Field research

Scientific papers, abstracts and posters from cooperation activities in Africa – 2022

MEDICI CON L'AFRICA CUAMM
Doctors with Africa

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MEDICI CON L'AFRICA
CUAMM
Doctors with Africa

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Con il contributo della Fondazione
Cassa di Risparmio di Padova e Rovigo

Fondazione
Cassa di Risparmio
di Padova e Rovigo

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e istituzioni e favorendo rapporti,
un tempo impensabili,
tra scienza di base e salute
pubblica».*

Giovanni Putoto,
Medici con l'Africa Cuamm

ENSURING THE FUTURE OF HEALTHCARE

Health systems in Italy and Africa have reached a critical turning point: already chronically underfunded, they are now also sapped by the COVID-19 pandemic and facing rising patient expectations as well as the privatization of services and political indifference. The most emblematic aspect of this difficult situation, however, is the crisis with regard to human resources: there are simply not enough health workers. It is estimated that by 2030 there will be shortfalls of some 30 to 40 thousand doctors and 60 to 70 thousand nurses in Italy, 4 million health workers across Africa, and 15 million globally. And this severe health worker shortage is just one part of the problem.

Also under way is a phenomenon known as "the Great Resignation", where growing numbers of health workers are opting to quit their professions early due to stress, inadequate remuneration and a lack of job satisfaction at the same time that more and more of their younger peers are moving abroad in search of "greener pastures". This is taking place against a backdrop of tension between more traditional training pathways and the need of health workers to develop new skills to better understand and address social determinants and inequities. Notwithstanding this difficult scenario, some positive developments are also being seen.

For more than 15 years the Italian Medical Students' Association (SISM) has provided medical students from 30 Italian universities with the opportunity to undertake a period of training in Africa. Those who have taken it up have reported positive impacts both professionally and personally, including increased motivation and resolve to carry on with their studies as well as greater personal awareness about health inequities and an intensified resolve to help tackle them[1].
The Junior Project Officer program is now two decades old, and has enabled over 300 medical students from Italy to train in Africa for six-month periods, taking on significant yet enriching challenges including a lack of resources, cultural diversity, interprofessional teamwork, mortality and research[2].
The number of doctoral scholarships offered by Italian universities to younger people in global health area is also on the rise. The same institutions, are also finally beginning to engage in interuniversity cooperation with African countries. An inspiring example is the second-level Master's degree program in pediatric and neonatal emergencies offered by the University of Padua and two Mozambican universities.
Last but not least, research conducted in the field has begun to truly come into its own, creating links between people and institutions and helping foster once unthinkable relationships between basic science and public health[3].
While these are but sprouts of hope, and clearly not enough to tackle the scope and complexity of the challenge vis-à-vis the lack of health workers, they are still promising signs that call for systematic nurturing and development. Indeed, a critically important part of caring for patients is caring for the health workforce itself.

Giovanni Putoto
Head of Operational Programming and Research,
Doctors with Africa CUAMM

LA RISORSA UMANA COME PROMESSA AL FUTURO

I sistemi sanitari in Italia e in Africa sono a un tornante cruciale della loro storia.
Usciti esausti dalla epidemia di Covid-19, soffrono di un cronico sotto finanziamento, patiscono la privatizzazione dei servizi e l'indifferenza della politica. Il tratto più emblematico di questo smarrimento, però, è la crisi profonda della risorsa umana: mancano gli operatori sanitari, i care givers. *Le stime variano dai 30-40 mila medici e 60-70 mila infermieri in Italia ai 4 milioni in Africa fino 15 milioni a livello globale previsti fino al 2030.*

C'è poi il fenomeno della Great Resignation *o del disimpegno: stress, condizioni retributive inadeguate e scarsa gratificazione professionale spingono molti lavoratori della salute a licenziarsi anzitempo mentre si ingrossano le fila dei più giovani che migrano all'estero in cerca di opportunità migliori. Sullo sfondo, la tensione tra percorsi formativi focalizzati sui meccanismi biologici della malattia e le esigenze di sviluppare nuove competenze per affrontare i determinanti e le disuguaglianze sociali e le sfide della salute globale.*
Uno scenario non confortante in cui qualcosa di positivo si sta muovendo, con nuove prospettive per i più giovani nella formazione e nella ricerca sul campo.
Il Segretariato Italiano degli Studenti di Medicina invia da oltre 15 anni in Africa studenti di medicina da 30 università italiane. L'impatto positivo, a detta degli studenti, è sia sul versante professionale, con una maggiore motivazione a proseguire gli studi, sia su quello personale, con un rinnovato impegno ad affrontare il tema delle diseguaglianze in salute[1].
L'iniziativa Junior Project Officer *è al suo ventesimo anno: oltre 300 specializzandi italiani hanno trascorso un periodo di formazione di 6 mesi in Africa affrontando sfide e difficoltà inedite e arricchenti, come le diversità culturali, la scarsità delle risorse, la collaborazione interprofessionale, la morte, la ricerca[2].*
Crescono anche le borse di dottorato offerte dalle università italiane su temi di salute globale. Spinte dalla necessità di allargare gli orizzonti internazionali e il dialogo con la società civile, le università si aprono alla cooperazione interuniversitaria anche in Africa. Ne è un esempio il Master di secondo livello in emergenze pediatriche e neonatologiche che coinvolge l'Università Padova e due Università Mozambicane.

Infine, la ricerca sul campo comincia ad avere una sua dignità, unendo persone e istituzioni e favorendo rapporti, un tempo impensabili, tra scienza di base e salute pubblica[3].

Sono germogli, piccole promesse, certamente insufficienti in rapporto alla vastità e alla complessità dei problemi che affliggono le risorse umane in sanità. Sono tuttavia segnali che vanno coltivati e diffusi in maniera sistematica. Prendersi cura dei pazienti significa anche e soprattutto prendersi cura della risorsa umana.

Giovanni Putoto
Responsabile della Programmazione e della Ricerca Operativa,
Medici con l'Africa Cuamm

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[1] Quaglio, GL et al. *Medical Electives in Sub-Saharan Africa: A 15-Year Student/NGO-Driven Initiative*. **J Community Health** 47, 273–283 (2022). https://doi.org/10.1007/s10900-021-01045-5.
[2] Quaglio GL, *Putoto G et al. International medical electives in Sub-Saharan Africa: Experiences from a 19-year NGO-driven initiative*, **BMC Medical Education**, submitted for publication.
[3] Alberto Mantovani, Maria Rescigno, Guido Forni, Francesca Tognon, Giovanni Putoto, Jerry Ictho and Peter Lochoro, *Covid-19 Vaccines and A Perspective On Africa*, **Trends in Immunology** (2023).

PARTNERING ON RESEARCH AND INTERVENTIONS TO GENERATE HEALTH

Studies, analyses and international partnerships to generate new know-how and integrate it into our programs on the ground: this describes both the aim and outcome of Doctors with Africa CUAMM's 2022 operational research.

This year saw not only the publication of 31 studies in international journals, but also research activities in every area of intervention and country with which CUAMM engages. While we focused in particular on newborn and child health – of vital importance for fostering healthy futures for individuals and communities alike – and infectious diseases, we also carried out numerous interventions in the areas of nutrition, chronic diseases and public health.

Our research encompassed studies on the management of newborns in low-resource settings and chronic diseases like diabetes (a critical matter in African countries affected by food insecurity) as well as one conducted in a pair of Angolan health centers with the aim of improving the care and management of tuberculosis (TB) patients through better data collection and tracing systems.

We also worked on a large and diverse group of studies dealing with various aspects of infectious and tropical diseases, especially HIV/AIDS, malaria and TB, with a focus on drug resistance, a mounting challenge both locally and globally.

A few studies continued to investigate the impact of the COVID-19 pandemic on already tenuous health systems in low-resource countries, and in exceptionally difficult situations such as the camps hosting refugees and IDPs in Mozambique and Ethiopia.

Finally, analyses were done of various sensitive health and social issues that have now made their way onto "Western" agendas as well, including the mental health of adolescents and vulnerable individuals such as HIV/AIDS patients and others who are particularly disadvantaged either from a socio-economic perspective and/or in terms of their lack of access to health services.

The decision by prominent international journals including BMC, Scientific Reports and Frontiers in Public Health to publish CUAMM's research this year testifies to the growing recognition of our organization's expertise and the quality of our research. Following the compulsory hiatus due to the COVID-19 pandemic, CUAMM's participation in conferences both in Italy and abroad is also on the rise, enabling us to share our work with our peers through oral and poster presentations.

It was certainly no foregone conclusion that an international development organization so busy in the field would have achieved such recognition. We are also pleased to note the number of health research institutions with which CUAMM collaborated in 2022: a total of 76, including nearly 30 in Africa and a growing number of partners in Italy, elsewhere in Europe and further abroad, from Thailand to the United States.

RICERCA E INTERVENTO, INSIEME PER COSTRUIRE SALUTE

Studi, analisi, partnership internazionali per produrre nuova conoscenza e integrarla ai programmi di intervento sul campo: è stata questa la ricerca operativa a firma Cuamm nel 2022.

31 ricerche pubblicate su riviste internazionali e un'attività di ricerca che ha coperto tutte le aree geografiche e di intervento in cui Cuamm opera; tra i temi toccati emerge una attenzione particolare alla salute infantile e neonatale, premessa necessaria per costruire un futuro di salute per i singoli e per la collettività, e alle malattie infettive ma con uno sguardo sempre ampio che non trascura la nutrizione, le malattie croniche e la salute pubblica.

Dagli studi sulla gestione del neonato nei Paesi a basse risorse a quelli sulle malattie croniche come il diabete, critico anche nei contesti africani di insicurezza alimentare, fino allo studio in due centri angolani per migliorare i processi di cura e gestione dei pazienti malati di tubercolosi tramite sistemi di raccolta dati e tracciamento.

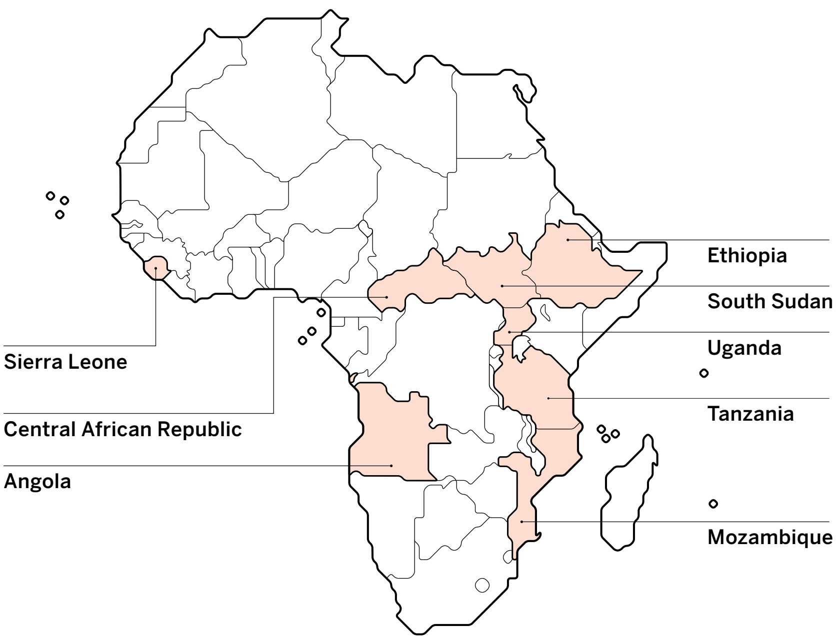
Rilevanti per numero e varietà sono le ricerche che approfondiscono i diversi aspetti delle malattie infettive e tropicali, in particolare HIV, malaria e tubercolosi, con un focus sul tema della farmaco-resistenza, di rilevanza crescente anche a livello globale.
Qualche linea di ricerca approfondisce ancora la pandemia di Covid-19, ponendo l'accento sull'impatto che ha avuto sui sistemi sanitari, già fragilissimi, dei Paesi a risorse limitate, e nelle situazioni particolarmente critiche come quelle dei campi che accolgono i profughi, i displaced people, e i rifugiati in Mozambico ed Etiopia.
Non mancano le analisi su temi delicatissimi sia sul piano sanitario sia sociale, ormai entrati anche nelle agende 'occidentali': si tratta della salute mentale e del suo impatto sugli adolescenti e sui soggetti fragili, siano essi malati di HIV o membri di comunità particolarmente svantaggiate a livello socio-economico e di accesso alla salute.

Le riviste che hanno ospitato i lavori del Cuamm – tra cui BMC, Scientific Reports, Frontiers in Public Health *– confermano una crescita di autorevolezza e posizionano l'organizzazione come autore di ricerca accreditato. Inoltre, dopo la pausa forzata legata al Covid-19, appare in crescita anche la partecipazione a convegni, in Italia e all'estero, in cui le ricerche a firma Cuamm sono state condivise con esperti e addetti ai lavori attraverso presentazioni orali e nelle poster session dedicate.*

Un posizionamento in ambito scientifico di valore e niente affatto scontato per un'organizzazione che si occupa di cooperazione e interventi sul campo. Lo conferma anche il numero di centri di ricerca e istituzioni che si occupano di salute e sanità con cui Cuamm ha collaborato nel 2022: 76 in totale, con una presenza di quasi 30 partner africani e un numero sempre crescente di partner italiani, europei e di altri Paesi, dalla Thailandia agli USA.

Doctors with Africa CUAMM

Medici con l'Africa Cuamm



Doctors with Africa CUAMM is the largest Italian NGO working to **improve the health of vulnerable communities in Sub-Saharan Africa**. CUAMM carries out **long-term projects in 8 countries** in the region and partners with **universities and research centers** in Italy and abroad to raise awareness about people's right to health care. CUAMM also organizes **courses on global health** for medical students and health professionals and conducts **research** with international partners, convinced that such endeavors are vital to developing **quality international healthcare programs**.

*Medici con l'Africa Cuamm è la più grande organizzazione italiana per la **promozione e la tutela della salute delle popolazioni africane**. Medici con l'Africa Cuamm realizza **progetti a lungo termine in 8 paesi** dell'Africa Sub-sahariana e collabora con **università e centri di ricerca in Italia e in Europa**. Organizza inoltre **corsi di Salute Globale** per studenti di Medicina e professionisti sanitari e lavora con partner internazionali a **progetti di ricerca**, nella convinzione che questi sforzi siano necessari per lo sviluppo di **programmi sanitari internazionali di qualità**.*

Doctors with Africa CUAMM currently operates in Angola, Central African Republic, Ethiopia, Mozambique, Sierra Leone, South Sudan, Tanzania and Uganda. / *Medici con l'Africa Cuamm attualmente lavora in Angola, Etiopia, Mozambico, Repubblica Centrafricana, Sierra Leone, Sud Sudan, Tanzania e Uganda attraverso:*

23
hospitals / *ospedali*

95
districts (for public health activities, mother-child care, the fight against HIV/AIDS, tuberculosis and malaria, training) / *distretti (iniziative per la salute pubblica, assistenza e cure per la salute materna e infantile, lotta contro l'HIV/AID, la tubercolosi e la malaria)*

4
nursing schools / *scuole per infermieri e ostetriche*

1
university (Mozambique) / *università (Mozambico)*

4,581
health workers, including / *collaboratori sanitari, che includono:*

500
from Europe and abroad / *europei e internazionali*

Operational research in 2022
Ricerca operativa nel 2022

31 research articles published in international journals on topics ranging from newborn health and infectious diseases to drug resistance and the mental health of youth and other particularly vulnerable individuals.
CUAMM's operational research in 2022 testified to our chosen methodological approach: to conduct studies based on, and in parallel with, our interventions on the ground in order to enhance the quality and effectiveness of the latter.
This year we were pleased to partner with **234** researchers from **76** research centers in Italy, Africa and elsewhere around the world, together producing fresh know-how and devising new programs to be implemented in low-resource settings.

31 *ricerche pubblicate su riviste internazionali: dalla ricerca sulla salute neonatale a quella sulle malattie infettive e sulla farmaco-resistenza fino all'approfondimento di alcuni temi più delicati, come la salute mentale e il suo impatto sui più giovani e sui fragili. Nel 2022 la ricerca operativa Cuamm è entrata nei temi di lavoro sul campo, dimostrando l'approccio metodologico che intendiamo perseguire: una ricerca che si integra all'intervento per garantire qualità. Abbiamo lavorato a fianco di* ***76*** *centri di ricerca italiani, africani e internazionali, coinvolgendo* ***234*** *ricercatori e ricercatrici che hanno collaborato per costruire nuova conoscenza e sviluppare progetti in Paesi con risorse limitate.*

Maternal and child health
Salute materna e infantile

Infectious and tropical diseases
Malattie infettive e tropicali

Public health and universal coverage
Copertura sanitaria universale ed equità

Nutrition
Nutrizione

Chronic diseases
Malattie croniche

OUR RESEARCH PARTNERS

The 76 research centers, universities and other organizations – in Africa, Europe (including Italy), and other countries around the world – with which Doctors with Africa CUAMM partnered on research 2022.
I 76 centri di ricerca, università e organizzazioni con cui Medici con l'Africa CUAMM ha collaborato per produrre la ricerca nel 2022.

AFRICA

1. St. John of the Cross, Tosamaganga Council Designated Hospital, Tanzania
2. St. Kizito Hospital, Matany, Uganda
3. Songambele Hospital, Simiyu, Tanzania
4. African Population and Health Research Center, Nairobi, Kenya
5. Faculty of Medicine, Ministry of Health, Eduardo Mondlane University, Maputo, Mozambique
6. Mozambican Diabetes Association (AMODIA), Maputo, Mozambique
7. National Directory of Public Health, Ministry of Health of Angola, Luanda, Angola
8. UNICEF Mozambique, Maputo, Mozambique
9. St. Luke Catholic Hospital & College of Nursing and Midwifery, Wolisso, Ethiopia
10. Tosamaganga Hospital, Iringa, Tanzania
11. Centre Hospitalier Universitaire Pédiatrique de Bangui (CHUPB), Bangui, Central African Republic
12. Institut Pasteur de Bangui, Bangui, Central African Republic
13. Faculté des Sciences de la Santé (FACSS), Université de Bangui, Bangui, Central African Republic
14. College of Health and Medical Sciences, Haramaya University, Dire Dawa, Ethiopia
15. Ministry of Health and Sanitation, Sierra Leone
16. The National Emergency Medical Service - NEMS, Ministry of Health and Sanitation, Freetown, Sierra Leone
17. Ministry of Health of Angola, Luanda, Angola
18. Department of Behavioural Sciences, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
19. Ministry of Health Community Development Gender Elderly and Children, Dar es Salaam, Tanzania
20. Muhimbili University of Health and Allied Sciences, Department of Epidemiology and Biostatistics, Dar es Salaam, Tanzania
21. St. John's XXIII Hospital Aber, Jaber, Uganda
22. African Network for Change, Kampala, Uganda
23. Missionary Catholic Hospital of Chiulo, Ombadja Municipality, Techiulo, Angola
24. Ngokolo Health Centre, Catholic Diocese of Shinyanga, Tanzania
25. Bugisi Health Centre, Catholic Diocese of Shinyanga, Tanzania
26. Disease Prevention and Control Directorate, Federal Ministry of Health, Addis Ababa, Ethiopia
27. Université du Kwango - UNIK, Kenge, Democratic Republic of the Congo

ITALY

1. University of Padua
2. Mabix srl
3. Department of Woman's and Children's Health, University of Padua
4. Department of Medicine, Diabetology Service, ULSS 2 Marca Trevigiana, Treviso
5. Department of Medicine, University of Padua
6. Department of Biomedical Sciences and Human Oncology, Clinic of Infectious Diseases, University of Bari
7. Association "Amici Per Il Centrafrica ODV", Limido Comasco (Como)
8. Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa
9. Management and Healthcare Laboratory, Institute of Management and Department EMbeDS, Sant'Anna School of Advanced Studies, Pisa
10. School of Advanced International Studies (SAIS) Europe, Bologna Institute for Policy Research (BIPR), Johns Hopkins University, Bologna
11. CRIMEDIM – Center for Research and Training in Disaster Medicine, Humanitarian Aid, and Global Health, University of Piemonte Orientale, Novara
12. Department of Surgical Sciences and Integrated Diagnostics, San Martino Policlinico Hospital IRCCS for Oncology, University of Genoa
13. Department of Intensive Care, University of Milan Bicocca, Monza
14. Department of Specialistic Surgery, Ophthalmology Service, ULSS 2 , Treviso
15. National Center for Global Health, National Institute of Health (ISS), Rome
16. Clinic of Infectious Diseases, University Hospital, University of Bari
17. FISSPA Department, University of Padua
18. Clinic of Infectious Diseases, Catholic University of the Sacred Heart, Rome
19. Department of Infectious Diseases, National Institute of Health (ISS), Rome
20. Department Woman and Child Health Sciences, Catholic University of the Sacred Heart, Rome
21. Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Laboratory and infectious diseases sciences, Rome
22. Department of Translational Medicine, University of Piemonte Orientale, Novara
23. Disaster Medicine Service 118, ASL CN1, Levaldigi (Cuneo)
24. Department of Diagnostics and Public Health, University of Verona
25. St John and Paul Hospital, Department of Child Health, Venice
26. Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital, University of Turin, Orbassano (Turin)
27. Department of Internal Medicine and Geriatrics, Geriatric Unit, University of Palermo
28. National Institute for Infectious Diseases Lazzaro Spallanzani - IRCCS, Rome
29. University of Bologna
30. Meyer Children's University Hospital, Florence

EUROPE

1. European Parliamentary Research Services, European Parliament, Brussels, Belgium
2. Department of HIV Medicine, Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom
3. Department of Intensive Care, Amsterdam University Medical Centers, Academic Medical Center, Amsterdam, The Netherlands
4. Pulmonary Engineering Group, Department of Anaesthesiology and Intensive Care Medicine, University Hospital Carl Gustav Carus and Technical University Dresden, Germany
5. Anaesthesia and Intensive Care Medicine, School of Medicine, National University of Ireland, and Galway University Hospitals Ireland, Galway, Ireland
6. Department of Global Health, Amsterdam Institute for Global Health and Development, University of Amsterdam, The Netherlands
7. ISGlobal - Barcelona Institute for Global Health, Hospital Clinic, University of Barcelona, Spain
8. Department of Global Health and Development London School of Health and Tropical Medicine, London, United Kingdom
9. Department of Microbiology, Immunology and Transplantation, Clinical and Epidemiological Virology, Institute for the Future, Rega Institute for Medical Research, KU Leuven, Leuven, Belgium
10. Department of Public Health and Primary Care, Academic Centre for Nursing and Midwifery, KU Leuven, Leuven, Belgium
11. Faculty of Economics and Business, Access To Medicine Research Center, KU Leuven, Belgium
12. Department of Earth and Environmental Sciences, Division of Bioeconomics, KU Leuven, Belgium
13. Research Group on Emergency and Disaster Medicine, Vrije Universiteit Brussels, Belgium
14. Centre for Health, Performance, and Wellbeing, Anglia Ruskin University, Cambridge, United Kingdom
15. Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom

OTHER COUNTRIES

1. School of Public Health and Preventive Medicine, Monash University, Australia
2. Department of Critical Care Medicine, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil
3. Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
4. Tufts University School of Medicine, Boston, USA

76 Research partners
partner di ricerca

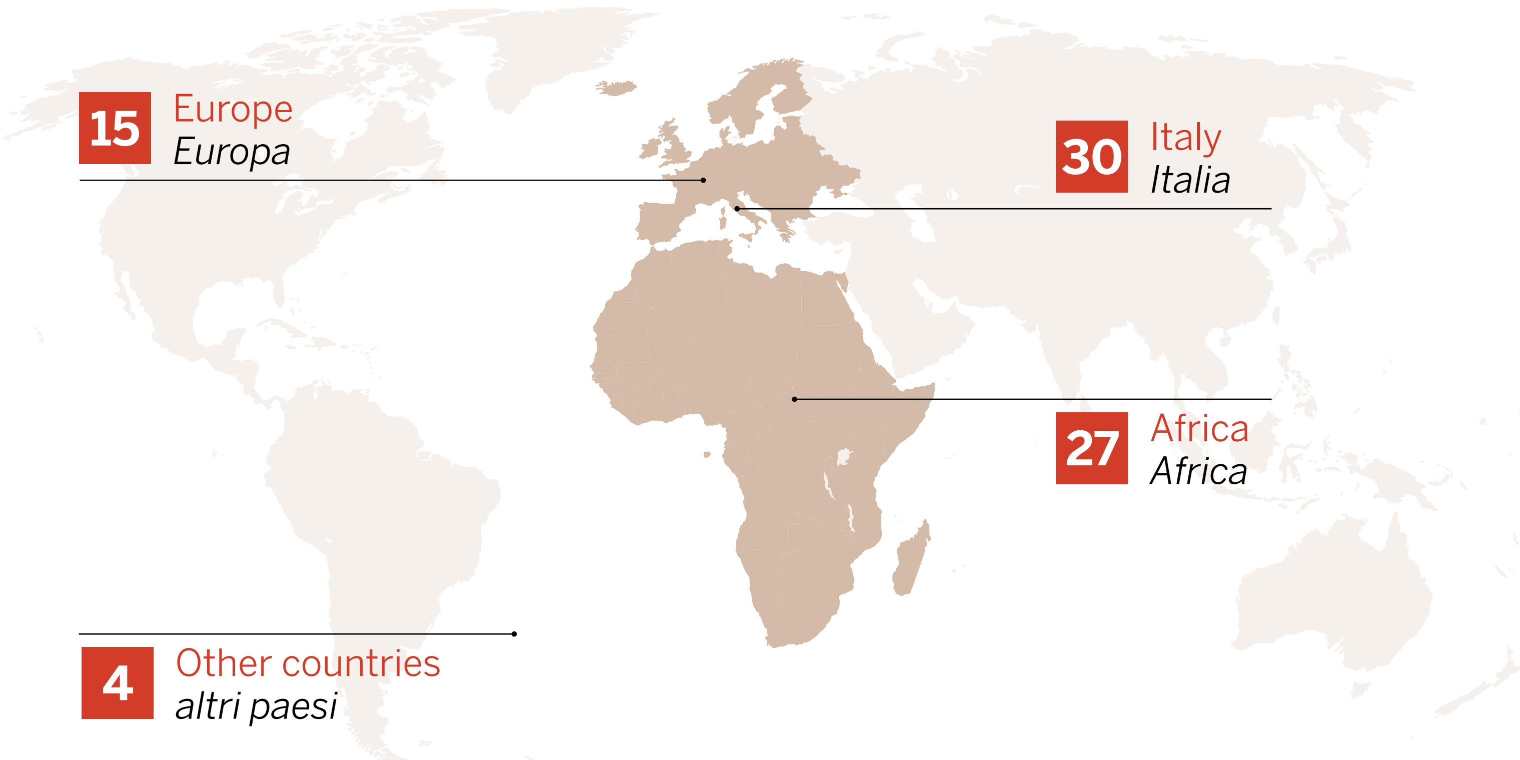


TABLE OF CONTENTS

PAPERS

Maternal and child health

POSTER PRESENTATIONS

85 **01 → Multi-countries**
23° Congresso Nazionale Agorà Simp
Genoa, Italy, 29 September - 1 October 2022
- Guadagno C. et al., *Relationship between Admission Temperature and Risk of Cerebral Palsy in Infants Admitted to Special Care Unit in a Low Resource Setting: A Retrospective Single-Center Study*

86 **02 → Tanzania**
23° Congresso Nazionale Agorà Simp
Genoa, Italy, 29 September - 1 October 2022
- Pietravalle A. et al., *Impact of Quality Improvement Bundle on Neonatal Mortality in a District Hospital in Tanzania*

87 **03 → Central African Republic**
23° Congresso Nazionale Agorà Simp
Genoa, Italy, 29 September - 1 October 2022
- Kiteze Nguinzanemou C.J. et al., *Neonatal seizures in the pediatric teaching hospital in Bangui: Epidemiology, etiologies and outcome*

88 **04 → Central African Republic**
23° Congresso Nazionale Agorà Simp
Genoa, Italy, 29 September - 1 October 2022
- Kiteze Nguinzanemou C.J. et al., *A first experience of neonatal cerebral ultrasound in the Central African Republic*

89 **05 → Tanzania**
Congress of Paediatric Association of Tanzania
Zanzibar, Tanzania, 13 October 2022
- Borellini M. et al., *Premature new-borns follow-up in a semi-rural facility: A two years' experience at Tosamaganga Hospital*

90 **06 → Uganda**
15th European Public Health Conference
Berlin, Germany, 9-12 November 2022
- Bertoncello C. et al., *Assessment of maternal and newborn services in Uganda based on the Effective Coverage framework*

147

Infectious and tropical diseases

PAPERS

Infectious and tropical diseases

POSTER PRESENTATIONS

Chronic diseases

POSTER PRESENTATIONS

349 **01 → Ethiopia**
XLVI Convegno Associazione Italiana di Epidemiologia (AIE)
Padua, Italy, 29 June - 1st July 2022
- Paiola E. et al., *Caratteristiche cliniche e rischio di chetoacidosi diabetica nei pazienti dell'Ospedale St. Luke in Etiopia: un'analisi spaziale geografica*

350 **02 → South Sudan**
14th European Epilepsy Congress
Geneva, Switzerland, 9-13 July 2022
- Scanagatta C. et al., *Nodding Syndrome Alliance - preliminary data on clinical management from a multi-sectorial initiative addressing nodding syndrome and other forms of epilepsy in Western Equatoria, South Sudan*

351 **03 → Ethiopia**
15th European Public Health Conference
Berlin, Germany, 9-12 November 2022
- Benoni R. et al., *Epidemiological factors affecting health service utilization in diabetic patients in Ethiopia*

352 **04 → Tanzania**
The 4th National Non-Communicable Diseases Scientific Conference
Mwanza, Tanzania, 10-11 November 2022
- Bazzanini et. al., *An Integrated Management System for the treatment of Noncommunicable Diseases: evidences from a program implementation in Iringa DC*

ORAL PRESENTATIONS

353 **01 → Ethiopia**
15th European Public Health Conference
Berlin, Germany, 9-12 November 2022
- Paiola E. et al., *Diabetic ketoacidosis among patients admitted to a general hospital in Ethiopia: a spatial analysis*

PAPERS

POSTER PRESENTATIONS

Maternal and child health

Relationship between Admission Temperature and Risk of Cerebral Palsy in Infants Admitted to Special Care Unit in a Low Resource Setting: A Retrospective Single-Center Study

PAPER

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Maternal and child health

Focus country
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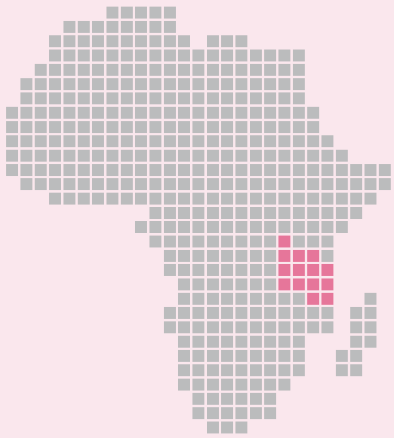

children

MDPI

Article

Relationship between Admission Temperature and Risk of Cerebral Palsy in Infants Admitted to Special Care Unit in a Low Resource Setting: A Retrospective Single-Center Study

Chiara Guadagno [1], Francesco Cavallin [2], Luca Brasili [1], Donald Micah Maziku [3], Dionis Erasto Leluko [3], Gaetano Azzimonti [1], Giovanni Putoto [4], Andrea Pietravalle [4,]* and Daniele Trevisanuto [5]

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Abstract: Background: Deviations from normothermia affect early mortality and morbidity, but the impact on neurodevelopment of the survivors is unclear. We aimed to investigate the relationship between neonatal temperature at admission and the risk of cerebral palsy (CP) at one month of age in a low-resource setting. Methods: This retrospective study included all inborn neonates admitted to the Special Care Unit of Tosamaganga Hospital (Tanzania) between 1 January 2019 and 31 December 2020. The neurological examination at one month of age was performed using the Hammersmith method. The relationship between the admission temperature and the risk of CP was investigated using logistic regression models, with temperature modeled as the non-linear term. Results: High/moderate risk of CP was found in 40/119 (33.6%) of the neonates at one month of age. A non-linear relationship between the admission temperature and moderate/high risk of CP at one month of age was found. The lowest probability of moderate/high risk of CP was estimated at admission temperatures of between 35 and 36 °C, with increasing probability when departing from such temperatures. Conclusions: In a low-resource setting, we found a U-shaped relationship between the admission temperature and the risk of CP at one month of life. Expanding the analysis of the follow-up data to 12–24 months of age would be desirable in order to confirm and strengthen such findings.

Keywords: birth; temperature; hypothermia; cerebral palsy; low-resource setting; neonate; neurological outcome

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1. Introduction

About 2.4 million neonates still die every year globally, with a greater risk in their first day of life [1]. As neonatal temperature early after birth seems to play a crucial role, the World Health Organization (WHO) guidelines focused on thermal control since 1993, in order to support health care providers in thermal management and prevention of thermal loss [2]. Deviations from normothermia have been demonstrated to be important contributors to neonatal morbidity and mortality in both high- and low-resource settings [3,4]. Thermal control at birth is a critical challenge in low-resource settings, where proper thermal care is often inadequate and thermal stability is underestimated in management protocols [5–8]. Despite WHO recommendations, deviations from normothermia remain a public health issue in low-resource settings, where it is often under-recognized, under-documented, and poorly managed [8,9]. Beyond early mortality and morbidity, it is reasonable to suspect that deviations from normothermia may also impact the neurodevelopment of survivors [10]. Cerebral palsy (CP) is the most frequent physical disability in children, with decreasing prevalence in high-income countries and uncertain rates in low/middle-income countries [11]. Although the diagnosis of CP usually occurs at 12–24 months of age, it can be made before six months of age [11]. This is desirable given the therapeutic opportunities during the period of greatest brain development and neuroplasticity, but effective implementation is hampered by inadequate diagnostic equipment in low-income countries. In such settings, alternative diagnostic tools can provide affordable and reliable assessment of neurological damage [11]. This study aimed to investigate the relationship between neonatal temperature at admission and risk of CP at one month of age in a low-resource setting. Furthermore, the relationship between the admission temperature and mortality was also investigated in order to strengthen the considerations of the findings.

2. Materials and Methods

2.1. Study Design and Setting

This is a retrospective study on the relationship between neonatal temperature at admission and risk of CP at 1 month of age. The study was performed at the Special Care Unit (SCU) of Tosamaganga Hospital, which is a district designated hospital situated in the district of Iringa, Tanzania. This is a referral facility for a geographical area that covers about 260,000 people for major obstetric emergencies and has also a SCU offering basic intensive care, such as intravenous therapies, phototherapy, and oxygen supplementation without non-invasive respiratory support and mechanical ventilation. About 3000 deliveries and 500 admissions to the SCU occur every year at Tosamaganga Hospital. Moreover, since January 2019, a neonatal follow-up clinic has been available to check clinic well-being, growth, and neurological development for all babies discharged from the SCU during their first year of life.

2.2. Patients

All neonates admitted to the SCU of Tosamaganga Hospital between 1 January 2019 and 31 December 2020 were evaluated for inclusion in this study. Exclusion criteria were (i) outborn neonates, (ii) being admitted to the SCU after the first day of life, and (iii) missing data about body temperature at admission.

2.3. Data Collection

Due to the retrospective design, relevant information was collected in an anonymized dataset from hospital charts. When a baby was admitted to the SCU, the attending nurse measured the axillary temperature with a digital thermometer (C202; Terumo, Tokyo, Japan), and replicated the measurement if the temperature was <35 °C or >39 °C. According to WHO indications, temperatures in the 36.5–37.5°C range were classified as normothermia, >37.5 °C as hyperthermia, 36–36.4 °C as mild hypothermia, and <36 °C as severe/moderate hypothermia [12]. Admission diagnosis was made according to clinical assessment due to limited availability of laboratory and instrumental exams. Birth asphyxia was defined as 5-min Apgar Score of < 7. Respiratory distress was diagnosed in presence of signs of increased work of breathing (measured by the Silverman Anderson Score) and/or hypoxemia with need for oxygen supplementation. Early- or late-onset sepsis was diagnosed in presence of clinical signs (i.e., fever, hypotonia, irritability) within or after the first 7 days of life. Hypoglycemia was defined as blood glucose of < 2.6 mmol/L at any time. Jaundice was diagnosed according to the Kramer's rule [13]. Weight loss was defined as body weight loss of >10%. Skin infection included abscess and omphalitis.

2.4. Neurological Examination

The neonatal follow-up program at Tosamaganga Hospital is scheduled at one, three, six, nine, and twelve months of corrected age for preterm infants and chronologic age for term infants. In this study, we chose to focus on the follow-up at 1 month of age, due to the high rate of lost to follow-up at later ages. As in many low-resource settings, the SCU lacked expensive diagnostic equipment (such as magnetic resonance imaging) and personnel trained in neurological examination. Hence, we identified affordable and reliable tools for neurological assessment, which were not time consuming or requiring specialized doctors. The neurological examination was performed using the standardized criteria provided by the Hammersmith method. We applied the Hammersmith Neonatal Neurological Examination (HNNE) by Spittle et al. [14], who used optimality scores between 10th–90th centile to define low risk, scores between 5th–10th, or 90th–95th, to define medium risk, and scores below 5th, or above 95th, to define high risk. Posters with images of neurological items by age were created and made available in the room where the examinations took place. The neurological examination was performed by healthcare providers with 6 month of on-the-job training (CG and LB) and each infant was classified at low risk, medium risk, or high risk of CP, as reported in Table 1 [14].

Table 1. Classification of risk of cerebral palsy according to the Hammersmith Neonatal Neurological Examination (HNNE).

Risk	HNNE
Low risk	27–33
Medium risk	25.4–26.9 or 33.1–33.5
High risk	<25.4 or >33.5

2.5. Statistical Analysis

Continuous data were summarized as median and interquartile range (IQR), and categorical data as number and percentage. The relationships between admission temperature and (i) mortality and (ii) risk of CP were investigated with logistic regression models where temperature was modeled with first-, second-, and third-order polynomials, and with restricted cubic splines. Furthermore, multivariable logistic regressions were applied to assess the effect of admission temperature on mortality (adjusting for birth weight, Apgar score at 5 min, major malformations, and meconium-stained amniotic fluid) and risk of CP (adjusting for birth weight and Apgar score at 5 min). The adjusting variables were chosen among the clinically relevant variables and according to the number of neonates with the event, while gestational age could not be included because it was largely missing. All tests were two-sided and a p-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria) [15].

3. Results

A total of 906 newborns were admitted to the SCU of Tosamaganga Hospital between 1 January 2019 and 31 December 2020. Of them, 450 were excluded from the analysis because they were outborn (n = 259) or were admitted after their day of birth (n = 191). A further three infants were excluded due to missing temperature data at admission (Figure 1). The remaining 453 newborns were included in this analysis and their characteristics are reported in Table 2. Information on the gestational age was largely missing (420/459, 91.5%). The median temperature at admission was 35.4 °C (IQR 34.7–36.1 °C; min 30.6 °C, max 37.5 °C). Severe/moderate hypothermia was reported in 316 of the neonates (69.7%), mild hypothermia in 66 (14.6%), normal temperature in 71 (15.7%), and no infants with a temperature higher than 37.5 °C were observed. The treatments included antibiotics (301 neonates, 66.4%), anticonvulsant (48 neonates, 10.6%), and aminophylline/caffeine

(78 neonates, 17.2%). Oxygen therapy was administered to 399 neonates (88.1%) for a median of two days (IQR 1–5). IV fluids were administered to 323 neonates (71.3%) for a median of five days (IQR 3–8). Phototherapy was offered to 67 neonates (14.8%).

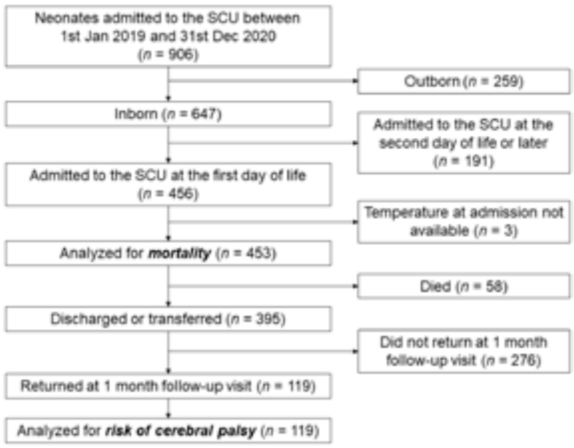

Figure 1. Flowchart of patient selection for analysis of mortality and risk of cerebral palsy among inborn neonates who were admitted on their day of birth to the Special Care Unit of Tosamaganga Hospital between 1 January 2019 and 31 December 2020.

Table 2. Characteristics of inborn neonates who were admitted on their day of birth to the Special Care Unit of Tosamaganga Hospital between 1 January 2019 and 31 December 2020 and those who attended the 1-month follow-up.

	Admitted Neonates (*n* = 453)	Newborns at 1 Month Follow-Up (*n* = 119)
Males	237 (52.3)	65 (54.6)
Birth weight, grams [a]	2750 (1940–3180)	2610 (1795–3055)
Birth weight:		
Normal birth weight (≥2500 g)	269 (59.4)	62 (52.1)
Low birth weight (1500–2499 g)	130 (28.7)	43 (36.1)
Very low birth weight (1000–1499 g)	42 (9.3)	14 (11.8)
Extremely low birth weight (<1000 g)	12 (2.6)	0 (0.0)
Temperature at admission, °C [a]	35.4 (34.7–36.1)	35.4 (24.8–35.9)
Temperature at admission:		
36.5–37.5 °C	71 (15.7)	16 (13.5)
36–36.5 °C	66 (14.6)	13 (10.9)
<36 °C	316 (69.7)	90 (75.6)
HIV-positive mother	35/450 (7.8)	13/118 (11.0)
Maternal VDRL [b]	7/438 (1.6)	1/117 (0.9)
Apgar score at 1 min [a]	5 (3–7)	5 (2–8)
Apgar score at 5 min [a]	7 (5–10)	8 (5–10)
PROM [c]	86 (19.0)	22 (18.5)
Meconium-stained amniotic fluid	133 (29.4)	34 (28.6)
Maternal fever	12 (2.6)	2 (1.7)

Table 2. *Cont.*

	Admitted Neonates (n = 453)	Newborns at 1 Month Follow-Up (n = 119)
Dexamethasone:		
None	414 (91.4)	99 (84.2)
Complete cycle (24 mg)	26 (5.7)	14 (11.8)
Incomplete cycle (12 mg)	13 (2.9)	6 (5.0)
Mode of delivery		
Spontaneous vaginal delivery	221 (48.8)	63 (52.9)
Assisted vaginal delivery	42 (9.3)	11 (9.3)
Caesarean section	190 (41.9)	45 (37.8)
Twin pregnancy	61/452 (13.5)	24 (20.2)
Birth asphyxia	171 (37.7)	49 (41.2)
Respiratory distress	308 (68.0)	83 (69.7)
Early-onset sepsis	22 (4.9)	6 (5.0)
Late-onset sepsis	18 (4.0)	5 (4.2)
Hypoglycemia	20/428 (4.7)	7/114 (6.1)
Jaundice	85 (18.8)	29 (24.4)
Weight loss	10 (2.2)	2 (1.7)
Skin infection	14 (3.1)	8 (6.7)
Major malformations or chromosomopathies [d]	19 (4.2)	2 (1.7)

Data were summarized as n (%) or [a] median (IQR). Definitions are provided in Methods section. HIV: human immunodeficiency virus. PROM: prolonged rupture of membranes. VDRL: venereal disease research laboratory test. [b] VDRL was treated in 5/7 mothers. [c] PROM prophylaxis in 18/88 mothers. [d] Major malformations included cardiac heart disease (n = 9), club feet (n = 3), conjoined sibling (n = 2), cranial malformation (n = 1), Down syndrome (n = 1), myelomeningocele and encephalocele (n = 1), imperforate anus (n = 1), arthrogryposis (n = 1) and hypospadias (n = 1).

After a median length of stay of six days (IQR 4–11), 58 neonates died (12.8%) while 390 were discharged (86.1%) and five were transferred to other health facilities (1.1%). The analysis suggested modelling the relationship between mortality and admission temperature with first-order polynomial ($p < 0.0001$), showing the highest mortality risk for decreasing temperature (Figure 2). At the multivariable analysis, temperature at admission was not an independent predictor of mortality ($p = 0.46$), adjusting for birth weight ($p < 0.0001$), Apgar score at 5 min ($p = 0.0008$), major malformations ($p < 0.0001$), and meconium-stained amniotic fluid ($p = 0.56$).

Overall, 119 out of 395 neonates (30.1%) returned at the follow-up visit at one month of age. The neurodevelopmental assessment suggested low risk of CP in 79 neonates (66.4%), moderate risk in 31 (26.0%), and high risk in nine (7.6%). The analysis suggested modelling the relationship between high/moderate risk of CP at one month of age and the admission temperature with second-order polynomial ($p = 0.04$), showing the lowest probability between 35–36 °C and increasing probability when departing from the 35–36 °C range (Figure 3). At the multivariable analysis, the temperature at admission was still associated with risk of CP ($p = 0.04$), adjusting for birth weight ($p = 0.002$) and Apgar score at 5 min ($p = 0.18$).

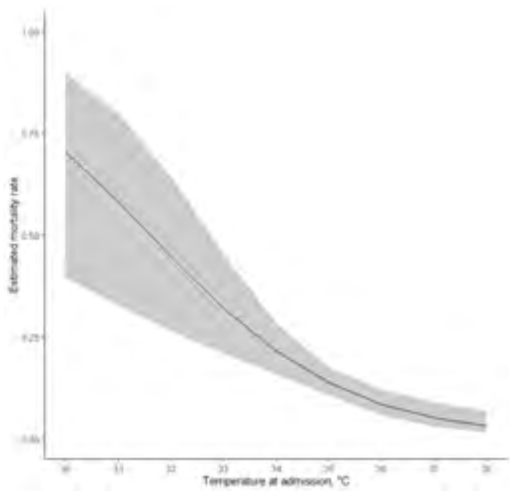

Figure 2. Estimated mortality rate according to neonatal temperature at admission as modeled with first-order polynomial. Shaded areas represent bootstrap 95% confidence intervals.

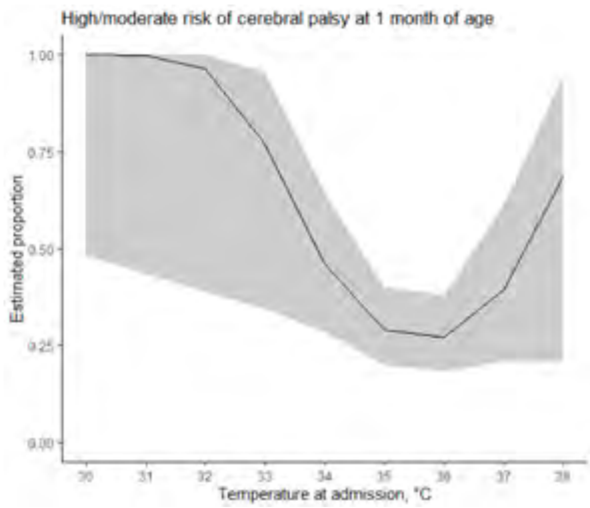

Figure 3. Estimated proportion of high/moderate risk of cerebral palsy at 1 month of age. Shaded areas represent bootstrap 95% confidence intervals.

4. Discussion

Our findings showed a small proportion of neonatal normothermia in a low-resource setting and a non-linear relationship between the admission temperature and the risk of CP at one month of life. To our knowledge, this is the first study to explore the variation in the risk of CP across a wide range of admission temperatures and to suggest a non-linear relationship between the admission temperature and the risk of CP in a low-resource setting. Our results extend previous reports on a U-shaped relationship between admission temperature and neonatal morbidity and mortality in high- and low-resource settings [3,4], suggesting a U-shaped relationship between the admission temperature and the risk of CP in survivors at one month of life. The study also has some limitations that should be considered by the reader. First, the retrospective design does not allow us to draw any causal relationships. Second, the compliance to follow-up visits was partial, hence limiting the representativeness of the findings for the original sample of the discharged neonates. Third, the short duration of the follow-up assessment only allows speculations about the clinical confirmation of the long-term neurological status. Finally, we applied the HNNE by Spittle et al. [14], hence we estimated the category of gestational age (moderate preterm infants, late preterm infants, term infants) by using the relationship between 50th percentile of birthweight and gestational age. Literature offers heterogeneous information about neonatal temperature at admission and neurological outcome. Previous studies mainly focused on hypothermia and intraventricular hemorrhage (IVH)—as high-grade IVH is an important cause of severe cognitive and motor neurologic impairment—in very preterm infants, and reported conflicting results. Laptook et al. [16], Wilson et al. [17], Chang et al. [18], and Ng'eny et al. [19] did not find any significant associations between admission temperature and severe IVH in very preterm infants in the United States, Europe, Taiwan, and South Africa. Of note, Chang et al. did not find any associations also with two-year neurodevelopmental impairment [18]. On the other hand, Miller et al. [20] and Yu et al. [21] reported an increased risk of IVH in hypothermic very preterm infants in the United States and China. In addition, Lyu et al. [3] showed a U-shaped relationship between admission temperature and severe neurological damage (IVH or periventricular leukomalacia) in very preterm infants in Canada. Our data suggest a similar U-shaped relationship between the admission temperature and moderate/high risk of CP during early follow-up. The lowest probability of moderate/high risk of CP was estimated at the admission temperature of between 35–36 °C, with increasing probability when departing from such temperature. However, the reader should be aware that lower admission temperature was associated with higher in-hospital mortality risk, but the analysis of risk of CP could be performed in the subgroup of survivors who returned at the one-month follow-up visit, thus preventing us from drawing a combined consideration. Overall, our results convey a similar message about such U-shaped relationship, although there are some differences in terms of the timing of the assessment (one month vs. before discharge), outcome measure (CP vs. IVH), population (term + preterm vs. very preterm infants), temperature range (30.6–37.5 °C vs. 32–41 °C), and study setting (low- vs. high-resource). We believe that such aspects may explain the slight difference in the estimated temperature range with the lowest risk of adverse neurological outcome (35–36 °C vs. 36.8 °C). In sub-Saharan Africa, the incidence of postnatal hypothermia is very high, with figures ranging from 32 to 85% [5]. In our study, we found a large proportion (84.3%) of neonates who were admitted with hypothermia, thus highlighting that the prevention of postnatal thermal loss is still an unsolved major challenge in these settings. In addition, the high proportion of birth asphyxia can be explained by the patient selection (inborn neonates who were admitted at the first day of life) and the referral role of the Tosamaganga Hospital. Of note, only one in three of the discharged neonates returned for the follow-up visits. In low-resource settings, this situation has been commonly reported in other pediatric situations, such as immunization or malnutrition [22,23]. Beyond limiting the representativeness of the findings about risk of CP, this information calls for actions to investigate the reasons for non-adherence to follow-up visits and to plan adequate interventions in order to overcome the barriers to adherence [24]. In addition, expanding the analysis of the follow-up data to 12–24 months of age would be desirable in order to strengthen the findings and confirm the U-shaped association between the admission temperature and the risk of CP.

5. Conclusions

In a low-resource setting, we found a U-shaped relationship between the admission temperature and the risk of CP at one month of life. Beyond the study limitations, these findings add a special alert about the possible association between the admission temperature and the risk of adverse neurological outcomes among newborns in low-resource settings. As disabilities have a large burden in low-resource settings, enhancing the efforts to prevent all of the identified associated conditions, such as deviations from normothermia, could be desirable.

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Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study and the use of anonymized data from hospital records.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest. Francesco Cavallin is an independent statistician and declares no conflict of interest.

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Viral Acute Respiratory Infections in Central African Republic Children: Epidemiological and Clinical Aspects

PAPER

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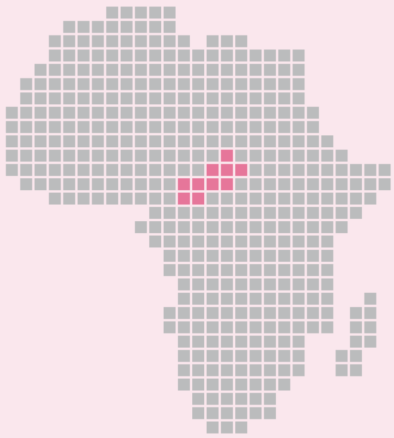

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Viral Acute Respiratory Infections in Central African Republic Children: Epidemiological and Clinical Aspects

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Abstract

Background: Acute respiratory infections (ARI) are recognized as an important cause of morbidity, mortality, and hospitalization among children in developing countries. **Objectives:** To identify the respiratory viruses circulating in Central African children before the SARS-COV2 pandemic and to assess the clinical manifestations. **Methodology:** This is a cross-sectional, descriptive, multicenter study, run from March 1, 2019, to March 31, 2020. Children aged 28 days to 15 year-old, with respiratory symptoms ≤10 days had been included. Nasopharyngeal swabs were taken and sent to the Institute Pasteur in Bangui (WHO National Referral Center for influenza). Virus research was done by cell and molecular culture techniques. Data were recorded and processed with Access 2019 software, then analyzed with STATA version 14 software. Chi-square test and ANOVA test were used to compare proportions at the $p < 0.05$ threshold. **Results:** Out of 659 children included during the study period, viruses were identified in 231 children, for an overall positivity rate of 35.05% (231/659). Rhinoviruses (RV) and influenza viruses were found in 66.23% and 16.88% respectively. Virus-virus co-infections were found in 10 (10/231) children (4.32%). Children under 5 years of age were more represented (78.60%). The main reasons for consultation were: fever (96.20%), cough (95.45%), runny nose (78.5%), and breathing difficulty (30.50%). ILI (Influenza-Like Illness) was found in 71.02% versus 28.98% of SARI (Severe

Acute Respiratory Infection). There was a statistically significant association between age < 5 years and severity of acute respiratory infection (p = 0.001). The outcome was known for the 122 children at the CHUPB site with a mortality rate of 17.21% (n = 21). **Conclusion:** Viral ARI is common in children in Central African Republic. Care givers should think about it in order to reduce the inappropriate prescription of antibiotics.

Keywords

Acute Respiratory Infections, Virus, Children, Central African Republic

1. Introduction

Respiratory viruses are ubiquitous and are present in all regions across the 5 continents of the world [1]. Each year, according to the World Health Organization (WHO), the influenza epidemic results in 3 to 5 million severe cases and 290,000 to 650,000 deaths worldwide [2]. ARI occurs in all age groups, with a high prevalence found in the pediatric population [3] [4] [5] [6] [7]. The prevalence of viruses in respiratory infections is difficult to estimate because they are rarely investigated routinely outside of epidemic context. Seroprevalence studies have shown that 60% - 84% of infants have significant antibodies against common respiratory viruses at birth (probably from mother). The maternal antibodies level decline to 7% - 25% in children aged 6 months to 1 year. Seroprevalence then increases to 30% - 55% in patients between 1 and 2 years of age, suggesting the acquisition of a primary infection. Approximately 38% - 70% of specimens between 2 and 5 years of age and 75% - 100% for children older than 5 years show serological evidence of exposure to respiratory viruses [1] [8] [9]. The profile of pathogens found depends on the type of respiratory infection, the age of the child and the epidemiological data of the country [10]. In the Central African Republic, the incidence of viral respiratory infections in 2014 in children under 5 years of age was 38.5% [11]. The current study following to the 2014 one aims to identify epidemiological variations of viruses circulating in children in the Central African Republic and describe clinical aspects within a period preceding and coinciding with the SARS-CoV2 pandemic.

2. Methodology

The influenza virus monitoring system is a collaborative partnership between the Ministry of Health and the Flu national reference laboratory, hosted by the Institute Pasteur in Bangui. The first sentinel sites were established in January 2008 in Bangui, the country's capital, inside the pediatric teaching hospital (CHUPB)—the only tertiary referral hospital for monitoring—and the Saint Joseph Health Center, which is a private center—run by Catholic missionaries—providing health care to very low-income populations. In 2010, monitoring was extended to public facilities of the Ministry of Health at the health district level

(Pissa health center, Boali health center, Bossembele hospital), which were selected on the basis of their accessibility, for rapid transport of case report forms and samples to the national influenza referrence laboratory. In early 2019 a pediatric emergency center managed by an independent Italian organization (AMICI Per Il Centrafrica) was added as the sixth influenza virus monotoring site in the Central African Republic.

The Institute Pasteur in Bangui—the national influenza referral laboratory—has an ABI 7500 platform (Applied Biosystems, Foster City, California, USA) with SuperScript III Platinum One-step Quantitative RT-PCR System (Invitrogen, Carlsbad, California, USA) that was used for the assays. In addition to influenza viruses, this platform detects other viruses leading to respiratory infections. In addition, the Institute Pasteur in Bangui is responsible for the monitoring supply management system, providing logistical and material support to the sentinel sites: standardized questionnaires, swabs, viral transport media, coolers and ice packs.

This study is a cross-sectional and descriptive one. It was conducted jointly on the six sentinel sites of influenza virus monitoring in the Central African Republic, from March 1, 2019, to March 31, 2020. After informed consent from their parents, children aged 28 Days to 15 years-old, presenting with fever greater than or equal to 38˚C with cough and/or other respiratory symptoms with onset within the past 10 days were included. Incomplete forms and parents' sampling rejection were the reasons for non-inclusion in the study.

Regarding the study's running, the following case definitions guided clinicians. "Influenza-like illness was defined as a temperature ≥ 38˚C and cough with onset within the past 10 days. Was considered severe acute respiratory infection a temperature ≥ 38˚C and cough with onset within the past 10 days, that required hospitalization." [12]. Following these definitions, the care givers involved in the monitoring, collected information from the parents or legal guardians of each child on the standardized questionnaire and on the survey, form including the nominative demographic characteristics; data from the interview: reasons for consultation, medical history, evolution of symptoms; data from the physical examination, paraclinical data after nasal or oropharyngeal swabbing, and the outcome of the disease (see **Appendix**). The swab from each case is placed in a tube with viral transport conditioning and stored at 2˚C - 8˚C in the sentinel site laboratory before delivery to the National Influenza Reference Laboratory within the same week, from Monday to Friday. Workshops were held quarterly to improve the monitoring system, and supervision of targeted clinical staff. The National Influenza Reference Laboratory provided weekly reports on the distribution of samples and the number of confirmed influenza cases to the Ministry of Health, sentinel sites, and WHO FluNet
(http://www.who.int/influenza/gisrs_laboratory/flunet/en/) [12].

3. Laboratory Procedures

Three aliquots were taken from each sample, two of which (1 ml each) were kept at less than 80˚C for external quality assessment (Centre for Health Protection, Department of Health, Hong Kong). The third aliquot of 140 µl was kept at 4˚C for RNA extraction with the QIAmp Viral RNA Mini Kit (QIAagen, Courtaboeuf, France) according to the manufacturer's protocol. Influenza virus was detected and subtyped by (RT-PCR) within 72 h of sample receipt [13]. All negative samples were analyzed by multiplex RT-PCR for the simultaneous detection of other respiratory viruses. The primers used are listed in **Table 1**.

Data from completed forms and laboratory results were recorded and processed by Access 2019 software. The diagnosis of upper or lower ARI was made on the basis of clinical symptoms for all children seen in consultation and included in the study. Children with the following clinical signs were classified as having

Table 1. Sense, anti-sense primers and double-labeled probes provided by CDC.

Primers and probes	Séquence (5' > 3')	Concentration
Primer Inf.A sense	GAC CRA TCC TGT CAC CTC TGA C	40 µM
Primer Inf.A anti-sense	AGG GCA TTY TGG ACA AAK CGT CTA	40 µM
Probes Inf.A	TGC AGT CCT CGC TCA CTG GGC ACG	10 µM
Primer A/H1 sense	AAC TAC TAC TGG ACT CTR CTK GAA	40 µM
Primer A/H1 anti-sense	CCA TTG GTG CAT TTG AGK TGA TG	40 µM
Probe A/H1	TGA YCC AAA GCC TCT ACT CAG TGC GAA AGC	10 µM
Primer A/H3 sense	AAG CAT TCC YAA TGA CAA ACC	40 µM
Primer A/H3 anti-sense	ATT GCR CCR AAT ATG CCT CTA GT	40 µM
Probe A/H3	CAG GAT CAC ATA TGG GSC CTG TCC CAG	10 µM
Primer SW A/H1 sense	GTG CTA TAA ACA CCA GCC TYC CA	40 µM
Amorce SW A/H1 anti-sens	CGG GAT ATT CCT TAA TCC TGT RGC	40 µM
Probe SW A/H1	CA GAA TAT ACA T CC RGT CAC AAT TGG ARA A	10 µM
Primer Inf.A/H5a sense	TGG AAA GTR TAA RAA ACG GAA CGT	40 µM
Primer Inf.A/H5a anti-sense	YGC TAG GGA RCT CGC CAC TG	40 µM
Probe Inf.A/H5a	TGA CTA CCC GCA G T A TTC AGA AGA AGC AAG ACT AA	10 µM
Amorce Inf.A/H5b sens	GGA ATG YCC CAA ATA TGT GAA ATC AA	40 µM
Amorce Inf.A/H5b anti-sens	CCA CTC CCC TGC TCR TTG CT	40 µM
Sonde Inf.A/H5b	TCA CCA TAC CAA CCA T CT ACC ATT CCC TGC CAT	10 µM
Amorce Inf.B sens	TCC TCA AYT CAC TCT TCG AGC G	40 µM
Amorce Inf.B anti-sens	CGG TGC TCT TGA CCA AAT TGG	40 µM
Sonde Inf.B	CCA ATT CGA GCA GCT GAA ACT GCG GTG	10 µM
Amorce RnaseP sens	AGA TTT GGA CCT GCG AGC G	40 µM
Amorce RnaseP anti-sens	GAG CGG CTG TCT CCA CAA GT	40 µM
Sonde RnaseP	TTC TGA CCT GAA GGC TCT GCG CG	10 µM

upper ARI: cough, rhinorrhea, nasal obstruction, fever and snoring. All children with cough, fever, dyspnea, chest pain, focal signs on auscultation and chest radiography were classified as having lower ARI.

To estimate age-specific disease prevalence, we categorized children by age: <5 years, 5 to <15 years [14]. Characteristic demographics of all children and positive cases by age and seasonal trends of circulating viruses were analyzed with Stata version 12 (StataCorp, Texas, USA). The chi-square test was used to assess differences in proportions and the ANOVA test to compare mean ages of children between sentinel sites. A value of $P < 0.05$ was considered statistically significant.

4. Results

A total of 659 children with ARF were included in the study, with 51.14% (n = 337) male and 48.86% (n = 322) female. The sex-ratio of 1.04. The under 5 years old were more represented 78.60% (n = 518) and 21.40% (n = 141) for the over 5 years old. The majority of samples were taken in rural areas 60.39% (n = 398). In urban areas, 39.61% (n = 261) were performed. Vaccination status was up to date in 75.72% of cases (n = 499); according to the Expanded Program of Immunization and 2.42% of children (n = 16) had traveled from one city to another in CAR during the 15 days preceding the symptomatology. The same symptomatology was found in the entourage of 7.73% (n = 51) of children. Antibiotic therapy had been instituted before sampling in 637 children (96.66%). The main reasons for consultation were: fever in 100.00% of cases (n = 659) with a duration of <5 days in 63.58% of children (n = 419), cough in 95.45% (n = 629), runny nose in 78.5% (n = 517) and breathing difficulty in 30.50% (n = 201) (See **Table 2**). The rapid malaria test was positive in 362 children (54.93%) (See **Table 3**). According to WHO global influenza standards monitoring ILI was found in 71.02% of cases (n = 468) versus 28.98% of SARI (Severe Acute Respiratory Infection) (n = 191). Of all the samples taken during the 13 months, viruses were identified in 231 children, for an overall positivity rate of 35.05% (231/659). Rhinoviruses (RV) were found in 66.23% of cases (n = 153), Influenza A and B viruses in 16.88% (n = 40), Respiratory Syncytial Viruses (RSV) in 9.09% (n = 21), Human Bocaviruses (HBoV) in 4.32% (n = 10), Human Metapneumoviruses (HMPV) in 1.73% (n = 4), Adenoviruses (ADV) in 1.29% (n = 3) and Para-influenza Viruses (PIV 1-3) in 0.43% (n = 1). Only rhinoviruses were constant throughout the year. The others had a seasonal occurrence (See **Figure 1**). Four subtypes of influenza A and B viruses were highlighted among the 33 positive cases: H1pdm 16 (48.48%), Victoria 12 (36.36%), H3N2 3 (9.09%) and Yamagata 2 (6.06%). Virus-virus co-infections were found in 10 (10/231) children or 4.32%. It was the association of influenza A and B viruses with Rhinovirus in 6 children (2.49%), Rhinovirus with Coronavirus 229E (HCoV-229E) in 0.43%, Rhinovirus with Coronavirus HKU1 (HCoV-HKU1) in 0.43%, Rhinovirus with Adenovirus in 0.43%, and Rhinovirus with Bocavirus in 0.43% (See **Figure 2**).

The hospitalization rate was 30.50% (n = 202). There was a statistically significant association between age < 5 years and severity of acute respiratory infection (p = 0.001). Rhinovirus was most associated with severity. But the difference was

Table 2. Distribution of children according to sociodemographic and anamnestic criteria.

Characteristics (N = 659)	Frequency	
	Number	Percentage
Sex		
M	337	51.14
F	322	48.86
Age in year		
< 5	322	48.86
>5	141	21.40
Study year (N = 659)		
2019	547	83.00
2020	112	17.00
Immunization status based on EIP		
No	160	24.28
Yes	499	75.72
Antibiotherapy before sample		
Yes	637	96.66
No	22	3.34
Duration of symptoms (days)		
[1 - 5[	419	63.58
[5 - 10]	240	36.42
Travel within 15 last days		
Yes	16	2.42
No	643	95.57
Presence of symptoms in surrounding		
Yes	51	7.73
No	608	92.26
Temperatures at the time of sampling		
Fever	464	70.41
Hyperthermia	170	25.79
Febricula	25	3.79
Suspicion of malaria after physical examination		
Yes	443	67.22
No	216	32.77

Table 3. Distribution of children according to malaria screening results.

Characteristics (N = 659)	Fréquence	
	Nombre	Pourcentage
Rapid test for malaria (RDT) done		
Yes	617	93.62
No	42	6.38
Malaria RDT results		
Positive	362	54.93
Négative	297	45.07
Thick drop made		
No	531	80.57
Yes	128	19.42
Results of the thick drop made		
Negative	609	92.41
Positive	50	7.59

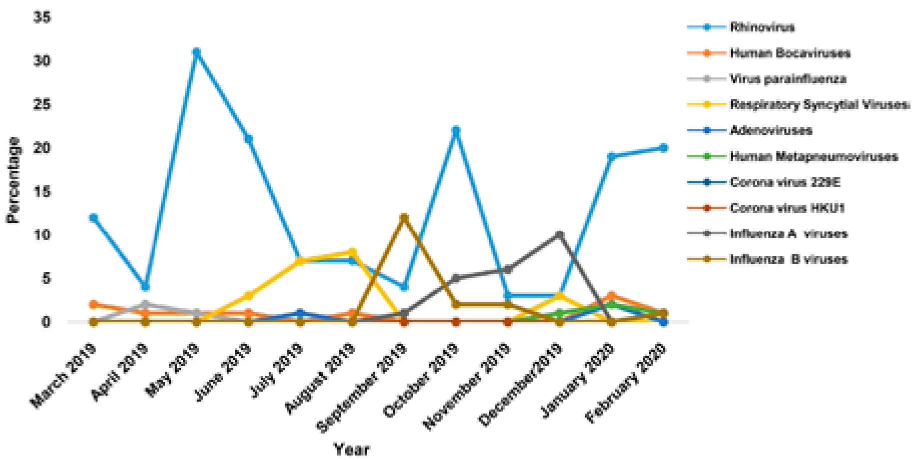

Figure 1. Distribution of viruses according to the seasons.

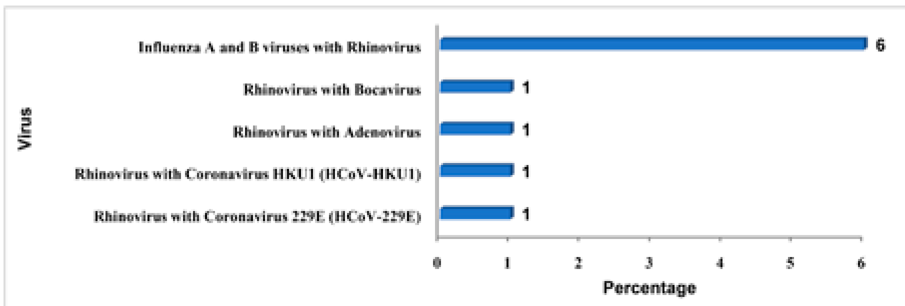

Figure 2. Distribution of children according to co-infections.

not statistically significant (P > 0.05). The outcome was known for the 122 children at CHUPB with a mortality rate of 17.21% (n = 21). Among the children who died, 95.23% (n = 20) were observed when the malaria RDT was positive P = 0.00; OR = 2000 [120 - 8323] (See Table 4).

5. Discussion

5.1. Epidemiological level

Out of 659 samples tested during the study period, at least one respiratory virus was detected in 231 children (35.05%). This prevalence is similar to that found by Bobossi *et al.* (38.5%) in 2014 in similar settings [11]; however, it is higher than Ghana's prevalence (25.7%) and lower than Zambia's one (63%) [5] [15]. The difference between these results, although concerning developing countries with a tropical climate, would be related to the viral epidemiology from one country to another, environmental factors, inclusion criteria, duration of the study, age, socioeconomic level, quality of the sample, diagnostic methods used, and the panel of viral agents tested [16]. The recent use of molecular biological methods has significantly improved the sensitivity ´of virus detection in respiratory infections [17]. The majority virus was rhinovirus (66.23%) followed by influenza A and B viruses (16.88%). Moreover, rhinovirus was found in all co-infections. The

Table 4. Distribution of viruses according to the severity of ARI by age group.

Characteristics	SARI (N, %)	ILI (N, %)	P	OR
Age (year)				
<5 (n = 190)	74 (38.94)	116 (61.06)	0.01	2.63[1.15 - 6.00]
≥5 (n = 41)	8 (19.51)	33 (80.49)		
Main Virus in children < 5 years				
Rhinovirus (n = 136)	58 (42.64)	78 (57.36)		
Virus grippaux A et B (n = 29)	10 (34.48)	19 (65.52)	0.41	1.4 [0.61 - 3.26]
Respiratory Syncytial virus (n = 17)	5 (29.42)	12 (70.58)	0.29	1.7 [0.59 - 5.34]
Other (n = 6)	1 (16.66)	5 (83.34)	0.20	3.71 [0.42 - 32.68]
Main virus in children ≥ 5 ans				
Rhinovirus (n = 22)	5 (22.72)	17 (77.28)		
Influenza A and B viruses (n = 12)	1 (8.33)	11 (91.67)	0.29	3.2 [0.33 - 31.53]
Respiratory Syncytial virus (n = 5)	1 (20)	4 (80)	0.89	1.17 [0.1 - 13.06]
Others (n = 2)	1 (50)	1 (50)	0.39	0.29 [0.01 - 5.59]
Evolution				
Rapid malaria test	**Dead**	**Favorable**		
Positive	20	1	0.00	2000 [120 - 8323]
Negative	1	100		

predominance of Rhinovirus in our study underlines its potential role in acute respiratory infections in children, and its circulation throughout the year with epidemic peaks would explain why it is mostly found in co-infection with other viruses. Viral co-circulation would be a reason for co-infections. Some have attributed viral co-detection to accidental overlap during seasonal epidemics. However, more complex mechanisms explain the onset of these co-infections. Viruses in general trigger an interferon-producing immunological mechanism that induces an antiviral state in the body [18]. It is possible that RV antagonizes interferon production, weakening the innate immune system and thereby promoting viral coinfection [18]. The ubiquitous character of rhinoviruses, their high frequency in communities, their airborne transmission, their mode of contamination by airborne vehicles [19] and their extreme resistance in the environment—giving the advantage of a long survival on an inert surface—would explain their permanent circulation. The absence of vaccination against influenza in the Central African Republic could explain the predominant place occupied by influenza viruses in our series [11]. The rate of co-infection in our series remains low compared to the series of Litwin (7%), Olofsson (10%), Mahonny (15%) and Daniel (25.5%) [11]. Did our series have few cases of immunodeficiency? We cannot answer this question because we did not investigate. Furthermore, we noted during the two monitoring analysis periods that coronavirus was already circulating in CAR in 2014. These are types 229E and HKU1 in 2014 and types 229E (HCoV-229E) and HKU1 (HCoV-HKU1) in the current round. This finding reinforces the hypothesis that African countries escaped the SARS-cov2 hecatomb because of the previous circulation of the coronavirus, which established a state of immunity.

5.2. Clinical and Therapeutic Aspects

The clinical manifestations observed are those known from upper or lower respiratory infections. Fever, present in all cases, proves the acute character of the manifestations in two children out of three. The immunocompromised or not of the children cannot be discussed here in view of what the fever suggests about the outcome of the respiratory disease: the frequent cause of immunodeficiency in the Central African Republic, mainly HIV, was not investigated and the questioning did not reveal the notion of taking immunosuppressive drugs or any clinical situation suggestive of immunodeficiency [20]. No virus seems to be specific for the topographical diagnosis; insofar as viruses with respiratory tropism initially replicate in the nose and pharynx before colonizing the lower airways according to a complex pathogenicity including the effects of the environment, the terrain and monoviral, polyviral or mixed bacterial and viral colonization [19] [21] [22] [23]. In this respect, respiratory difficulty was encountered in one child out of three in our analysis and syndromic grouping according to the WHO global influenza surveillance standards resulted in 71.02% of influenza-like illness (ILI) versus 28.98% of severe respiratory infection (SARI). Severe clinical manifestations are more prevalent in children under 5 years of age. The susceptibility to viral respiratory infections and the predisposition to severity in this age group is reported in the literature [16] [22] [24]. The immaturity of the humoral immune system essential in the defense against respiratory viruses would be a reason [16] [25]. In addition, some authors believe that viruses such as RSV and HMPV predispose to clinical severity. In addition, certain co-infections can make the prognosis pejorative. This is the case of RSV and adenovirus [20] [22]. However, the virus-host relationship is regulated by the immune status of the patient [20]. Chorazy, went in the same direction by proving that monoviral or polyviral colonization does not influence the occurrence of severe forms of acute respiratory infections [23]. Concerning the attenuation of clinical forms, we refer to the recent work of Dee [26] where it is shown that the first colonization of rhinovirus16 induces the secretion of interferons likely to block the proliferation of SARS-Cov2. Beyond bacterial and viral co-infections, what role could malaria play? The comorbidity of malaria and SARS is very poorly documented. In the present study, the risk of death was very high in children who had a positive rapid diagnostic test (RDT) for Plasmodium falciparum. Malaria has been identified as a poor prognostic factor in Congo in children with severe respiratory infection, increasing the risk of death by 2.98 [27]. However, the lack of precision of the form of malaria (neurological or other) and the small sample size do not allow us to generalize the conclusions. The existence of co-infections (malaria-virus) may make it difficult to establish the causal link between the viruses and the respiratory symptomatology [21]. Severe forms of malaria related to severe anemia, pulmonary oedema and acidosis induce respiratory distress. This justifies the systematic performance of a malaria RDT which is easily accessible in the presence of any febrile respiratory difficulty. Moreover, as reported earlier, antibiotic therapy is instituted prior to sampling in 96.66% of children before admission. This is a real challenge in developing countries like the Central African Republic. Although immunization programs have changed the microbial epidemiology of respiratory infections in favor of a viral predominance, the inaccessibility of viral diagnostic tests and the absence of specific antiviral treatment motivate the clinician to systematically use antibiotics with the risk of resistance [19].

6. Conclusion

This analysis highlighted the virus epidemiological characteristics of children in the Central African Republic. These are: the permanent circulation of RV and the presence of influenza viruses. Clinically, children under 5 years of age are the most affected; the influenza syndrome predominates over severe acute respiratory infections with a high risk of death when associated with malaria. The review of the literature revealed the lack of research about co-morbidity with immunodeficiency or bacteria, and ultimately the limitations of the choice of anti-infective. In the future, immunization and rapid detection tests for viruses and bacteria must be popularized and the community must be made aware of the harm of self-prescribing antibiotics if we want to protect anti-infective drugs and reducing the cost of care.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

FEVER MONITORING	**No……………………. Last name and First name:** ………………………………………………………….			
Reporting criteria: any axillary temperature (corrected) greater than or equal to 38˚C				
Date of consultation: |__|__| / |__|__| /|__|__|__|__|		**Center:** ………………………………………………		
Care giver name: |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|				
Patient number in the center's registry: |__|__|__|__|__|__|				
Sex Male Female	Date of Birth: |__|__|/|__|__|/|__|__|__|__| Age: |__|__|years |__|__|months			
Address: |__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|__|			Phone: |__|__|__|__|__|__|__|__|__|__|	
SUSPICION AND DIAGNOSIS				
Axillary temperature (corrected) upon admission: |__|__|,|__| °C		**Duration since onset of fever:** |__|__| days		
Cough	**Suspected Malaria**	**RDT done:** no yes	**RDT Result:** Positive Negative	
		Thick blood film done: no yes	**Thick blood film Result:** Positive Negative	
	Flu Syndrome	**Case type**	ILI SARI	
		Consent request for sampling	no yes	
		Sampling done	no yes	
		Nature of the sampling	Sampling Date	
		Nasal swab	|__|__| / |__|__| /|__|__|__|__|	
		Throat swab	|__|__| / |__|__| /|__|__|__|__|	
		Blood	|__|__| / |__|__| /|__|__|__|__|	
Others Signs: (Check boxes if the sign is present)				
Sore throat	Nausea	Clinical anemia	Splenomegaly	
Runny rose	Vomiting	Asthenia	Headache	
Oculo-nasal catarrh	Diarrhea	Myalgia	Others………………………………….	
Sub-costal retractions	Chills	Convulsion		
Dyspnea	Inability to drink or breastfeed			
Risk Factors (Check boxes if the risk factor is present)				
Asthma	Diabetes	Sick cell disease		
Heart disease	Malnutrition	Obesity		
Travel within the last 15 days	no	yes	if yes, specify location: ……………………	
Presence of other people with the same symptomatology surrounding: no yes				
Treatment before admission no yes (Check the box if treatment prescribed)				
Antibiotics	Antimalarias	Antihistamines	Antipyretics	
Bronchodilators,	Others………………………………………………………………………..			
SARI Diagnosis (Choose one option)				
Isolated upper respiratory disease	Lower respiratory disease with wheezing		Exacerbation of asthma	

Continued

Upper and lower respiratory diseases Bronchiolitis Other................................		
ILI Diagnosis (Choose one option)		
Yes No		
Outcome		
Cured(e) Alive dead if yes date of death |__|__| / |__|__| /|__|__|__|__|		
Number of days of hospitalization: |__|__|		
Date of sampling reception: |__|__| / |__|__| /|__|__|__|__| **Num of tube:** |__|__|__| |__|__|__| |__|__| |__|__|__|__|__| Area District Year Case number		
BIOLOGIC DIAGNOSIS		
Flu viruses: Yes ☐ No ☐ **If, yes, specify types**: A ☐ B ☐ **Sub-types:**	**Other viruses:** Yes ☐ No ☐ If yes, specify:...	

Training on the Silverman and Andersen score improved how special care unit nurses assessed neonatal respiratory distress in a low-resource setting

PAPER

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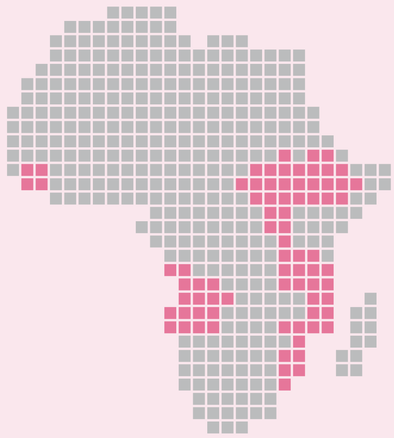

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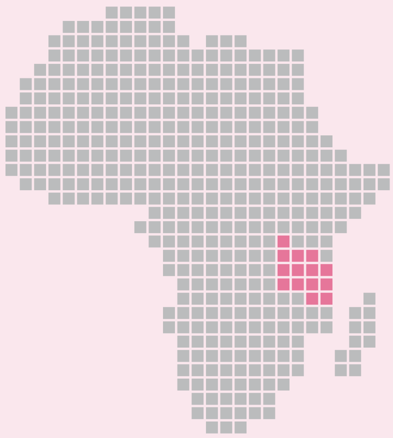
Impact of Quality Improvement Bundle on Neonatal Mortality in a District Hospital in Tanzania

PAPER



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Article

Impact of Quality Improvement Bundle on Neonatal Mortality in a District Hospital in Tanzania

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Abstract: Background: The poor quality of care received by mothers and neonates in many limited-resource countries represents a main determinant of newborn mortality. Small and sick hospitalized newborns are the highest-risk population, and they should be one of the prime beneficiaries of quality-of-care interventions. This study aimed to evaluate the impact on neonatal mortality of quality improvement interventions which were implemented at Tosamaganga Council Designated Hospital, Iringa, Tanzania, between 2016 and 2020. Methods: A retrospective comparison between pre- and post-intervention periods was performed using the chi-square test and Fisher's exact test. Effect sizes were reported as odds ratios with 95% confidence intervals. Results: The analysis included 5742 neonates admitted to the Special Care Unit (2952 in the pre-intervention period and 2790 in the post-intervention period). A decrease in mortality among infants with birth weight between 1500 and 2499 g (overall: odds ratio 0.49, 95% confidence interval 0.27–0.87; inborn: odds ratio 0.50, 95% confidence interval 0.27–0.93) was found. The analysis of cause-specific mortality showed a decrease in mortality for asphyxia (odds ratio 0.33, 95% confidence interval 0.12–0.87) among inborn infants with birth weight between 1500 and 2499 g. Conclusions: A quality improvement intervention was associated with decreased mortality among infants with birth weight between 1500 and 2499 g. Further efforts are needed to improve prognosis in very-low-birth-weight infants.

Keywords: neonatal mortality; low birth weight infants; quality improvement; B.A.B.I.E.S. Matrix tool

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1. Introduction

Poor neonatal outcomes represent a significant global health burden [1], with a large proportion of neonatal deaths occurring in low-resource settings [2]. Over the years, under-five-year-old mortality (U5M) declined more significantly than neonatal mortality did, resulting in a larger contribution of neonatal deaths to the U5M rate [3]. The poor quality of care received by mothers and babies in many limited-resource countries contributes to the high levels of newborn mortality [4]. Quality improvement (QI) is defined as "better patient experience and outcomes achieved through changing provider behavior and organization through using a systematic change methods and strategies" [5] Recent evidence shows that quality improvement initiatives can reduce the burden of mortality and morbidity for hospitalized newborns in developing countries [6–8].

The aim of the present study was to evaluate the impact on neonatal mortality of quality improvement interventions implemented at Tosamaganga Council Designated Hospital, Iringa, Tanzania, between 2017 and 2020.

2. Materials and Methods

2.1. Study Design

This retrospective study compared "pre-intervention" (1 January–31 December 2016) and "post-intervention" (1 January–31 December 2020) mortality data of newborns admitted to the neonatal Special Care Unit (SCU) of Tosamaganga Hospital, Iringa, Tanzania. The periods were separated by a 3-year time span (2017–2019) which was needed to implement the quality improvement bundle.

2.2. Setting

Tosamaganga Hospital is a District Designated Hospital in the District of Iringa (Tanzania) and is the referral hospital for major obstetric emergencies for around 260,000 people living in the area. Every year, around 3000 deliveries and 500 admissions to the SCU occur at Tosamaganga Hospital. The SCU offers basic intensive care such as intravenous therapies, phototherapy and oxygen supplementation without non-invasive respiratory support and mechanical ventilation. Since January 2019, all babies discharged from the SCU are offered regular follow-up visits (to monitor clinical wellbeing, growth and neurological development) at the neonatal follow-up clinic during their first year of life.

2.3. Patients

All newborns admitted to the SCU of Tosamaganga Hospital (Iringa, Tanzania) during the study periods were included.

2.4. Interventions

During 2017–2019, a structured quality improvement process was implemented by Doctors with Africa CUAMM, an Italian nongovernmental organization operating in the field of healthcare in developing countries [9]. The interventions focused on improving infrastructure, equipment, training and use of clinical protocols, with a specific target on low-birth-weight infants (LBW, <2500 g) and pathologic newborns. Table 1 summarizes the area of interventions, timing and actions which were implemented during the process.

Table 1. Summary of the quality improvement process which was implemented in 2017–2019 at Tosamaganga Hospital (Iringa, Tanzania).

Area of Intervention	Year	Action
Infrastructures	January 2017	A Neonatal ward was constructed near the Maternity Ward, divided into three areas: Neonatal Intensive Care Unit (one room), Neonatal Sub-intensive Care Unit (one room) and Kangaroo Mother Care Unit (two rooms)
Equipment	January 2017	Four oxygen concentrators (increased over the years up to 10), two phototherapy machines, four infusion pumps and a syringe pump, a capillary hemoglobin dosing machine and an electric aspirator were purchased. The staff received training on their use.
Protocols	2017 and 2019	Operational protocols were updated and presented to the staff in dedicated training sessions. Laminated copies of the most commonly used protocols were displayed for quick consultation even by on-call staff during night shifts and holidays. A further update of the ward guidelines was carried out in 2019, in light of the publication of the first edition of the national neonatal guidelines.
Procedures	January 2017	New procedures were introduced: antenatal administration of dexamethasone for lung maturity and magnesium sulfate for neuroprotection, positioning of an umbilical venous catheter in newborns weighing <1200 g, administration of paracetamol in newborns with suspected patent ductus arteriosus, administration of hydrocortisone in newborns with oxygen dependence and suspected bronchopulmonary dysplasia.
Staff	2017	A dedicated nursing team was created, consisting of 5 nurses (increased over the years up to 8). From February 2017, a Tanzanian doctor started working in Neonatology.

Table 1. *Cont.*

Area of Intervention	Year	Action
Training activity	2017–2019	Over years, the Neonatal Unit and Maternity Ward staff were periodically trained on partogram use and interpretation, management of a complicated pregnancy (gestational hypertension, gestational diabetes, prolonged rupture of the membranes); management of labor and delivery (1st, 2nd, 3rd stage), prolonged rupture of the membranes, complicated labor and the most common maternal peripartum complications, neonatal resuscitation, management of common neonatal severe conditions (sepsis, jaundice, asphyxia, prematurity, respiratory distress syndrome), essential newborn care and care of low-birth-weight and very-low-birth-weight infants.

2.5. Outcome Measures

The main indicators were derived from the World Health Organization (WHO) B.A.B. I.E.S. Matrix tool (Birth weight group, Age at death, Boxes for an Intervention Evaluation System) [10], which is described in paragraph 2.7. The primary outcome measures included deaths/live births before discharge <1499 g (B.A.B.I.E.S. Matrix Cell 3), deaths/live births before discharge 1500–2499 g (B.A.B.I.E.S. Matrix Cell 7), and deaths/live births before discharge $\geq$2500 g (B.A.B.I.E.S. Matrix Cell 11). The secondary outcome measures included the mortality rates from asphyxia, infection and prematurity, according to the main causes of death (as defined by the tool for cells 3, 7 and 11).

2.6. Data Collection

All data were retrospectively and anonymously collected from hospital charts by a researcher who was not involved in clinical activity. The researcher was not masked to the intervention period. Retrieved data did not contain any information that might be used to identify individual patients.

2.7. Definitions

The B.A.B.I.E.S. Matrix tool works by segregating, organizing, analyzing and transforming data regarding fetal and neonatal deaths. Through stratification of data by weight and by moment of death, the tool guides identifications of the main problems related to pregnancy, labor, delivery and postnatal management, suggesting the causes and the appropriate interventions needed to reduce neonatal mortality (Figure 1). The stratification works on three birth weight categories (<1499, 1500–2499 and $\geq$2500 g) and on four time categories (during pregnancy: from 28 weeks of gestational age to the beginning of labor; during labor: from the beginning of labor to delivery time; pre-discharge: from delivery time to discharge time; post-discharge: from discharge to 28 days of life).

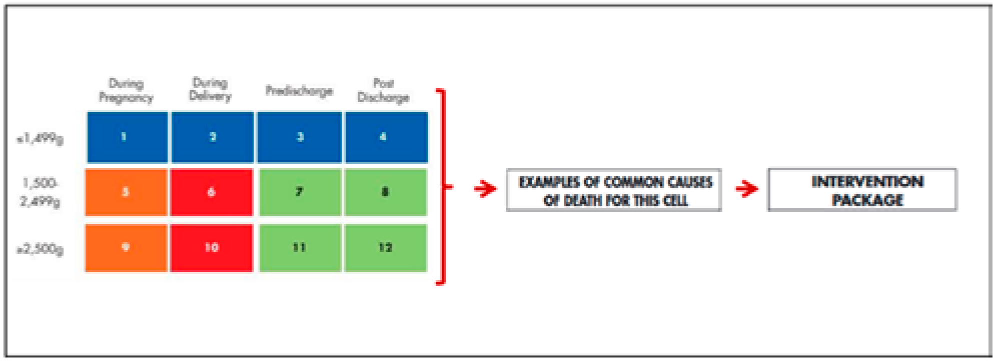

Figure 1. World Health Organization B.A.B.I.E.S. Matrix tool, modified from Joy Lawn et al. [10].

To identify the cause-specific mortality, the criteria reported by Mmbaga et al. [11] were used: (a) Birth asphyxia: birth asphyxia with weight >1000 g or gestational age >27 weeks; birth asphyxia and prematurity with gestational age ≥33 weeks and birth weight ≥2500 g or birth weight ≥1800 g if gestational age is unknown; neonatal encephalopathy with 5-min Apgar lower than 7; (b) Prematurity: prematurity; prematurity and asphyxia with gestational age <33 weeks and birth weight <2500 g or birth weight <1800 g if gestational age is unknown; respiratory distress syndrome in preterm; necrotizing enterocolitis; birth asphyxia gestational age <27 weeks or birth weight <1000 g; infection with gestational age <33 weeks; (c) Infection: neonatal infection; sepsis/septicemia; meningitis; pneumonia; impetigo neonatorum.

2.8. Statistical Analysis

Categorical data were summarized as frequencies and percentages. Comparisons between pre- and post-intervention periods were performed using the chi-square test and Fisher's exact test. Effect sizes were reported as odds ratios with 95% confidence intervals for each outcome measure. All tests were 2-sided, and a *p*-value less than 0.05 was considered statistically significant. Adjustment for multiple testing was not performed due to the exploratory purpose of the study. Statistical analysis was performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria) [12].

3. Results

The analysis included 2952 neonates admitted to the SCU in the pre-intervention period and 2790 neonates admitted to the SCU in the post-intervention period. The characteristics of deliveries and neonates are reported in Table 2. The baseline characteristics were clinically comparable between the two periods, with small changes in cesarean sections (36.4% vs. 30.7%, $p < 0.0001$), inborn neonates (97.9% vs. 96.6%, $p < 0.0001$) and LBW neonates (10.4% vs. 13.7%; $p < 0.0001$).

Table 2. Baseline characteristics of neonates admitted to the SCU in the pre- vs. post-intervention periods.

	Pre-Intervention Period:	Post-Intervention Period:	*p*-Value
Deliveries	N = 2901	N = 2732	-
Mode of delivery:			<0.0001
Caesarean section	1056/2901 (36.4%)	840/2732 (30.7%)	
Vaginal delivery	1845/2901 (63.6%)	1892/2732 (69.3%)	
Twin deliveries	50/2901 (1.7%)	55/2732 (2.0%)	0.48
Neonates	N = 2952	N = 2790	
Inborn neonates	2890/2952 (97.9%)	2675/2790 (95.6%)	<0.0001
Males	1472/2952 (49.9%)	1370/2790 (49.1%)	0.58
Birth weight:			<0.0001
≤1499 g	24/2952 (0.8%)	63/2790 (2.3%)	
1500–2499 g	282/2952 (9.6%)	318/2790 (11.4%)	
≥2500 g	2646/2952 (89.6%)	2409/2790 (86.3%)	
5-min Apgar score < 7 (only inborn)	121/2890 (4.2%)	109/2675 (4.1%)	0.89

Data were summarized as n/N (%).

A comparison of neonatal mortality between pre- and post-intervention periods is summarized in Table 3. Overall mortality did not change after the implementation of the interventions (odds ratio 1.05, 95% confidence interval 0.78 to 1.41). However, there was a decrease in overall mortality among infants with birth weight between 1500 and 2499 g (odds ratio 0.49, 95% confidence interval 0.27–0.87) and in inborn neonates of the same birth weight category (odds ratio 0.50, 95% confidence interval 0.27–0.93).

Table 3. Comparison of mortality of neonates admitted to the SCU in the pre- vs. post-intervention periods.

Outcome Measure	Pre-Intervention Period:	Post-Intervention Period:	Post vs. Pre Comparison: Odds Ratio (95% Confidence Interval)	*p*-Value
All neonates	**N = 2952**	**N = 2790**	-	-
Overall mortality	87/2952 (2.9%)	92/2790 (3.3%)	1.05 (0.78 to 1.41)	0.49
Mortality in BW categories:				
≤1499 g	13/24 (54.2%)	31/63 (49.2%)	0.81 (0.32 to 2.10)	0.86
1500–2499 g	34/282 (12.1%)	20/318 (6.3%)	0.49 (0.27 to 0.87)	0.02
≥2500 g	40/2646 (1.5%)	41/2409 (1.7%)	1.12 (0.72 to 1.75)	0.67
Mortality for prematurity	21/2952 (0.7%)	36/2790 (1.3%)	1.82 (1.03 to 3.29)	0.04
Mortality for asphyxia:				
Overall	44/2952 (1.5%)	40/2790 (1.4%)	0.96 (0.62 to 1.47)	0.94
≤1499 g	0/24 (0.0%)	0/63 (0.0%)	NA	NA
1500–2499 g	15/282 (5.3%)	7/318 (2.2%)	0.40 (0.16 to 1.00)	0.07
≥2500 g	29/2646 (1.1%)	33/2409 (1.4%)	1.25 (0.75 to 2.07)	0.45
Mortality for infection:				
Overall	12/2952 (0.4%)	6/2790 (0.2%)	0.52 (0.19 to 1.40)	0.29
≤1499 g	0/24 (0.0%)	0/63 (0.0%)	NA	NA
1500–2499 g	5/282 (1.8%)	2/318 (0.6%)	0.35 (0.06 to 1.82)	0.26
≥2500 g	7/2646 (0.3%)	4/2409 (0.2%)	0.62 (0.18 to 2.14)	0.55
Inborn neonates	**N = 2890**	**N = 2675**	-	-
Overall mortality	77/2890 (2.7%)	73/2675 (2.7%)	1.02 (0.74 to 1.41)	0.94
Mortality in BW categories:				
≤1499 g	10/15 (66.7%)	22/30 (73.3%)	1.37 (0.35 to 5.27)	0.90
1500–2499 g	29/249 (11.6%)	18/287 (6.3%)	0.50 (0.27 to 0.93)	0.04
≥2500 g	38/2626 (1.4%)	33/2358 (1.4%)	0.96 (0.60 to 1.54)	0.98
Mortality for prematurity	15/2890 (0.5%)	26/2675 (1.0%)	1.88 (0.99 to 3.55)	0.07
Mortality for asphyxia:				
Overall	43/2890 (1.5%)	33/2675 (1.2%)	0.82 (0.52 to 1.30)	0.48
≤1499 g	0/15 (0.0%)	0/30 (0.0%)	NA	NA
1500–2499 g	15/249 (6.0%)	6/287 (2.1%)	0.33 (0.12 to 0.87)	0.03
≥2500 g	28/2626 (1.1%)	27/2358 (1.1%)	1.07 (0.63 to 1.82)	0.90
Mortality for infection:				
Overall	10/2890 (0.3%)	5/2675 (0.2%)	0.53 (0.18 to 1.57)	0.38
≤1499 g	0/15 (0.0%)	0/30 (0.0%)	NA	NA
1500–2499 g	4/269 (1.5%)	2/287 (0.7%)	0.46 (0.08 to 2.55)	0.44
≥2500 g	6/2626 (0.2%)	3/2358 (0.1%)	0.55 (0.13 to 2.22)	0.51

Table 3. *Cont.*

Outcome Measure	Pre-Intervention Period:	Post-Intervention Period:	Post vs. Pre Comparison: Odds Ratio (95% Confidence Interval)	*p*-Value
Outborn neonates	**N = 62**	**N = 115**	-	-
Overall mortality	10/62 (16.1%)	19/115 (16.5%)	1.02 (0.44 to 2.37)	0.99
Mortality in BW categories:				
≤1499 g	3/9 (33.3%)	9/33 (27.3%)	0.75 (0.15 to 3.65)	0.69
1500–2499 g	5/33 (15.2%)	2/31 (6.5%)	0.38 (0.06 to 2.15)	0.42
≥2500 g	2/20 (10.0%)	8/51 (15.7%)	1.67 (0.32 to 8.66)	0.71
Mortality for prematurity	6/62 (9.7%)	10/115 (8.7%)	0.88 (0.30 to 1.57)	0.99
Mortality for asphyxia:				
Overall	1/62 (1.6%)	7/115 (6.1%)	3.95 (0.47 to 32.89)	0.26
≤1499 g	0/9 (0.0%)	0/33 (0.0%)	NA	NA
1500–2499 g	0/33 (0.0%)	1/31 (3.2%)	3.29 (0.12 to 89.97)	0.48
≥2500 g	1/20 (5.0%)	6/51 (11.8%)	2.53 (0.28 to 22.49)	0.66
Mortality for infection:				
Overall	2/62 (3.2%)	1/115 (0.9%)	0.26 (0.02 to 2.96)	0.28
≤1499 g	0/9 (0.0%)	0/33 (0.0%)	NA	NA
1500–2499 g	1/33 (3.0%)	0/31 (0.0%)	0.34 (0.01 to 8.76)	0.99
≥2500 g	1/20 (5.0%)	1/51 (2.0%)	0.38 (0.02 to 6.38)	0.48

Data were summarized as n/N (%).

The analysis of cause-specific mortality found a decrease in mortality for asphyxia (odds ratio 0.33, 95% confidence interval 0.12–0.87) among infants with birth weight between 1500 and 2499 g and an increase in overall mortality for prematurity (odds ratio 1.82, 95% confidence interval 1.03–3.29). No statistically significant differences in mortality were observed among outborn neonates.

4. Discussion

Recent evidence suggests that an effective implementation of quality improvement in the care of small and sick newborns is possible in low-resource settings [6–8]. The literature indicates limitations in staff, equipment and protocols as the main barriers for such implementation and underlines the opportunity for meso-level and educational interventions [6]. This study reports neonatal mortality outcomes after a quality improvement intervention in a sub-Saharan setting. According to indications drawn from the literature, our quality improvement approach involved the use of meso and micro interventions (such as strengthening the facility's infrastructure, continuous quality improvement, supervision, feedback, in-service training, distribution of referencing materials to providers, decision support and care coordination) and used mortality as the main outcome measure [6]. The decrease in mortality among infants with birth weight between 1500 and 2499 g supports the effectiveness of the implementation of specifically targeted interventions and indirectly underlines the importance of the B.A.B.I.E.S Matrix as a guiding tool for improving quality of neonatal care. The decrease in mortality for asphyxia among infants with birth weight between 1500 and 2499 g suggested an improvement in stabilization practices immediately after birth for low-birth-weight infants. Of note, we found increased overall mortality due to prematurity, which might likely be due to a bias in the definition of prematurity. As gestational age is rarely available in low-resource settings, a birth weight <1800 g was used to define prematurity [11]. Within this category, there was a larger number of babies with birth weight <1500 g in 2020 vs. that in 2016. Very-low-birth-weight newborns (<1500 g) are extremely fragile, and their mortality varies considerably among high-income (12–15%) and low–middle-income countries (21–43%) [13–15]. Unfortunately, reducing mortality in this subgroup of newborns requires massive human and economic resources, and the B.A.B.I.E.S Matrix tool suggests interventions on pre-pregnancy health and high-tech neonatal care that are very difficult to implement in low-resource settings.

The reader should be aware that reducing neonatal mortality may come at the cost of increased post-discharge morbidity in such vulnerable subjects. A follow-up service for high-risk newborns is currently active at the study site, but unfortunately, the high dropout rate makes any assessment difficult.

The present study has some limitations that should be considered by the reader. First, the retrospective design limited both the availability and quality of data. Second, the quality improvement was implemented in a sub-Saharan referral hospital, hence the generalizability of the findings should be limited to similar settings. Third, adjustment for multiple testing was not performed due to the exploratory purpose of the study, hence we suggest caution in the interpretation of the results. Finally, we could not discriminate the specific impact of each component of the bundle.

Future interventions for reducing morbidity and mortality in this setting would focus on applying new strategies such as the use of devices for non-invasive respiratory support and improving good practices of infection prevention, nutritional support and maintenance of normothermia. Hypothermia, hypoglycemia and infections are the main causes of death in the neonatal period, and their prevention is even more important in very-low-birth-weight newborns. To this end, it would be necessary to pay even greater attention to the management of vascular access, parenteral fluids and enteral nutrition. Strengthening Kangaroo mother care and close monitoring of temperature and blood sugar would also be essential.

5. Conclusions

A quality improvement process based on meso and micro interventions was associated with decreased mortality among infants with birth weight between 1500 and 2499 g. Further efforts are needed to improve prognosis in very-low-birth-weight infants.

Author Contributions: Conceptualization: A.P.; data curation: A.P., M.P., C.Z. and L.B.; formal analysis, F.C. and A.P.; investigation: M.P., C.Z., L.B., D.M.M. and D.E.L.; project administration: A.P., G.A. and G.P.; supervision: F.C., D.T. and G.P.; visualization: A.P. and F.C.; writing—original draft preparation: A.P. and F.C.; writing—review and editing: M.P., C.Z., L.B., G.A., D.M.M., D.E.L., G.P. and D.T. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study and the use of anonymized data from hospital records.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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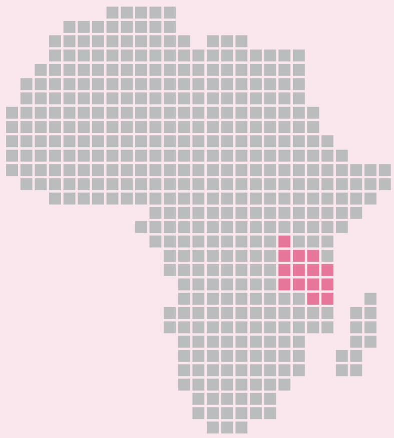
Comparison of alternative gestational age assessment methods in a low resource setting: a retrospective study



PAPER

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RESEARCH Open Access

Comparison of alternative gestational age assessment methods in a low resource setting: a retrospective study

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Abstract

Background: Accurate gestational age (GA) determination allows correct management of high-risk, complicated or post-date pregnancies and prevention or anticipation of prematurity related complications. Ultrasound measurement in the first trimester is the gold standard for GA determination. In low- and middle-income countries elevated costs, lack of skills and poor maternal access to health service limit the availability of prenatal ultrasonography, making it necessary to use alternative methods. This study compared three methods of GA determination: Last Normal Menstrual Period recall (LNMP), New Ballard Score (NBS) and New Ballard Score corrected for Birth Weight (NBS + BW) with the locally available standard (Ultrasound measurement in the third trimester) in a low-resource setting (Tosamaganga Council Designated Hospital, Iringa, Tanzania).

Methods: All data were retrospectively collected from hospital charts. Comparisons were performed using Bland Altman method.

Results: The analysis included 70 mother-newborn pairs. Median gestational age was 38 weeks (IQR 37–39) according to US. The mean difference between LNMP vs. US was 2.1 weeks (95% agreement limits − 3.5 to 7.7 weeks); NBS vs. US was 0.2 weeks (95% agreement limits − 3.7 to 4.1 weeks); NBS + BW vs. US was 1.2 weeks (95% agreement limits − 1.8 to 4.2 weeks).

Conclusions: In our setting, NBS + BW was the least biased method for GA determination as compared with the locally available standard. However, wide agreement bands suggested low accuracy for all three alternative methods. New evidence in the use of second/third trimester ultrasound suggests concentrating efforts and resources in further validating and implementing the use of late pregnancy biometry for gestational age dating in low and middle-income countries.

Keywords: Gestational age, Last menstrual period, Ultrasound, Neonatal examination

Introduction

Accurate determination of gestational age (GA) is of great importance in clinical practice, allowing correct management of high-risk, complicated or post-date pregnancies and prevention or anticipation of prematurity-related complications [1]. The ultrasound (US) measurement in the first trimester (up to and including 13 6/7 weeks of gestation) is considered the gold standard for GA determination and is followed in accuracy by ultrasound in second and third trimester [1]. In low- and middle-income countries, the availability of prenatal ultrasonography is limited by elevated costs, lack of skills and poor

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maternal access to health service, making it necessary to use alternative methods [2]. The Last Normal Menstrual Period recall (LNMP) and the neonatal physical and neurological maturity assessments with the New Ballard Score (NBS), constitute reasonable measurements for gestational age when compared to ultrasound, and acceptable methods when assessing gestational age in low-resource settings [3–7]. Compared with first trimester ultrasound, LNMP and NBS have a mean bias of 0.2 and 2.8 days, respectively, with 95% limits of agreement of ±26 days [2, 8]. LNMP shows high sensitivity (84.7%) and specificity (90.5%) for identifying preterm newborns (<37 weeks) [2], while NBS has moderate sensitivity (64%) but high specificity (95%) [8]. A modified birthweight-sensitive Ballard method (NBS+BW) seems to improve, in routine clinical practice, the assessment of gestational age and correct for errors caused by low birthweight [9].

This study compared three methods of GA determination (LNMP, NBS and NBS+BW) with the locally available standard (US measurement in the third trimester) in a low-resource setting, under real field conditions. The purpose was to identify the best method for GA determination in a low-resource setting.

Materials and methods

Setting

This study was carried out at the St. John of the Cross Hospital of Tosamaganga (Iringa, Tanzania), the only Comprehensive Emergency Obstetric and Newborn Care Center in Iringa Rural District. Designated as referral hospital of Iringa Rural District Council, it serves an estimated population of 265 000 inhabitants, handling approximately 2300 deliveries per year. The hospital has a total of 165 beds, 48 of which are in the maternity department, including 12 obstetrics, 18 in vaginal postpartum and 18 in CS postpartum. A labour room, a neonatal resuscitation room and a Neonatal Special Care Unit are also present [10].

Patients

All the mother-newborn pairs with complete data on the three different methods of determining GA were included in the study.

Outcome measures

The agreement in GA estimation between different methods.

Data collection

All data were retrospectively and anonymously collected from hospital charts and did not contain any information that might be used to identify individual patients. Maternal data included: age, weight, BMI, number of pregnancies, mode of delivery, GA by LNMP recall, GA by ultrasound measurement in the third trimester. Neonatal data included: sex, birth weight, APGAR score, GA by NBS and NBS+BW.

Definitions

The GA refers to the duration of time between conception and delivery. The LNMP recall is the difference between the first day of the last menstrual period and the delivery date. A US is defined as of the third trimester when executed at 28 0/7 weeks of gestation and beyond [1]. Late ultrasound GA determination was performed using the INTERGROWTH-21st project estimation method [11]. The NBS consists in a procedure, performed postnatally up to 96 h after birth, that asses physical and neuromuscular maturity of the neonate to determine its gestational age [12]. NBS+BW refers to the NBS adjusted considering birth weight in the score calculation [9].

Comparisons

The US measurement in the third trimester was separately compared with LNMP recall, NBS and NBS+BW.

Statistical analysis

The sample size calculation was based on information from available literature [8]. Assuming a mean difference of 0 weeks with a standard deviation of 3 weeks, a minimum of 64 subjects were required to have an 80% chance of detecting, as significant at the 5% level, an agreement interval of 8 weeks in the Bland-Altman plot. The final sample size was rounded up to 70 subjects (reaching an estimated power of 85%). Sample size calculation was performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria) [13].

Categorical variables were summarized as frequency and percentage. Continuous variables were summarized as mean and standard deviation (SD) or median and interquartile range (IQR). The agreement in GA estimation between different methods was assessed using Bland Altman plot (showing mean difference and 95% agreement limits). The correlation between continuous variables was assessed using Pearson correlation coefficient. Inter-rater reliability between the clinicians was evaluated using intra-class correlation coefficient (ICC) in a subsample of 30 newborns with double assessments. All tests were two-sided and a p-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria) [13].

Results

The analysis included 70 mother-newborn pairs. Maternal and neonatal characteristics are reported in Table 1. Data on GA by LNMP recall, GA by US, GA by NBS and GA by NBS + BW were available for all newborns ($n = 70$).

The agreement in GA estimation between LNMP and US is shown in Fig. 1. Mean difference between LNMP and US was 2.1 weeks (95% agreement limits −3.5 to 7.7 weeks). There was a mild correlation between difference and average GA value (Pearson correlation coefficient 0.36, $p = 0.002$), which suggested an increasing overestimation of LNMP over US in late GAs. The difference between LNMP and US was not associated with maternal age (Pearson correlation coefficient 0.01, $p = 0.98$), maternal BMI (Pearson correlation coefficient −0.24, $p = 0.11$) or number of pregnancies (Pearson correlation coefficient 0.01, $p = 0.93$).

The agreement in GA estimation between NBS and US is shown in Fig. 2. Mean difference between NBS and US was 0.2 weeks (95% agreement limits −3.7 to 4.1 weeks), without any correlation between difference and average value (Pearson correlation coefficient −0.11, $p = 0.38$).

The agreement in GA estimation between NBS + BW and US is shown in Fig. 3. Mean difference between NBS + BW and US was 1.2 weeks (95% agreement limits −1.8 to 4.2 weeks), without any correlation between difference and average value (Pearson correlation coefficient −0.15, $p = 0.20$).

In a subsample of 30 newborns, ICC showed good inter-rater reliability for NBS score (ICC = 0.99), NBS neuromuscular subscore (ICC = 0.96) and NBS physical subscore (ICC = 0.95).

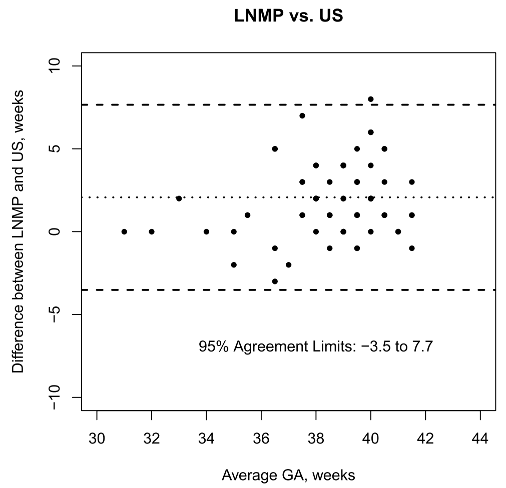

Fig. 1 Agreement in GA estimation between LNMP and US: Bland Altman plot (the average of the two measurements for each sample is allocated on the x-axis and the difference between the two measurements on the y-axis)

Discussion

In our low-income setting, the modified NBS (NBS + BW) was the less biased method for GA determination as compared to NBS alone and LNMP. In addition, the good inter-rater reliability of NBS suggested that it could be consistently used by the health care staff thank to the low subjectivity. On the other hand, our data indicated low agreement between the alternative methods (LMNP, NBS, NBS + BW) and the

Table 1 Maternal and neonatal characteristics

Mothers and newborns	Variable	N (%) or median (interquartile range)
Mothers ($n = 70$)	Age, years [a]	25 (22–28)
	Weight, kg [b]	64 (59–74)
	BMI, kg/m^2 [c]	28.0 (24.2–31.6)
	Number of pregnancies [a]	3 (1–3)
	Mode of delivery: [a] vaginal delivery (assisted) caesarean section vaginal delivery (spontaneous)	1 (1%) 40 (58%) 28 (41%)
Newborns ($n = 70$)	Gestational age according to US, weeks	38 (37–39)
	Males	40 (57%)
	Birth weight, grams	2795 (2702–3345)
	Apgar score at 1 min	8 (7–8)
	Apgar score at 5 min	10 (10–10)

Data not available in [a]1, [b]14 and [c]25 subjects

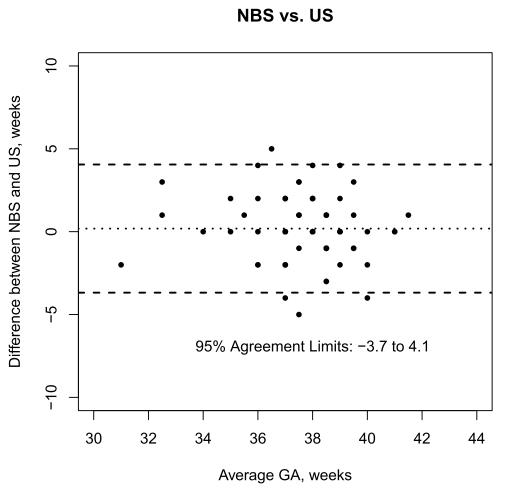

Fig. 2 Agreement in GA estimation between NBS and US: Bland Altman plot (the average of the two measurements for each sample is allocated on the x-axis and the difference between the two measurements on the y-axis)

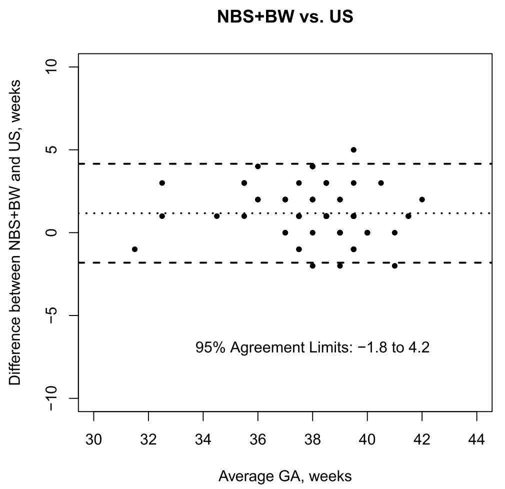

Fig. 3 Agreement in GA estimation between NBS + BW and US: Bland Altman plot (the average of the two measurements for each sample is allocated on the x-axis and the difference between the two measurements on the y-axis)

locally available standard (US measurement in the third trimester).

In low-income countries, the lack of accessible or accurate data on GA is a critical barrier to the correct management of high-risk pregnancies and preterm births. The limited availability of prenatal US suggested the opportunity of investigating alternative methods of GA determination in low-resource settings [2–7]. Unfortunately, we found low accuracy for some alternative methods (LMNP, NBS, NBS + BW) compared with the locally available standard. Overall, our deviations were in broad agreement with previous data reported in available literature [2, 8], thus supporting the unreliability of such alternative methods for GA determination. The deviations of the alternative methods indicated possible underestimation of GA up to 3.7 weeks and overestimation up to 7.7 weeks. As accurate determination of GA is crucial for prevention and anticipation of prematurity-related complications, such magnitude implies the impossibility of discriminating between term and preterm newborns (and among degrees of prematurity) by the health care provider. Given such results, a Reviewer suggested the intriguing idea of combining these methods to improve accuracy of estimated GA. However, NBS and NBS + BW could not be jointly used due to high multicollinearity (NBS + BW values are based on NBS values), hence leading to two options: (i) combining LMNP and NBS, or (ii) combining LMNP and NBS + BW. In both cases, the contribution of LMNP was negligible (data not shown), thus the estimated values were based on NBS or NBS + BW, respectively. Of note, we acknowledge that US measurement in the third trimester may represent a suboptimal reference standard, as dedicated literature suggests US measurement in the first trimester or accurate LMNP recall as the preferred reference standards for testing the validity of alternative methods of GA determination [2, 8]. However, the unavailability of such preferred reference standards forced the use of US measurement in the third trimester as the only viable option in our setting.

Recent evidence suggested that using US in second/third trimester with a novel parsimonious formula might narrow accuracy to ± 10.5 days (between 24 0/7 weeks and 29 6/7 weeks of gestation) and of ± 15.1 days (between 24 0/7 weeks and 29 6/7 weeks of gestation) [14]. These results suggest that concentrating efforts and resources in further validating and implementing the use of late pregnancy biometry for gestational age assessment may be valuable in settings where the preferred reference standards are unavailable.

To our knowledge, this is the first study evaluating the accuracy of the modified birthweight-sensitive Ballard method (NBS + BW) elaborated by Feresu et al. [10], under real field conditions.

Our study has also some limitations that should be considered by the reader. First, US measurement in the third trimester may represent a suboptimal reference standard. Second, the retrospective nature of the study limited data availability. Third, the generalizability of the findings should be limited to similar settings. In addition, our study included few preterm newborns hence caution is suggested in the interpretation of our findings in such subpopulation.

Conclusions

In a low-income setting, NBS + BW was the least biased method for GA determination as compared with the locally available standard (US measurement in the third trimester). However, wide agreement bands suggested low accuracy for all three alternative methods (LNMP, NBS, NBS + BW. New evidence in the use of second/third trimester ultrasound suggests concentrating efforts and resources in further validating and implementing the use of late pregnancy biometry for gestational age dating in low and middle-income countries.

Abbreviations

GA: gestational age; US: ultrasound; LNMP: Last Normal Menstrual Period; NBS: New Ballard Score; NBS + BW: NBS + Birth Weight.

Acknowledgements

We are very grateful to the nurses and medical staff of the St. John of the Cross, Tosamaganga Council Designated Hospital for the passion they show in their daily work.

Authors' contributions

Conceptualization: AP and SS and LB; data curation: AP and SS and LB; formal analysis, FC and AP; investigation: SS and LB and VG and DM and DL; project administration: AP and GA and GP; supervision: FC and DT and GP; visualization: AP and FC; writing—original draft preparation: AP and FC and DT; writing—review and editing: SS and LB and VG and GA and DM and DL and GP. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

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Availability of data and materials

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All methods were performed in accordance with the relevant guidelines and regulations.The study was approved by the Institutional Review Board of Tosamaganga Hospital (protocol number DOIRA/TCDH/VOL.016/5, date 08/09/2021), which waived the need for written informed consent given the retrospective nature of the study and the use of anonymized data from hospital records.

Consent for publication

NA (Not applicable).

Competing interests

The authors declare no conflict of interest.

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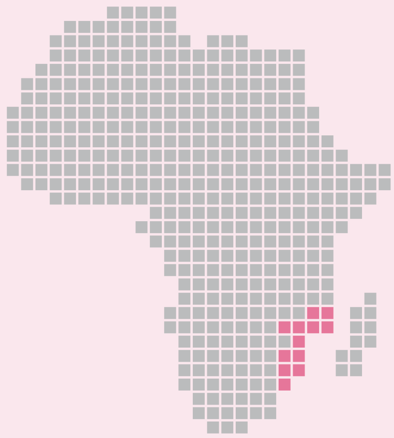

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Article

Implementation of the South African Triage Scale (SATS) in a New Ambulance System in Beira, Mozambique: A Retrospective Observational Study

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Abstract: In 2019, an urban ambulance system was deployed in the city of Beira, Mozambique to refer patients from peripheral health centres (HCs) to the only hospital of the city (Beira Central Hospital—HCB). Initially, the system worked following a first-in–first-out approach, thus leading to referrals not based on severity condition. With the aim of improving the process, the South African Triage Scale (SATS) has been subsequently introduced in three HCs. In this study, we assessed the impact of SATS implementation on the selection process and the accuracy of triage performed by nurses. We assessed 552 and 1608 referral charts from before and after SATS implementation, respectively, and we retrospectively calculated codes. We compared the expected referred patients' codes from the two phases, and nurse-assigned codes to the expected ones. The proportion of referred orange and red codes significantly increased (+12.2% and +12.9%) while the proportion of green and yellow codes decreased (−18.7% and −5.8%). The overall rates of accuracy, and under- and overtriage were 34.2%, 36.3%, and 29.5%, respectively. The implementation of SATS modified the pattern of referred patients and increased the number of severe cases receiving advanced medical care at HCB. While nurses' accuracy improved with the routine use of the protocol, the observed rates of incorrect triage suggest that further research is needed to identify factors affecting SATS application in this setting.

Keywords: emergency medical service; triage; prehospital care; low- and middle-income country; South African Triage Scale

1. Introduction

In low- and middle-income countries (LMICs), formal emergency medical services (EMSs) rarely exist and, when present, are often hampered by structural inefficiencies, such as poor transportation and infrastructure, the shortage of skilled medical staff and resources, and a lack of comprehensive referral protocols [1,2]. To address the transportation gap, many nongovernmental organisations (NGOs) working in LMICs have implemented EMSs at the local or regional level using different means of transport, including even motorbike and bicycle ambulances [3–5]. Nonetheless, the absence of well-established protocols for patient transfer frequently leads to the inappropriate transport of uncomplicated cases to referral hospitals, overwhelming their personnel and impacting already scarce available resources [6,7]. In this scenario, the implementation of patient prioritisation strategies is pivotal in managing the challenges associated with the existing mismatch between the demand for emergency care and the available resources, thus avoiding the inappropriate use of national referral hospitals and all the consequences associated with it. While prehospital triage criteria for patient transport are frequently adopted in upper-middle- and high-income countries [8], there is a lack of the scientific literature on the implementation of triage systems in LMICs' prehospital settings, and no consensus on which triage tool works better in these contexts exists [9,10]. More broadly, only recently have LMICs started incorporating triage tools into emergency department practice by either adapting existing protocols or implementing new tools such as the South African Triage Scale (SATS) [11–13].

SATS, a triage protocol expressly designed for LMICs, is a four-level triage algorithm based on a list of emergency conditions and on the evaluation of seven different vital signs (mobility, respiratory rate, heart rate, systolic blood pressure, temperature, neurologic status, and history of trauma). Using three different tables (for adults, younger, and older children) containing reference values, the so-called Triage Early Warning Score (TEWS) is calculated. Patients who present one of the predetermined emergency conditions listed in the SATS protocol (obstructed airway, facial burns and inhalation, severe hypoglycaemia, and cardiac arrest) are immediately classified within the maximal priority category (red), while others have codes assigned according to the TEWS [11]. The use of objective vital-sign data renders the SATS a robust, simple, and rapid tool to be taught to inexperienced staff [14,15]. While the use of SATS has been extensively validated in different emergency departments located in resource-constrained settings, effectively reducing patient waiting time, hospital length of stay, and mortality [15–21], its performance in the prehospital field and in the assessment of nontrauma cases has not been thoroughly evaluated. Indeed, the formal assessment of the SATS utilisation by prehospital providers has been performed only through indirect methodologies, such as written clinical vignettes or focus-group discussions [22–24].

SATS has been recently integrated in the urban ambulance system of Beira, the second largest city of Mozambique with more than 530,000 inhabitants. The ambulance system was established immediately after the 2019 Cyclone Idai by NGO doctors with Africa CUAMM (Padova, Italy) in collaboration with the Centre for Research and Training in Disaster Medicine, Humanitarian Aid, and Global Health (CRIMEDIM, Università del Piemonte Orientale, Novara, Italy), with the aim of reducing hospital care referral time. The 24/7 free-of-charge referral service started its activities on 1 June 2019, linking Beira Central Hospital (HCB) with 15 peripheral health centres (HCs) through a fleet of five ambulances stationed in five different HCs, selected according to their geographical position and to the number of patients treated per day (Figure 1).

Upon its inception, the service did not contemplate a standardised prioritisation protocol for patient referral, but rather followed a first-in–first-out approach, thus often leading to a saturation of the service's referral capacity. Therefore, SATS has been incorporated to improve referrals and regulate the number of severe cases accessing HCB from the three HCs of Chingussura, Munhava, and Manga Mascarenhas. From 27 to 30 November 2019, 75 nurses working in the above-mentioned HCs were trained on the use of SATS, and instructed to refer patients when deemed necessary according to the priority codes. Specifically, nurses underwent a single two-day course (Table A1) and were instructed to follow a specific protocol for patient transport from the three HCs to HCB (Figure A1). This is the first example of SATS integration and assessment within the referral protocol of an urban ambulance system in a low-income country. The purpose of this study was to assess whether the implementation of the SATS varied the pattern of acute patients referred from HCs to HCB. In addition, we evaluated the correct use of the SATS performed by nurses in the HCs, defined as the accuracy related to the application of the tool.

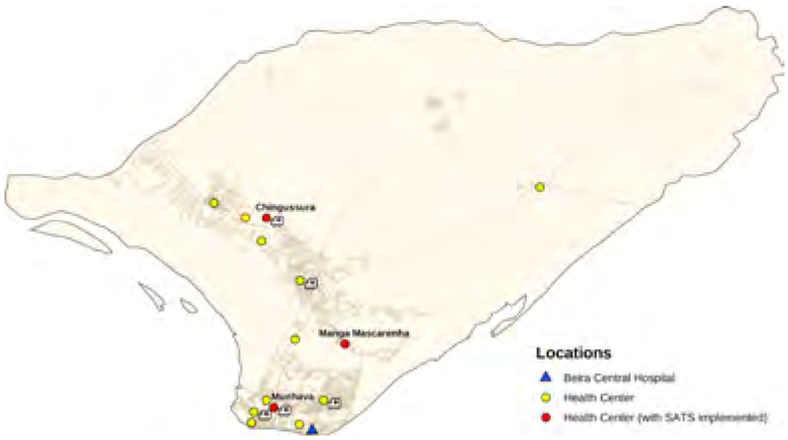

Figure 1. Distribution of health centres (HCs) and ambulances in Beira.

2. Materials and Methods

2.1. Study Design

This was a retrospective observational study that included all the referral transports performed from 8 October 2019 to 1 June 2020 from the three HCs of Chingussura, Manga Mascarenhas, and Munhava to HCB. The study consisted of two consecutive phases: a preimplementation phase (from 8 October to 7 December 2019) during which the assessment of patients and their subsequent referral to the HCB did not involve the use of SATS, and a postimplementation phase (from 8 December 2019 to 1 June 2020) involving the use of SATS.

2.2. Study Setting

The Chingussura and Munhava HCs (35 and 31 staffed beds, respectively) are classified as urban Type A health centres and were designed to serve a population of 40,000–100,000 inhabitants within a 1–4 km range. They are located at 18 and 6.5 km from HCB, respectively, and each one is equipped with one ambulance immediately available for referrals. The HC of Manga Mascarenhas (19 staffed beds) is classified as an urban Type B health centre, assisting 18,000–40,000 inhabitants within a 2–4 km range. It is 9.5 km from HCB and served by one ambulance stationed in the HC of Macurungo (at 8 km away), available upon request via phone call. Both types of urban HCs were designed to provide basic ambulatory services eventually followed by a short observational stay, such as general adult and paediatric examination, basic laboratory tests, and drug administration, while they cannot provide long-term patient hospitalisation, specialised consultation, surgery procedures, or advanced emergency care [25]. In the postimplementation phase, nurses in the three HCs were instructed to refer to HCB patients triaged with yellow, orange, and red codes, while minor green codes had to be treated at the HC level (Figure A1).

2.3. Data Collection

We used data from an electronic database storing all information recorded by trained nurses during transport using a patient's referral chart (Figure A2). After collecting patients' referral charts at HCB, dedicated local personnel trained by CUAMM performed data entry in this electronic database. Data accuracy was monitored through weekly inspections by CUAMM supervisors. Variables extracted for the present analysis were sex, age, disease category (medical, surgical/trauma, paediatric, obstetric/gynaecological), nurse-assigned priority codes (green, yellow, orange, red), and vital signs. Data were anonymised, and incomplete records for which it was not possible to retrospectively calculate the expected triage code (e.g., with one or more vital signs not recorded, or with missing age) were excluded from the statistical analysis.

2.4. Statistical Analysis

The researchers retrospectively assessed the expected triage code for all patients transported during the pre- and postimplementation phases using the SATS protocol. To evaluate variation in the pattern of referred acute patients, we compared the expected codes of patients transported to HCB before and after the implementation of SATS. The chi-squared test was used to evaluate changes in the proportion of the different expected triage codes.

The correct use of the SATS tool was assessed by comparing nurse-assigned and expected codes, the latter being used as the gold standard. We defined under- and overtriage as nurse-assigned codes lower or higher than the gold standard, respectively. The proportion of incorrect triage was defined as the sum of the observed proportions of under- and overtriage. To assess the inter-rater agreement, we used the quadratic weighted Fleiss' kappa, since it was used in previous triage studies [21].

We used logistic regression to investigate the possible association between nurses' accuracy of each referral, coded as a dichotomous variable (matching or not matching the expected code) and gender, age, and time since the implementation of SATS (independent variables). In all statistical analyses, a p-value of 0.05 or less was deemed to be statistically significant. We performed the analysis using Stata 15 (StataCorp, 2017, College Station, TX, USA).

3. Results

During the observation period, a total of 2636 referral charts were collected, and 159 and 317 records (from the pre- and postimplementation phases, respectively) were excluded. Table 1 summarises the demographic information of the considered patients. Our analysis comprised a total of 552 and 1608 referral charts for the pre- and postimplementation phases, respectively. Referral rate did not change appreciably over time. In both phases, referred patients were mainly women, and most of the referrals regarded obstetric or gynaecological and paediatric complaints (Table 1).

Table 1. Demographic information of referred patients before and after SATS implementation.

	Preimplementation	Postimplementation
Sex, n (%)		
Male	171 (30.0%)	474 (29.5%)
Female	381 (70.0%)	1134 (70.5%)
Pregnant	183 (48.0%)	609 (53.7%)
SATS age classes		
0–2 years (younger child)	88 (15.9%)	270 (16.8%)
3–12 (older child)	68 (12.3%)	147 (9.1%)
12+ (adult)	396 (71.7%)	1191 (74.1%)
Health centre		
Chingussura	356 (64.5%)	827 (51.4%)
Manga Mascarenhas	79 (14.3%)	177 (11.0%)
Munhava	117 (21.2%)	604 (37.6%)
Disease category		
Medical	97 (17.6%)	332 (20.7%)
Obstetric/gynaecological	141 (25.5%)	652 (40.6%)
Paediatric	118 (21.4%)	422 (26.2%)
Surgical/trauma	57 (10.3%)	202 (12.6%)
Missing	139 (25.2%)	0 (0.0%)
Observation time (days)	61	176
Transport rate (patients/day)	9.1	9.1
Total	552	1608

After the implementation of SATS, there was an increase in orange and red codes (+12.2%; +12.9%, respectively), and a reduction in green and yellow codes (−18.7%; −5.8%, respectively) referred to the HCB (Table 2). Figure 2 shows how this phenomenon took place gradually and lasted for the whole study period.

Table 2. Expected codes of referred patients before and after SATS implementation.

Code	Preimplementation	Postimplementation	*p*-Value
Green	174 (31.5%)	206 (12.8%)	
Yellow	181 (32.8%)	434 (27.0%)	
Orange	121 (21.3%)	539 (33.5%)	<0.0005
Red	76 (13.8%)	429 (26.7%)	
Total	552	1608	

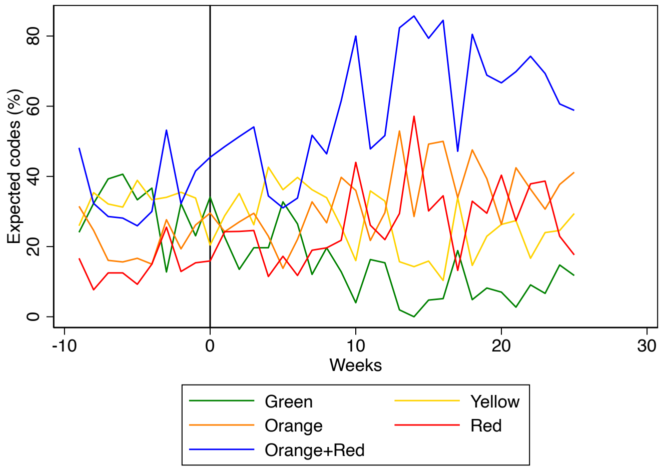

Figure 2. Proportion of expected triage codes before and after the implementation of the SATS (black line).

Table 3 shows the accuracy of SATS codes assigned by nurses during the postimplementation phase. The overall rate of nurses' accuracy, and under- and over-triage were 34.2%, 36.3% and 29.5% respectively. Tables A2 and A3 report the accuracy for obstetric or gynaecological and paediatric cases subgroups. The overall inter-rater agreement was 0.25 (95% confidence interval (CI) 0.21–0.29); in obstetric or gynaecological and paediatric cases, it was 0.17 (95% CI 0.10–0.25) and 0.16 (95% CI 0.06–0.25), respectively.

Figure 3 reports the association between time and accuracy, displaying an increasing trend from December 2019 (29.4%) to May 2020 (42.0%). This result was confirmed in the logistic regression, showing a statistically significant association between time since implementation and accuracy in the application of the tool (p-value < 0.0005). In contrast, the gender and age of patients did not influence nurses' accuracy in applying the SATS protocol.

Table 3. Comparison of the triage code originally assigned by local personnel and the code retrospectively obtained by researchers. The results in italics represent the number of correct triages performed by local personnel; those above and below them identify the percentage of over- and undertriage per category, respectively.

		Expected				Undertriage	Overtriage	Total
		Green	**Yellow**	**Orange**	**Red**			
Assigned	**Green**	*29 (23.0%)*	67	25	5	97 (77.0%)	-	126
	Yellow	62	*142 (31.3%)*	173	79	252 (55.3%)	62 (13.6%)	456
	Orange	94	181	*268 (34.5%)*	235	235 (30.2%)	275 (35.4%)	778
	Red	21	44	73	*110 (44.4%)*	-	138 (55.7%)	248
	Total	206	434	539	429	584 (36.3%)	475 (29.5%)	1608

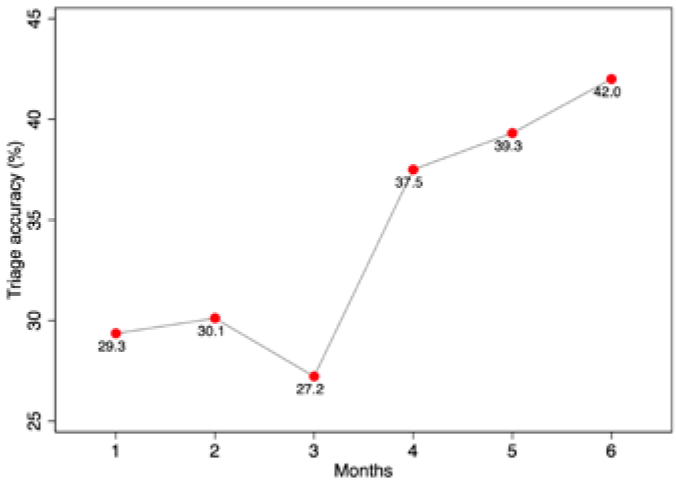

Figure 3. Triage accuracy (proportion of assigned codes matching with expected codes) in the postimplementation phase.

4. Discussion

The integration of SATS in the urban ambulance system of Beira modified the pattern of transported patients, improving the selection process and enabling local staff to become acquainted with the notions of triage and referral protocols, concepts that are still uncommon in Mozambique [23].

The increase in the proportion of severe transported cases followed a continuous progressive trend, suggesting that the concept of patient prioritisation and the SATS protocol might need time to be fully mastered by local professionals. Gradually, the first-in–first-out approach that aimed purely at reducing the pressure on constantly overcrowded HCs was replaced by a more coordinated system that has the utmost goal of addressing the limited resources available in postcyclone Mozambique to the most severe cases, optimising the use of the few ambulances, healthcare staff, and hospital assets [26]. The daily transport rates were similar before and after the SATS implementation, suggesting that the service worked from the beginning at its maximal capacity, and highlighting the importance of regulating the referral process through a standardised and rational approach.

To the best of our knowledge, this is the first formal assessment of the integration of SATS in the referral protocol of a low-income country. The decision to introduce the SATS to improve the existing referral service stemmed from its proven suitability for a low-resource context, evidenced by its algorithm-based approach, the availability of ready-to-use charts and training manuals, and the inclusion of easy-to-record vital signs [18,27,28].

Nevertheless, the use of SATS in this prehospital setting was associated with high rates of incorrect triage compared to the thresholds of 15% and 10% for over- and undertriage, respectively, which are usually deemed to be acceptable in hospital settings [24]. Our results are consistent with those of Mould-Millman and colleagues reporting high rates of undertriage among prehospital providers asked to assess clinical vignettes and assign a final SATS triage colour [24]. The authors suggested that the degree of miscalculation of TEWS, identified as one the most frequent causes of error in assigning the final triage colour could be further exacerbated under stressful real-life circumstances, such as the management of acute patients. The incorrect identification of predetermined emergency conditions and the incorrect selection of clinical discriminators are other common errors reported in the literature [24,29].

Furthermore, our analysis focused exclusively on under- and overtriage rates without investigating the root causes behind the decisions by nurses. The low inter-rater agreement and overall high rates of incorrect triage could have been amplified by the specific context. Indeed, the triage process is a complex activity, often performed in a stressful, distracting environment [30] that can influence the triage code assigned by nurses independently from the intrinsic reliability of the protocol [31]. This could, at least partially, justify the poorer SATS performance when compared to that in vignette-based studies [24].

This suggests the need for further studies to better assess the practical limitations for the implementation of SATS in a prehospital setting.

On the other hand, the main aim of the referral protocol implemented in the urban ambulance system of Beira was to avoid the transportation of green codes to HCB. The misclassification of yellow, orange, and red codes did not affect the referral indication. Among the 126 green-code patients erroneously referred to HCB, the vast majority were undertriaged (Table 3). This could mean that nurses could have recognised the mismatch between the assigned green code and the actual clinical condition, subsequently deciding to refer patients to HCB anyway, a frequent phenomenon already described in the literature [22,24,29]. Despite this procedure being contemplated in the SATS [32], it could have led to an apparent incorrect triage due to the contrast between recorded clinical parameters and triage codes assigned retrospectively.

Furthermore, the delivered training course might not have been sufficient in terms of content, duration, and teaching methodologies to provide sufficient skills and knowledge to the nurses. On the other hand, the available literature highlights a great heterogeneity among SATS training, thus indicating that no standardisation currently exists; for example, the duration of courses varies from 1-h [19,20] to 2-day courses [21]. In addition, the official SATS training manual [32] does not provide a suggested duration nor a specific teaching approach.

Moreover, this referral service represents, especially for the vulnerable strata of population, one of the few chances to reach HCB. Subsequently, nurses could have decided to refer patients with specific health needs even if not presenting an urgent condition recognised by SATS. Despite this approach overtaking the initial design and objectives of the referral system, it is very common and could be considered acceptable in the specific low-resource context [33]. In the same vein, the SATS has been implemented without any specific adaptation. Despite this approach being deemed necessary to provide a reliable and evidence-based tool, it does not take in consideration the specific needs and peculiarities of Beira's prehospital context.

Hence, whether SATS represents the best available option to regulate acute patients' referral in the prehospital setting is still under debate. Studies that assess the practical implications, benefits, and limitations of SATS implementation are needed to better understand its use in this context, and whether any adaptation is required to adjust the algorithm according to prehospital and local particularities.

Our findings should be interpreted considering some limitations. First, the study was performed immediately after the introduction of SATS, thus intercepting the learning curve of local nurses, and not investigating the long-term effects of the implementation. In addition, data used for this study were gathered from patients' referral charts, thus only including information on transported patients. Therefore, we are unaware of the actual number of patients assessed and treated at each HC in the selected timeframe, and we could not estimate the proportion of the different codes assigned to patients who have not been referred to the HCB. Additionally, as available data do not provide the outcome after hospitalisation, we were unable to establish whether the prioritisation of severe cases in the referral system effectively translated into improved health outcomes.

5. Conclusions

The integration of SATS in the Beira urban ambulance referral system has the potential to regulate the transport of acute patients to the central hospital, thus increasing the number of severe cases receiving advanced medical care. Despite nurses' performance being ameliorated with the routine application of the protocol, the use of SATS in this setting was associated with high rates of incorrect triage, suggesting a possible scope for improvement. For instance, the implementation could be strengthened by specific context-based tailoring, and the training might be designed and delivered taking into consideration the local professionals' expertise and habits.

A similar approach can be replicated in analogous settings to further investigate factors that might impact SATS application in prehospital settings, and to explore possible strategies for protocol adaptation and training improvement.

Author Contributions: Conceptualisation, A.C., D.S., M.C. and F.B.-A.; methodology, F.B.-A., M.C. and L.R.; formal analysis, A.C., D.S. and M.C.; investigation, A.C., D.S. and G.P.; resources, G.P. and M.M.; data curation, A.C., D.S., G.D.M., E.D.V. and L.L.R.; writing—original draft preparation and A.C., D.S. and M.C.; writing—review and editing, G.P., I.H., F.D.C., L.R. and F.B.-A.; visualisation, A.C., D.S., M.M.; supervision, I.H., F.D.C., L.R. and F.B.-A.; project administration, G.P., M.M., G.D.M. and E.D.V. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the AOU Maggiore della Carità di Novara, ASL BI, ASL NO, ASL VCO (Novara, Italy). Registration ID: 723/CE; approval ID: CE161/21.

Informed Consent Statement: Patient consent was waived due to the impracticability to identify and contact the subjects.

Data Availability Statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

LMIC	Low- and middle-income country
EMS	Emergency medical services
NGO	Nongovernmental organisation
SATS	South African triage scale
TEWS	Triage early warning score
HCB	Beira Central Hospital
HC	Health centre
CI	Confidence interval

Appendix A

Appendix A.1. SATS Course Agenda and Learning Objectives

Table A1. SATS course agenda.

Slots (1 h each)	Day 1	Day 2
Slot 1	Introduction to the course and pretest	Introduction to adult and paediatric SATS triage
Slot 2	Introduction to basic principles of triage	Exercise on SATS (adult and paediatric)
Slot 3	Introduction to the proposed referral protocol	Data collection and referral chart use
Slot 4	Vital signs (reference values, how to measure them, meaning of abnormal values)	Exercise on SATS (adult and paediatric)
Slot 5	Introduction to the SATS	Post-test and feedback questionnaire

Learning objectives

- To acquire the basic principles of triage.
- To acquire the ability to measure and to understand vital signs.
- To understand the importance of patient prioritisation.
- To understand the newly implemented referral protocol.
- To learn how to apply the SATS to both adult and paediatric patients.
- To acquire the ability to collect data using the referral chart.

Appendix A.2. Referral Protocol Specifications

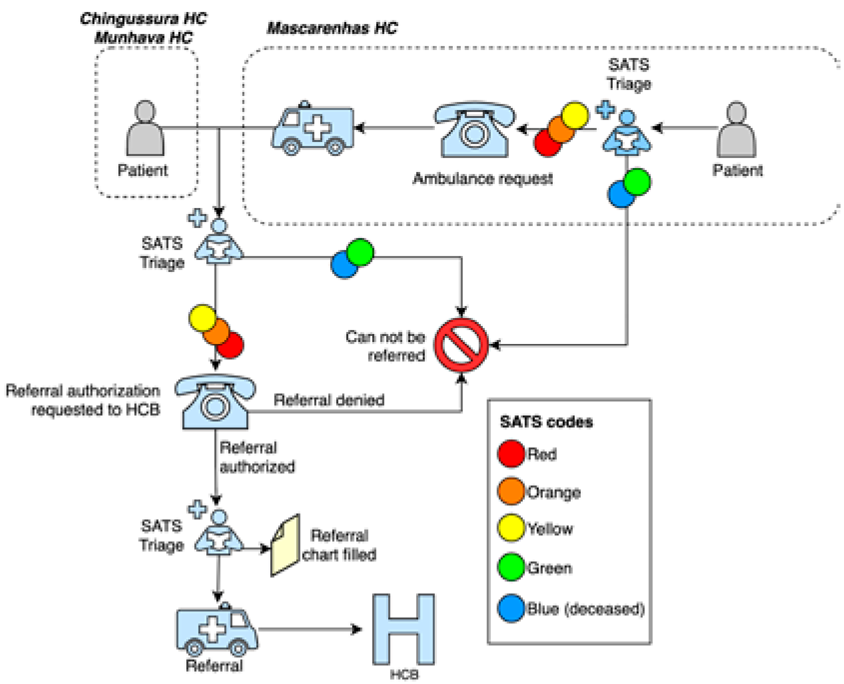

Figure A1. Dispatch protocol.

BEIRA CUAMM Ambulance Service - ECHO/-SF/BUD/2019/91002
Standardized referral chart

Date:	Ambulance nurse name:	Ambulance driver name:

Part 1 - Patient Information

General Information

Sex	❒ Male ❒ Female
Name	
Surname	
Date of birth	
Age (if date of birth unknown)	
Pregnant	❒ Yes ❒ No
Date and time of patient arrival	
Nurse requesting referral	

Observations

Part 2 – Referral information

Requesting HC

❒ CER Cerâmica	❒ CHI Chingussura
❒ CHA Chamba	❒ INH Inhamízua
❒ CHO Chota	❒ MAN Manga Loforte
❒ MAC Macurungo	❒ MAS Mascarenhas
❒ MAR Marocanhe	❒ MUN Munhava
❒ MAT Matadouro	❒ NAN Nhangau
❒ NAC Nhaconjo	❒ SAO São Lucas
❒ PON Ponta Gêa	❒ OUT Outro CS
❒ Transfer aborted (specify):	

Referral times

H1 Dispatch time	:
H2 Arrival time at the HC	:
H3 Depart. time from the HC	:
H4 Arrival time at HCB	:
H5 Return time back to HC	:

Part 3 – Main reason for the referral

A - Emergency	**C - Surgical**
❒ A01 Obstructed airway – Not breathing	❒ C01 Acute Abdomen
❒ A02 Convulsions (current)	❒ C02 Fracture
❒ A03 Facial burn or intoxication	❒ C03 Infected wound
❒ A04 Hypoglic. <3mmol/L	❒ C04 Bleeding
❒ A05 Cardiac arrest	❒ C05 TEC
❒ A06 Psychomotor agit.	❒ C06 Animal bite
B - Medical	**D – Obst./Gyn.**
❒ B01 Asma	❒ D51 High obstetric risk
❒ B02 Pneumonia	❒ D52 Obstetric hemorrhages
❒ B03 Severe or cerebral malaria	❒ D53 Abortion
❒ B04 Severe anemia	❒ D54 Dystocia
❒ B05 Sepsis	❒ D55 Abnormal presentation
❒ B07 Hypertension	❒ D56 Broken amniotic sac
❒ B08 Central cianosis	❒ D57 RPM
❒ B09 Severe respiratory difficulty	❒ D58 Eclampsia
❒ B10 Severe dehydration	❒ D59 Severe preeclampsia
❒ B11 Hypergl. >11mmol/L	❒ D60 Fetal distress
❒ B12 Meningitis	**E - RN**
	❒ E01 Neonatal Asphyxia
	❒ E03 Prematurity
	❒ E04 Neonatal Sepsis
	❒ E05 Congenital malformation
	❒ E06 Necrotizing Enterocolitis
	❒ E07 Doenc. menb. hial. DMH
F00 – Other (specify)	

Part 4 – Vital Signs

Time	BP	HR	RR	Temp.	AVPU
Depart.	/				
:	/				
:	/				

Mobility
❒ M1 Normal
❒ M2 With help
❒ M3 Immobile/on stretcher

Event type
❒ T0 Non traumatic
❒ T1 Trauma

Part 5 - Hospital

Final destination
❒ RE Patient rejected
❒ FA Patient deceased during referral
❒ AE Patient hospitalized in the emergency department
❒ AS Patient hospitalized in the delivery room
❒ AP Patient hospitalized in the pediatric department
❒ AG Patient hospitalized in the Gynecological department
❒ AO Patient hospitalized in other departments (specify):

Outcome (space reserved for M&E):

M&E reserved space: ❒ Added to database \\ ❒ Data acquired from HCB	**ID Number** /

Figure A2. Patient's referral chart (English translation: the original chart was developed and implemented in Portuguese).

Appendix A.3. Obstetric/Gynaecologic and Paediatric Cases Accuracy

Table A2. Comparison of the triage code originally assigned by local personnel and the code retrospectively obtained by researchers for obstetric/gynaecological cases. The results in italics represent the number of correct triages performed by local personnel; those above and below them identify the percentage of over- and undertriage per category, respectively.

		Expected				Undertriage	Overtriage	Total
		Green	**Yellow**	**Orange**	**Red**			
Assigned	**Green**	*20 (24.7%)*	48	11	2	61 (75.3%)	-	81
	Yellow	34	*63 (34.6%)*	73	12	85 (46.7%)	34 (18.7%)	182
	Orange	60	100	*119 (36.2%)*	50	50 (15.2%)	160 (48.6%)	329
	Red	12	17	14	*17 (28.3%)*	-	43 (71.7%)	60
	Total	126	228	217	81	196 (30.1%)	237 (36.3%)	652

Table A3. Comparison of the triage code originally assigned by local personnel and the code retrospectively obtained by researchers for paediatric cases. The results in italics represent the number of correct triages performed by local personnel; those above and below them identify the percentage of over- and undertriage per category, respectively.

		Expected				Undertriage	Overtriage	Total
		Green	**Yellow**	**Orange**	**Red**			
Assigned	**Green**	*3 (21.4%)*	4	6	1	11 (78.6%)	-	14
	Yellow	8	*27 (25.0%)*	39	34	73 (67.6%)	8 (7.4%)	108
	Orange	12	37	*77 (35.3%)*	92	92 (42.2%)	49 (22.5%)	218
	Red	4	9	32	*37 (45.1%)*	-	45 (54.9%)	82
	Total	27	77	154	164	176 (41.7%)	102 (24.2%)	422

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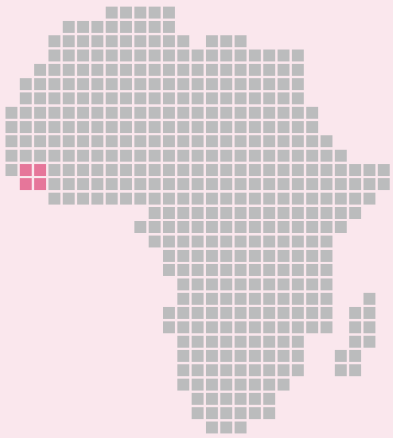
Prognostic role of TOPS in ambulance-transferred neonates in a low-resource setting: a retrospective observational study



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Prognostic role of TOPS in ambulance-transferred neonates in a low-resource setting: a retrospective observational study

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Abstract

Background: Assessing the severity of transferred neonates at admission can improve resource allocation. This study evaluated the role of TOPS (illness severity score including temperature, oxygen saturation, skin perfusion and blood sugar) in predicting mortality in neonates transferred by ambulance in a low-resource setting.

Methods: The study was conducted at Beira Central Hospital (Mozambique). Infants who were transferred by ambulance to the Neonatal Intensive Care Unit between 16th June and 16th October 2021 were included. The association between TOPS and mortality was investigated with a logistic regression model. Receiver-operating characteristics (ROC) curve was derived for TOPS; area under the ROC curve, sensitivity and specificity were calculated.

Results: In-transport mortality was 2/198 (1.0%) and in-hospital mortality was 75/196 (38.3%). Median gestational age and birthweight were 38 weeks and 2600 g. Main causes of admission were asphyxia (29.3%), prematurity (25.3%) and sepsis (22.7%). Hypothermia and oxygen desaturation at admission were 75.8% and 32.3%. TOPS ≥ 1 was associated with increased mortality risk (odds ratio 7.06. 95% confidence interval 1.90 to 45.82), with 0.97 sensitivity and 0.26 specificity.

Conclusions: The high mortality rate calls for interventions and quality initiative studies to improve the transfer process and the conditions at admission. TOPS can be used to identify neonates at risk of mortality and concentrate efforts of health care providers. Interventions preventing hypothermia and oxygen desaturation should be implemented in pre-transport stabilization and care during transport.

Keywords: Neonatal transport, Mortality, TOPS, Low-resource setting

Introduction

According to the last report by the United Nations International Children's Emergency Fund (UNICEF), over 5 million under-5 children died in 2020, including 2.4 million newborns [1]. While under-5 mortality has been significantly decreasing in the last three decades, a slower reduction rate has been observed in neonatal mortality [1]. Around 1 million of neonatal deaths occurred in

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sub-Saharan Africa, accounting for 43% of worldwide neonatal mortality [1].

While the centralization of high-risk deliveries is the preferred option, postnatal transport is inevitable when maternal transfer was not performed or possible, or specialized neonatal care was not anticipated before birth [2–5]. Neonatal inter-facility transport is a key aspect of perinatal care that aims to offer the appropriate care to preterm or sickest infants [4].

In low-income countries, many births occur in rural settings or at home, hence several efforts have been focused on promoting institutional births [6]. However, these usually take place in peripheral health centers with basic equipment and health care providers with limited formal training, thus sick babies require transport to a referral facility [6]. While neonatal transport is well established as part of regionalized perinatal care networks in high-income countries [7], transport modalities in low/middle-income countries remain suboptimal and transportation routes are difficult and time-consuming [6, 8–10]. In addition, pre-transport stabilization and care during transport are often inadequate, with potential serious consequences on infant outcome [11].

Assessing the severity at admission to the referral facility can improve resource allocation by health care providers and be used in the evaluation of the improvement in the transport process. TOPS score is an illness severity score for transferred newborns which was created as a simple and useful bedside method including four parameters (temperature, oxygenation, capillary refill time, and blood sugar) [11].

This study aimed to evaluate the role of TOPS in predicting mortality in neonates who were transferred by ambulance in a low-resource setting, with the purpose of identifying opportunities for improvement.

Methods

Study design

This retrospective observational study described the neonates who were transferred by ambulance to the Beira Central Hospital (Mozambique). The study was approved by the Comité Interinstitucional de Bioética para Saúde—CIBS/Sofala (prot.005/CIBS/Sofala) and written informed consent was obtained from the parents/caregivers of the newborns.

Setting

Beira Central Hospital (BCH) is the referral Hospital for the Sofala Province in Mozambique, and accounts for around 6,000 deliveries per year. The health care system in Sofala Province includes 158 health centers (primary level), one district hospital and four rural hospitals (secondary level) and the BCH (referral center) [12].

The Neonatal Intensive Care Unit (NICU) of the BCH is the second largest in the country and admits around 2,200 neonates every year, 56% of them are referred from other health centers or home. NICU staff includes a pediatrician, two general doctors, two residents, 26 nurses and six health workers. The NICU has 14 beds and is equipped with incubators, infant warmers, oxygen, bubble continuous positive airway pressure (CPAP), peristaltic and syringe pumps, phototherapy, and a portable ultrasound machine. Parenteral nutrition, invasive ventilation and therapeutic hypothermia are not available. Kangaroo Mother Care is offered in a dedicated 16-bed room.

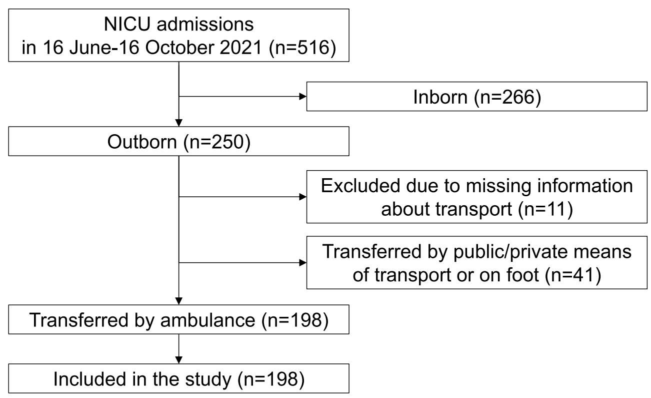

Fig. 1 Flowchart of patient inclusion (16 June 2021- 16 October 2021)

Neonates can be referred to BCH by ambulance, public transport (i.e. vans and bus), private vehicles (vans, cars, three-wheel motorbike) or on foot. Ambulances transfer neonates from health centers to BCH, and are equipped with oxygen, self-inflating bag and face mask, thermometer, peripheral venous line, stethoscope, gloves, and delivery-kit. The transport incubator is not available, and neonates are usually transferred in parent's arms. The transport involves a health care provider (usually a pediatric nurse) when indicated. The service is free-of-charge.

Patients

Outborn infants who were admitted to the NICU of BCH between 16th June and 16th October 2021 were eligible for inclusion in the study. Infants who were transferred by ambulance were included in the main analysis, while infants transferred by other means of transport and those with incomplete information about transport were excluded.

Data collection

Data were collected from NICU and transport records, and neonatal medical charts. Two researchers (AC and NA) retrieved the data independently and any inconsistencies were resolved by a third researcher (BM). Retrieved data included patient characteristics at birth, transport data, interventions before and during transport, information at admission and outcome. Gestational age was calculated according to the Last Normal Menstrual Period recall or assessed by using the New Ballard Score [13, 14]. Information on neonatal temperature (< 36.5 °C), oxygenation (SpO2 < 90%), capillary refill time (≥ 3 s) and blood sugar (< 40 mg/dl) at NICU admission were used to calculate the TOPS score (ranging from 0 to 4) in infants with birthweight ≥ 1,000 g and no life-threatening malformations (according to the selection in Mathur et al.) [11].

Statistical analysis

Numerical data were summarized as median and interquartile range (IQR), and the categorical data as absolute frequency and percentage. Comparisons between groups were performed using Mann–Whitney test (numerical data) and Chi Square test or Fisher's test (categorical data). The association between TOPS and mortality was investigated with a logistic regression model, adjusting for imbalances at NICU admission. Effect sizes were reported as odds ratio (OR) with 95% confidence interval (CI). Receiver-operating characteristics (ROC) curve was derived for TOPS predicting mortality; area under the

Table 1 Characteristics of outborn infants transferred by ambulance to Beira Central Hospital

Outborn infants transferred with the ambulance	198
Maternal age, years: [a]	22 (20–29)
Homebirth	21 (10.6)
Mode of delivery:	
Vaginal delivery	195 (98.5)
Caesarean section	3 (1.5)
Males	113 (57.1)
Females	85 (42.9)
Gestational age, weeks [a]	38 (34–39)
Gestational age:	
< 28 weeks	5 (2.5)
28–31 weeks	26 (13.1)
32–36 weeks	39 (19.7)
37–42 weeks	128 (64.6)
Birth weight, grams: [ab]	2600 (1778–3000)
Birth weight: [b]	
< 1000 g	6/194 (3.1)
1000–1499 g	24/194 (12.4)
1500–2499 g	55/194 (28.3)
2500–4000 g	107/194 (55.2)
> 4000 g	2/194 (1.0)
5-min Apgar score:	
0–3	13 (6.6)
4–6	40 (20.2)
7–10	117 (59.1)
Unknown	28 (14.1)
Distance, km [a]	13 (7–32)
Age at admission, days [a]	0 (0–3)
Age at admission:	
≤ 24 h	129 (65.2)
> 24 h	69 (34.8)
Weight at admission, grams [a]	2498 (1668–3025)
Diagnosis at admission:	
Asphyxia	58 (29.3)
Prematurity	50 (25.3)
Sepsis	45 (22.7)
Congenital malformation [c]	21 (10.6)
Respiratory distress	7 (3.5)
Gastrointestinal diseases [d]	7 (3.5)
Cutaneous or musculoskeletal diseases [e]	4 (2)
Metabolic problems [f]	2 (1)
Convulsions	2 (1)
Poor growth or weight loss	2 (1)

Data expressed as n (%) or [a] median (IQR)

Data not available in [b]4 neonates

[c] Congenital malformations included spina bifida (*n* = 10), abdominal wall defects (*n* = 6), imperforazione anale (*n* = 1), club foot (*n* = 1), hydrocphalus (*n* = 1), neck mass (*n* = 1), sacrococcygeus teratoma (*n* = 1)

[d] Abdominal distension, diarrhea, vomiting

[e] Abscesses, cellulitis, fractures, birth trauma

[f] Hypoglycemia, jaundice

ROC curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were calculated with their 95% CIs. All tests were 2-sided and a p-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria) [15].

Results

Patient selection

Overall, 516 newborns were admitted to the NICU of BCH between 16 June and 16 October 2021 (Fig. 1). Of them, 277 were excluded from the analysis because they were inborn infants ($n = 266$) or outborn infants with missing information about transport ($n = 11$; Supplementary Table 1). Further 41 outborn infants were excluded because were transferred by other means of transport (15 by public/private van, 11 by local three-wheel motorbike, 10 by personal car, four on foot, and one by public local bus) (Supplementary Table 2). The remaining 198 outborn infants who were transferred by ambulance were included in this analysis.

Characteristics of included patients

Table 1 displays the patient characteristics. The majority was admitted at their first day of life (129/198, 65.2%). The most frequent diagnosis at admission included asphyxia (58/198, 29.3%), prematurity (50/198, 25.3%) and sepsis (45/198, 22.7%). Median distance was 13 km (IQR 7–32).

Interventions before and during transport

Interventions before and during transport are reported in Table 2. Most transports had a written referral letter (170/198, 85.9%), while a pre-transfer phone call to the referral center was less frequent (52/198, 26.3%). Health care providers were present during 160/198 transports (80.8%).

TOPS components at admission

Vital signs at admission are shown in Table 3. Regarding the TOPS components, body temperature < 36.5 °C was found in 150/198 neonates (75.8%), oxygen saturation < 90% in 64/198 (32.3%), capillary refill time ≥ 3 s

Table 2 Interventions before and during transport of outborn infants transferred by ambulance to Beira Central Hospital

Phase	Aspects	Description	Outborn infants transferred by ambulance ($n = 198$)
Before transport	Interventions	Warming	98 (49.5)
		Suctioning airway	70 (35.4)
		Oxygen administration	44 (22.2)
		Face Mask Ventilation	44 (22.2)
		Chest compressions	30 (15.2)
		Adrenaline	3 (1.5)
		Sodium chloride 0.9% infusion	2 (1)
		Dextrose infusion	8 (4)
		Antibiotic therapy	10 (5.1)
		Neonatal prophylaxis (ocular, umbilical)	46 (23.2)
		Breastfeeding	68 (34.3)
	Communication and documentation	Pre-transfer phone call to the referral center	52 (26.3)
		Written referral letter	170 (85.9)
During transport	Interventions	Skin-to-skin contact	40 (20.2)
		Breastfeeding	33 (16.7)
		Oxygen administration	37 (18.7)
		Face Mask Ventilation	4 (2)
		Chest compressions	1 (0.5)
		Adrenaline	0 (0.0)
		Sodium chloride 0.9% infusion	0 (0.0)
		Dextrose infusion	0 (0.0)
		Antibiotic therapy	0 (0.0)
	Health care provider	Nurse	159 (80.3)
		Medical doctor	1 (0.5)
		None	38 (19.2)

Data expressed as n (%)

Table 3 Vital signs at admission of outborn infants transferred with the ambulance to Beira Central Hospital

Aspect	Variable at admission	Outborn infants transferred by ambulance ($n = 198$)
Clinical parameters	Heart rate:	
	≤ 60 bpm	7 (3.5)
	60–100 bpm	7 (3.5)
	101–180 bpm	182 (92.0)
	> 180 bpm	2 (1.0)
	Respiratory rate:	
	Apnea	8 (4.0)
	< 40 breaths/min	23 (11.6)
	40–60 breaths/min	104 (52.6)
	> 60 breaths/min	63 (31.8)
	Oxygen Saturation:	
	< 80%	27 (13.6)
	80–91%	45 (22.7)
	> 92%	126 (63.6)
	Body temperature:	
	< 32 °C	4 (2.0)
	32–35.9 °C	107 (54.1)
	36–36.4 °C	39 (19.7)
	36.5–37.5 °C	40 (20.2)
	> 37.5 °C	8 (4.0)
TOPS components	Body temperature < 36.5 °C	150 (75.8)
	Oxygen saturation < 90%	64 (32.3)
	Capillary refill time ≥ 3 s	22 (11.1)
	Blood sugar < 40 mg/dl[a]	14/177 (7.9)

Data expressed as n (%)

[a] Data not available in 21 neonates

in 22/198 (11.1%) and blood sugar < 40 mg/dl in 14/177 (7.9%). Hypothermia was found in 31/40 (77.5%) neonates receiving skin-to-skin contact and 119/158 (75.3%) not receiving skin-to-skin contact ($p = 0.94$). Among 64 neonates with transcutaneous oxygen saturation < 90% at admission, 18 (28.1%) received supplemental oxygen during transport.

Outcome

Two neonates expired at the arrival at the NICU of BCH (one late preterm, asphyxiated infant with 5-min Apgar score of 4 who was transferred after birth with body temperature of 34 °C; one full term, asphyxiated infant with 5-min Apgar score of 3 who was transferred at the 13th day of life with body temperature < 32 °C) and 196 were admitted to the NICU of BCH. Median length of stay was 4 days (IQR 2–8). In-hospital mortality was 75/196 (38.3%).

Role of TOPS in predicting mortality

Among the 171 outborn infants with birthweight ≥ 1,000 g and no life-threatening malformations (selected according to Mathur et al.) [11], increasing TOPS score was associated with higher mortality risk ($p < 0.0001$; Fig. 2A). The ROC curve suggested sensitivity of 0.97 (95% CI 0.88 to 0.99), specificity of 0.26 (95% CI 0.18 to 0.36), positive predictive value of 0.43 (95% CI 0.35 to 0.52) and negative predictive value of 0.93 (95% CI 0.76 to 0.99) for TOPS ≥ 1; 0.64 (95% CI 0.50 to 0.76), specificity of 0.80 (95% CI 0.71 to 0.87), positive predictive value of 0.65 (95% CI 0.51 to 0.77) and negative predictive value of 0.79 (95% CI 0.70 to 0.87) for TOPS ≥ 2; 0.22 (95% CI 0.13 to 0.35), specificity of 0.99 (95% CI 0.95 to 0.99), positive predictive value of 0.93 (95% CI 0.66 to 0.99) and negative predictive value of 0.69 (95% CI 0.60 to 0.76) for TOPS ≥ 3 (AUC = 0.77, 95% CI 0.70 to 0.84; Fig. 2B). Similar sensitivity and specificity were found when analyzing neonates transferred by ambulance or any other means of transport (Supplementary Table 3).

Mortality risk factors

In outborn infants (with birthweight ≥ 1,000 g and no life-threatening malformations) who were transferred by ambulance, higher mortality rate was associated with higher TOPS score and its components, lower gestational age, lower birth weight, no pre-transfer phone call, and breastfeeding during transport (Table 4). Multivariable analysis confirmed TOPS ≥ 1 as independent risk factor for mortality (OR 7.06. 95% CI 1.90 to 45.82, $p = 0.01$), adjusting for pre-transfer phone call (OR 0.41, 95% CI 0.17 to 0.92, $p = 0.03$), birth weight (OR 1.00, 95% CI 0.99 to 1.00, $p = 0.24$) and breastfeeding during transport (OR 0.43, 95% CI 0.11 to 1.33, $p = 0.17$). Gestational age was not included in the model due to collinearity with birth weight.

Discussion

Our findings underlined the high rate of hypothermia and desaturation among transferred infants by ambulance in a low-resource setting, and suggested a prognostic role of TOPS.

Despite the promotion of institutional births in low/middle-income countries, the limited resources in peripheral health centers usually force the transfer of sick babies to a referral facility [6]. In agreement with dedicated literature, our data showed that asphyxia, prematurity, and sepsis were the main causes for postnatal transfer, and most babies were transferred during the first day of life [6, 16].

Pre-transport stabilization and care during transport are crucial aspects in the management of these patients [6, 11]. Our data showed suboptimal warming care (half

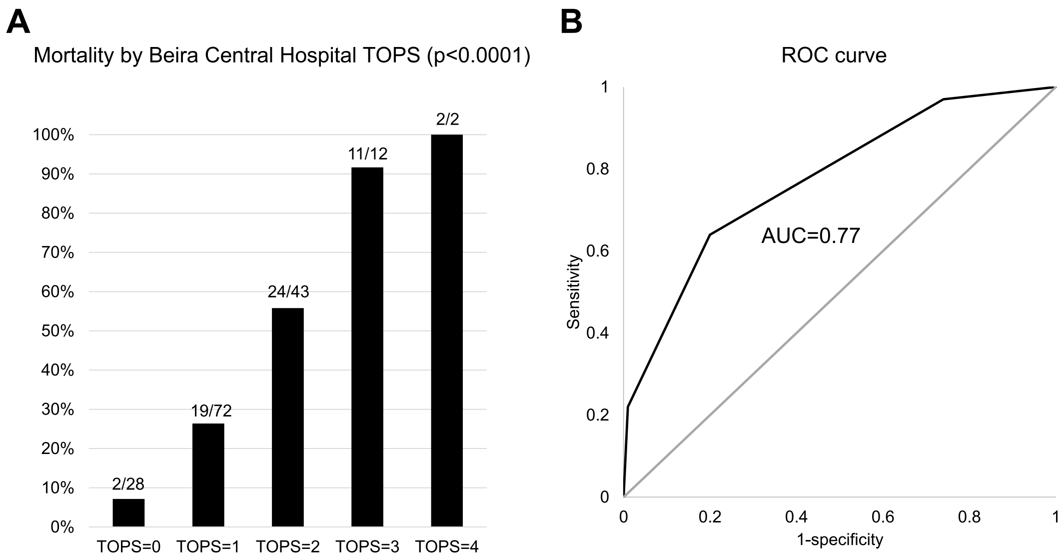

Fig. 2 Mortality risk according to TOPS score (**A**) and ROC curve for TOPS predicting mortality (**B**)

of the babies before transport and none during transport) and high rate of hypothermia at admission to the referral center (75.8%), hence highlighting the need for improvements in thermal management before and during transport. While skin-to-skin contact has been suggested as an effective approach during neonatal transport [17], only one out of five transported babies received skin-to-skin contact. We believe that this finding requires further investigation on application of skin-to-skin contact and/or considerations about alternative warming methods in this setting [18, 19]. Our data also suggested a large underestimation of hypoxia during transport, since most desaturated infants at admission to the referral hospital had not received supplemental oxygen before. Clinical evaluation of cyanosis can be difficult as there is limited agreement between infant color and oxygen saturation, hence a pulse oximeter should be included in the ambulance equipment [20]. These problems occurred despite the frequent presence of a nurse during the transport, which was higher compared to previous studies in low/middle-income countries [9, 21, 22]. Specific training on management of neonates during transport should be offered to health care providers who are involved in this activity. Of note, the referral center often received a written referral letter but was rarely informed before transfer, as previously reported [9, 21]. Our data identified pre-transfer phone call to the referral center as a protective factor for mortality, thus underling the importance of prompt communication between referring and referral centers. We may speculate that both sides can benefit from such communication, as the referring center may receive consultation for pre-transfer stabilization and the referral center may be ready for patient's arrival.

In our study, we found a high mortality rate in babies who needed postnatal transport, in agreement with literature [9, 23, 24]. Therefore, assessing the severity of transferred babies can improve resource allocation by health care providers at the referral center. Nonetheless, some limitations of the referral center (such as the lack of mechanical ventilation) underline the need for strengthening the local care. Our study evaluated TOPS as simple illness severity score (including temperature, oxygenation, capillary refill time, and blood sugar at admission) which has been suggested as useful predictor of mortality risk in low-middle resource settings [11]. Our data confirmed that TOPS at NICU admission was an independent predictor for mortality in a low-resource setting. We found that at least one derangement in any TOPS component was able to identify almost all neonates at risk of mortality (sensitivity 99%), who would benefit from greater resource allocation. On the other hand, the low specificity (26%) implied a high proportion of babies with low mortality risk who would receive unnecessary attention, hence reducing optimization of resource allocation. Of note, we also reported positive and negative predictive values for TOPS thresholds in the Results section; when considering such findings, the reader should remember that mortality prevalence impacted those

Table 4 Mortality risk factors in outborn infants (birthweight ≥ 1,000 g, no life-threatening malformations) transferred by ambulance

Variable	Discharged ($n = 111$)	Dead ($n = 60$)	p-value
Body temperature < 36.5 °C	79 (71.2)	52 (86.7)	0.04
Oxygen Saturation < 90%	20 (18.0)	37 (61.7)	< 0.0001
Capillary refill time ≥ 3 s	2 (1.8)	15 (25.0)	< 0.0001
Blood sugar < 40 mg/dl [b]	5/99 (5.1)	8/58 (13.8)	0.07
TOPS: [b]			< 0.0001
0	26/99 (26.3)	2/58 (3.4)	
1	53/99 (53.5)	19/58 (32.8)	
2	19/99 (19.2)	24/58 (41.4)	
3	1/99 (1.0)	11/58 (19.0)	
4	0/99 (0.0)	2/58 (3.4)	
Maternal age, years: [a]	24 (20–30)	22 (20–28)	0.27
Homebirth	9 (8.1)	7 (11.7)	0.63
Males	64 (57.7)	34 (56.7)	0.99
Females	47 (42.3)	26 (43.3)	
Gestational age:			0.03
28–31 weeks	10 (9.0)	14 (23.3)	
32–36 weeks	21 (18.9)	12 (20.0)	
37–42 weeks	80 (72.1)	34 (56.7)	
Birth weight, grams [a]	2750 (2000–3058)	2380 (1538–2900)	0.02
5-min Apgar score:			0.12
0–3	3 (2.7)	6 (10.0)	
4–6	27 (24.3)	9 (15.0)	
7–10	69 (62.2)	37 (61.7)	
Unknown	12 (10.8)	8 (13.3)	
Distance, km [a]	13 (7–23)	11 (6–25)	0.23
Age at admission:			0.32
≤ 24 h	69 (62.2)	42 (70.0)	
> 24 h	42 (37.8)	18 (30.0)	
Diagnosis at admission:			0.07
Asphyxia or respiratory distress	37 (33.3)	18 (30.0)	
Prematurity	21 (18.9)	21 (35.0)	
Sepsis	30 (27.1)	15 (25.0)	
Other	23 (20.7)	6 (10.0)	
Before transport:			
Warming	55 (49.5)	31 (51.7)	0.87
Suctioning airway	42 (37.8)	23 (38.3)	0.99
Oxygen administration	29 (26.1)	14 (23.3)	0.72
Face Mask Ventilation	27 (24.3)	15 (25.0)	0.99
Chest compressions	19 (17.1)	9 (15.0)	0.83
Antibiotic therapy	5 (4.5)	5 (8.3)	0.32
Neonatal prophylaxis	30 (27.0)	10 (16.7)	0.14
Breastfeeding	45 (40.5)	16 (26.7)	0.09
Pre-transfer phone call	39 (35.1)	10 (16.7)	0.01
Written referral letter	98 (88.2)	51 (85.0)	0.63
During transport:			
Kangaroo mother care	21 (18.9)	12 (20.0)	0.84
Breastfeeding	21 (18.9)	4 (6.7)	0.04
Oxygen administration	23 (20.7)	10 (16.7)	0.69
Nurse or medical doctor during the transport	91 (82.0)	49 (81.7)	0.99

Data expressed as n (%) or [a] median (IQR)

[b] Data not available in 14 neonates. Other diagnoses included respiratory distress ($n = 6$), congenital malformation ($n = 6$), gastrointestinal diseases ($n = 7$), cutaneous or musculoskeletal diseases ($n = 4$), metabolic problems ($n = 2$), convulsions ($n = 2$), poor growth or weight loss ($n = 2$)

statistics. Previous studies suggested a different threshold (derangements of 2 or more components) with better sensitivity/specificity balance (81.6%/77.4% in Mathur et al.; 81.5%/70.6% in Verma et al.; 71.9%/80.8% in Begum et al.) which may result in improved resource allocation but higher mortality [11, 23, 25]. In our data, derangements of 2 or more components provided comparable specificity but lower sensitivity, due to higher mortality among neonates with only one deranged component. Such discrepancy may be due to the different setting (sub-Saharan Africa vs. India), the different transferring system (referring center, transport service and referral center) and means of transport (by ambulance vs. ambulance and any other means). We replicated our analysis in neonates transferred by ambulance or other means of transport (Supplementary Table 3), and found similar results (comparable specificity but lower sensibility with respect to previous studies), hence we may speculate that different setting and transferring system may explain the discrepancy in sensitivity. Of note, the primary analysis focused on transport by ambulance because being transferred by ambulance or other means implied different subpopulations (for example, neonates transported by other means were older, less sick and cared for by unspecialized caregivers), as confirmed in Supplementary Table 2. In addition, there was a high heterogeneity among the other means of transport, including public van, private van, local three-wheel motorbike, personal car, public bus, or on foot. Further investigations in larger samples and different settings may provide more information on the optimal alert signal to stratify risk of mortality in transferred neonates.

Our study adds information on the prognostic role of TOPS in neonates transferred by ambulance in a low-resource setting, and offers useful insights about the care before and during the transport. This study has some limitations that should be considered. First, this is a single-center study hence the generalizability of the findings should be limited to similar settings. Second, the retrospective design precludes any causal relationship. Third, TOPS at referring centers and data on transport time were not available.

Conclusions

The high mortality rate calls for interventions and quality initiative studies to improve the transfer process and the conditions at admission. TOPS can be used to identify neonates at risk of mortality and concentrate efforts of health care providers. Interventions preventing hypothermia and oxygen desaturation should be implemented in pre-transport stabilization and care during transport.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-022-05060-9.

> **Additional file 1: Supplementary Table 1.** Characteristics of outborn infants who were excluded due to incomplete information about transport. **Supplementary Table 2.** Information about outborn infants admitted to Beira Central Hospital according to means of transport. **Supplementary Table 3.** Sensitivity and specificity of TOPS score for prediction of mortality in 210 outborn infants with birthweight ≥1,000 grams and no life-threatening malformations (who were admitted to Beira Central Hospital between 16 June and 16 October 2021) transferred by ambulance or other means of transport.

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Authors' contributions
FC performed the statistical analysis, contributed to data interpretation, writing of the manuscript and critically reviewed the manuscript. AC, NA performed the literature review, collected the data in Mozambique, drafted the initial manuscript and critically reviewed the manuscript. BM, AHAS and BRC contributed to the collection of data in Mozambique, contributed to data interpretation and critically reviewed the manuscript. SC performed the literature review, contributed to data interpretation, contributed to writing of the manuscript and critically reviewed the manuscript. GP and DT conceptualized the study, contributed to data interpretation, writing of the manuscript and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Comité Interinstitucional de Bioética para Saúde—CIBS/Sofala (prot.005/CIBS/Sofala). Written informed consent was obtained from the parents/caregivers of the newborns. We confirm that the study was performed in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Relationship between Admission Temperature and Risk of Cerebral Palsy in Infants Admitted to Special Care Unit in a Low Resource Setting: A Retrospective Single-Center Study

POSTER PRESENTATIONS

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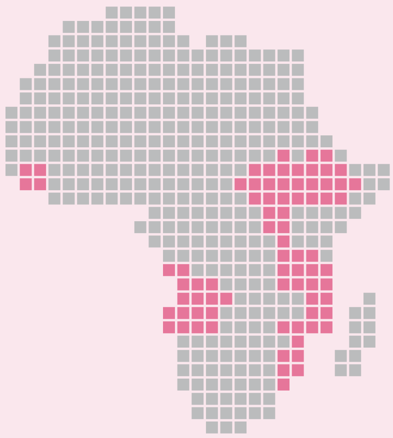

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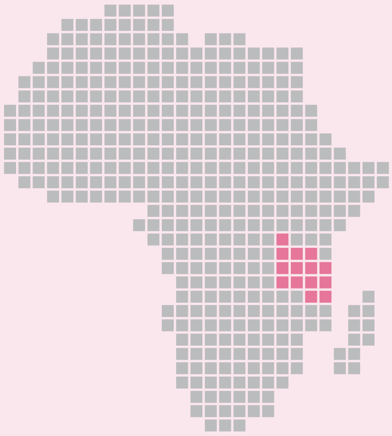

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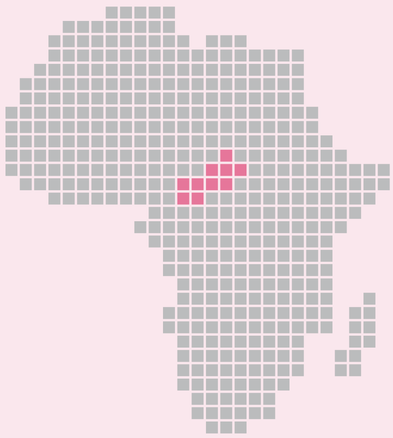

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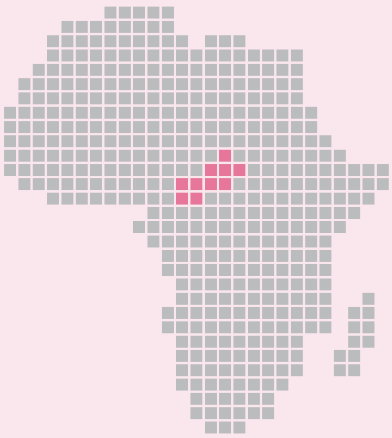

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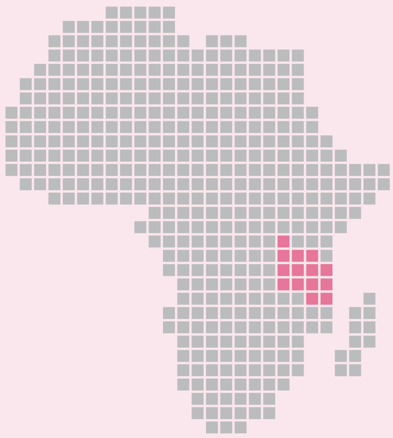

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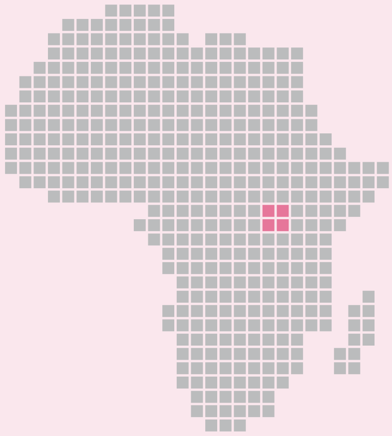

Public health and universal coverage

“This Is Not Our Disease”: A Qualitative Study of Influencers of COVID-19 Preventive Behaviours in Nguenyyiel Refugee Camp (Gambella, Ethiopia)

PAPER

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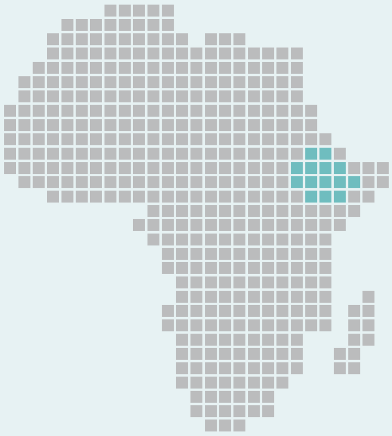

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"This Is Not Our Disease": A Qualitative Study of Influencers of COVID-19 Preventive Behaviours in Nguenyyiel Refugee Camp (Gambella, Ethiopia)

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The COVID-19 pandemic has infected more than 263 million people and claimed the lives of over 5 million people worldwide. Refugees living in camp settings are particularly vulnerable to infection because of the difficulty implementing preventive measures and lack of medical resources. However, very little is known about the factors that influence the behavioural response of refugees towards COVID-19. There is an urgent need for field evidence to inform the design and implementation of a robust social and behaviour change communication strategy to respond to the threat posed by COVID-19 in humanitarian settings. This study examines factors influencing COVID-19-related behavioural decisions in the Nguenyyiel refugee camp located in Gambella, Ethiopia using data collected from focus group discussions and key informant interviews in September 2020. The evidence suggests that while a number of factors have been facilitating the adoption of COVID-19 prevention measures, including good general knowledge about the virus and the necessary preventive strategies and the active engagement by community leaders and non-governmental organisations, important structural and cultural factors have hindered the uptake of COVID-19 prevention measures. These include: difficultly staying at home to minimise physical contact; overcrowding in the camp and within home dwellings; a lack of hand sanitizers and masks and of funds to purchase these; inconsistent use of facemasks when available; COVID-19 denial and misconceptions about the disease, and other cultural beliefs and habits. Overall, the study found that refugees perceived COVID-19 to pose a low threat (susceptibility and severity) and had mixed beliefs about the efficacy of preventive behaviours. This study identified gaps in the existing information education and communication strategy, including a lack of consistency, inadequate messaging, and a limited use of communication channels. While awareness of COVID-19 is a necessary first step, it is not sufficient to increase adoption of prevention measures in this setting.

The current communication strategy should move beyond awareness raising and emphasise the threat posed by COVID-19 especially among the most vulnerable members of the camp population. This should be accompanied by increased community support and attention to other barriers and incentives to preventive behaviours.

Keywords: COVID-19, refugee camp, refugees, SBCC, Gambella, Nguenyyiel, Ethiopia

INTRODUCTION

Since the WHO declared a Public Health Emergency in January 2020, COVID-19 has infected more than 260 million people and claimed the lives of almost 5.2 million people worldwide by 26th November 2021 (1). Ethiopia has reported close to 271,000 cases and 6,700 deaths (1), although these numbers are likely to represent gross underestimations (1). Refugees and IDPs have been particularly hard hit. Those living in camp settings, most of whom are in middle-income countries (LMICs), are particularly vulnerable to infection because of overcrowding and a general lack of access to water, sanitation and hygiene (WASH) services, and medical resources.

The COVID-19 pandemic has created a global health crisis unprecedented since the outbreak of the Spanish Flu a century ago. Until the recent development of successful vaccines, the only means to protect oneself and prevent the spread of the virus was through the strict observation of social distancing, quarantines, lockdowns, and the promotion of basic preventive measures, like frequent hand washing, self-isolation, and the use of face masks in public. These measures are particularly difficult to observe in marginalised and over-crowed refugee camp settings, where access to facemasks, water, soap, heath facilities, and proper healthcare is limited.

At the outbreak of the pandemic, experts form UNHCR and IOM described refugee camps as "ticking time bombs waiting to explode," and warned that COVID-19 could have a devastating effect and spread like "wild fire" if it reached the world's largest refugee camps. There are over 26 million refugees in the world, about a third of whom live in camps. An additional 48 million people are internally displaced as a result of conflict and human rights violations (2). This population includes more than a million Rohingya refugees in Bangladesh, 3.6 million Syrian refugees in Turkey, 289,000 in Iraq, 232,000 South Sudanese in Uganda and 189,000 in Kenya (3).

Having fled violence and social collapse, this population is already highly vulnerable. Refugees live in precarious and overcrowded conditions, suffer from a high prevalence of physical and mental health problems, and are constantly facing the risk of deportation and an uncertain future. Their access to health care is limited due to financial, administrative, legal, and language barriers (4). Most LMICs that host the overwhelming majority of refugees and IDPs lack enough vaccines, COVID-19 tests, hospital beds, intensive care units, or ventilators to treat their own populations.

As of the time of publication, no large outbreaks of COVID-19 have been reported in refugee or IDP camps. This may be partially explained by the fact that cases in many LMICs that host refugees have yet to peak and many refugee camps are located in isolated places. It is also very likely that COVID-19 has taken hold in some camps, but that the virus has been under-reported due to a lack of testing, and fear of stigmatisation on the part of the refugees. The refugee populations also tend to be relatively young, which affords a certain degree of protection. A modelling study of the potential impact of a COVID-19 outbreak in a Rohingya refugee camp in the Kutupalong-Balukhali area of Bangladesh, for example, projected that an outbreak would be characterised by a high transmission but a low death rate. Even if refugee camp residents manage to avoid getting ill as a result of COVID-19, the pandemic is likely to take a tremendous toll on these vulnerable populations.

With over 814,535 refugees and IDPs, Ethiopia is host to one of the largest forced migrant populations in the world. According to UNHCR, 368,822 of them (45.3%) are refugees that have fled the conflict in South Sudan (5). Approximately 82,614 of these refugees reside in the Nguenyyiel Refugee Camp, in Ethiopia's Gambella region (6).

In refugee camps and regions with fragile health systems, the range of medical and epidemiological responses to emerging disease outbreaks can fall short, as was demonstrated by the response to the Ebola outbreak in West Africa (7). In these contexts community-based responses are critical to preventing the spread of infections.

Community-based responses, however, are affected by local perceptions of the threats posed by the disease and of the efficacy of the proposed protection measures. The perceptions of threat are a combination of people's perceived susceptibility to infection and perceived severity of the disease. Perceived efficacy, on the other hand, represents a combination of *response efficacy*, or the perceived effectiveness of the recommended response to avoid the threat, and perceived *self-efficacy*, or people's belief in their own ability to adequately perform the recommended response. Both concepts are derived from the extended parallel process model of Social and Behaviour Change Communication (SBCC) for emergency preparedness. This model is recommended for emergency situations because it takes into account the increased risk perception that populations are likely to experience as a result of an emergency (8). An effective SBCC strategy design must also take into account the various levels of influence that interact to influence behaviour. The Social Ecological Model, informed by Bronfenbrenner's 1979s seminal work (9), recognises four levels of influence: (1) individual; (2) family and peer networks; (3) community; and (4) social/structural levels (10). Ideally, a messaging strategy should be evidence-based, respond to misinformation present within the community, and induce rational, adaptive, and protective behaviours in the population. In humanitarian settings, however, very little is usually known about the complex interplay among the changing epidemiology, media coverage, the measures put in place to control the epidemic, the public's perception of risk, and their behaviours. Considering this, the design and implementation of a robust SBCC response to COVID-19 in humanitarian settings needs to be informed by evidence generated through action research. West Africa's experience with Ebola clearly illustrated that SBCC interventions were critical in changing harmful health practises that were contributing to the rapid spread of Ebola (11).

Unpublished preliminary reports produced by community outreach agents showed evidence of a significant "knowledge-action gap" with regards to COVID-19 in the Nguenyyiel Refugee Camp (12). While camp residents were aware of the existence of COVID-19, they perceived it to be a low risk. The disease was mostly seen as a "*Ferenj*" affair, or a disease that only affects white people and to which Black Africans are immune. It became increasingly apparent that humanitarian agencies' communication strategies that had focused exclusively on COVID-19's modes of transmission and means of prevention were not bringing about the desired behavioural changes. Crowded camp conditions and a lack of infrastructure also presented significant challenges to the implementation of COVID-19 preventive measures and the adoption of health recommendations. This study was conducted to generate evidence to inform the design of more effective communication strategies that could bring about the desired behavioural changes to prevent the transmission of COVD-19 in the camp.

More specifically, this study sought to explore factors that influence refugees' response to COVID-19 at the different levels—individual, family, community, and social/structural—as identified by the Social Ecological Model. The study also sought to identify the perceived threats and efficacy beliefs that influence responses to prevention and control of COVID-19 and to identify opportunities for actions in the camp. The evidence generated would help to develop and implement appropriate messages to support specific interventions targeting all camp residents including vulnerable groups to adopt prevention measures. The evidence would also contribute to the development of appropriate SBCC messages tailored to the existing local community-based organisations such as youth clubs, self-help mothers' associations, mutual help associations, sport and religious groups, to support the COVID-19 response.

METHODS

The Nguenyyiel Refugee Camp, located in Itang Woreda, is the largest and newest camp in Ethiopia's Gambella region (13). The camp is home to 82,744 South Sudanese refugees, all of them from the Nuer tribe (13). It is divided into four zones, each with about 20,000 people. In total, there are 17,613 households, 51,150 children below age 15, and 14,281 women of reproductive age (14). As of the end of 2020, there were 13 reported COVID-19 cases and no deaths in the camp (14). The camp was selected for this study because Doctors With Africa Collegio Aspiranti e Medici Missionari (CUAMM) has been implementing a health project there providing medical services to the refugees specifically focusing on maternal and child health services.

This study was designed as a qualitative action research project using focus group discussions (FGDs) and key informant interviews (KIIs) with adult male and female populations of refugees residing in the Ngunyyiel Refugee Camp. Focus groups are used to explore views on health issues, programs, and interventions. The group interaction encourages respondents to explore and clarify individual and shared perspectives. This method was thus deemed most appropriate to answer our research objectives of exploring factors that influence refugees' response to COVID-19 and identifying the perceived threats and efficacy beliefs that influence their responses to COVID-19 prevention and control measures. KIIs were used to provide information from an expert's perspective to complement and triangulate the information from FGDs. All adult residents of the camp who were able to provide informed consent were eligible to participate in the study.

FGD participants were chosen through sampling techniques to guarantee fair representation according to geographic distribution throughout the camp, demographic indicators, and their social position in the camp. FGDs were conducted with the following groups: elderly men (aged > 60 years), elderly women (aged > 60 years), middle-aged men (aged 30–59 years), middle-aged women (aged 30–59 years), male youth (aged 18–29 years),, female youth (aged 18–29 years), and members of the refugee central committee. The FGD participants were identified from the refugee register maintained by the UNHCR. **Table 1** shows the makeup of the FGDs. The FGDs included 41 participants including 10 elderly women and men, 10 middle-aged men and women, 11 Refugee Central Committee (RCC) members and 10 male and female youth. The RCC is the main decision making and coordination body for refugees in the camp. Most of the participants (41.5%) had 1–8 years of schooling and about a third had no formal education, with the elderly being more likely to be non-educated. Most (73.2%) had stayed in the camp for 4–5 years.

Participants of KIIs included community leaders and humanitarian organisation staff members with knowledge of COVID-19 prevention and response. KIIs were conducted with three NGO staff involved in SBCC activities and three community leaders in the camp.

Data was collected in September 2020 by trained field interviewers (facilitators) using open-ended KIIs and FGD interview guides. The interview guides were written in English and translated into the Nuer language in which the interviews were conducted. All KII and FGD sessions were audio recorded with the consent of participants, and field notes were taken to document non-verbal cues. FGDs were conducted in venues close to respondents' houses while KIIs were conducted in respondents' offices or homes.

Two teams, each composed of three field interviewers fluent in Nuer and English, collected data. A field supervisor supervised the teams. A team composed of female field interviewers facilitated women's FGD sessions while a team composed of male interviewers facilitated FGDs involving men.

TABLE 1 | Characteristics of participants of focus group discussions.

Characteristics	Elderly men and women ($n = 10$)	Middle-aged men and women ($n = 10$)	RCC members ($n = 11$)	Male and female youth ($n = 10$)	Total ($n = 41$)
Age*, Median (min–max)	65 (61–70)	36 (33–49)	41.5 (38–45)	23 (18–28)	40 (18–70)
Sex, *n* (%)					
Female	5 (50)	5 (50)	5 (45.5)	5 (50)	20 (48.9)
Male	5 (50)	5 (50)	6 (54.6)	5 (50)	21 (51.2)
Education level, *n* (%)					
None	7 (70)	4 (40)	3 (27.3)	0 (0)	14 (34.2)
Grade 1–8	3 (30)	3 (30)	6 (54.6)	5 (50)	17 (41.5)
Above grade 9	0 (0)	3 (30)	2 (18.2)	5 (50)	10 (24.4)
Duration in the camp, *n* (%)					
2–3 years	1 (10)	2 (20)	5 (45.5)	3 (30)	11 (26.8)
4–5 years	9 (90)	8 (80)	6 (54.6)	7 (70)	30 (73.2)

*Data on age were missing for five Refugee Central Committee (RCC) members.

All audio recordings were transcribed verbatim, translated to English, and uploaded into *Atlas.ti* for inductive coding and thematic analysis. After reading through the transcripts, the research team members developed and reviewed a coding framework. Data were then summarised under four broad themes, namely: (1) Factors facilitating prevention of COVID-19; (2) factors hindering COVID-19 prevention; (3) unintended consequences of COVID-19 prevention measures; and (4) SBCC interventions. Lower-level themes were presented under each broad theme and pieced together to provide an overview of the content relating to that specific theme. Quotes from respondents were selected to represent a typical response or to illustrate a deviant opinion.

Ethical approval for the study was provided by the Gambella Region Health Bureau Ethics Review Committee and The Agency for Returnees and Refugees Affairs (ARRA). All participants in this study provided verbal informed consent.

RESULTS

The FGDs and KIIs explored a few key themes. The section below discusses the factors that facilitated and that hindered the uptake of COVID-19 preventive measures among the refugee population living in the camp. In both cases, a distinction is made between factors affecting behaviour at the individual, household, and community/social levels. The study then proceeds to identify refugees' perceived threats and efficacy beliefs that influenced their behaviour towards the pandemic. Finally, it explores the measures taken in the camp and some unintended consequences produced by these measures.

FACTORS FACILITATING THE UPTAKE OF COVID-19 PREVENTION MEASURES

Awareness About COVID-19 (Individual Level)

Refugees in the camp, for the most part, exhibited a high level of awareness and knowledge about COVID-19. Participants felt that they had received sufficient information about the virus, and they attributed this to the sensitisation work that humanitarian organisations had been conducting in the camp since the outbreak of the pandemic.

> *"As my colleagues explained it more, we have been made aware by many institutions about the symptoms of coronavirus which include fever, cough, diarrhoea, sneezing."* FGD, Elderly Men

> *"The information given to us about COVID is enough. All NGOs are working hard to teach us on how we can protect ourselves from coronavirus."* FGD, Middle-aged women

As a result of the sensitisation campaigns, COVID-19 was a common topic of conversation within the camp. Participants believed that the problem in the camp was not a lack of awareness about the virus, but that people were failing to take preventive measures.

> *"We discuss about COVID at home. This coronavirus has dominated all the dialogues at homes and on streets."* FGD, Elderly men

> *"I don't think there is a problem on awareness. The problem is taking the preventive measures."* KII, NGO staff

Participants showed a high level of awareness about the measures that needed to be taken if they or others began exhibiting symptoms of COVID-19. Among the measures mentioned were visiting the health facility, self-isolating at home, and staying away from symptomatic individuals.

> *"Everyone who feels sick should go to the closest health facilities whenever they have some symptoms. No one should stay at home while sick."* FGD, Elderly men

> *"If a person has a cough, she/he can't sleep together with other persons. If a child has fever, other individuals should distance themselves from the child"* FGD, Elderly women

Participants also showed a high level of knowledge about COVID-19 prevention strategies. Most were able to recall with ease the recommended public health strategies including hand washing, social distancing, avoiding handshakes, staying away from symptomatic individuals, using face masks, and not sharing them with others.

> *"We have to keep our social distance; we should wear face masks and we should avoid handshakes."* FGD, Male youth

> *"COVID-19 preventive measures are important things like avoiding handshakes, keeping social distance and staying far from sick persons."* FGD, RCC Men

> *"We have learned many things. We use soap, we maintain our distance, we stay far from the person who has fever, we stay far from the person who has a cough, we stay far from a person who has a common cold and far from persons who sneeze; the masks should be worn by only one person. Masks should not be used by two or more people even among family members."* FGD, Elderly men

Respondents had a generally good understanding about the means through which COVID-19 is transmitted from person to person.

> *"We heard that air droplet transmission occurs when a person is in close contact with an infected person and exposure to potentially infective respiratory droplets occurs, for example, through coughing, sneezing or very close personal contact resulting in the transfer of air droplet through the mouth and the nose."* FGD, Elderly men

> *"We know that coronavirus transmits from person to person through coughing and sneezing."* FGD, Male youth

Participants were also aware that COVID-19 could sometimes result in death, and that there was no known treatment for the disease.

> *"We are taking care of coronavirus because we have heard that there is no treatment for it."* FGD, Elderly men

> *"This disease is very dangerous. There is no treatment for it."* FGD, Female youth

There were, however, some misconceptions and inaccurate information about the severity of COVID-19. Some respondents, for example, believed that the disease killed instantly.

> *"What we hear about coronavirus is that it kills persons immediately after infection."* FGD, RCC men

> *"It kills people immediately after it has reached the person's lung."* FGD, RCC men

Communication Within Households (Household Level)

COVID-19 prevention messaging was clearly spreading within households in the camp. The study revealed that men were the primary recipients of the information, because they were also the ones most likely to venture out of the home and to become exposed to health messages. They, in turn, transmitted this information to the women in the home and to other family members.

> *"I told to my wife emphasizing that children can do a lot to keep themselves and others safe. I introduce the idea of social distancing, standing further away from friends, avoiding large crowds, not touching people."* FGD, Elderly men

> *"Even though I don't get information about COVID, my husband will tell me what he has heard. Men do not sit at home like women and you have to follow what they say."* FGD, Middle-aged women

Role of Community Leaders and Humanitarian NGOs (Community/Social Level)

Community leaders played a key role in promoting COVID-19 prevention measures in the camp. They raised awareness about COVID-19 when food was distributed in the camp, in the streets using megaphones, and during house to house visits and public gatherings in churches and schools. Community leaders also provided refugees with the means to wash their hands, ensuring that people adhered to social distancing guidelines when in public, for example, while waiting in food distribution lines. They also acted as critical links between the community, the authorities, and the NGOs.

> *"We pass the information to the community during food distribution. We arrange water for washing; we ensure their hands are washed. We also maintain social distance during food distribution time. We report the inadequacy of resource allocation to the bodies concerned."* FGD, RCC men

> *They visit our homes and tell us not to share many things with our neighbours, not to share drinking cups even with home members, and not to share eating utensils with our neighbours."* FGD, Elderly men

> *"The community leader has told us day and night to wash our hands with soap and water and to keep social distance."* FGD, Elderly women

Participants expressed a high level of trust in the NGOs that were involved in raising awareness about COVID-19 and that were promoting preventive measures. They particularly recognised the work that OXFAM was doing.

> *"I trust the international non-governmental organization who brought us here, I know they are working hard for us and they will bring masks."* FGD, RCC men

> *"The OXFAM plays a great role to provide us training, provide us water, soap, and increase our awareness to fight against the diseases. They provide us places for hand washing, carry out campaigns, and provide information using megaphones."* FGD, Elderly men

NGOs working in the camp (particularly OXFAM), had ensured that water and soap were available for the people to wash their hands.

> *"The use of soap and water has been a very good thing and the soap has been available here in the camp; you can see people washing their hands with soap and water along the roads and even at home people are doing it."* FGD, Elderly men

Preventive Measures Taken (Individual Level)

FGD participants mentioned several measures that they were taking to prevent COVID. These included washing hands with soap, changing clothes after venturing outside of the house, properly disposing of used tissue paper, using coughing/sneezing etiquette, avoiding handshakes, avoiding symptomatic individuals, and exercising social distancing.

> *"First of all, we wash our hands with soap and water. We ask guests to wash their hands before coming into our house."* FGD, RCC men

> *"We cover our nose and mouth while sneezing or coughing with a flexed elbow. We don't throw used tissue papers everywhere."* FGD, Elderly men

> *"If I need to cough, I have to turn to the side to avoid the transmission of the disease and also I don't greet friends by shaking hands."* FGD, Elderly women

FACTORS HINDERING THE UPTAKE OF COVID-19 PREVENTION MEASURES

Despite having a basic understanding about COVID-19 and the measures that should be taken to prevent infection, refugees living in the camp were not always able or willing to follow preventive guidelines consistently. Discussions with community participants and key informants showed increasing evidence of a "knowledge-practise" gap.

Individual Level Factors

Individuals had difficulty observing social distancing recommendations and limiting physical contact with others because of the need to venture out of the home in search of sources of livelihoods and because of a strong tradition of visiting relatives.

> *"People who are working among us get only 800 Ethiopian Birr (US$21). This money is not enough to bring food to our family; it should be supplemented by wild foods. We are on the run; I cannot close my door and stay at home. We are suffering with hunger so we can't stay home and starve."* FGD, RCC men

> *"Yeah, we will spend our time everywhere because here in this camp we are visiting our relatives on daily basis."* FGD, Female youth

The camp residents claimed that they lacked money to buy COVID-19 supplies such as face masks and hand sanitizers.

> *"We have no money. Only a few people have this mask; these two things are not available."* FGD, middle-aged women

> *"The refugees don't have money to buy soap and face mask. They are not wearing face masks because they don't have them."* KII, Humanitarian NGO staff

When available, face masks were used inconsistently. Individuals tended to use facemasks only in situations where they were mandatory, for example, when riding public transportation.

> *"I have seen little change recently; I have seen masks worn by women when they were the first people who refused masks. They were forced to wear masks before getting into buses to go to Gambella."* FGD, RCC men

Although masks were available at local shops, the majority of the camp's residents could not afford to buy them. A lack of hand sanitizers also meant that most people had to wash their hands with soap and water to maintain hand hygiene.

> *"How many people are there in your home? You mean all your family can wear the same mask? It may be only you who can afford to buy a mask. Some people cannot afford to buy masks for all family members."* FGD, RCC men

> *"We don't have enough facemask, and we don't have sanitizers. We try to use them but it's challenging."* FGD, Women

Overcrowding at Home (Household-Level Factors)

Families live in crowded conditions because of large family sizes and inadequate housing. The camp is overcrowded making it very difficult for residents to observe social distancing and creating potentially risky conditions for the spread of infectious diseases.

> *"When the number of families and relatives increase, people start to congest in the same house."* FGD, Middle-aged women

> *"You may find five to ten people sleeping in the same house."* FGD, RCC men

Misconceptions About COVID

There were a few shared misconceptions about COVID-19 that were responsible for hindering the uptake of preventive measures. The most common one, perhaps, was the belief that COVID-19 was a disease that only affected white people, and that Africans living in warmer climates were somehow immune to it.

> *"Some people say: I'm sorry you are believing white people. Just leave it. This is not our disease. But I would tell them that this disease is for everyone."* FGD, Middle-aged women

> *"There are people who say this disease is only for white people and it can't be transmitted to black people."* FGD, Women

> *"Some people say COVID-19 does not affect the people living in hot environments, which is not true. Some people in the beginning were saying COVID-19 could not affect black people."* KII, Humanitarian NGO staff

There were also shared misconceptions about preventive measures and cures. For example, some believed that drinking alcohol and smoking cigarettes could prevent infection.

> *"When you hear the young men talking, they will say things like: why are you not drinking wine or smoking cigarettes? If you drink, you will not be infected by the Corona virus."* FGD, Male youth

Some individuals ignored COVID-19 prevention guidelines despite being aware of what they were supposed to do.

> *"... some people don't understand things easily, they ignore the disease even if it is considerably evident."* FGD, RCC men

> *"...of course, the community knows how to prevent COVID-19. Nevertheless, they don't apply the preventive strategy. They are ignoring the presence of COVID-19."* KII, Humanitarian NGO staff

At one extreme, some camp residents denied the existence of COVID-19 all together.

> *"When trying to tell people about COVID, they never understand saying this is false, this is a false thing."* FGD, RCC men

> *"...people don't accept the presence of the disease called COVID-19"* KII, Humanitarian NGO staff

Others failed to follow the guidelines because they believed that COVID-19 was not particularly severe as evidenced by the very small number of reported cases and deaths in the camp.

> *"The reason they ignore the disease is that they have heard of people recovering very quickly of coronavirus. They don't believe the disease is serious enough to kill people."* KII, Humanitarian NGO staff

Those who denied the existence of the virus did so mainly because they had never seen someone who was sick or had died from COVID-19.

> *"People ask questions like: if it is real, let me see persons who are affected by coronavirus. If coronavirus is really true, I have to see real patients."* FGD, RCC men

Perceived Low Severity of COVID-19 (Individual)

Overall, camp residents did not perceive the threat of COVID-19 to be particularly severe. This is because the camp was not particularly affected.

> *"The community does not believe that the disease is serious enough to kill people. They ignore the disease considering it not that serious."* KII, Humanitarian NGO staff

Individuals attempting to observe COVID-19 prevention measures where often under pressure not to do so by those who denied the existence of the virus.

> *"We are forced to shake hands with those who ignore this disease saying: this is false; there is no disease."* FGD, RCC men

> *"People are discouraged by others. If they see you wearing the mask, they may say 'why are you wearing this mask?' There is no coronavirus."* FGD, Elderly women

> *"When you keep your distance, they will challenge you saying wrong words and we try to tell them about COVID, but they don't believe the disease exists."* FGD, Female youth

Culture and Tradition (Community/Society-Level Factors)

The study identified a number of social and cultural factors particular to Nuer society, which hindered the uptake the recommended protective measures.

Social gatherings such as small group meetings, communal meals, worshipping and working together, are a central part of the Nuer culture. Observing social distancing guidelines in this context thus proved to be particularly challenging. During social gatherings, COVID-19 prevention measures are often ignored.

> *"It is difficult to prevent Nuer form sitting and gathering together. If you go to the market you see many people sitting together."* FGD, Female youth

> *"According to our tradition, we should be together, sit together, eat together and work together."* FGD, male youth.

The Nuer believe that eating together is unavoidable. Eating alone, or not sharing food is seen as a sign of selfishness.

> *"Nuer people share things together; when a person refuses to share food in order to avoid COVID, he should be called selfish." FGD, RCC men*

Because of high unemployment rates among the refugees, the issue of boredom and idleness also presents a challenge. Unemployed refugees prefer to spend their time meeting with friends and relatives to chat or play games.

> *"We the refugees feel that staying at home alone is boring, so every man including me spend our time at our local cafeterias; We drink coffee and tea there. We share some conversation about our country there. We listen to some news from our country and sometimes it brings pleasure."* FGD, Elderly men

> *"But how can we spend our days? We sit together and talk."* FGD, Elderly men

Avoiding the habit of shaking hands as a form of greeting one another has been particularly difficult. Handshaking is an integral part of Nuer culture. It was considered inappropriate or impolite to avoid handshakes.

> *"Nuer culture is one of several serious factors affecting the prevention of COVID-19. In Nuer culture, they love shaking hands with others. The people promote handshakes. It is offensive not to shake hands as a greeting. A Nuer person does not allow covering*

of nose with something." FGD, RCC men

"There are many things in Nuer culture which influence the prevention of coronavirus, one of them is handshakes…" FGD, RCC men

Avoiding a handshake as a preventive measure, in fact, was considered rude and as something that could lead to conflict in the community.

"Coronavirus prevention causes conflict in our community. When trying to avoid shaking hands with a person from a rural area, they feel something bad. These are not good for Nuer culture." FGD, RCC men

The Nuer tradition of visiting relatives and people who are ill also presented a risk for viral transmission of COVID-19. Preventing people from visiting a sick person and having physical contact with that person was seen as unacceptable.

"For example, my neighbour's son was sick yesterday. I visited him today early in the morning before coming to work. My visit is not only to see him and turn my back without touching. He may condemn me if I don't touch him. To avoid being condemned by my neighbour, I touched him. I don't know if the disease was COVID." FGD, RCC men

Participants found it very difficult to require guests to wash their hands when visiting their homes.

"When a guest comes home and you give him an order to wash his hands before sitting down; saying 'go there and wash your hands,' it can bring conflict. I don't feel comfortable telling people to wash their hands." FGD, RCC men

Another challenge to the uptake of the recommended protective measures, derived from Nuer culture, was the presence of traditional healers in the camp who claimed to be able to treat COVID-19 using traditional medicine.

"Yes, there are traditional healers here in the camp." FGD, RCC men

"Yes, there are traditional healers for corona; they treat cough and chest pain. I know some traditional medicines among plant roots including 'wangmach,' and 'chiok buoka.' These are good medicine for Corona." FGD, RCC men

"If you have a cough, there are healers. You will go to them and they will give you the medicines from the forest and you will be healed." FGD, Female youth

Some participants recognised that a certain sense of fatalism, inherent in Nuer culture, may also have hindered, to some extent, the uptake of preventive measures in the camp. The Nuer considered death to be a normal thing that should not be feared. This means that people are not too afraid of dying of COVID-19 and are therefore not very likely to adopt preventive measures.

"Death is not new, and you can't occupy the soil after death. These kind of sayings are most influential in discouraging people from taking preventive measures." FGD, RCC men

"If a person is trying to take preventive measures, other Nuer will say death is not new thing." FGD, RCC men

Finally, participants noted that, for the large part, children in the camp were not observing any COVID-19 prevention measures.

"Children are not stoppable, while a person may try to keep himself at home; the children are impossible to keep at home." FGD, RCC men

PERCEIVED THREATS AND EFFICACY BELIEFS THAT INFLUENCE THE RESPONSE TO COVID-19

Perceived Threat

Initially, people did not feel threatened because they did not believe that COVID-19 was real. After a number of cases were reported in other refugee camps in Gambella, some individuals began feeling susceptible to infection.

"We didn't believe that the disease was real. But when coronavirus reached the camp, all of us became afraid and understood that what we were told was true." FGD, Elderly men

"When we were given an announcement that coronavirus had come, we did not believe it, but when it was announced that it affected people here in the camp it caught our attention that this disease was for real." FGD, Middle-aged women

Despite a number of confirmed cases, some camp residents continued to believe that COVID-19 was a white people's disease that could not harm people living in warm regions. These individuals did not view COVID-19 as a threat.

Many minimised the severity of the disease, likening it to other common illnesses present in the community. They did not believe they had any good reason to fear COVID-19.

"The community does not believe that the disease is serious enough to kill the people. They ignore the disease considering it not that serious." KII, Humanitarian NGO staff
"Old people are saying COVID is simple. It is like common cold or malaria. They don't take it as a serious disease." FGD, Male youth.

This was mainly because death from COVID-19 was rare in the camp.

"When people see that it is not killing a lot of people, they say that it is not a serious disease." KII, Humanitarian NGO staff.

Some, however, did believe that COVID-19 was a severe disease that could result in death.

"This disease is very dangerous. There is no treatment for it." FGD, Female youth

"We understand that coronavirus can kill people." FGD, Elderly men.

Efficacy Beliefs

Overall, FGD participants accepted that the COVID-19 prevention methods being promoted, including frequent hand washing, the use of face masks in public, and social distancing, were effective in preventing transmission.

"We understand that masks can help prevent the spread of the virus from the person wearing the mask to others, but we don't have enough masks." FGD, Elderly men

"If you shake hands with everyone you will transmit the disease. If you wear facemask even though you have a cough, there is no way to transmit the disease." FGD, Female youth

There were, however, a mixture of self-efficacy beliefs. Some FGD participants felt that COVID-19 had been brought about by God to punish humanity. These participants believed that prevention measures were futile, and that only God could protect them.

"I suspect that this disease is brought to us by God through air. God wants to punish his people. God should have brought the poison to the earth through something like air." FGD, Elderly men

"We will not succeed in prevention by ourselves; we will be protected by God." FGD, RCC Men

Others expressed low self-efficacy to prevent infection because they lacked the recommended protection supplies.

"It is difficult for us to prevent the disease. We have no prevention equipment." FGD, Elderly men

Overall, most FGDs participants felt that they were capable of taking preventive measures to protect themselves against COVID-19. This sense of confidence derived in part from their wartime experience, which they had survived, and which they saw as significantly more threatening than COVID-19. They felt that protecting themselves from this virus in the camp would be easier than surviving the violence in their own country.

"It is a dangerous disease. If we are responsible enough to protect our health, we can prevent it. It will not be as difficult as preventing deaths from war. Millions of people have died in South Sudan due to war. COVID is not difficult like war. We can prevent the disease." FGD, Elderly women

Surviving violence in South Sudan could also result in the adoption of a cavalier attitude towards COVID-19 within the camp.

"We are victims of war that occurred in South Sudan. We sometimes have trauma. You can see many people here don't care about serious things." FGD, Elderly men

Additional Consequences of COVID-19 Prevention Measures

An added consequence of the promotion of COVID prevention measures has been the improvement of sanitary conditions in the refugee camp.

"No hand washing practice before this disease, now people are well aware. Being clean in your area, avoid eating un-boiled food. This disease has improved sanitary awareness in the family" FGD, RCC men

"I wake up in the morning and start to clean the home, and my wife, child and the whole family join me in cleaning the home. We also clean the place of my cattle; now my children have learned that, and they now wake up before me. They started cleaning their houses, they reach the outside and move on to other places of my home." FGD, Elderly men.

Social and Behaviour Change Communication Interventions

Humanitarian organisations principally made use of megaphones and loudspeakers to broadcast IEC messages in the camp. Community leaders also delivered IEC messages via house-to-house visits. Respondents, however, recognised that this method also increased the risk of transmitting the disease. They believed that there was a need for radio broadcasting IEC messages.

"Currently, community leaders walk house to house to deliver health information. However, walking by feet is not good because there may be contact. We need a radio station here in the camp to pass information to everybody in the camp." FGD, RCC men

"OXFAM provides information to the whole camp using megaphones mounted on a vehicle. It provides information to the whole camp. We need these kinds of things in this camp." FGD, RCC men

"the way health messages are delivered to us is through the use of megaphone, loudspeakers and so on in the language of the communities by health care workers." FGD, Female youth

Posters were also displayed in the marketplaces to convey COVID-related messages.

"There are also mass awareness raising activity at the community level using megaphones and loudspeakers. There are also a lot of key message posted around market centres. The community can easily look and identify what has to be done to prevent COVID-19." KII, Humanitarian NGO staff

Some individuals first became aware of COVID-19 after attending training sessions in the camp.

"Our awareness has improved; we attended so many trainings and learned about COVID." FGD, Elderly men

IEC messaging in the camp focused principally on people's need to observe social distancing, avoid shaking hands, wear masks, wash hands frequently, and avoid individuals exhibiting flu-like symptoms.

> *"We have been told that there is disease and there is no need for handshakes, and we have been told to wear masks. We have been told also to stay clean. All home members should frequently wash their hands. These are the ways to protect ourselves."* FGD, RCC men

> *"If you are giving your kids food, you have to wash your hand, if you are going to the market to buy something you have to use a mask and you cannot greet anyone on the road and if there is anyone who greets you, you have to say hi without touching his/her hand. This is the information we are given"* FGD, Elderly women

> *". . . so, we are told that people cannot sit in one place or be together, we have to wash our hand with soap. If you see someone coughing or having common cold, you should not be close to her/him. The third thing is we have to wear a face mask."* FGD, Middle-aged women

Respondents identified a number of gaps in the existing IEC messaging. They thought, for example, that IEC activities were conducted very sporadically, giving people the impression that COVID-19 was no longer a threat.

> *"In this community everyone knows coronavirus. However, the IEC activities are not continuously conducted. If there is no follow up from us, we may think that coronavirus does not exist."* FGD, RCC men

With regards to the content of the messages broadcasted, participants believed that the severity of COVID-19 was not being emphasised well enough. This was leading camp residents to believe that COVID-19 was not very severe, and to relax the observation preventive measures.

> *"They don't have that much promotion regarding the seriousness of the disease. Different partners are focusing on raising awareness about COVID. Most of the IEC activities focus on awareness raising activities not giving emphasis on seriousness of the disease."* KII, Humanitarian NGO staff

> *"The severity of the disease is not reported by different organizations especially in the Gambella region. So, the community understands that there is no death from COVID-19 and are not serious enough to take preventive measures."* KII, Humanitarian NGO staff

> *"The community has some information regarding COVID-19, but the seriousness of COVID-19 is not given much emphasis."* KII, Humanitarian NGO staff

There was also a general perception that the IEC delivery methods were largely ineffective in reaching everyone, especially those who stay at home. As previously noted, women who stay at home tended to receive their information regarding COVID-19 from their husbands who ventured outside of the home.

> *"The people who have information about COVID are the ones who attend churches and go to the market areas. Those people who are sitting at home are not getting adequate information about COVID-19."* FGD, Male youth

Participants believed that existing IEC activities could be made more effective with the use of more pictures and symbols. They also believed that more extensive use could be made of existing social networks as well of existing community, administrative, and religious structures.

> *"It is good to show pictures to people showing the cause of the disease, picture of infected persons and picture of someone who takes preventive measures."* FGD, RCC men

> *"It is good to establish community social network to improve the communication system. If we have such network, once the information reaches to COAs, it can easily pass to the subsequent community structures."* KII, Humanitarian NGO staff

Camp residents were most likely to trust information conveyed by health workers, community and religious leaders, NGO staff, and people who speak the same language as they do.

> *"In my view, we trust you because we have the same language and the same traditional way of life. When I was in Dima the humanitarian staffs didn't provide us the real information like you do now. The life in Dima was difficult. Now we enjoy this camp because we get services from the people who share the same language and the same historical background with us."* FGD, Elderly men

> *"The one who will encourage me to take preventive actions are the people who work in the community because they are teaching us in the community, and those humanitarian workers, including RCC leaders, zonal leaders, block leaders, and all the people who have knowledge about this disease. They encourage me to take action."* FGD, Female youth

> *"Yeah, in my view, the community trusts the church leaders. Any information that pass through the church is accepted by the community."* KII, Humanitarian NGO staff

DISCUSSION

This study found that refugees in the Nguenyyel Camp in Gambella, Ethiopia had good general awareness about COVID-19, the strategies they needed to follow to prevent contagion, and the measures they needed to take when and if symptoms occurred. Community leaders and NGOs have been actively transmitting this information within the community and this knowledge has been passed along within households. The uptake of preventive behaviours has also been facilitated by greater availability of water and soap, and a greater awareness of the importance of frequent hand washing.

The study also found that important factors were hindering the uptake of COVID-19 prevention measures. These included some structural factors, such as overcrowded living conditions, challenges practising social distancing by staying at home, lack of money to purchase hand sanitizer and facemasks, and inconsistent use of facemasks.

The uptake of effective prevention measures was also hindered by a general low severity perception of the disease, particularly in light of other safety risks faced by refugees, cultural obstacles to social distancing, and the acceptance of death as a normal event that is out of people's control.

Overall, the participants had a low risk perception of the threat posed by the COVID-19 virus. Their responses showed that they did not believe that they were very susceptible to the disease or that the disease was very severe. These perceptions were clearly reinforced by the fact that the virus has not impacted the camp very severely.

Participants also showed a mixture of efficacy beliefs. While most believed that the prevention measures promoted in the camp were indeed effective (response efficacy), some participants felt that there was not much they could personally do to prevent from becoming infected (self efficacy).

House-to-house visits by volunteers and use of megaphones and loudspeakers were the most common methods for the dissemination COVID-related IEC messages in the camp. These messages were focused primarily on promoting social distancing, mask wearing, and frequent handwashing. This study, however, identified a number of gaps in the existing IEC strategy. These included a lack of consistency in awareness raising, inadequate content, particularly with regards to the severity of the disease, and limited use of available communication channels.

Our study's findings are generally consistent with the findings of other studies of refugee populations living in camp settings. A study conducted on South Sudanese and Congolese refugees in Uganda showed that most refugees and asylum seekers were well-informed about COVID-19 and about the measures they needed to take to protect themselves from infection (15). For the most part, the refugee population in Uganda was following the proscribed COVID-19 measures but also experienced some difficulty practising social distancing, staying at home, and wearing facemasks. This study also showed evidence of the spread of misinformation and misconceptions about contracting, avoiding, and treating COVID-19. Like in Ethiopia, a common misconception was that the virus affected only whites and foreigners and that black Africans were immune. One of the limitations of the Ugandan study, however, was that it only included community leaders, so it is unclear whether ordinary members of the community shared the same perceptions.

Another study of Syrian refugees living in Turkey showed a very high level of COVID-19 awareness (16). Unlike the refugees in Nguenyyiel Camp, however, refugees in Turkey had access to television, social media, and the internet as sources of information about COVID-19, which facilitated the diffusion of IEC. Despite a high level of awareness, community members became less inclined to adhere to the proscribed preventive measures overtime as a type of lockdown fatigue settled in. As in Nguenyyiel Camp, some refugees in Turkey denied the existence of COVID-19 and minimised the risk it posed to them (16).

CONCLUSION

The study in Gambella shows that while general knowledge about COVID-19 is a necessary first step to prevent the spread of infection, it does not guarantee the uptake of preventive measures within the community. Both significant structural and cultural challenges to the adoption of preventive measures must also be addressed. Further emphasis should be placed on the susceptibility and severity of COVID-19, particularly among the most vulnerable members of the population such as the elderly and individuals with underlying health conditions. Self-efficacy should be further encouraged. A comprehensive SBCC strategy must address the widespread misconceptions and the cultural factors that are hindering the adoption of preventive measures.

Additional material support to the community, making available face masks and hand sanitizer, largely out of reach to refugees, can also go a long way in promoting the adoption of preventive behaviours.

This qualitative study offers an initial yet valuable insight into the prevailing community perceptions related to COVID-19 within a refugee camp setting. The findings outlined in this study applied to all groups targeted. Within our sample, we did not note any major differences across demographic groups with regards to knowledge of the virus or risk adversity. A more in-depth quantitative inquiry that looks at a larger sample may further identify the factors that best predict community adherence to the recommended preventive measures. In light of this study's findings, we have proposed a SBCC communication strategy (**Appendix 1**), and have developed a list of key messages to educate the refugee population and counter some prevailing myths on COVID-19 (**Appendix 2**).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Gambella Region Health Bureau Ethics Review Committee. The Agency for Returnees and Refugees Affairs (ARRA) also approved the study. Participants provided verbal informed consent. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AT, FM, MB, GP, MD'A, and AA contributed to conception of the study. AT, CW, and GP contributed to design of the study. AT, DF, and MB facilitated the collection of and transcription of the data. AT and CW analysed and wrote the first draft of the study report. FM and GP reviewed the first draft report. GC-F wrote the first draft of the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.723474/full#supplementary-material

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The impact of the COVID-19 pandemic on health service use in sub-Saharan Africa

PAPER

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The impact of the COVID-19 pandemic on health service use in sub-Saharan Africa

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SETTING: Six hospitals in four sub-Saharan African countries.

OBJECTIVE: To examine the indirect effects of COVID-19 on health service utilisation and to explore the risk of bias in studies on prediction models.

DESIGN: Monthly data were analysed using interrupted time-series modelling. We used linear mixed-effect models for the analysis of antenatal care visits, institutional deliveries, vaccinations, outpatient visits and hospital admissions, and generalised linear mixed-effect models for hospital mortality.

RESULTS: During 2018–2020, the six hospitals recorded a total of 57,075 antenatal care visits, 38,706 institutional deliveries, 312,961 vaccinations, 605,925 outpatient visits and 143,915 hospital admissions. The COVID-19 period was associated with decreases in vaccinations (–575 vaccinations, $P < 0.0001$), outpatient visits (–700 visits, $P < 0.0001$) and hospital admission (–102 admission, $P = 0.001$); however, no statistically significant effects were found for antenatal care visits ($P = 0.71$) or institutional deliveries ($P = 0.14$). Mortality rate increased by 2% per month in the pre-COVID-19 period; however, a decreasing trend (by 2% per month) was observed during the COVID-19 period ($P = 0.004$). Subgroup and sensitivity analyses broadly confirmed the main findings with only minor inconsistencies. A reduction in outpatient visits was also observed in hospitals from countries with a higher Stringency Index and in urban hospitals.

CONCLUSIONS: The pandemic resulted in a reduction in health service utilisation. The decreases were less than anticipated from modelling studies.

The COVID-19 pandemic has become one of the main causes of death in many countries, and the real number of deaths are at least double if not triple those confirmed.[1] The magnitude of the COVID-19 pandemic has created unprecedented challenges for health authorities, as well as concerns about disrupted healthcare provision and access.[2] This may weigh most heavily in settings such as sub-Saharan Africa (sSA).

As reported during the West African Ebola virus outbreak, the response of the health institutions led to restrictions in the coverage of health services, both directly and indirectly.[3–8] Available evidence suggests that disrupting healthcare provision may have a long-term impact on demand, as it erodes trust in providers and patients may continue to avoid providers for fear of infection even when services resume.[9–11]

At the beginning of the COVID-19 crisis, it was forecast that sSA might well record large numbers of cases and deaths.[12] To date, however, the region seems relatively less affected (i.e., fewer confirmed cases and deaths) than other continents and regions.[13,14] However, it is unclear to what extent these figures are due to lower testing rates, less severe clinical presentation, or other factors.[15,16] Nonetheless, the pandemic has placed a strain sSA healthcare systems and disrupted healthcare provision and access.[2,17]

Only a few observational studies investigated the pandemic's impact on the use of health services in sSA, finding a decrease in obstetric and paediatric health services,[18–20] as well as barriers to care and fear of COVID-19 infection.[19] Outside sSA, evidence suggests declines in vaccinations, institutional deliveries and healthcare use during the COVID-19 pandemic.[21–23]

Modelling studies may provide useful insights into the projected 'collateral damage' of the current epidemic.[24] However, their accuracy in predicting outcomes depends on the model used, assumptions made, and quality of available data.[25] This can be challenging at the beginning of an outbreak or in low-resource settings, where data quality is often poor. A systematic review of the impact of COVID-19 on healthcare utilisation worldwide found no eligible studies from sSA.[21] Another systematic review of 40 studies assessed the collective evidence on the effects of the pandemic on maternal, foetal and neonatal outcomes. The report found one eligible study from sSA.[26]

While the epidemic is ongoing, it is difficult to assess the entire impact of COVID-19 on health service access and health outcomes. The present study aimed to evaluate the indirect impact of COVID-19 pandemic on antenatal care visits, institutional deliveries, vaccinations, outpatient visits, hospital admissions and hospital mortality in six hospitals of four sSA countries: Ethiopia, Sierra Leone, Tanzania and Uganda.

METHODS

Setting

This study evaluates the indirect impact of the COVID-19 outbreak in six hospitals in four sSA countries: Ethiopia, Sierra Leone, Tanzania and Uganda. Table 1 shows the progress of the pandemic in these countries. In the four countries considered, the first case of COVID-19 was identified between the second week of March (Ethiopia) and the first week of April (Uganda). Schools were closed in all four countries in

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TABLE 1 COVID-19 indicators by country

Country	First reported case	First reported death	Schools closed	Mass gatherings events prohibited	Average Stringency Index*
Ethiopia	13 March	5 April	16 March	16 March	67
Sierra Leone	31 March	23 April	20 March	20 March	42
Tanzania	16 March	31 March	19 March	2 April	27
Uganda	21 March	23 July	18 March	18 March	71

*The stringency index is a composite measure based on nine response indicators, including school closures, workplace closures and travel bans, rescaled to a value from 0 to 100 (100 = strictest).

the second half of March (16 March in Ethiopia, 31 March in Sierra Leone). Mass gatherings were prohibited, home confinement was mandated and borders were closed, with different modalities and times, between the second week of March and the first week of April.

It was not clear which aspects of the restrictive measures to contain the epidemic would impact on health services. Measures were implemented differently in different settings, and included a broad range of restrictions. Restrictive measures are presented here according to COVID-19 Stringency Index. This index is a composite based on nine response indicators and ranges from 0 to 100 (100 = strictest) (Figure 1 and Table 1).[27,28] Doctors with Africa (DwA) CUAMM *(Collegio Universitario Aspiranti Medici Missionari)* is an Italian non-governmental organisation (NGO) working in 23 sSA hospitals.[29] The low quality of data collection precluded the participation of some hospitals where DwA provides only technical support without a continuous presence of staff (which means that monthly records are not available) and other hospitals where the presence of DwA personnel was intermittent due to the pandemic, and continuous data collection was not possible. This study looked at data from hospitals where DwA has been working for years and where there has been ongoing consolidated data collection without interruption during the pandemic. Data came from Wolisso Hospital (Ethiopia), Pujeuhun Hospital (Sierra Leone), Tosamaganga and Songambele Hospitals (Tanzania), and Aber and Matany Hospitals (Uganda). Table 2 gives general information about these hospitals. The six hospitals analysed did not discontine or reduce healthcare services during the pandemic.

Data collection

The outcome measures included antenatal care visits, institutional deliveries, vaccinations, outpatient visits, hospital admissions and hospital mortality. To include a pre-COVID-19 period with adequate length for comparison, aggregate data were taken from monthly hospital records from January 2018 to December 2020. Data extraction was carried out by a researcher who was not involved in any clinical activities.

Analytical strategy

This was a retrospective, observational, multi-centre, multi-country study. Monthly data were analysed using interrupted time-series modelling to evaluate the indirect impact of the COVID-19 pandemic by changes in the level and slope of the time series of each outcome measure. As the pre-COVID-19 and COVID-19 periods included different subsets of months, seasonality was expected to contribute to the observed change between the two periods without being associated with the pandemic itself. We ruled out the option of comparing similar months in the two periods due to disadvantages in reducing the amount of data and limiting the estimation capability of the time trends. Since the indirect impact of the pandemic could be measured by the change in the trend component of the time series, we estimated the trend component and the seasonal component of each time series separately, and further analyses focused on the trend component.

We used linear mixed-effect models in the analysis of data on antenatal care visits, institutional deliveries, vaccinations, outpatient visits and hospital admissions, and generalised linear mixed-effect models using the beta distribution family for hospital mortality. The models included the time (January 2018–December 2020), the period (pre-COVID-19 period vs. COVID-19 period) and the interaction term time*period, with the centre contributing as random effect.

Given the heterogeneity of the participating hospitals in terms of setting and health policies, a subgroup analysis was performed for each country to provide further insights. For the subgroup analysis, linear regression models were used for prenatal care vis-

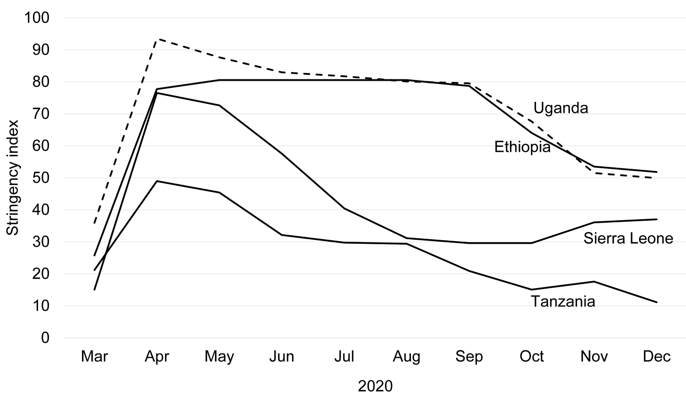

FIGURE 1 COVID-19 Stringency Index by country.

TABLE 2 General information on the six participating hospitals, sub-Saharan Africa, 2020

Hospital, country	Served population	Location	Beds	Outpatients	Admissions	Antenatal visits	Births	Vaccinations	Total staff	Qualified staff
Wolisso, Ethiopia	1,198,149	Urban	200	66,522	12,578	5,794	3,950	8,296	353	228
Pujeuhun, Sierra Leone	397,171	Rural	59	5,558	2,067	3,361*	1,081	NA	121	71
Tosamaganga, Tanzania	687,460	Rural	165	38,210	5,812	1,349	2,659	8,859	165	109
Songambele, Tanzania	123,400	Rural	84	12,882	2,600	1,965	903	8,879	79	71
Aber, Uganda	217,141	Rural	178	36,133	10,521	6,837	2,637	35,037	163	110
Matany, Uganda	159,409	Rural	250	33,946	14,761	4,391	1,531	37,108	267	149

*Data of 2019.
NA = not available.

its, institutional deliveries, vaccinations, outpatient visits, and hospital admissions, whereas beta regression models were used for hospital mortality. The models included the time (January 2018–December 2020), the period (pre-COVID-19 period vs. COVID-19 period), the centre (when more hospitals participated from the same country) and all interaction terms.

In the main and the subgroup analyses, the pre-COVID-19 period ranged from January 2018 to February 2020, while the COVID-19 period ranged from March 2020 to December 2020. However, it was uncertain if data from March 2020 would show the impact of the COVID-19 outbreak. Therefore, a sensitivity analysis was also performed with the pre-COVID-19 period ranging from January 2018 to March 2020, and the COVID-19 period ranging from April 2020 to December 2020.

Further sensitivity analyses explored the possible indirect effects on the study of the restrictive measures to contain the epidemic (measured by the Stringency Index) and the location of the hospital (urban or rural). In these sensitivity analyses, additional interaction terms were included in the models (see Supplementary Data). All tests were two-sided, and $P < 0.05$ was considered statistically significant. Statistical analysis was performed using R v4.1 (R Computing, Vienna,Austria).[30]

Ethics statements and patient involvement

Ethical clearance for accessing and using data for scientific purpose was granted by the Ethics Committee of each participating hospital. This study used hospital-level data only, and no personal information was retrieved from hospital charts. As this research was performed without patient involvement, informed consent was not required.

RESULTS

Main analysis

During 2018–2020, the six hospitals recorded a total of 57,075 antenatal care visits, 38,706 institutional deliveries, 312,961 vaccinations, 605,925 outpatient visits and 143,915 hospital admissions, with an average hospital mortality rate of 5.0%. Figure 2 shows overall trends in antenatal care, institutional deliveries and vaccinations during the study period. The COVID-19 period was associated with a reduction in average monthly vaccinations (–575 vaccinations, $P < 0.0001$), while no statistically significant effects on the number of monthly antenatal care visits ($P = 0.71$) or institutional deliveries ($P = 0.14$) were estimated.

Overall trends in outpatient visits, hospital admission and hospital mortality during the study period are shown in Figure 3. The COVID-19 period saw a drop in the average monthly outpatient visits (–700 visits, $P < 0.0001$) and hospital admissions (–102 admissions, $P = 0.001$). Mortality rate was increasing by 2% per month before the COVID-19 period, while a decreasing trend (by 2% per month) was observed during the COVID-19 period ($P = 0.004$). Full details of the analysis are reported in Supplementary Table S1.

Subgroup analysis

When data from each country's hospitals were analysed separately, it was observed that the COVID-19 period showed widely disparate local changes in antenatal care visits and vaccines. The findings of the main analysis of institutional deliveries, outpatient visits, hospital admissions and mortality were locally confirmed by most hospitals, but some differences were observed in a

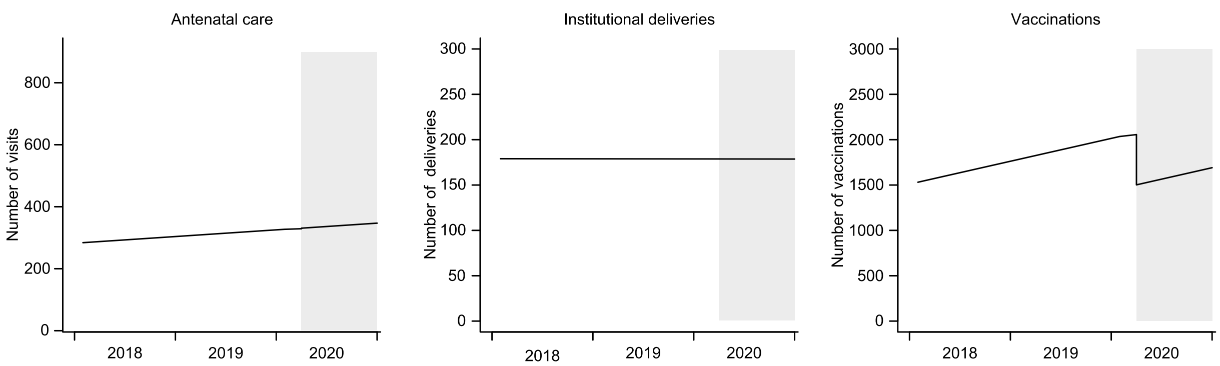

FIGURE 2 Interrupted time series of antenatal care, institutional deliveries and vaccinations in six sub-Saharan African hospitals in 2018–2020. White background = pre-COVID-19 period (January 2018–March 2020); grey background = COVID-19 period (April–December 2020); line = predicted trend based on the regression model.

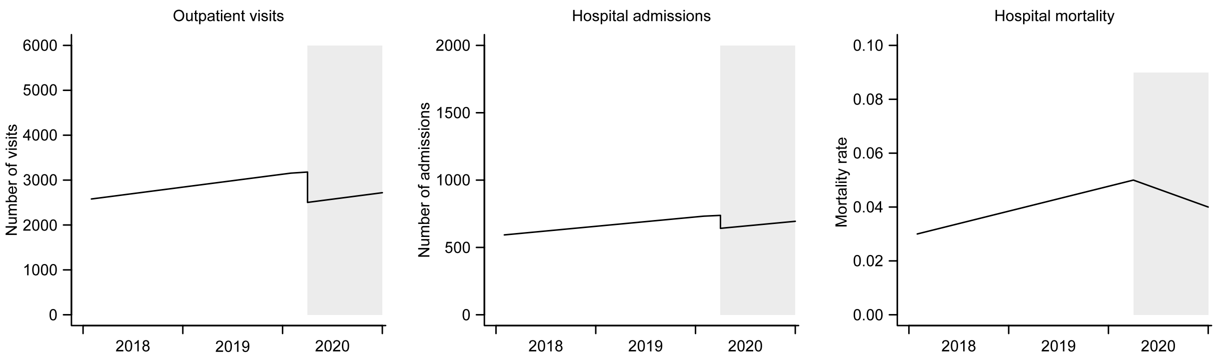

FIGURE 3 Interrupted time series of outpatient visits, hospital admission, and hospital mortality in six sub-Saharan African hospitals in 2018–2020. White background = pre-COVID-19 period (January 2018–March 2020); grey background = COVID-19 period (April–December 2020); line = predicted trend based on the regression model.

few hospitals. Full details are provided in Supplementary Figures S1–S4 and Supplementary Tables S2–S5.

Sensitivity analyses

When we shifted the beginning of the COVID-19 period from March to April 2020, the sensitivity analysis confirmed the findings of the main analysis and the subgroup analysis, with minor changes in the estimated effects of the COVID-19 period. Full details are reported in Supplementary Figures S5–S10 and Supplementary Tables S6–S10.

In the investigation of the possible indirect effects of the restrictive measures and the location of the hospital, the findings of our analysis suggested a reduction in the average monthly antenatal care visits (–31 visits, $P = 0.03$) and outpatient visits (–903 visits, $P < 0.0001$) in hospitals from countries with a higher Stringency Index, i.e., Uganda and Ethiopia. In addition, urban hospitals showed reductions in the average monthly antenatal care visits (–62 visits, $P = 0.0002$), institutional deliveries (–58 deliveries, $P < 0.0001$), outpatient visits (–1921 visits, $P < 0.0001$), hospital admissions (–306 admissions, $P < 0.0001$) and hospital mortality rates (–3.4%, $P = 0.03$) with respect to rural hospitals (Supplementary Data).

DISCUSSION

In the six hospitals studied in four sSA nations (Ethiopia, Sierra Leone, Tanzania, and Uganda), our findings regarding the indirect effects of COVID-19's on health service utilisation were inconsistent. The COVID-19 period was associated with a reduction in vaccinations, outpatient visits and hospital admissions. No significant effects were seen on antenatal care visits and institutional deliveries. The mortality rate, which had been increasing in the pre-COVID-19 period, began to decrease in the COVID-19 period. Overall, we did not observe decreases in health service utilisation or the higher mortality rates that had been predicted by modelling studies at the outset of the pandemic.[24,31,32] For example, Abbas et al., have estimated the additional maternal and under-5 child deaths resulting from the potential disruption of health systems due to COVID-19 in LMICs: under different scenarios, these deaths would represent a 9.8–44.7% increase in under-5 child deaths per month and an 8.3–38.6% increase in maternal deaths per month across the 118 countries.[32]

Changes in healthcare utilisation might occur concurrently with shifts in health seeking behaviour and trust in the healthcare system. Trust is affected by how patients and the community perceive the infection risk, service availability, and cost of health centres.[19] We can speculate that limited decrease in healthcare utilisation is, above all, related to the perceived level of the threat. During the 2013–2016 Ebola outbreak, the largest decreases in service utilisation were seen in the districts with the highest Ebola incidences.[7] Unlike Ebola, the number of cases and reported case fatalities has remained low in the current pandemic, and the public probably did not see the disease as a serious life-threatening infection.

Previous studies from sSA reported some reduction in healthcare access during the pandemic. In rural South Africa, a single-centre study found no significant change in total admissions, but did find significant changes between subgroups of admissions, with a large decline in the use of health services among children.[18] Hospital-level data from South Africa and Nigeria showed that the number of antenatal visits had fallen. Evidence was mixed for facility-based deliveries and caesarean sections.[19] Wanyana et al. reported that the utilisation of 13 maternal and child health services across Rwanda had decreased since the COVID-19 outbreak, particularly in the use of services related to health facility deliveries and child vaccinations.[20] Chelo et al. assessed the effect of the COVID-19 pandemic on hospitalisations, as well as the mortality of children in a paediatric hospital in Cameroon. A drastic drop in the number of hospitalisations was reported, with a parallel increase in the number of deaths.[33] Caniglia et al. evaluated the association between the COVID-19 period and the adverse birth outcomes in Botswana: they found that the number of deliveries remained constant and no significant difference in adverse birth outcomes was observed.[34]

Our findings showed a decrease in vaccinations and outpatient visits at the beginning of the pandemic. The decrease in outpatient visits was more marked in urban hospitals and in hospitals located in countries with higher restrictive measures to contain the epidemic. We also observed that vaccinations and outpatient visits did not return to pre-pandemic levels at the end of 2020, suggesting medium-term effects, with the possibility of more long-term impact. A recent risk-benefit study warned that the deaths prevented by sustaining routine childhood immunisation in Africa could outweigh the excess risk of COVID-19 deaths associated with vaccination clinic visits, especially for vaccinated children. Routine childhood immunisation should be sustained in Africa as much as possible, taking into account logistical constraints and reallocation of resources during the COVID-19 pandemic.[32]

We can speculate that the informative impact and the economic impact of the pandemic, as well as the limitations on access to care, were greater in urban compared to rural settings.[19] It is hard to disentangle the extent to which restrictive measures and stigma/fear drove the change in care-seeking behaviour. Nonetheless, the fact that the reduction in some health services was greater in hospitals of countries with the highest Stringency Index suggests that reduction in care-seeking for some types of visits was an unintended negative consequence of the restrictive measures to contain the epidemic. This finding is remarkable, especially in light of the fact that these unintended consequences could outlast the duration of the policy.

After an early drop at the beginning of the pandemic, the sensitivity analysis also showed an increase in hospital admissions during the second half of 2020, which might be explained by the relaxing of the restrictive measures and the delayed access to hospital care.[18] However, this increase did not coincide with an increase in hospital mortality that was reported elsewhere.[18] In fact, we observed a decrease in hospital mortality during the pandemic, which may suggest that the most vulnerable people did not access hospital care. The absence of concurrent rising trends in hospital admissions and hospital mortality during the pandemic may imply a higher external mortality (i.e., those who did not seek care and died at home may not have been included in the hospital mortality statistics).[35] It is reasonable to assume that several factors, including fear of contracting COVID-19, restrictive measures and changes in resource allocation, might have contributed to limiting access to care.[19] In sSA, approximately 90% of people are employed in the informal sector with low productivity.[36] This sector was greatly affected during the pandemic, and faced serious financial difficulties.

Overall, prenatal care visits and institutional deliveries in the hospitals surveyed were unaffected by the pandemic, in contrast to other studies from South Africa and Asia that reported significant declines in the use of these health services.[11,19,20] We believe that pregnant women may have preferred the hospital to the health centres, as they viewed the hospital to be a safer environment.

The subgroup analysis showed some heterogeneity in the effects of the pandemic on the participating hospitals. Such differences might be explained by a complex mix of local factors, such as the role of the hospital in the community, organisational features (urban hospitals showed a larger reduction in monthly antenatal care visits, institutional deliveries, outpatient visits and hospital admissions), country-level response to the pandemic (hospitals from countries with higher restrictive measures showed a larger reduction in monthly antenatal care visits and outpatient visits) and population factors (fear, affordability of healthcare service, income loss).[37] Hence, understanding the local constraints on access to care is crucial in ensuring healthcare coverage during the ongoing epidemic.

Our study has strengths and limitations that should be considered when interpreting the results. First, the multi-centre, multi-country design provided a wide overlook at the indirect impact of COVID-19 pandemic on sSA healthcare and increased the generalisability of the findings. On the other hand, generalisability was limited by possible selection bias when selecting participating hospitals (i.e., sSA hospitals where DwA had worked for years and where a consolidated data gathering methodology had been established over time). Second, the analysis benefited from the inclusion of a wide time series covering adequate pre-COVID-19 and COVID-19 periods; this allowed an adequate estimation of the indirect impact of the COVID-19 pandemic by using interrupted time-series modelling and seasonality adjustments. However, monthly hospital-level data precluded any patient-level analyses (including stratification for patient age), and the quality of the retrospective data collection may have been wanting. Finally, the large sample size and the sensitivity analyses strengthened the interpretation of the findings.

Our study showed indirect effects of the COVID-19 pandemic on health service utilisation in six hospitals in four sSA countries. The decreases in health service utilisation were less than anticipated from modelling studies, but long-term effects should be expected. From a policy perspective, understanding the role of several factors – such as availability and accessibility of services, fear and financial access – can shed light on the underlying causes of the observed changes. Therefore, a regular monitoring of health service utilisation in epidemics plays an important role in guiding and evaluating public health response measures. Integrating health information system data analysis with social sciences evidence can contribute to a better and more comprehensive interpretation of the data.

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CONTEXTE : Six hôpitaux de quatre pays d'Afrique subsaharienne.
OBJECTIF : Examiner les effets indirects de la COVID-19 sur l'utilisation des services de santé et analyser le risque de biais dans les études utilisant des modèles de prédiction.
MÉTHODES : Des données mensuelles ont été analysées en utilisant une modélisation de séries chronologiques interrompues. L'analyse principale a mis en place des modèles linéaires à effets mixtes (pour les consultations anténatales, les accouchements en institutions, les vaccinations, les consultations ambulatoires et les admissions à l'hôpital) et des modèles linéaires généralisés à effets mixtes (pour la mortalité hospitalière).
RÉSULTATS : En 2018–2020, les six hôpitaux ont enregistré un total de 57 075 consultations anténatales, 38 706 accouchements en institutions, 312 961 vaccinations, 605 925 consultations ambulatoires et 143 915 admissions hospitalières. La période de la COVID-19 a été associée à une baisse des vaccinations (–575 vaccinations, $P<0{,}0001$), des consultations ambulatoires (–700 consultations, $P < 0{,}0001$) et des admissions hospitalières (–102 admissions, $P = 0{,}001$). Cependant, aucun effet statistiquement significatif n'a été observé pour les consultations anténatales ($P = 0{,}71$) ou les accouchements en institutions ($P = 0{,}14$). Le taux de mortalité augmentait de 2% par mois avant la période de la COVID-19, mais nous avons observé une tendance à la baisse (de 2% par mois) pendant la période de la COVID-19 ($P = 0{,}004$). Les analyses des sous-groupes et de sensibilité ont globalement confirmé les résultats principaux ; seules des incohérences mineures ont été observées. Une diminution des consultations ambulatoires a également été observée dans les hôpitaux des pays dont l'Indice de sévérité des mesures publiques était plus élevé, ainsi que dans les hôpitaux urbains.
CONCLUSIONS : La pandémie a été associée à une utilisation réduite des services de santé. Ces diminutions étaient moindres que celles anticipées par les études de modélisation.

An integrated hospital-district performance evaluation for communicable diseases in low-and middle-income countries: Evidence from a pilot in three sub-Saharan countries

PAPER

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RESEARCH ARTICLE

An integrated hospital-district performance evaluation for communicable diseases in low- and middle-income countries: Evidence from a pilot in three sub-Saharan countries

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Data Availability Statement: At health district level, we used publicly available data that were extracted from the District Health Information

Abstract

Introduction

The last two decades saw an extensive effort to design, develop and implement integrated and multidimensional healthcare evaluation systems in high-income countries. However, in low- and middle-income countries, few experiences of such systems implementation have been reported in the scientific literature. We developed and piloted an innovative evaluation tool to assess the performance of health services provision for communicable diseases in three sub-Saharan African countries.

Material and methods

A total of 42 indicators, 14 per each communicable disease care pathway, were developed. A sub-set of 23 indicators was included in the evaluation process. The communicable diseases care pathways were developed for Tuberculosis, Gastroenteritis, and HIV/AIDS, including indicators grouped in four care phases: prevention (or screening), diagnosis, treatment, and outcome. All indicators were calculated for the period 2017–2019, while performance evaluation was performed for the year 2019. The analysis involved four health districts and their relative hospitals in Ethiopia, Tanzania, and Uganda.

Results

Substantial variability was observed over time and across the four different districts. In the Tuberculosis pathway, the majority of indicators scored below the standards and below-average performance was mainly reported for prevention and diagnosis phases. Along the

Systems (DHISs) of the countries involved in the study. At hospital level, data were extracted from each hospital's registers. All relevant data are within the paper and its Supporting information files. More particularly, data on all indicators listed in Table 1 are included in the report "Performance Evaluation System of hospital and health districts in Ethiopia, Uganda and Tanzania", that is available at the link report in Supporting information (S3). Additionally, in Supporting information (S4) we provided all data elements related to the indicators listed in Table 2.

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Competing interests: The authors have declared that no competing interests exist.

Gastroenteritis pathway, excellent performance was instead evaluated for most indicators and the highest scores were reported in prevention and treatment phases. The HIV/AIDS pathway indicators related to screening and outcome phases were below the average score, while good or excellent performance was registered within the treatment phase.

Conclusions

The bottom-up approach and stakeholders' engagement increased local ownership of the process and the likelihood that findings will inform health services performance and quality of care. Despite the intrinsic limitations of data sources, this framework may contribute to promoting good governance, performance evaluation, outcomes measurement and accountability in settings characterised by multiple healthcare service providers.

Introduction

Despite steady global improvements, the burden of disease due to communicable diseases (CDs) remains high in certain regions of the world, including sub-Saharan Africa. Lower respiratory infections, diarrhoeal diseases and sexually transmitted infections (including HIV) still rank high among the causes of morbidity and death [1]. Dedicated public health strategies have been designed and rolled out over the decades to tackle CDs in sub-Saharan Africa, often engaging multiple partners for their implementation. Global initiatives such as the Global Fund to Fight AIDS, Tuberculosis (TB) and Malaria and Stop-TB, have greatly accelerated progress by fostering multi-stakeholders' collaborations and resources mobilization [2]. Healthcare provision in certain areas of sub-Saharan Africa relies also on the presence of external agencies and entities such as non-governmental organizations (NGOs) [3, 4].

The heterogeneity of the healthcare services (HS) scenario poses additional challenges for performance assessment, especially in countries where national monitoring systems are suboptimal. Performance evaluation of healthcare provision is extremely relevant to i) assess the impact of different stakeholders' efforts and contributions towards the achievement of health goals; ii) monitor activities and plan policy-related initiatives; iii) set and promote quality improvement actions at national/local level; and iv) ensure accountability towards national health institutions and donors [5, 6].

In recent years, an extensive effort to design, develop and implement Performance Evaluation Systems (PESs) in healthcare have been made by institutions in single high-income countries as well as by international agencies [6–8]. The added value of PES rests on the integrated approach, taking into consideration multiple dimensions and indicators related to efficiency, structure, process, quality of care, appropriateness, and equity [9] as well as the interests of several stakeholders in the healthcare system, from a population-based perspective [10]. Yet, in low- and middle-income countries (LMICs), few experiences of PESs implementation have been reported in the scientific literature [11, 12]. Shortage of human and technical resources, unavailability and unreliability of data, lack of culture of data-driven decision making are all coexisting factors that hamper the set-up and the maintenance of coherent and integrated PES in LMICs [13–15]. Additionally, a larger body of evidence relates to the application of monitoring and evaluation frameworks of global health strategies, which usually have a vertical approach and are geared towards the assessment of progresses towards global goals rather than towards the assessment of performance [16, 17]. In this scenario, quality of health data on

CDs, as compared to other dimensions or health conditions, may have benefitted from more intense and coordinated efforts along the past decades, targeting LMICs and the sub-Saharan region in particular.

The present study aimed at investigating the feasibility of using a bottom-up and integrated PES, and at assessing the performance of health services provision related to CDs (PES-CDs) in three selected sub-Saharan countries. For this purpose, we adapted and tailored the framework developed to assess Italian regional healthcare systems performance through an iterative multi-stakeholders process [9], engaging local HSs, academia, and an Italian-based non-governmental organization (NGO) delivering health care in the target countries.

Material and methods

Country/Setting brief description: Similarities and differences

The analysis involved the following four hospitals and their relative health districts: i) St.Luke—Wolisso Hospital (Wolisso) and five "Woredas" in the region of Oromia in Ethiopia (Wolisso Area); ii) Tosamaganga District Designated Hospital (Tosamaganga) and the Iringa District Council (Iringa District) in the region of Iringa in Tanzania; iii) St. Kizito—Matany Hospital (Matany) and the Napak District and iv) Pope John XXIII—Aber Hospital (Aber) and the Oyam District in the northern region in Uganda, as shown in Fig 1.

The details of the analysed hospitals and their relative health districts are included in the supporting information (S1 Table).

These settings differ not only in terms of population served, the surface area covered, and, consequently, population density, but also with respect to some relevant and intrinsic factors, which include different environmental characteristics, epidemiological priorities and issues, organizational and governance models, levels of development of transport, energy, and ICT infrastructures.

Despite such differences, they were selected because of some similar characteristics inherent to all four contexts, which are related to: i) the organization of healthcare delivery across levels of care; ii) the institutional setting of the hospitals, i.e. private, faith-based and not for profit; and iii) the funding model through which hospitals are financed. Most importantly, in all these contexts clinical and administrative activities are supported by the same NGO, Doctors with Africa CUAMM (CUAMM) which contributed to strengthening health systems in LMICs through the allocation of financial and human resources, including expatriate professionals, for several decades.

Data sources and analyses

We sourced health-related data on TB, Gastroenteritis and HIV/AIDS for the years 2017–2019. Hospital level metrics were derived from health and administrative registers, whereas district level metrics were extracted from the District Health Information Systems (DHISs) in each context of interest. In all four hospitals, TB, Gastroenteritis, and HIV/AIDS related-data were retrieved from digital and paper-based administrative department registers, which include laboratory, pharmacy, outpatient (e.g. ART clinic, TB clinic), and inpatient departments records. At health district level, data were electronically extracted from specific DHIS registers provided by the Ministry of Health of each country involved in this study. For example, TB data related to the two Ugandan sites were sourced from the Ugandan DHIS in the register 106a:3.1. Data sources are further detailed in Table 1.

Data extraction was carried out by local staff in each study context. Disease-specific datasets were created by extracting aggregated data on pre-defined variables (Table 1) from existing databases into excel spreadsheets and subsequently elaborated. Data were aggregated per

Country	Health District	Reference Hospital	TB incidence rate at national level, per 100 000 population (1)	Percentage of deaths caused by diarrhoea in children under 5 years of age at national level (2)	Prevalence of HIV at district level (% of population aged 15-49) (3)
Ethiopia	Five «Woredas» in the Shoa-west zone	St. Luke – Wolisso Hospital	140	8%	1%
Tanzania	Iringa District Council	Tosamanga District Designated Hospital	237	8%	9.5%
Uganda	Napak District	St. Kizito – Matany Hosptital	200	7%	5.2%
Uganda	Oyam District	Pope John XXIII – Aber Hospital	200	7%	7%

Sources: (1) World Health Organization, year 2019; (2) Unicef, year 2017; (3) World Bank, year 2019

Fig 1. Analysed settings. List of the four analysed hospitals and their respective health districts. Reprinted from Doctors with Africa CUAMM under a CC BY license, with permission from PLOS ONE, original copyright 2021.

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Table 1. List of the indicators included into the CDs care pathways: Tuberculosis, gastroenteritis and HIV/AIDS.

Phase	Indicator code	Indicator name	Numerator	Denominator	Computation level	Type of indicator	Sources
List of the indicators related to the Tuberculosis Pathway.							
Prevention	IDPT01	Percentage of treatments with isoniazide (IPT)	Number of treatments with isoniazide (IPT) (x100)	Total number of eligible treatments	Health District	Evaluation	Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPT02	Percentage of TB cases undergoing the HIV screening	Number of TB cases undergoing the HIV screening (x100)	Number of TB diagnosed patients	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
Diagnosis	IDPT03	Percentage of positive TB cases on number of tests	Number of positive TB cases (confirmed by lab tests or Xpert) (x100)	Number of tests (presumptive cases)	Health District	Observation	Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources) and WHO global tuberculosis reports
	IDPT04	Percentage of confirmed TB cases on diagnosed cases	Number of positive PTB cases (bacteriologically confirmed) (x100)	Number of TB diagnosed patients	Health District	Evaluation	Hospitals registers—laboratory departments (electronic and paper-based sources)
	IDPT05	Percentage of confirmed PTB	Number of positive PTB cases (bacteriologically confirmed) (x100)	Number of PTB cases	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPT06	Percentage of positive Xpert cases	Numer of positive Xpert cases (x100)	Number of Xpert cases	Hospital	Evaluation	Hospitals registers—laboratory departments (electronic and paper-based sources)
	IDPT06.1	Percentage of positive Xpert RR	Number of positive Xpert RR (x100)	Number of positive Xpert	Hospital	Observation	Hospitals registers—laboratory departments (electronic and paper-based sources)
Treatment	IDPT07	Percentage of treatments for extrapolmunary TB	Number of treatments "initiated" for extrapolmunary TB (x100)	Number of TB diagnoses	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)

(*Continued*)

Table 1. (Continued)

Phase	Indicator code	Indicator name	Numerator	Denominator	Computation level	Type of indicator	Sources
Outcome	IDPT08	Percentage of PTB MDR initiated treatments	Number of MDR initiated treatments (x100)	Number of MDR TB diagnoses	Hospital	Observation	Hospitals registers—laboratory departments (electronic and paper-based sources)
	IDPT09	Percentage of cured patients	Number of cured patients (x100)	Number of PTB+ (bacteriologically confirmed)	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPT10	Percentage of completed treatments	Number of completed treatments (x100)	Number of treated cases	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPT11	Percentage of deaths	Number of deaths (x100)	Number of treated cases	Health District	Observation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPT12	Percentage of treatment interrupted	Number of treatments interrupted (x100)	Number of treated cases	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPT13	Percentage of admitted patients due to TB	Number of admitted patients for TB in reference hospital (x100)	Total number of TB cases at residence level	Health District	Observation	Hospitals registers—medical departments (electronic sources) and Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
List of the indicators related to the Gastroenteritis Pathway.							
Prevention	B7.9	Vaccination coverage for rota virus	Number of children under one year of age who have received 2nd dose of Rotavirus vaccine (x100)	Number of infants aged less than 1 year	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian DHIS2, Ugandan eHMIS/DHIS2 (electronic source)
	IDPD02	Average number of water sources by Hospital	Number of water taps	Total wards and outpatient rooms	Hospital	Evaluation	Hospital technical departments
	IDPD03	Availability of an hand washing programme (Hospital)	-	-	Hospital	Observation	Hospital technical departments
	IDPD04	Average number of toilets per beds in IPD	Number of toilets	Number of beds	Hospital	Evaluation	Hospital technical departments
	IDPD05	Average number of toilets in OPD per number of rooms	Number of toilets in OPD	Number of rooms in OPD	Hospital	Evaluation	Hospital technical departments

(*Continued*)

Table 1. (Continued)

Phase	Indicator code	Indicator name	Numerator	Denominator	Computation level	Type of indicator	Sources
Diagnosis	IDPD06	Percentage of positive stool tests (for parasites)	Number of positive stool tests (for parasites) (x100)	Total faeces examinations	Hospital	Observation	Hospitals registers—laboratory departments (electronic and paper-based sources)
	IDPD07	Percentage of gastroenteritis diagnosed (<5 years—Outpatient)	Number of gastroenteritis diagnosed (<5 years) in OPD and HCs (x100)	Number of OPD access for children <5yr	Health District	Observation	Tanzanian DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPD08	Percentage of gastroenteritis diagnosed (>5 years—Outpatient)	Number of gastroenteritis diagnosed (>5 years) in OPD and HCs (x100)	Number of OPD access >5yr	Health District	Observation	Tanzanian DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPD09	Percentage of diarrhoea cases with severe dehydration due to gastroenteritis and diarrhoea	Number of diarrhoea cases with severe dehydration (x100)	Total number of cases	Hospital	Observation	Wolisso and Matany hospital's registers, Tanzanian DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPD10	Percentage of discharged patients for diarrhoea and gastroenteritis	Number of discharged patients for diarrhoea and gastroenteritis (x100)	Total number of discharged patients (adults and children)	Hospital	Evaluation	Wolisso and Matany hospital's registers, Tanzanian DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPD11	Percentage of diarrhoea cases (<1 year)	Number of diarrhoea cases (<1 year—acute cases) (x100)	Total number of diarrhoea cases	Health District	Observation	Tanzanian DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
Treatment	IDPD12	Average number of ORS packages delivered per patient with diarrhoea (<5years)	Number of ORS packages delivered (Hospital + HCs)	Total number of diarrhoea cases (<5 years)	Health District	Evaluation	Ugandan eHMIS/DHIS2 (electronic sources)
	IDPD13	Average number of Zinc Tablets doses delivered per patient with diarrhoea (<5years)	Number of Zinc Tablets doses delivered (Hospital + HCs)	Total number of diarrhoea cases (<5 years)	Health District	Evaluation	Ugandan eHMIS/DHIS2 (electronic sources)
Outcome	IDPD14	Percentage of deaths with a diagnosis of gastroenteritis	Number of deaths diagnosed with gastroenteritis (patients aged < 5 years) (x100)	Number of discharged patients with a diagnosis of gastroenteritis (patients aged < 5 years)	Hospital	Evaluation	Wolisso and Matany hospitals registers, Tanzanian DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPD15	ALOS for gastroenteritis	Number of inpatient days for gastroenteritis	Total number of inpatients (for gastroenteritis)	Hospital	Observation	Wolisso and Matany hospitals registers—medical department (electronic sources)

List of the indicators related to the HIV/AIDS Pathway.

(Continued)

Table 1. (Continued)

Phase	Indicator code	Indicator name	Numerator	Denominator	Computation level	Type of indicator	Sources
Screening	CPHIV01	Percentage of HIV screening coverage	Number of performed tests (x100)	Number of admissions in OPD (hospital and HCs) and IPD	Health District	Observation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	CPHIV02	Percentage of performed tests to pregnant women	Number of HIV performed tests to pregnant women followed in RCH (x100)	Total number of pregnant women with at least one ANC visit	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	IDPT02	Percentage of TB cases undergoing the HIV screening	Number of TB cases undergoing the HIV screening (x100)	Number of TB diagnosed patients	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	CPHIV03	Percentage of HIV + cases undergoing the TB screening	Number of HIV cases undergoing the TB screening (sputum, symptom questionnaire, Xpert) (x100)	Number of HIV+ cases	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	CPHIV03.1	Percentage of HIV patients screened for TB with Xpert	Number of HIV patients screened with Xpert for TB (x100)	Number of HIV + screened patients for TB	Hospital	Observation	Hospitals registers—laboratory departments (electronic and paper-based sources) and Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
Diagnosis	CPHIV04	Percentage of new diagnosed patients with CD4 < 350cell/ml	Number of diagnosed patients with CD4 < 350cell/ml (x100)	Number of new diagnosed HIV + patients	Hospital	Observation	Hospitals registers—laboratory departments (electronic and paper-based sources) and Ugandan eHMIS/DHIS2 (electronic sources)
	CPHIV05	Percentage of HIV + patients with opportunistic infections (or advanced HIV)	Number of HIV+ patients with opportunistic infections diagnosed at the time of HIV diagnosis (x100)	Number of new HIV + patients diagnosed	Hospital	Observation	Hospitals registers—laboratory departments (electronic and paper-based sources) and Ugandan eHMIS/DHIS2 (electronic sources)
	CPHIV06	Percentage of malnourished patients followed in a HIV unit	Number of HIV + malnourished patients currently on ART in a HIV unit (x100)	Number of patients currently in HIV unit	Health District	Observation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)

(*Continued*)

Table 1. (Continued)

Phase	Indicator code	Indicator name	Numerator	Denominator	Computation level	Type of indicator	Sources
Treatment	CPHIV07	Percentage of new HIV + linked to ART	Number of HIV+ starting ART (x100)	Number of new patients tested HIV+ in OPD and IPD	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	CPHIV08	Coverage rate of the therapy	Number of HIV+ patients currently on ART therapy (x100)	Number of HIV + residents (estimated)	Health District	Evaluation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	CPHIV09	Average number of nutritional supplements delivered per patients currently on ART therapy	Number of nutritional supplements (Plumpinat, enriched flawour ect.) delivered	Number of patients currently on ART therapy	Health District	Observation	Ugandan eHMIS/DHIS2 (electronic sources)
	CPHIV10	Percentage of VL tests over the patient undergoing ART therapy	Number of patients undergoing VL tests (x100)	Number of patients currently on ART therapy	Health District	Evaluation	Hospitals registers—ART clinic/CDC departments (paper-based sources) and Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
Outcome	CPHIV11	Percentage of patients undergoing ART therapy and tested with VL with suppression of viremia	Number of patients undergoing VL tests with viremia suppression (x100)	Number of patients currently on ART therapy and tested with VL within last 12 months	Hospital	Evaluation	Hospitals registers—ART clinic/CDC departments (paper-based sources) and Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	CPHIV12	Percentage of deaths undergoing ART therapy (within 12 months)	Number of patients undergoing ART therapy who died within 12 months from the beginning of the therapy (x100)	Number of patients who started ART therapy as of at least 12 months	Hospital	Observation	Ethiopian HMIS/DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)
	CPHIV13	ALOS (HIV admitted patients)	Number of inpatient days for HIV and its complication	Number of inpatients for HIV and its complications	Hospital	Observation	Wolisso and Matany hospitals registers—medical department (electronic sources)

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variable of interest and per year of study. Disease-specific datasets were successively shared with Italian partners for analyses validation purposes. Data analyses and relative visual representations were run using SAS (Statistical Analysis System) version 9.4.

CDs care pathways development

This pilot study represents the result of constructive research carried out by two Italian academic research centres on healthcare economics and management, public health in collaboration with CUAMM. The study protocol/research approach used has been previously described elsewhere [Belardi et al., under review].

A multidisciplinary team elaborated the list of indicators populating the PES-CDs and a total number of 42 indicators, 14 for each specific CD care pathway, were selected. Additionally, 20 indicators were calculated at hospital level and 22 at health district level (Table 1).

Indicators were derived from international reference sources, including WHO relevant global monitoring frameworks [18–23]. Reference indicators were revised and adapted based on local needs or to data availability at hospital and health district levels. The final list of indicators with reference sources is presented in Table 1.

All the indicators were calculated for the years 2017–2019. For 16 indicators (three for TB, seven for Gastroenteritis, six for HIV/AIDS) data sources were not available for at least in one setting. Subsequently, each of the indicators calculated was assessed according to five dimensions [24], namely: relevance (is the indicator appropriate in relation to the peculiarities of the context analysed?); validity (is the indicator compliant with the purposes for which has been defined?); reliability (is the data and its sources authentic, solid, and reliable?); interpretability (does the indicator provide a univocal indication on how to interpret the data?); feasibility (can the indicator be calculated by using the existent information flows?; a reference standard is available?; is the reference standard appropriate for all contexts studied?). Using a consensus-building approach, a sub-set of 23 indicators per each disease-specific PES-CD was derived, covering all phases of care (prevention or screening, diagnosis, treatment and outcome) (Table 2). Evaluation was performed for the year 2019.

The evaluation standards were determined based on: i) international and global targets, when available; ii) on the guidelines already implemented by the Italian Inter-Regional Performance Evaluation System (IRPES) [9, 25]; or iii) on benchmarking assessment of indicators' values statistical distribution (i.e. by applying 0 to 5 scores to five bands that consider the statistical distribution of indicators values).

The indicators were evaluated using the approach already adopted for the development of the IRPES in Italy [9, 25], and subsequently applied in some OECD countries [26–28]. To provide an integrated and continuous view of performance across different settings and providers, each care pathway was represented by the music stave (the "stave") [9]. The staves illustrate strengths and weaknesses characterizing patient's pathway along the continuum of care.

Results

Overall, the 2017–2019 trend was analysed for the 42 indicators. Substantial variability was observed over time and across the four different settings (Fig 5 and supporting information (S1 File)).

Here we present the performance results of the three staves (Figs 2–4) and one selected indicator for each stave (Fig 5).

Stave and indicators related to the TB care pathway performance

Fig 2 shows the stave related to the TB care pathway performance evaluation for the four geographical areas considered in this study.

More particularly, in Wolisso Area, the indicators evaluating the TB prevention phase scored on the orange band, while the ones belonging to the diagnosis phase from red to yellow. Average performance was also observed for the indicator evaluating the treatment phase, while the outcome phase included indicators with scores ranging from poor to excellent performance.

In Iringa District, the performance of the indicator assessing the percentage of isoniazide preventive therapy (IPT) (IDPT01) scored on the red band, while the performance of the percentage of TB patients who underwent an HIV screening (IDPT02) scored excellent. Additionally, the indicators included in the diagnosis phase scored very poor, whereas an excellent performance was registered for the indicator evaluating the treatment phase. Finally, an ups and downs trend emerged by observing the outcome indicators.

With reference to Napak District, the stave reported a very poor or poor performance for all the evaluated indicators along the four care pathway phases.

Finally, in Oyam District, the performance of the two indicators regarding the prevention phase scored very poor and poor, respectively. Higher performance scores were registered,

Table 2. Care pathways' indicators.

Care pathway	Phase	Indicator code	Indicator name	Computation level	Numerator	Denominator	Sources	Standard
Tuberculosis	Prevention	IDPT01	Percentage of treatments with isoniazide (IPT)	Health District	Number of treatments with isoniazide (IPT) (x100)	Total number of eligible treatments	Tanzanian ETL/ DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)	International standard (WHO)
		IDPT02	Percentage of TB cases undergoing the HIV screening	Health District	Number of TB cases undergoing the HIV screening (x100)	Number of TB diagnosed patients	Ethiopian HMIS/ DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
	Diagnosis	IDPT04	Percentage of confirmed TB cases on diagnosed cases	Health District	Number of positive PTB cases (bacteriologically confirmed) (x100)	Number of TB diagnosed patients	Hospitals registers —laboratory departments (electronic and paper-based sources)	International standard (WHO)
		IDPT05	Percentage of confirmed PTB	Health District	Number of positive PTB cases (bacteriologically confirmed) (x100)	Number of PTB cases	Ethiopian HMIS/ DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
		IDPT06	Percentage of positive Xpert cases	Hospital	Numer of positive Xpert cases (x100)	Number of Xpert cases	Hospitals registers —laboratory departments (electronic and paper-based sources)	International standard (WHO)
	Treatment	IDPT07	Percentage of treatments for extrapolmunary TB	Health District	Number of treatments "initiated" for extrapolmunary TB (x100)	Number of TB diagnoses	Ethiopian HMIS/ DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
	Outcome	IDPT09	Percentage of cured patients	Health District	Number of cured patients (x100)	Number of PTB+ (bacteriologically confirmed)	Ethiopian HMIS/ DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
		IDPT10	Percentage of completed treatments	Health District	Number of completed treatments (x100)	Number of treated cases	Ethiopian HMIS/ DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
		IDPT12	Percentage of treatment interrupted	Health District	Number of treatments interrupted (x100)	Number of treated cases	Ethiopian HMIS/ DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)

(*Continued*)

Table 2. (Continued)

Care pathway	Phase	Indicator code	Indicator name	Computation level	Numerator	Denominator	Sources	Standard
Gastroenteritis	Prevention	B7.9	Vaccination coverage for rota virus	Health District	Number of children under one year of age who have received 2nd dose of Rotavirus vaccine (x100)	Number of infants aged less than 1 year	Ethiopian HMIS/ DHIS2, Tanzanian DHIS2, Ugandan eHMIS/DHIS2 (electronic source)	International standard (IRPES)
		IDPD02	Average number of water sources by Hospital	Hospital	Number of water taps	Total wards and outpatient rooms	Hospital technical departments	International standard (Infection Prevention Control of WHO)
		IDPD04	Average number of toilets per beds in IPD	Hospital	Number of toilets	Number of beds	Hospital technical departments	International standard (Infection Prevention Control of WHO)
		IDPD05	Average number of toilets in OPD per number of rooms	Hospital	Number of toilets in OPD	Number of rooms in OPD	Hospital technical departments	International standard (WHO)
	Diagnosis	IDPD10	Percentage of discharged patients for diarrhoea and gastroenteritis	Hospital	Number of discharged patients for diarrhoea and gastroenteritis (x100)	Total number of discharged patients (adults and children)	Wolisso and Matany hospital's registers, Tanzanian DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	Benchmarking assessment of values statistical distribution
	Treatment	IDPD12	Average number of ORS packages delivered per patient with diarrhoea (<5years)	Health District	Number of ORS packages delivered (Hospital + HCs)	Total number of diarrhoea cases (<5 years)	Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
		IDPD13	Average number of Zinc Tablets doses delivered per patient with diarrhoea (<5years)	Health District	Number of Zinc Tablets doses delivered (Hospital + HCs)	Total number of diarrhoea cases (<5 years)	Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
	Outcome	IDPD14	Percentage of deaths with a diagnosis of gastroenteritis	Hospital	Number of deaths diagnosed with gastroenteritis (patients aged < 5 years) (x100)	Number of discharged patients with a diagnosis of gastroenteritis (patients aged < 5 years)	Wolisso and Matany hospitals registers, Tanzanian DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	Benchmarking assessment of values statistical distribution

(Continued)

Table 2. (Continued)

Care pathway	Phase	Indicator code	Indicator name	Computation level	Numerator	Denominator	Sources	Standard
HIV/AIDS	Screening	CPHIV02	Percentage of performed tests to pregnant women	Health District	Number of HIV performed tests to pregnant women followed in RCH (x100)	Total number of pregnant women with at least one ANC visit	Ethiopian HMIS/ DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
		IDPT02	Percentage of TB cases undergoing the HIV screening	Health District	Number of TB cases undergoing the HIV screening (x100)	Number of TB diagnosed patients	Ethiopian HMIS/ DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
		CPHIV03	Percentage of HIV + cases undergoing the TB screening	Health District	Number of HIV cases undergoing the TB screening (sputum, symptom questionnaire, Xpert) (x100)	Number of HIV + cases	Ethiopian HMIS/ DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
	Treatment	CPHIV07	Percentage of new HIV+ linked to ART	Health District	Number of HIV + starting ART (x100)	Number of new patients tested HIV + in OPD and IPD	Ethiopian HMIS/ DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
		CPHIV08	Coverage rate of the therapy	Health District	Number of HIV + patients currently on ART therapy (x100)	Number of HIV + residents (estimated)	Ethiopian HMIS/ DHIS2, Tanzanian ETL/DHIS2, Ugandan eHMIS/ DHIS2 (electronic sources)	International standard (WHO)
		CPHIV10	Percentage of VL tests over the patient undergoing ART therapy	Health District	Number of patients undergoing VL tests (x100)	Number of patients currently on ART therapy	Hospitals registers —ART clinic/CDC departments (paper-based sources) and Tanzanian ETL/ DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)	International standard (WHO)
	Outcome	CPHIV11	Percentage of patients undergoing ART therapy and tested with VL with suppression of viremia	Hospital	Number of patients undergoing VL tests with viremia suppression (x100)	Number of patients currently on ART therapy and tested with VL within last 12 months	Hospitals registers —ART clinic/CDC departments (paper-based sources) and Tanzanian ETL/ DHIS2, Ugandan eHMIS/DHIS2 (electronic sources)	International standard (WHO)

List of the evaluated indicators included into the CDs pathways.

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instead, along the diagnosis and treatment phases, with a negative deterioration in both indicators of the outcome phase, which scored on the red band.

Fig 3 reports the three-year trend of the percentage of TB patients who completed the treatment in the reference year (indicator IDPT10, outcome phase). The target of 90% was set

Fig 2. Tuberculosis care pathway. Performance of care pathways related to tuberculosis.

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Fig 3. Gastroenteritis care pathway. Performance of care pathways related to gastroenteritis.

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Fig 4. HIV/AIDS care pathway. Performance of care pathways related to HIV/AIDS.

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Fig 5. One selected indicator per each stave. Three-year trend indicators (panels on the left), and their respective evaluated scores for 2019 (panel on the right), one for each CD pathway.

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based on the WHO guidelines [29]. The indicator values ranged from 38% in the Oyam District to 93% in the Wolisso Area and scored 45% and 85% in Napak and Iringa Districts respectively. For Napak District, this observation was consistent with the other indicators along the TB care pathway. The highest percentage of patients who interrupted the treatment (S1 Fig, IDPT12) and those who resulted positive to the Xpert rifampicin-resistance test (S1 Fig, IDPT06.1) were in fact reported in Napak District.

Stave and indicators related to the gastroenteritis care pathway performance

From the analysis of the stave representing the gastroenteritis care pathway evaluation (Fig 3), it emerged that in Wolisso Area all the indicators related to the prevention phase showed excellent performance, with the exclusion of the indicator IDPD05, i.e. average number of toilets in OPD per number of rooms, which scored on the red band. Moreover, the performance of the indicators included in the diagnosis and outcome phases were registered with average and good scores, respectively. Indicators evaluating the treatment phase were not available for this setting.

With respect to Iringa District, the prevention phase showed heterogeneous results, with indicators scoring from poor to excellent performance. The indicator evaluating the diagnosis phase, i.e. the percentage of discharged patients for diarrhoea and gastroenteritis at hospital level (IDPD10), performed very well, while the one belonging to the outcome phase, namely the percentage of deaths with a diagnosis of gastroenteritis (IDPD14), scored on the orange band. Indicators evaluating the treatment phase were not available for this setting.

As in the previous stave, in Napak District the prevention phase showed diversified results in terms of performance scores, from excellent (indicators B7.9 and IDPD04) to average (IDPD02) and very poor (IDPD05). Moreover, the indicator evaluating the diagnosis phase performed poor, while higher performance scores were registered for the treatment and outcome phases.

With reference to Oyam District, the stave displayed excellent performance, except for the indicator regarding vaccination coverage for rota virus (B7.9). Additionally, the indicator related to the diagnosis phase scored poorly, whereas the indicators belonging to the other two phases showed a very good or excellent performance.

The histogram in Fig 5 shows the three-year trend of the percentage of deaths with a diagnosis of gastroenteritis and diarrhoea among hospitalized patients aged less than five years (indicator IDPD14, outcome phase). The target of 0,4% was set based on data assessment in benchmarking among the hospitals analysed. In the three-year period examined a fluctuating trend emerged. Except for Tosamaganga, the indicators values were homogeneous among districts. When comparing this indicator with the percentage of patients diagnosed with severe dehydration (S1 Fig, IDPD09), we observe some discrepancies regarding Tosamaganga. In 2019, when the highest death rate (2.0%) was reported, the hospital registered the lowest percentage of severe cases diagnosed (2.5%). Furthermore, Matany and Wolisso showed similar death rates, but widely different percentages of severe cases.

Stave and indicators related to the HIV/AIDS care pathway performance

The stave representing the HIV/AIDS care pathway (Fig 4) did not include indicators assessing primary prevention and diagnosis activities.

In Wolisso area, the performance of all evaluated indicators belonging to the screening and treatment phases scored very poor, with the exception of the percentage of HIV positive cases undergoing the TB screening (CPHIV03) that had an excellent score. Data on outcome measures were not available.

In Iringa District, the three indicators related to the screening phase scored average to excellent. Excellent performance results emerged from indicators belonging to the treatment phase, while those indicators evaluating treatment outcomes scored on the red band.

With respect to Napak District, the three indicators related to the screening phase scored poor to excellent, the indicators evaluating the treatment phase scored good to excellent, and those related to outcomes scored on the low and average bands.

In Oyam District, the screening phase showed heterogeneous results, with performance scores ranging from poor to good. Additionally, the two indicators evaluating the treatment phase (CPHIV07 and CPHIV08) scored on the dark green and red bands respectively, as well as those evaluating treatment outcomes (CPHIV10 and CPHIV11). Fig 5 illustrates the three-year trend of the HIV coverage rate of HIV therapy among residents at residence level (indicator CPHIV08, treatment phase). The denominator consists of the estimation of HIV prevalence among residents in the areas considered. The target of 95% was fixed according to WHO standard [30]. The graph shows that in the Napak and Oyam Districts almost all the estimation of HIV positive residents were enrolled on ART therapy over three years, while in the Wolisso Area and Oyam District this percentage was under 50%.

Discussion

In LMICs, performance evaluation tools are often used for reporting on achievement against international targets, providing baseline assessments under specific monitoring programmes or related to definite project goals, and ensuring accountability to donors [16, 17]. Indeed, these frameworks usually imply top-down approaches intended to evaluate outcomes at macro or project level. Here, we described the pilot experience in developing and implementing a PES-CDs in three sub-Saharan African countries using a bottom-up approach.

Indeed, the PES-CDs framework was developed through a north-south cooperation involving a NGO, two research centres and local health authorities and providers. This multisectoral cooperation benefitted from the commitment of the NGO, local stakeholders and partners to strengthen health systems activities using a data-driven and evidence-based approach and represented a fundamental condition for the development of the appropriate tool. The NGO's knowledge of the institutional and epidemiological contexts allowed the design of the system rapidly and facilitated the process of interaction and integration with local communities and professionals. Local stakeholders' involvement contributed to raise awareness and foster a common understanding of the jointly conceived PES-CDs, to ensure high degree of participation during all phases of development and to engage a multidisciplinary team. Moreover, this collaboration would not have been possible without the scientific contribution of academia, whose know-how guaranteed the application of rigorous methodology to PES-CDs development and data analyses taking advantage of previous experience in other healthcare systems.

The innovative contribution of this study lies in the development of a set of indicators aimed at measuring and evaluating the performance of the patient pathway along the continuum of care within the local healthcare system. Since HSs in each geographical area involve a plurality of organizations, the design of an evaluation framework that integrates different providers and their respective perspectives becomes fundamental. The PES-CDs added value relied in the assessment of the capacity of local healthcare systems to perform along the continuum of care and through the integrations of different organizations [31]. In other words, the focus of this evaluation shifted from an organization-centred approach to a patient-focused perspective [32], thus highlighting how local healthcare systems are capable of creating value for their reference populations [9, 10].

In our experience, the use of the stave as an intuitive and effective visual representation of the results proved to be a successful approach to highlight strengths and weaknesses along the patients' care pathway. In particular, it provided policy makers and healthcare managers with an integrated and continuous view of the performance across different healthcare settings [9].

In particular, from the TB stave analysis emerged that both TB primary (IDPT01) and secondary prevention (IDPT02) could be greatly improved in all the contexts considered, even if secondary prevention performed slightly better. When assessing outcomes, the percentage of cured patients (IDPT09) scored differently across settings, and appeared not to be related to the diagnostic or treatment performance, but rather to the rate of drop out. For example, in Oyam District, where the indicators belonging to the diagnosis and treatment phases scored high, IDPT09 scored very poor. This could be attributed to the still low treatment adherence rates due to the lack of patients awareness of the importance to complete the treatment [33]. Napak District scored poorly along the whole TB pathway, registering a low rate of treatment completion, thus highlighting the challenges in ensuring adherence to treatment in an area of predominantly nomadic population. On the contrary, Iringa and Wolisso Districts registered the highest percentages of cured TB patients suggesting a good service organization and patient's follow-up system. Appropriate and locally tailored strategies to increase treatment compliance are necessary to ensure a wider proportion of treated patients resolve the infection [34].

The Gastroenteritis care pathway was least complete due to data unavailability at both health district and hospital levels. A wide variation was observed across different settings, especially concerning the vaccination coverage for rota virus (B7.9). Indeed, such remarkable differences may be explained by the difficulty of complying with the international target (98% coverage), which is particularly challenging in these settings due to many reasons (i.e. interruption of the vaccine cold chain, natural events as well as duration of raining seasons) [35]. Information on treatment and disease outcomes was less consistent and not always available. The capacity of diagnosing and defining severe cases and their attributable deaths were not uniform across different contexts. The lack of reliability in defining causes of death is a well-known phenomenon in LMICs [36]. For example, deaths with a diagnosis of gastroenteritis and diarrhoea among hospitalized children aged <5 ranged from very poor to excellent and were not related to treatment performances. Finally, Hygiene and sanitation prevention measures met the WHO standards when implemented at the hospital level, while scored worse at the residential level, with important implications in terms of investment beyond the healthcare sector.

The HIV care pathway benefitted from a robust tradition of regional and global monitoring and vertical investments [37]. Performance indicators related to screening rarely achieved the international standards. Moreover, it was likely to have an under-reporting of HIV cases in the contexts analysed. This may have affected the estimation of treatment performance indicators and, particularly, the coverage rate of the therapy (CPHIV08), which was calculated using HIV prevalence estimates. As a consequence, the assessment of single indicators, as compared to the stave, may not provide an accurate and complete understanding of HSs provision gaps. Outcomes indicators also were affected by local practices and data availability, resulting in low accuracy and validity of the data. The most relevant example was perhaps the indicator measuring proportion of patients undergoing ART therapy and with suppression of viremia (CPHIV11) which scored from excellent to very poor across the different settings, but was likely to be severely affected by the fact that proportion of patients tested for HIV viral load during treatment scored very poorly in all the reference hospitals. This might be a very relevant finding considering that suppression of viral load is one of the key global indicators to assess country performance against WHO goals for HIV control [38].

By applying the PES-CDs to four settings located in three different countries, we tested the tool's scalability and replicability in diversified contexts, building on previous experiences [39, 40]. This supra-national benchmarking exercise was made possible by the adoption of targets and standards defined and already in use at international level. Consequently, based on our experience, the PES-CDs indicators and graphical representation could be used by other organizations providing HS in LMICs at various levels, regardless of the epidemiological context or the organizational model.

As in high-income countries, where the HSs provision heterogeneity has been studied for over 40 years [41], in LMICs unwarranted clinical variation is also common. Our results highlighted substantial variability across all care pathway's phases and between the four settings by mean using standardised indicators and targets. The relative weight of the underlying determinants will need to be further analysed with local stakeholders.

Health professionals' motivation and engagement in PES-CDs may also vary as different monitoring activities (e.g. data capturing, collection, analysis, interpretation) are not always prioritized in the daily routine and often derive from top-down initiatives [42, 43]. Therefore, the commitment to capturing data of sufficient quality and reliability is often limited and clinicians are rarely involved in or responsible for the use of PES-CDs data for monitoring or planning improvements. In this scenario, the PES-CDs promoted data sharing between local healthcare system providers in the study settings and facilitated the development of local competencies in data collection, analysis and interpretation, including problem-solving. In addition, by using data obtained through hospitals and health districts' information systems, the PES-CDs seeks to foster synergies between existing public information sources.

For all these reasons, the main aim of the PES-CDs remains its use at local level (e.g. hospital level, district level) to boost performance evaluation over time and to promote and guide hospital/district internal quality improvement efforts.

Over and above data handling limitations already mentioned, this study constituted a pilot experience and the extent of the impact on the local settings has not been evaluated yet. Future rounds of data collection, analyses and sharing with local stakeholders are planned in the coming years with the aim of turning PES-CDs into a routine activity. Further developments of the PES-CD may also be considered to assess, among others, usefulness and impact on health system financing as well as the inclusion of additional measures to investigate the dimension of equity in healthcare access.

Conclusion

We described an innovative approach to develop and roll-out a PES-CDs of health services provision along three CDs care pathways in three sub-Saharan African countries through multidisciplinary and north-south collaboration. Despite the intrinsic limitations of data sources, our results demonstrated that this system has great potential to strengthen the culture of data collection and monitoring at local level, ultimately fostering data-driven policy making and planning in healthcare. The bottom-up approach and stakeholders' engagement increased the likelihood of local ownership of the process and engagement to implement changes needed to improve HS performance and quality of care. In health systems characterized by multiple actors (governmental entities, private funders and providers), the proposed PES-CDs may contribute to achieve good governance in HSs provision, by stimulating performance evaluation, outcomes measurement and accountability.

Supporting information

S1 Fig. Trend and evaluated indicators related to the three CDs care pathways.
(PDF)

S1 Table. List of the analysed hospitals and their relative health districts or catchment area.
(PDF)

S1 File. Link to the report "Performance Evaluation System of hospital and health districts in Ethiopia, Uganda and Tanzania".
(PDF)

S2 File. Data elements related to the indicators listed in Table 2.
(PDF)

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Response to Mass-Casualty Incidents and Outbreaks: A Prehospital Disaster Training Package Developed for the National Emergency Medical Service in Sierra Leone

PAPER

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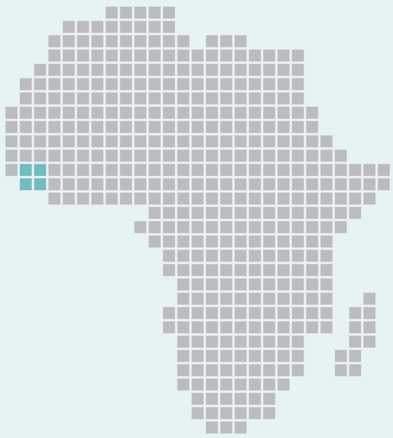

FIELD REPORT

Response to Mass-Casualty Incidents and Outbreaks: A Prehospital Disaster Training Package Developed for the National Emergency Medical Service in Sierra Leone

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Abbreviations:
CRIMEDIM: Center for Research and Training in Disaster Medicine, Humanitarian Aid, and Global Health
CUAMM: Doctors with Africa
DTP: Disaster Training Package
MCI: mass-casualty incident
MoHS: Ministry of Health and Sanitation
NEMS: National Emergency Medical Service
OC: operation center
PAL: peer-assisted learning
ToT: training-of-trainers

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Abstract
Sierra Leone is a country highly prone to disasters, still recovering from the catastrophic 2014 Ebola epidemic. In 2018, the country launched its first National Emergency Medical Service (NEMS) aiming to strengthen the provision of essential health services to the population with the long-term goal of creating a resilient health system able to effectively respond to and recover from emergencies. The Center for Research and Training in Disaster Medicine, Humanitarian Aid, and Global Health (CRIMEDIM), together with the Italian NGO Doctors with Africa (CUAMM), under the direct supervision of the Ministry of Health and Sanitation (MoHS), developed a prehospital Disaster Training Package (DTP) to be delivered to all NEMS personnel to boost the prehospital management of mass-casualty incidents (MCIs) and outbreaks. The DTP included a first phase in which NEMS local trainers underwent a training-of-trainers (ToT) course, enabling them to deliver cascade trainings to 16 district ambulance supervisors, 441 paramedics, 441 ambulance drivers, and 36 operators working in the NEMS operation center. This on-going training package represents the first Disaster Medicine training course for prehospital health professionals in Sierra Leone.

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Introduction

In the last three decades, the African continent experienced over 2,000 disasters, a trend that is likely to continue given the rapid and unplanned urban growth and the escalating impact of climate change.[1] Sierra Leone, one of the least developed low-income countries, ranks among the ten African countries reporting the highest disaster death toll in the past 20 years as a consequence of a number of disastrous events, including the regional epidemic of Ebola Virus Disease in 2014 and a series of mass-casualty incidents (MCIs) resulting from torrential rains, floods, and landslides.[2] In 2015, the government of Sierra Leone issued a post-Ebola recovery plan with the ultimate goal of building a resilient national system, enabling the health sector to provide essential health services, and to develop an integrated disaster risk management system.[3] As part of the essential health services package, the plan envisaged to improve the national prehospital referral transport system, a goal that was achieved in 2018 with the official launch of the first National Emergency Medical Service (NEMS).[4,5] The NEMS is a coordinated prehospital referral system that entails a fleet of 84 ambulances, 441 paramedics, and 441 prehospital care drivers working to provide timely prehospital care and transportation of patients to the nearest referral hospital under the supervision of 16 district ambulance supervisors and with the support of 36 operation center (OC) operators. Before taking service, NEMS personnel underwent a series of ad-hoc basic training courses developed by the Center for Research and Training in Disaster Medicine, Humanitarian Aid, and Global Health (CRIMEDIM; Università del Piemonte Orientale; Novara, Italy) and delivered with the support of the Italian NGO Doctors with Africa (CUAMM; Padova, Italy) under the direct supervision of the Ministry of Health and Sanitation (MoHS; Freetown, Western Area, Sierra Leone).[4] The courses embraced different topics, including the management of medical, trauma, obstetrics, gynecology, and pediatric emergencies and Basic Life Support and resuscitation maneuvers without the support of automated external defibrillator.[4] In addition, a series of refresh courses have been delivered to all NEMS personnel to improve their technical and attitudinal performances, with specific focus in those areas where gaps in knowledge, attitude, and practice were highlighted.

In its first three years of service, the NEMS has been challenged by a series of events that tested its resilience, including the 2019 Lassa Fever outbreak and the COVID-19 pandemic, the latter requiring a number of structural adaptation to ensure both the delivery of routine services and the proper management of COVID-19 patients.[6] A COVID-19 Special Training has also been provided to the prehospital health care teams and to the operators working at the NEMS OC focusing on the correct use of personal protective equipment; infection, prevention, and control procedures; case definition; triage; and dispatch procedures.[6] In line with the national recovery plan[3] and according to the governmental willingness to reinforce disaster risk management institutions and capacities in the country,[7] in 2021, CRIMEDIM and CUAMM with the support of the MoHS developed a training package with the goal of strengthening the capacity of the NEMS to manage MCIs and respond to outbreaks. The aim of this paper is to describe the prehospital Disaster Training Package (DTP) implemented for the NEMS in Sierra Leone.

Report

Training Needs and Learning Methodology

The DTP was designed following the six-step approach to curriculum and training development[8] with the ultimate goal of creating a workforce comprising qualified emergency responders with specific professional competencies to respond to outbreaks and MCIs. Since NEMS represents the first structured prehospital Emergency Medical Service of Sierra Leone, there was no previous experience in disaster and MCI training and education for prehospital providers in the country. In fact, to the best of the authors' knowledge, no similar training existed in the African continent at the time of writing of this manuscript, a gap that the World Health Organization (Geneva, Switzerland) Emergency Medical Teams initiative has started addressing in 2021 with the first Mass-Casualty Management course held in Ethiopia which, however, focused mainly on hospital response.[9] Therefore, to set the targeted learning objectives of the DTP, existing Disaster Medicine curricula designed by CRIMEDIM and other existing courses[10,11] were reviewed and adapted to produce a training package tailored to the local needs and based on local resources and capabilities. As such, the development process had to consider: (1) the country institutional architecture and national mechanism of response to disasters and MCIs; (2) the NEMS organizational structure; (3) the high burden represented by outbreaks and epidemics; (4) the medical resources present on the ambulances and current medical competences of the NEMS paramedics; and (5) the need to train all NEMS prehospital personnel, thus including approximately 1,000 providers, within a one-year timeframe. To guarantee the capillarity of the DTP throughout the 16 districts of the country and to enable its sustainability over time, the presence of the NEMS national trainers was leveraged, a pool of seven qualified trainers with health backgrounds, specifically as registered nurses or community health officers, responsible for all the NEMS educational activities. Therefore, the first task of the DTP was to develop a one-week training-of-trainers (ToT) course to equip national trainers with both basic knowledge in Disaster Medicine and the necessary skills to transfer this knowledge to all NEMS personnel through a peer-assisted learning (PAL) approach.[12] The ToT courses aimed to prepare national trainers to critically replicate and lead the same types of exercises, promoting learners' engagement, reflective practice, critical thinking, and skill acquisition. The second task was to develop a one-week cascade training to be delivered by national trainers to district ambulance supervisors, prehospital teams, and OC operators in the 16 districts of the country. The utmost goal of the cascade training activities was to help prehospital teams and OC operators familiarize with disaster concepts, but also to improve their attitudinal, behavioral, and technical performance, strengthening their existing professional skills and developing context-specific capacities to achieve an effective team performance. The educational strategy adopted included a blended methodology based on adult learning principles, combining traditional classroom teaching methodologies with practical exercises, group discussions, table-top simulations, and drills using mannequins and role players. The curriculum has then been presented to the MoHS representatives at NEMS to obtain support and financing and to identify and address potential barriers to its implementation. Lastly, an evaluation tool was designed to assess the individual performance of learners in a summative way, thus evaluating knowledge retention, and to assess their participation and awareness during the practical sessions.

Curriculum and Training Structure

In Table 1, the ToT course curriculum is reported, including modules, learning objectives, teaching methods, and time allocated. Trainees were also exposed to a drill reproducing a mass-casualty scenario in which they were asked to perform specific tasks regarding scene assessment, proper communication and reporting to health authorities, primary triage using the Simple Triage and Rapid Treatment (START) algorithm,[13] and evacuation procedures. The objective of the drill was to exercise the newly acquired skills inside a realistic scenario, both as individuals and within the team, under the supervision of expert evaluators in charge of

Module	Learning Objectives	Teaching Methods	Time
Introduction to Disaster Medicine	1. To understand the main features and functional attributes of disasters 2. To explain the common characteristics of disasters and MCIs 3. To understand the impact of disasters and MCIs 4. To get acquainted with concepts related to disaster risk (ie, hazard, exposure, vulnerability, capacity) 5. To understand and describe the different component of the disaster cycle (ie, response, recovery, preparedness, mitigation)	Classroom lecture	1hour
Triage During MCIs	1. To understand the basic principles of triage in a context of multiple casualties and limited resources 2. To describe the key concepts related to triage during MCIs 3. To get acquainted with the START algorithm 4. To efficiently perform the START algorithm	Classroom lecture; Practical session: table-top exercise, group discussions, live simulations	6hours
Prehospital Response to MCIs	1. To understand the difference between different MCIs according to type, setting, and events 2. To perform scene assessment and gather the necessary information to deliver the initial report and alert the system of impending MCI 3. To perform scene size-up and identify different areas (ie, advanced command post, patient collecting, and loading areas) 4. To understand basic concepts of communication during MCIs 5. To establish roles within the team, understanding the importance of the chain of command and control 6. To understand the importance of a coordinated scene evacuation	Classroom lecture; Practical session: table-top exercise, group discussions, live simulations	8hours
Infectious Diseases	1. To explain the difference between outbreaks, epidemics, and pandemics 2. To get acquainted with International Health Regulations 3. To describe the role of infectious diseases as disasters 4. To describe the main features and risks pertaining the occurrence of infectious diseases after a natural or technological disaster	Classroom lecture	1hour
IPC & PPE	1. To understand and explain basic concepts pertaining to the infectious disease transmission cycle (ie, agent, reservoir, modes of transmission) 2. To understand and describe the standard precautions to protect operators and prevent operators from spreading infections among patients (ie, hand hygiene, use of PPE, respiratory hygiene and cough etiquette, sharps safety, clean and disinfected environmental surfaces) 3. To review and refresh existing COVID-19 knowledge on policy, procedures, and protocols 4. To be familiar with all parts of PPE and know how to don and doff 5. To understand the decontamination process	Classroom lecture Practical session	6hours
National Response Mechanism to MCIs and Outbreaks	1. To get familiar with national institutional architecture to manage disasters and emergencies in Sierra Leone 2. To understand the different steps pertaining the national response mechanism in case of MCI and outbreaks 3. To understand the role and responsibilities of NEMS within the national response mechanism	Classroom lecture	2hours
Planning of Cascade Trainings	1. To get acquainted with the practical sessions to be critically led during the cascade training 2. To understand how to perform effective debriefing sessions after simulation activities 3. To discuss the cascade training schedule according to NEMS operational needs 4. To plan the cascade training activities and material	Group work and discussion	12hours

Table 1. Overview of the Training-of-Trainers Curriculum within the Prehospital Disaster Training Package Developed for the National Emergency Medical Service in Sierra Leone
Abbreviations: MCI, mass-casualty incidents; START, Simple Triage and Rapid Treatment; IPC, infection prevention and control; PPE, personal protective equipment; NEMS, National Emergency Medical Service.

observing trainees' performances and leading a post-drill debriefing session. The course was delivered by two qualified training managers with backgrounds in disaster and emergency medicine, supported by CRIMEDIM's experts. The ToT course comprised a final examination that consisted of 24 multiple-choice questions to assess content knowledge, and test results were expressed as a score out of 100 with a minimum passing score of 60. Trainees' participation and awareness during practical sessions were also evaluated using a one-to-five score. Participation was defined as "active engagement with course content, faculty, and fellow students" while trainees' awareness encompassed a combination of social awareness (related to social connections within the

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	Final Examination	Practical Sessions	
		Participation	Awareness
Trainer 1	75	5	5
Trainer 2	87	5	5
Trainer 3	84	5	5
Trainer 4	75	3	4
Trainer 5	71	4	4
Trainer 6	75	4	5
Trainer 7	80	4	4

Table 2. Evaluation of the NEMS Local Trainers Exposed to the Training-of-Trainers Course on Outbreaks and Mass-Casualty Incidents
Note: The final written examination included 24 multiple choice questions with a cut-off score for passing of 60 out of 100. Practical sessions were evaluated with a 1 to 5 score.
Abbreviation: NEMS, National Emergency Medical Service.

group), task awareness (related to the steps needed to complete tasks), and concept awareness (related to the trainees existing knowledge in respect to the tasks).[14] At the end of the course, the national trainers with the support of training managers, CRIMEDIM's experts, and relevant stakeholders reviewed the cascade trainings to be delivered to NEMS paramedics, ambulance drivers, and OC operators. A group discussion was held to agree on the topics to be included, which comprised the same modules delivered in the ToT course in addition to a review session focusing on NEMS communication and handover procedures. A final examination consisting of 24 multiple-choice questions and a course evaluation questionnaire were also produced.

Outcomes

Starting on July 19, 2021, the ToT course was delivered to the seven national trainers. All trainers successfully passed the final examination and achieved high scores in the practical sessions, demonstrating active participation, commitment to the project, and good awareness (Table 2). The use of a hybrid learning approach featuring frontal lectures and practical sessions, a modality that has already been adopted during the delivery of NEMS basic training courses,[4] allowed to achieve excellent results concerning students' engagement and knowledge retention. Following the ToT course, the series of cascade trainings started on August 2, 2021, delivered by the just-trained national trainers under the direct supervision of the two training managers. After three-month stop due to financial issues related to delays in external financing, the cascade trainings are currently on-going with the objective of reaching 1,000 NEMS prehospital providers by the end of the year.

Discussion and Conclusions

The NEMS' DTP is the very first Disaster Medicine training course delivered to prehospital health care providers in Sierra Leone. The curriculum development process followed a concrete educational framework,[8] and the curriculum was tailored according to local needs. The adoption of a PAL approach, a modality that has been successfully implemented in several training programs for health professionals and also in the delivery of disaster medicine courses,[15–17] was beneficial both for NEMS national trainers and trainees. Indeed, the former had the chance to improve their individual competencies and skills, boosting their self-confidence and autonomy in the provision of training activities, while the latter had the possibility to learn in a "social and cognitive congruent" environment, where trainers and trainee sharing the same social role feel more encouraged to express informally and exchange ideas.[18,19] The abovementioned considerations indicate that the provision of the DTP to all NEMS personnel has the potential to improve Disaster Medicine culture among health professionals in Sierra Leone. While education and training are the cornerstones of disaster preparedness and response, results in the literature clearly point out the lack of Disaster Medicine trainings in medical schools world-wide,[20] a deficiency that contributes to leaving health professionals unprepared when facing the consequence of disastrous events, which can rapidly overwhelm local resources and the ability to deliver comprehensive medical care. Few sporadic steps were made in the past years to provide Disaster Medicine education in African countries,[9] and in most cases, involved health professionals in South Africa, the most developed country of the continent.[21,22]

The authors strongly believe that the DTP delivered to NEMS personnel represents an important step towards the strengthening of disaster risk management efforts in the country, with the possibility to be extended to other emergency responders such as the police and fire department, as well as all the partners involved in the national response plan. Moreover, this experience has the potential to expand beyond its national borders and to foster the implementation of similar projects at the global level.

Author Contributions

Marta Caviglia conceived the presented idea; participated in project administration, data curation, formal analysis, and investigation; drafted the article, designed figures and tables, and provided final approval of the version to be submitted.

Josè Alberto da Silva-Moniz participated in project administration, investigation, and interpretation of results; critical revision of the article; and provided final approval of the version to be submitted.

Francesco Venturini provided study resources, participated in critical revision of the article, interpretation of results, and provided final approval of the version to be submitted.

Amara Jambai provided study resources, participated in critical revision of the article, and provided final approval of the version to be submitted.

Matthew Jusu Vandy provided study resources, participated in critical revision of the article, and provided final approval of the version to be submitted.

Abdul Wurie provided study resources, participated in critical revision of the article, and provided final approval of the version to be submitted.

Moi Tenga Sartie provided study resources, participated in critical revision of the article, and provided final approval of the version to be submitted.

Giovanni Putoto provided study resources, participated in critical revision of the article, and provided final approval of the version to be submitted.

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Luca Ragazzoni participated in the study design, project administration, and supervision; participated in critical revision of the article, interpretation of results, and provided final approval of the version to be submitted.

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Sviluppo di uno strumento multidimensionale di integrazione tra Project Management e Implementation research per la Cooperazione Sanitaria Internazionale

ORAL PRESENTATIONS

Conference
VII Congresso Coordinamento Universitario per la Cooperazione allo Sviluppo CUCS: Capacity Building, Science Diplomacy e Open Science nei rapporti tra Nord e Sud del mondo nel nuovo contesto globale

Location
Naples, Italy

Presentation date
21-23 April 2022

Authors
Bertoncello C. et. al.

Focus country
Multi-countries

Performance Evaluation System of Hospitals and Health Districts in Ethiopia, Tanzania and Uganda. A focus on Iringa District Council/ Tosamaganga District Designated Hospital

ORAL PRESENTATIONS

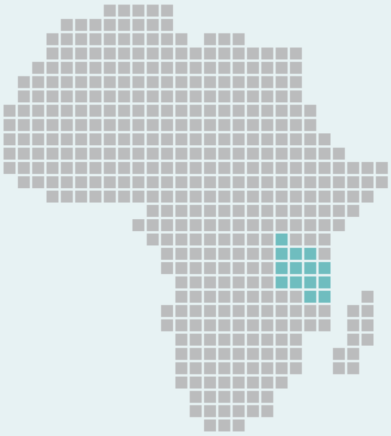
Conference
1st Tanzania Monitoring, Evaluation and Learning Week

Location
Dodoma, Tanzania

Presentation date
27-28 April 2022

Authors
Belardi P. et. al.

Focus country
Tanzania



An integrated care pathway for maternal and childcare: evidence from Ethiopia, Tanzania, and Uganda

ORAL PRESENTATIONS

Conference
European Public Health Conference

Location
Berlin, Germany

Presentation date
9-12 November 2022

Authors
Corazza et. al.

Focus country
Multi-countries

Infectious and tropical diseases

Beyond viral suppression: Quality of life among stable ART clients in a differentiated service delivery intervention in Tanzania

PAPER

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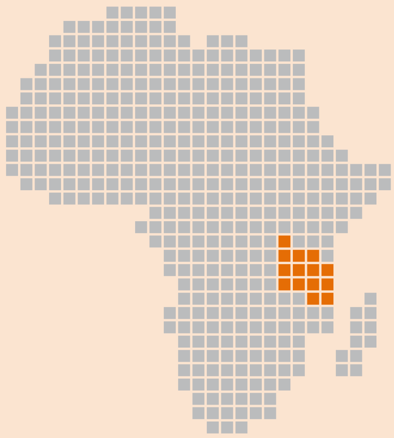

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Beyond viral suppression: Quality of life among stable ART clients in a differentiated service delivery intervention in Tanzania

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Abstract

Background With antiretroviral therapy, more people living with HIV (PLHIV) in resource-limited settings are virally suppressed and living longer. WHO recommends differentiated service delivery (DSD) as an alternative, less resource-demanding way of expanding HIV services access. Monitoring client's health-related quality of life (HRQoL) is necessary to understand patients' perceptions of treatment and services but is understudied in sub-Saharan Africa. We assessed HRQoL among ART clients in Tanzania accessing two service models.

Methods Cross-sectional survey from May–August 2019 among stable ART clients randomly sampled from clinics and clubs in the Shinyanga region providing DSD and clinic-based care. HRQoL data were collected using a validated HIV-specific instrument—Functional Assessment of HIV infection (FAHI), in addition to socio-demographic, HIV care, and service accessibility data. Descriptive analysis of HRQoL, logistic regression and a stepwise multiple linear regression were performed to examine HRQoL determinants.

Results 629 participants were enrolled, of which 40% accessed DSD. Similar HRQoL scores *[mean (SD), p-value]*; FAHI total [152.2 (22.2) vs 153.8 (20.6), p 0.687] were observed among DSD and clinic-based care participants. Accessibility factors contributed more to emotional wellbeing among DSD participants compared to the clinic-based care participants (53.4% vs 18.5%, $p = < 0.001$). Satisfactory (> 80% of maximum score) HRQoL scoring was associated with (OR [95% CI], p-value) being male (2.59 [1.36–4.92], p 0.004) among clinic participants and with urban residence (4.72 [1.70–13.1], p 0.001) among DSD participants.

Conclusions Similar HRQoL was observed in DSD and clinic-based care. Our research highlights focus areas to identify supporting interventions, ultimately optimizing HRQoL among PLHIV.

Keywords Quality of life · FAHI · Wellbeing · Emotional · Social · Differentiated service delivery

Abbreviation

ART	Anti-Retroviral Therapy
ARV	Antiretroviral
AUC	Area Under Curve
AYPLHIV	Adolescent and Young People Living with HIV
CF	Cognitive Functioning
CI	Confidence Interval
CHW	Community Health Worker

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CTC	Care and Treatment Centre
DSD	Differentiated Service Delivery
EWB	Emotional Wellbeing
FAHI	Functional Assessment of HIV Infection
FGWB	Functional and Global Wellbeing
HIC	High Income Country
HIV	Human Immunodeficiency Syndrome
HCW	Health Care Worker
HRQoL	Health-Related Quality of Life
LMIC	Low- and Middle-Income Country
NACP	National AIDS Control Program
NIMR	National Institute for Medical Research
MOHCDGEC	Ministry of Health, Community Development, Gender, Elderly, and Children Tanzania
PLHIV	People Living with HIV
PWB	Physical Wellbeing
QoL	Quality of Life
ROC	Receiver Operative Characteristics
SD	Standard Deviation
SSA	Sub-Saharan Africa
SWB	Social Wellbeing
T & T	Universal Test & Treat
VL	Viral Load
VLS	Viral Load Suppression
WHO	World Health Organization

Background

Access to effective antiretroviral therapy (ART) has contributed to an increased number of people living with HIV (PLHIV) being virally suppressed and living longer [1–4]. However, the physical consequences of long-term exposure to ARVs have yet to be fully elucidated and evidence associates PLHIV on ART with an increased risk of cardiovascular disease, liver disease, and various malignancies [5–8]. While PLHIV report significantly lower health-related quality of life (HRQoL) when compared to the general population in high-income countries (HIC) [9], HRQoL among PLHIV is understudied in low and middle-income countries (LMIC), especially in sub-Saharan Africa (SSA). With an increasing number of PLHIV on ART who are aging in SSA, monitoring of HRQoL becomes a priority in this setting [10, 11].

HRQoL is a multidimensional concept depicting an individual's subjective perception of current health status and outlook of the future [12, 13]. HRQoL studies assess individuals' perception of their health and how it affects or is affected by other aspects of life [13]. Among PLHIV, ART impacted HRQoL positively, especially in LMIC when ART start was guided by CD4 thresholds [1, 14, 15]. Subsequent studies predicted factors associated with good HRQoL among PLHIV e.g. being married, absence of co-morbidities, higher education, living in an urban setting, status disclosure, being on ART longer, being employed, fewer pills, and good adherence [16–21]. Conversely, factors found to be associated with lower HRQoL included stigma, same-sex relationships, being symptomatic, illiteracy and not being sexually active [18, 19, 22–24]. HRQoL studies among virally suppressed PLHIV are limited in LMIC [9, 23, 25].

In SSA, HRQoL studies have mostly been conducted among clients who access ART in clinical settings [24, 26–28]. Differentiated service delivery (DSD) is a patient-centered approach which offer virally suppressed PLHIV alternative models of HIV care both within clinic (e.g. multiple month scripting, fast-track refills, adherence/ART clubs etc.) and out-of-clinic (e.g. community ART, community drug distribution points, ART clubs etc.) [29–33]. DSD models benefit both the health system by reducing over-crowding in clinics, improving work efficiency among healthcare workers (HCW), and clients, by fostering self-management, peer support, and reducing time spent seeking care. Out-of-clinic DSD models limit contact with the formal health system and rely upon community health workers (CHW) who are trained volunteers for service delivery. Most evaluations of such models focused on adherence and quality of care yet change in delivery models of care may also affect HRQoL.

With 1.6 million PLHIV and a prevalence of 4.6% among adults in 2018, it was estimated that only 62% of PLHIV on ART in Tanzania are virally suppressed [34]. Though studies show favorable patient-related outcomes with DSD interventions elsewhere, there is a dearth of evidence within the Tanzanian context [35–37]. Additionally, it was not clear how limited contact with the health system, more peer support, less frequent travels impacted the QoL of clients. Our study therefore aimed to assess HRQoL among stable ART clients accessing ART care in a flagship Test and Treat (T&T) project in north-western Tanzania. We compared HRQoL scores and determinants of HRQoL between stable ART clients receiving either standard clinic-based care or ART clubs DSD care.

Methods

Study setting and population

The T&T project is hosted by the Catholic Diocese of Shinyanga which covers both Shinyanga and Simiyu regions in north-western Tanzania. Besides Shinyanga urban, Kahama urban, and Bariadi districts, the regions are largely rural. Project sites are four HIV care and treatment centers (CTC) referred to as hubs, two hubs each in the Shinyanga (Ngokolo and Bugisi) and Simiyu (Songambele and Mwamapala) regions. Standard of HIV care in Tanzania is clinic-based and includes one clinic visit every one to three months for consultation, health screening, routine labs and ART refill. DSD in ART clubs was rolled out in the T&T project from July 2018, details of which have been described elsewhere [38]. Briefly, ART clubs are CHW managed groups of 15–30 clients living within the same locality who meet every 3 months for routine health screening and ART distribution. Club members have a clinical consultation every year. Data were collected from May to August 2019. Participants were recruited at the two hubs in the Shinyanga region and their related ART clubs. Eligibility criteria included being adults ≥ 18 years and stable on ART according to the Tanzanian guidelines: on ART 1st line regimen ≥ 6-months, viral load < 50 copies/ml, and no current chronic illness [39]. At the hubs, participants were randomly sampled from a list of all eligible clients who had a clinic appointments within the data collection period. Eligible participants were approached as they attended clinic appointments. All clubs that had a meeting during the data collection period and were at least 6 months or older, were visited. At the clubs, all members were approached as stability was an eligibility criterion for DSD participation. Those clients who gave written consent, completed the interviewer-administered questionnaire.

Data collection

We used an HIV-specific HRQoL tool that has been validated for the low literacy Swahili population, the Kiswahili translation of the Functional Assessment of HIV Infection (FAHI) [40]. Outcomes of interest were the total and domain-specific FAHI scores. The FAHI is a 47-item tool with five domains namely physical wellbeing (PWB) – 10 items, emotional wellbeing (EWB) – 10 items, functional & global wellbeing (FGWB) – 13 items, social wellbeing (SWB)-8 items, and cognitive functioning (CF) – 3 items [41]. Scores ranged for each item between 0 and 4. We derived (a) domain scores by summing respective item scores – ranges for PWB and EWB were 0 to 40, FGWB 0 to 52, SWB 0 to 32, and CF 0 to12; (b) total FAHI scores by summing all five domain scores – ranging between 44 and 176—note that three items in the PWB domain were not scored as recommended by the FAHI scoring document [42]; (c) FAHI proportional score by calculating each individual score as a proportion of the maximum possible total or domain scores; and (d) a dichotomous (satisfactory/less than satisfactory FAHI HRQoL) variable for total and domains. We considered a score in the highest quintile i.e. ≥ 80% of FAHI total or domain scores as satisfactory to capture all participants who report at least ≥ 4 on the 5-point FAHI tool. This represents all those who report at least above "Somewhat" (i.e. 3 – the midpoint) for all items in all domains of the FAHI instrument.

Secondary outcomes were factors associated with satisfactory HRQoL and domain scores. Three categories of additional data were collected to assess these factors: socio-demographic (location, sex, age, educational level, marital status, employment status, and income level), HIV care (duration on ART, CD4 count at ART start and recency of viral load result) and service access (location, time spent during clinic visit/club meeting[wait time], time spent traveling to clinic/club[travel time] and frequency of service delivery). Data entry, collation, and cleaning were done using EpiData [43].

Sample size and statistical analysis

Our sample size calculation was based on EQ-index scores and extrapolated to proportional FAHI scores. We assumed a difference in proportional scores of 0.10 (0.80 to 0.90) between the clinic and DSD participants, a standard deviation of 0.40 as determined by Louwagie et al. in South Africa, and a 10% refusal rate requiring thus a minimum of 542 participants overall with 271 participants per service delivery group to have 80% power to reject the null hypothesis of no difference [1].

Categorical variables were presented as percentages and continuous variables as means (± standard deviation) or medians (± interquartile range) as appropriate. Comparisons between clinic and DSD participants were done using Mann Whitney or Kruskal Wallis tests. Association between socio-demographic, HIV care, and service access factors and satisfactory FAHI HRQoL were examined using logistic regression. Sex, age, marital status, and variables showing significant bivariate association at the p-value of < 0.1 were included in the multivariable model. A 3-step hierarchical multiple linear regression was used to quantify the contribution of the three-factor categories to the variance of FAHI scores observed. Socio-demographic variables were entered in the model in the first step, followed by HIV care variables and lastly, service access variables.

We examined variables for multicollinearity using tolerance values and variance inflation factor (VIF) statistics. We generated a Receiver Operative Characteristic (ROC) i.e. area under the curve (AUC) to test the discriminative ability of the model (with all covariates included) to categorize observations as satisfactory/less than satisfactory HRQoL. We assessed the 33 and 28 missing observations dropped from the clinic and DSD in step 3 hierarchical linear models, respectively, to observe any significant differences in mean FAHItotal. All analyses were performed using STATA software version 16.0.

Ethical approval for the study was obtained from the National Institute for Medical Research (NIMR; approval number NIMR/HQ/R.8c/Vol. I/674).

Results

Characteristics of the study population

Of 667 PLHIV approached to participate, 641 consented to participate (response rate of 96.1%), and 629 were included in the final analysis (12 excluded due to missing data). While the overall majority of participants were female (63%), there were significantly more men in clinic-based care compared to DSD, and DSD participants were also significantly older (see Table 1). The mean numbers of years-on-ART and mean CD4 count at ART start were significantly longer (4.9 vs 4.1 years, $p<0.001$) and higher (398.1 vs 341.4 cells/mm^3, $p<0.001$) for DSD participants. They also spent shorter time on travel (84.7 vs 34.3 min, $p<0.001$) and during club meetings (140.2 vs 83.8 min, $p<0.001$). There were more DSD participants in the urban area (60.6% vs 39.4%). Table 1 provides details on the characteristics of study participants according to the service delivery model.

FAHI total and domain scores by service access model

Clinic and DSD participants show comparable mean HRQoL scores across domains with only slight differences in the physical and emotional wellbeing domains (36.4 vs 35.5, max-40 $p<0.01$) and (32.1 vs 32.8, max-40 $p<0.05$) (Fig. 1a). No differences were observed in satisfactory HRQoL percentages across domains except for FGWB where more clinic participants revealed satisfactory HRQoL as compared to DSD. Satisfactory HRQoL overall was highest in the CF domain (89.2 vs 93.6) and lowest in the EWB (68.8 vs 68.5) and SWB (74.1 vs71.7) domains (Fig. 1b).

Associations between sociodemographic, HIV care, and service access factors and satisfactory overall HRQoL

Satisfactory overall HRQoL was associated with being male ((odds ratio 2.59, 95% confidence interval 1.36–4.92) among clinic participants and with living in an urban setting (4.72, 1.70–13.1) in DSD care (see—Table 2). Less than satisfactory HRQoL was observed with increasing age among clinic participants, and with increasing income, and increased meeting duration among DSD participants. HIV care factors were generally not associated with satisfactory overall HRQoL.

Associations between sociodemographic, HIV care and service access factors and satisfactory domain HRQoL

Compared to being single, satisfactory HRQoL was associated with being married in the PWB domain for both clinic and DSD. Being married or separated, divorced, or widowed was positively associated with satisfactory HRQoL for both clinic and DSD participants in the SWB domain and only among DSD participant in the FGWB domain. Living in an urban area was significantly associated with satisfactory HRQoL for both clinic and DSD participants in the EWB domains and only among DSD participants in the SWB and PWB domains. Across domains, declining age was generally not associated with satisfactory HRQoL. Significantly less satisfactory HRQoL was only seen among clinic participants aged over 65 years in the PWB and FGWB domains. Surprisingly, less satisfactory HRQoL was linked with increased income levels in the EWB domain among clinic and DSD participants. Generally, HIV care factors were not associated with satisfactory HRQoL. Among service access factors, DSD participants alone reported less than satisfactory HRQoL for spending longer time during service access in the PWB, EWB, and SWB domains (Table 2 and Additional file 1 [for additional results of FGWB & CF domains]).

Contribution of sociodemographic, HIV care, and service access factors to variance observed in HRQoL.

Table 3 shows the contribution of sociodemographic, HIV care, and service access factors to the variance observed in HRQoL scores. The analyses revealed that among clinic participants, the variance in overall HRQoL score FAHI total explainable by sociodemographic variables in the first step was 10.2%. The addition of HIV care variables in the second step increased the variance explained to 14.5%. Finally, service access variables in the third step brought the total to 14.9%. For DSD participants, the variance explained was 22.9%, 28.9%, and 43.5% in the first, second, and third steps, respectively. Across all domains, the variance in HRQoL explainable by the 3-step hierarchical model for clinic participants was modest (see Table 3). The highest was reported in the EWB domain i.e. 8.5%, 11.4%, and 18.5%, and lowest in the CF domain i.e. 5.9%, 9.1%, and 9.8%, respectively. A much higher proportion of variance was explained in overall FAHI 43.5%, PWB 30.2%, EWB 53.4%, and SWB 35.1% among DSD participants. Additional file 2 shows the details of the hierarchical linear regression with coefficients of all covariate in each step.

Table 1 Socio-demographic, HIV care, and service access-related characteristics according to service delivery model

	Clinic-based ($n=378$)	DSD ($n=251$)	p-value*
Sociodemographic information			
Location, n (%)			
Bugisi (Rural)	324 (65.8)	168 (34.1)	< 0.001
Ngokolo (Urban)	54 (39.4)	83 (60.6)	
Sex (n, %)			
Female	224 (59.3)	172 (68.5)	0.018
Male	154 (40,7)	79 (31.5)	
Age in years, median (IQR)	39.3 (33.3–48.1)	44.7 (37.6–54.0)	< 0.001
Age-groups, n, (%)			
< 25	25 (6.61)	6 (2.40)	< 0.001
25–34	96 (25.1)	35 (13.9)	
35–44	137 (36.2)	91 (36.3)	
45–54	75 (19.8)	62 (24.7)	
55–64	33 (8.73)	40 (15.9)	
≥ 65	13 (3.4)	17 (6.8)	
Educational level, n (%)			
No education	97 (25.7)	60 (23.9)	0.744
Primary	261 (69.1)	180 (71.7)	
≥ Secondary	20 (5.3)	11 (4.4)	
Marital status (n, %)			
Single	94 (24.9)	80 (31.9)	0.092
Married	144 (38.1)	78 (31.1)	
Separated/Divorced/Widowed	140 (37.0)	93 (37.1)	
Employment status (n, %)			
Unemployed	53 (14.0)	60 (23.9)	0.002
Income level (TSH), median (IQR)	87,000 (50,000- 172,000)	80,000 (50,000- 150,000)	
< 100,000	206 (54.5)	148 (59.0)	0.315
100,000–300,000	116 (30.7)	63 (25.1)	
> 300,000	56 (14.8)	40 (15.9)	
HIV care information			
Years on ART, median [IQR]	4.1 [2.1–5.8]	4.9 [2.2–7.3]	0.001
Years on ART group around the mean			
≤ 4.4 years	219 (57.9)	130 (51.8)	0.316
> 4.4 years	150 (39.7)	114 (45.4)	
Missing	9 (2.38)	7 (2.79)	
CD4 at ART start in cells/mm^3, median [IQR]	341.4 [155–449]	398.1 [184.5–513.5]	0.003
CD4 at ART start groups			
< 200	126 (33.3)	63 (25.1)	0.07
≥ 200	236 (62.4)	173 (68.9)	
Missing	16 (4.23)	15 (5.98)	
Viral load in copies/ml, median [IQR]	10 [10]	10 [10]	0.876
Viral load group			
< 50 copies/ml	375 (99.2)	237 (94.4)	< 0.001
≥ 50	-	9 (3.6)	
Missing	3 (0.8)	5 (2.0)	
Time since last VL record, n (%)			
≤ 6 months	179 (47.4)	113 (45.0)	< 0.001
6 months – 1 year	170 (44.9)	85 (33.9)	
> 1 year	26 (6.9)	49 (19.5)	
Missing	3 (0.8)	4 (1.6)	

Table 1 (continued)

	Clinic-based ($n=378$)	DSD ($n=251$)	p-value*
Service access information			
Time spent in clinic/club in minutes, median [IQR]	140.2 [60–180]	83.8 [30–120]	< 0.001
Length of stay, n (%)			
Short (≤ 1 h 30 min)	129 (34.1)	177 (70.5)	< 0.001
Long (> 1 h 30 min)	246 (65.1)	71 (28.3)	
Missing	3 (0.8)	3 (1.2)	
Time spent traveling to clinic/club in minutes, median [IQR]	84.7 [30–120]	34.3 [10–30]	< 0.001
Travel time group, n (%)			
Short (≤ 1 h)	214 (56.6)	232 (92.4)	< 0.001
Long (> 1 h)	161 (42.4)	17 (6.8)	
Missing	3 (0.8)	2 (0.8)	
Frequency of visits/meetings, n (%)			
More (≤ every 2 months)	355 (93.9)	121 (48.2)	< 0.001
Less (> every 2 months)	23 (6.1)	130 (51.8)	

**p*-values presented are calculated using Mann Whitney U or Kruskal Wallis tests as appropriate. *n* number, % percentage, *SD* standard deviation, *TSH* Tanzanian shilling, *IQR* interquartile range, *ART* antiretroviral treatment, *VL* viral load

Internal consistency and Goodness of fit statistics

In the present study, Cronbach alpha was 0.68, 0.73, 0.67, 0.71, and 0.81 for the PWB, EWB, FGWB, SWB, and CF domains, respectively, indicating acceptable internal consistency. Tolerance values ranged from 0.16 to 0.84 while the VIF values were from 1.19 to 6.3 suggesting that multicollinearity had no impact on the variables included. The AUC for our logistic regression model was 0.81 showing the acceptable ability of our model to discriminate – the effective range is usually from 0.5 to 1. There was no significant difference in mean FAHI total scores when the step 3 models in the hierarchical regression were compared with step 1 models.

Discussion

Our study compared factors influencing HRQoL among stable ART clients accessing care at either HIV clinics or DSD clubs in the Shinyanga region of Tanzania. Most participants in our study rate their HRQoL as satisfactory. Our results revealed that service access factors contributed considerably to HRQoL among DSD participants. We found that time spent during clinic/club and the settings of service delivery were factors significantly associated with perceived HRQoL.

Understanding HRQoL in African studies is relevant in the current era of expanded treatment" and DSD. Previous HRQoL studies compared HIV positive and negative people and/or PLHIV not on and on ART [2, 2]. Similar HRQoL among stable clients seen in our study strengthens the case for DSD which may likely impact positively on care delivery to unstable clients concurrently who are more likely to have special needs [44, 45]. The complex effect of service access factors on overall HRQoL suggests that other non-measured factors are likely also to influence HRQoL.

Service access factors are more commonly studied about patient satisfaction and retention in care than in HRQoL but both are likely to be related. The shorter time spent accessing service observed as positively associated with HRQoL in our study may reflect the value placed on other meaningful engagements made possible by the time saved from care seeking in this setting. Being predominantly farmers, reduction of productivity loss due to care seeking likely impacts HRQoL. In Malawi and Uganda, reduced time spent in DSD models was reported as a favorable outcome predicting retention and satisfaction [46, 47]. Reduced travel time has also been identified as beneficial for DSD participants and enabling its success, although it was not independently associated with HRQoL in our study [48, 49].

As per HRQoL domains, the literature reveals that social and psychological/emotional domains score the lowest in most HRQoL studies among PLHIV [16, 21, 25, 50–54] which is in line with our findings. Reasons adduced for this include stigma and discrimination due to fear and lack of awareness as HIV continues to isolate those infected from meaningful relationships. The slight difference in the PWB domain scores is likely not clinically significant as HRQoL was generally not associated with most covariates except for those age > 65 years or married in the clinic. The variance explainable due to service access factors was notably largest i.e. 53.4% in the EWB domain suggesting some significance of the contribution of DSD in supporting participants who

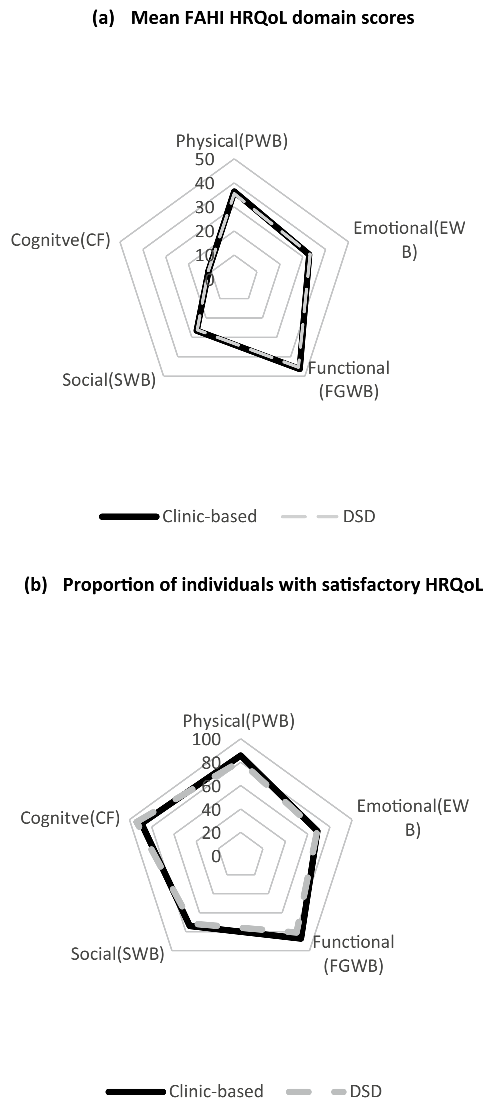

Fig. 1 FAHI HRQoL scores by service access model. Mean FAHI HRQoL domain scores (b) Proportion of individuals with satisfactory HRQoL. *PWB* Physical wellbeing, *EWB* Emotional wellbeing, *FGWB* Functional and Global wellbeing, *SWB* Social wellbeing, *CF* Cognitive Functioning

likely face different psychological, emotional, and social dilemmas. [16, 17, 51].

While our finding that being male was associated with a more satisfactory HRQoL aligns with evidence from Tanzania, Burkina Faso, Ghana, and Ethiopia [18, 55–57], other studies reveal either no association [23, 25, 58] or favor higher HRQoL among women [22, 50, 59]. Although these studies did not target stable clients, they illustrate the complexity of associations between gender and HRQoL. We note across studies that women living in male dominated settings (as is the case in our study) tend to report lower HRQoL when compared with settings where women have social support.

Similar to findings with gender, age reveals intricacies of associations in literature, showing evidence of declining HRQoL with age [54, 55, 57, 59] among PLHIV, as well as improvement or no association [18, 23, 60]. Given that DSD participants in our study were significantly older, our finding a trend of declining HRQoL with age mainly among clinic participants suggests a protective effect of DSD on HRQoL with increasing age. Older adults may enjoy fewer social ties than younger adults and thus reap a larger emotional benefit from DSD. As the PLHIV population on ART ages and comorbidities increase, emotional support will become increasingly important and DSD could serve as a springboard for additional interventions.

Context such as place of residence has been associated with HRQoL in LMIC [20, 21]. Our study showed that urban participants had higher HRQoL scores across most domains than did their rural counterparts. Better living conditions, greater awareness about HIV, and the anonymity people generally enjoy living in an urban setting likely creates a less-stigmatizing space for PLHIV. Our findings that educational level, employment, and income level was not associated with HRQoL however differs from reports in the literature which associates a better HRQoL among PLHIV with a higher level of education [18, 20, 53–55]; with employment [19, 59, 61] and relatedly to higher income levels [19, 62]. The prevailing socio-economic circumstances which are similar among participants irrespective of setting could provide an explanation.

Despite viral suppression, HIV infection predicts suboptimal HRQoL [9, 25]. The assumption of 'normalcy' in all areas as PLHIV attain viral suppression may be ambitious especially in the context of stigma, living in socio-economically difficult circumstances, or with other chronic illnesses. The need to do more in these areas has been advocated especially for PLHIV in the rural areas, for women, and adolescents, and young people living with HIV [18, 24, 25, 61, 63].

Strengths and limitations

Our study is among few HRQoL studies conducted recently in SSA in the era of DSD. It provides useful insights into factors influencing HRQoL in an African population. Our participants were drawn from different geographical settings that mimic the reality of our population and generated valuable information about the impact of DSD in these settings. Though observational with

Table 2 Logistic regression with robust variance: Multivariable association between sociodemographic, HIV care, and service access variables and satisfactory FAHI QoL scores#

	FAHItotal		PWB		EWB		SWB	
	Clinic	DSD	Clinic	DSD	Clinic	DSD	Clinic	DSD
Sociodemographic	Odds ratios and confidence intervals							
Sex	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Female	2.59**	1.11	1.02	0.71	1.39	0.87	1.98*	1.95
Male	1.36–4.92	0.49–2.51	0.51–2.04	0.31–1.62	0.83–2.33	0.36–2.12	(1.14–3.43)	(0.89–4.27)
Age								
18–25	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
25–35	0.16	1.15	0.17	2.12	0.61	0.18	0.33	1.32
	0.02–1.43	0.01–22.62	0.02–1.55	0.11–39.4	0.20–1.83	0.00–1.45	(0.08–1.34)	(0.11–15.78)
35–45	0.0.09*	1.33	0.17	2.86	0.62	0.43	0.21*	1.19
	0.01–0.78	0.07–23.91	0.02–1.52	0.18–46.3	0.21–1.84	0.00–3.28	(0.05–0.84)	(0.11–12.91)
45–55	0.06*	0.62	0.16	1.29	0.49	0.16	0.26	0.67
	0.01–0.59	0.03–11.3	0.02–1.56	0.08–20.7	0.15–1.58	0.00–1.27	(0.06–1.09)	(0.06–7.40)
55–65	0.08*	0.55	0.25	1.78	0.81	0.14	0.33	1.08
	0.01–0.85	0.03–10.5	0.02–2.82	0.10–31.3	0.21–3.05	0.00–1.11	(0.07–1.63)	(0.09–12.82)
> 65	0.04*	0.36	0.05*	0.58	0.58	1.19	0.35	0.76
	0.00–0.52	0.02–7.96	0.00–0.59	0.03–11.2	0.11–2.98	0.01–1.17	(0.06–2.12)	(0.05–10.43)
Education								
None	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Primary	1.18	0.8	0.74	0.65	0.98	0.87	1.33	0.23**
	0.62–2.20	0.33–1.93	0.35–1.52	0.26–1.61	0.57–1.69	0.32–2.36	(0.76–2.31)	(0.09–0.58)
≥ Secondary	0.43	1	0.31	1	0.77	1	0.96	0.59
	0.12–1.60		0.07–1.32		0.24–2.52		(0.28–3.30)	(0.05–6.44)
Marital status								
Single	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Married	1.98	2.22*	2.22*	3.92*	1.77	1.49	4.08**	4.93**
	0.96–4.07	0.89–5.50	1.01–4.89	1.37–11.2	0.95–3.30	0.53–4.12	(2.11–7.87)	(2.06–11.75)
Separ/Divorc/Wid	1.72	1.53	1.54	1.53	1.26	0.73	1.91*	6.35**
	0.85–3.49	0.62–3.79	0.71–3.30	0.63–3.76	0.68–2.33	0.26–2.00	(1.04–3.52)	(2.60–15.53)
Employment								
Unemployed vs Employ			Ref.	Ref.				
			1.44	0.39				
			0.58–3.56	0.14–1.14				
Income level								
< 100,000	Ref.	Ref.			Ref.	Ref.		
100,000–300,000	0.45*	0.43			0.48**	0.6		
	0.24–0.84	0.18–1.02			0.28–0.82	0.22–1.62		
> 300,000	1.09	0.28*			0.46*	0.23*		
	0.43–2.79	0.11–0.78			0.23–0.91	0.07–0.77		
Location								
Bugisi	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Ngokolo	1.88	4.72**	3.05	3.94*	4.81**	17.1**	0.94	3.79**
	0.74–4.81	1.70–13.13	0.94–9.89	1.34–11.5	1.86–12.42	4.63–62.8	(0.45–1.98)	(1.62–8.86)
Wait time mins	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
< 90 min	0.9	0.23**	0.89	0.43*	0.64	0.05**	0.75	0.24**
> 90 min)	0.47–1.73	0.11–0.47	0.44–1.79	0.21–0.92	0.37–1.10	0.02–0.12	(0.42–1.32)	(0.12–0.48)

*p < 0.01; **p < 0.001. # See Additional file 1 for table with FGWB and CF domain results.

Table 3 Contribution of sociodemographic, HIV care, and service access factors to variance observed in HRQoL scores

Variance explained by three-factor categories (N = clinic vs DSD)	FAHItotal		PWB		EWB		FGWB		SWB		CF	
	Clinic	DSD	Clinic	DSD	Clinic	DSD	Clinic	DSD	Clinic	DSD	Clinic	DSD
*Step 1 R^2 (n = 378 vs 251)	0.102	0.229	0.103	0.205	0.085	0.184	0.119	0.222	0.118	0.217	0.059	0.058
^Step 2 R^2 (n = 351 vs 226)	0.145	0.289	0.146	0.243	0.114	0.268	0.169	0.253	0.139	0.258	0.091	0.086
#Step 3 R^2 n = 345 vs 223	0.149	0.435	0.149	0.302	0.185	0.534	0.167	0.297	0.148	0.351	0.098	0.099
AIC Step 3	8.803	8.692	5.969	6.077	6.603	6.415	6.258	6.63	6.723	6.523	4.034	4.081

*Step 1—Contribution of sociodemographic factors to variance observed; ^Step 2—Contribution of HIV care factors to variance observed and #Step 3 – Contribution of service access variables to variance observed from Hierarchical Multiple Linear Regression. Additional file 2 shows the regression coefficients for variables included in the models in steps 1–3.

known biases, the analytical design of our study allowed for comparisons that produced a rich resource useful for informing implementation and policy.

Clinic participants were selected for stability as defined by the Tanzanian guideline at the time of data collection while DSD participants were assumed to be stable. This might have biased our results in favor of clinic participants, however, viral load-related variables were similar in both groups and not independently associated with HRQoL in our study.

The project sites were mission clinics which may limit the generalizability of our findings. However, we might expect that larger differences in HRQoL scores would be found when comparing DSD and clinics outside the mission hospital setting, as better funding and service which characterize our setting likely obscured the effect of DSD.

Conclusion

Our results reveal comparable HRQoL between clinic and DSD participants. The similarity was also observed across HRQoL domains only differing in the PWB and EWB domains where clinic participants score higher. Better HRQoL was associated with being male among clinic participants and with being married, urban residence and shorter duration of wait during service access among DSD participants. While DSD shows promise in improving acceptability among clients and, therefore, the sustainability of such services, our research highlights future areas to explore to further improve HRQoL among PLHIV. Service providers will need to engage PLHIV and the community at large to identify supporting interventions relevant for adapting acceptable DSD interventions to maximize their benefit.

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Authors contribution NEO, GBG, SH, DN, and TRW contributed to the conceptualization and design of the study. NEO conducted the field study and data collection. ONE was responsible for data analysis and interpretation with guidance from DN. NEO, GBG, SH, JdK, TRW were all involved in the interpretation of the results. TRW was responsible for the overall scientific management of the study. NEO wrote the initial draft of the manuscript. All authors contributed to drafts of the manuscript, read, and approved the final version.

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Availability of data and materials The dataset used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval Ethics approval for this research study was obtained from NIMR i.e. NIMR/HQ/R.8c/Vol. I/674. Written consent was obtained from individuals who agreed to participate in the study using appropriate forms that had been approved for the same as part of the ethics application.

Consent for publication Not Applicable.

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PAPER

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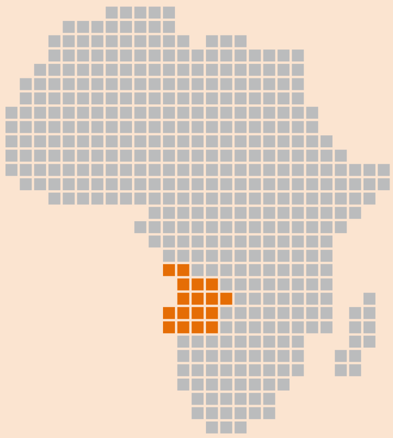

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Improving TB Surveillance and Patients' Quality of Care Through Improved Data Collection in Angola: Development of an Electronic Medical Record System in Two Health Facilities of Luanda

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TB Programs should promote the use of digital health platforms, like Electronic Medical Records (EMR) to collect patients' information, thus reducing data incompleteness and low accuracy and eventually improving patients' care. Nevertheless, the potential of digital health systems remains largely unexploited in low-resource settings. Angola is one of the 14 countries with a triple burden of TB, TB/HIV and MDR-TB (multidrug-resistant TB) and it is among the three countries, together with Congo and Liberia that have never completed a drug-resistance survey so far. The Sanatorium Hospital of Luanda and the Tuberculosis Dispensary of Luanda are the two reference health facilities in Luanda dealing with most of the TB cases, and they both rely entirely on paper-based data collection. The aim of this paper is to describe a three-stage process for the development of a TB EMR system in these two health facilities of Luanda and to share the lessons learned. The description is focused on the activities that took place from March 2019 to January 2020. Main lessons learned were identified in the importance of engaging all the stakeholders in the development process, in the mainstream of the "think digital" transition, in the promotion of a monitoring and evaluation (M&E) culture and in the planning of the system's sustainability. This approach may be replicated in similar contexts where the development of a TB EMR system is sought, and the lessons learned could assist and facilitate the programming of the interventions.

Keywords: TB, surveillance, Angola, Electronic Medical Record (EMR), quality

INTRODUCTION

The Tuberculosis (TB) pandemic, including its multidrug-resistant (MDR-TB) form, is a global health threaten. TB is one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent. An estimated 10 million people fell ill with TB in 2019 and 1.2 million people died (1).

The WHO End TB Strategy aims to end the global TB epidemic, with targets to reduce TB deaths by 95% and incidence by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic expenses due to TB (2). In the years 2015–2019, TB incidence rate dropped by 9%, however this was less than halfway to reach the End TB Strategy milestone of 20% incidence reduction between 2015 and 2020 (3).

To achieve the End TB strategy goals and improve patients' management, effective surveillance systems are needed to measure and monitor the burden and the determinants of the disease. Implementing a functional TB surveillance system often remains challenging in many low- and middle-income countries (4). TB programs should promote the use of digital health platforms to collect patients' information, to reduce time and efforts to fill paper forms and to avoid common mistakes like data incompleteness and low accuracy. Digital health interventions can strengthen surveillance and monitoring, program management and ultimately patients' care (5).

Introducing a new digital health system needs an enabling environment and to deploy a formative stage to document bad and good practices, pivotal for the uptake of the new system (6). Therefore, a comprehensive approach is required, that starts with gaps and needs identification and the description of the patient's pathway for TB care (7).

Angola is among the 14 high burden countries for TB, TB/HIV and MDR-TB prevalence and is among the three countries, together with Congo and Liberia, that have never completed a drug-resistance survey so far (1). Moreover, according to the WHO country profile, Angola had a treatment success rate of 25% in 2017, much lower as compared to a pooled rate of 76.2% in sub-Saharan Africa countries in the last decade, according to a recent systematic review (8).

The Angola TB network is made of Sanatoriums, TB Dispensaries (DAT), Diagnostic and Treatment Units (UDT with smear laboratory), and Treatment Units (UT without smear laboratory). The TB surveillance system in Angola is weak, with main gaps regarding cases notification, data reporting and elaboration, and quality of data collected (9). The Angolan TB National Program (PNCT) uses a digital database to collect aggregated data from the network, however countrywide TB facilities continue to rely on paper-based tools leading to incompleteness, poor accuracy of data and delays in reporting. Therefore, it is imperative to enhance data collection and management in order to strengthen TB surveillance, programmatic decisions and patient's management. To this purpose, the implementation of user-friendly Electronic Medical Record (EMR) systems could improve data quality and strengthen the continuum of care by ensuring adherence to clinical guidelines and reducing errors in data recording and reporting. A study based in Malawi documented the positive outcomes of a point-of-care EMR system for HIV-TB patients in a public clinic (10). In Rwanda the use of EMR data for evidence-based clinical decisions improved HIV patients monitoring (11). A study in Kenya reported significant improvements in data quality through the implementation of a cloud-based EMR system for maternal and child health (12).

A systematic review showed that the factors that challenged the widespread use of EMR systems in Sub-Saharan Africa were the high costs of procurement and maintenance of the EMR system, poor implementation planning, issues with electricity supply and internet connectivity, and user's limited computer skills (13). Strategies such as phased implementation planning, financial sustainability, appropriate EMR system and training of users, showed positive results in EMR systems implementation.

CONTEXT

Luanda is the capital city of Angola with one-third of the Angolan population living in conditions of overcrowding and poor sanitation. Luanda has the highest TB mortality rate in the country (13.9*100.000 inhabitants) and 245 MDR-TB cases over 534 (46%) notified at country level in 2018 (14). A recent study also showed that in Luanda chronic diseases like diabetes are an important comorbidity for TB patients (15).

The Sanatorium Hospital of Luanda (HSL) and the Anti-Tuberculosis Dispensary (DAT) of Luanda are the two reference health facilities in Luanda dealing with most of the TB cases, and being also reference centers for the diagnosis and management of MDR-TB (HSL) and provincial reference center for the PNCT (DAT). These two health facilities collect clinical and surveillance data entirely on paper medical records and registries and this may result in poor quality of data and ultimately poor patients' care.

The project "Stop TB and TB/HIV in Angola: Improving Access to TB and HIV treatment by enhancing diagnostic quality and patient management in the Province of Luanda" funded by the Italian Cooperation Agency (AICS—Agenzia Italiana per la Cooperazione allo Sviluppo) and implemented by the Italian non-governmental organization "Doctors with Africa CUAMM" with the technical support of the "Italian National Institute of Health" (ISS) aimed at improving the quality of diagnosis and management of TB and TB/HIV patients at the HSL and the DAT of Luanda. The project, among other activities, included the development of a TB EMR system, based on an enhanced TB medical record and the setting up of software and hardware features, to be piloted in the two health facilities. The EMR system development was a three-stage process and included first a situation analysis, second the development of an enhanced medical record and finally the development of the EMR system. The situation analysis supported the identification of the patients' flow and actual gaps and needs in data recording and reporting at the HSL and the DAT of Luanda. The results of the situation analysis were used to develop an enhanced medical record that aimed at filling the gaps and needs identified, and finally in the development of the EMR system. The process was consolidated through a workshop for the staff of the two health facilities (around 40 people) involved in the data collection with the double aim of promoting awareness about the importance of data quality and getting acquainted with the TB EMR system.

The aim of this paper is to describe the three-stage process for the development of the EMR system and share the lessons learned. The description is focused on the activities that took place from March 2019 to January 2020.

TABLE 1 | SWOT analysis.

Strengths	Weaknesses (areas of improvement)
Key stakeholders' commitment to the EMR system development and implementation; Previous similar experiences to benefit from; Presence of local technical expertise to draw upon.	Suboptimal data collection and management, and ultimately patients' care; Manual for clinical and programmatic management of TB and MDR-TB only available as an electronic draft, and not widely distributed (at the time of the study); Gaps and delays in the reporting process; Poor data/information quality; No M&E functioning system.
Opportunities	**Threats**
Window for capacity building initiatives; Reducing workload of HCWs related to paper-based data collection; Strengthening national surveillance system; EMR system could be scaled up in other health facilities and for community follow-up.	Disturbance of daily activities during the system roll-out; HCWs poor digital skills; HCWs high workload; System uptake resistance; Financial sustainability.

The process could be replicated in other health facilities in Angola and other similar contexts to improve TB surveillance, control and quality of care, to boost the achievement of the WHO END TB strategy.

STAGE 1: LAY THE FOUNDATION FOR THE EMR SYSTEM DEVELOPMENT

Stakeholders' Engagement

A series of meetings, interviews, site visits and observations were arranged involving local stakeholders in order to engage them in the design of the EMR system and to promote ownership and sustainability of the system. Representatives of the Ministry of Health and local authorities, key staff of the two health facilities, health care workers (HCWs), international organizations and other local NGOs with similar experiences were involved in this step, to gain their insights and recommendations, discuss perceived barriers and come to a consensus on a plan of actions for the implementation of the EMR system and ensure its adherence to the national guidelines. The process involved around 20 stakeholders that were constantly consulted along the duration of the project.

Situation Analysis

From March to September 2019 the EMR expert team, including two epidemiologists from the Italian National Institute of Health, CUAMM project manager, a TB specialist consultant and a software developer consultant, conducted specific site visits at the two health facilities to gain full knowledge and understanding of the patients' flow and data collection system. The final aim was to design a user-friendly EMR system that could meet the stakeholders needs, while improving data collection and reporting. During the visits, the TB patients' flow was analyzed from the entrance to the discharge and the data collection points, established by the health facilities in accordance with the patient's assistance and care pathway, were identified and described, including the data collection tools in use.

Interviews with key staff and HCWs at the two health facilities were also carried out to feed their suggestions into the development of the EMR system. A purposive sample of data was collected and analyzed with the aim of assessing the quality of the information collected.

The situation analysis allowed to identify strengths and weaknesses of the current data collection system in the two health facilities and to define areas of improvement. Moreover, this stage identified opportunities and threats to the implementation of the EMR system.

Strengths, weaknesses, opportunities, and threats (SWOT) that resulted from the situation analysis are reported in **Table 1**.

Areas of Improvement (Weaknesses)

Data collection and reporting presented some gaps and inaccuracies, mostly linked to the great flow of data to be collected on paper-based tools, which could also undermine data privacy and security. Main areas of improvement were identified in the use of multiple forms and codes for the same patient that could lead to misinterpretation of data, including patients' identification, or loss of information. In addition, the need to improve the timeliness and accuracy of internal and external reports that rely only on paper-based registers emerged as an important issue, to support programmatic decision-making and TB surveillance. Finally, some cruxes along the pathway of patient's care do not provide for the collection of data, thus some essential information for patients' management is lost.

An adequate M&E system should be implemented, and data/information quality should be enhanced, particularly regarding the quality of patient's information recorded (eg., completeness, readability, numeration etc.,); quality of clinical management of patients' information (eg., bacilloscopy results/timing, HIV test result, body weight etc.,); quality of data flow information (eg., timing of internal reports, coherence between registries and reports, reports availability etc.,). As an example, patients that do not perform bacilloscopy (BK) are often reported as BK negative, while they should be reported as not assessed. Reported cases of relapses are very few, raising the question that relapses might be often treated as new cases without ascertaining the possible development of a resistant form of TB. The final treatment outcome is most of the time absent in the registries, possibly linked to the poor patient's follow-up.

At the time of visiting the facilities there was no updated TB manual providing consolidated guidelines about recording and reporting procedures, which might at least partially explain the occurrence of the shortcomings noticed above. The same can be said for the management of MDR-TB.

TABLE 2 | Examples of indicators of weaknesses in the current data collection system and the correspondent EMR system response.

Weakness (areas for improvement)	EMR system response
Lack of registration of the patients dismissed after the first visit because not considered suspect TB cases. The whole facility workload is therefore missing.	All the patients are registered at their 1st access to the health facility.
Use of multiple forms and codes for the same patient.	Univocal code, univocal record saved indefinitely and accessible from each established data collection point.
Delays and incompleteness of internal and external reports.	Specific reporting feature of the system to ensure delivering of internal and external reports in accordance with the requirements of the national reporting system.
Poor or inexistent data collection system at some cruxes of the patient's care pathway.	All the needed data collection points of the patient's care pathway are included as active units of the EMR system.
Data quality.	Guided choice, mandatory answers, improved M&E system.

The areas of improvement identified suggested the need to enhance the medical record currently in use and refine the current data collection and reporting system, to improve patients' management and quality of care (**Table 2**).

STAGE 2: ENHANCING THE TB MEDICAL RECORD

After discussing the gaps and needs of the current data collection system emerged during the situation analysis, the EMR expert team fed the results in the elaboration of an enhanced TB medical record. To this purpose, the two medical records and patients' forms in use at the two health facilities were used as a starting point. The DAT used the standard clinical record adopted by the National TB Program with essential information about diagnosis and treatment. The HSL medical record was based on the National TB Program standard record, but included more information, reflecting its role in the management of complex cases and MDR-TB cases.

A preliminary version of the enhanced TB medical record was discussed with key stakeholders to assess information clarity, content and sequencing, and compliance to national guidelines, and adjusted accordingly.

A formative workshop was arranged in January 2020 in the two health facilities to introduce the HCWs (around 40) to the enhanced medical record and to instruct them about their use for the digitalised data collection. The formative workshop allowed the HCWs to increase their awareness about the importance of data collection for TB surveillance, for the quality of the patient management and to enhance the accuracy of data reported to the National TB Programme for programmatic decisions.

The enhanced medical record is divided into several sections that follow the patient's clinical pathway (**Table 3**).

STAGE 3: SETTING UP THE EMR SYSTEM

The EMR expert team fed the results of the situation analysis and the contents of the enhanced medical record in the design of the EMR system. Software and hardware components were defined, according to the stakeholders' needs and recommendations. The EMR system has been designed as a real-time, point-of-care, internet-based system based on open-source software that employs C# and Java language and the MSSQL server 2017. The system is available in Portuguese and English. Although the system is web based, and it allows to work online and offline, so far it has been configured to be used on a LAN (Intranet) at the health facility level in offline modality only.

The system is accessible only to authorized staff that has been provided with username and password and keeps an audit trail by tracking users, locations, and time for all the accesses. Data is encrypted during offsite data back up using secure encryption protocols. The system owns the technical features needed to communicate with the District Health Information Software 2 (DHIS2) (16), the Health Management Information System that is increasingly being used by the TB National Program for aggregate data reporting. The system can produce internal and external reports according to formats and indicators in use in the two health facilities and within the TB National Program. Multiple testing sessions assessed the usability of the EMR system.

A print screen of the EMR system is shown in **Figure 1**.

LESSONS LEARNED

The following lessons learned were collected during the project, through a continuous consultation process with the stakeholders involved.

Engage the Stakeholders

Local stakeholders were identified as the representatives of local health authorities, key staff and HCWs of the two health facilities and other TB health facilities, representatives from international organizations and NGOs working in the same area. Engaging all the stakeholders in an inclusive process allowed to promote the ownership and buy-in of the final product and its sustainability, to encourage trust among all the actors, to share a common vision about how to overcome the challenges and to identify capacity building needs (10).

Introducing innovation in information systems needs to be supported by an enabling environment, since it could be perceived by the final users more as a challenge than an advantage, unless tangible benefits are clearly communicated (17). As an example, all the stakeholders agreed that the reporting process was time-consuming, resulting in delays and inaccuracies, therefore the new EMR system aimed at simplifying

TABLE 3 | Enhanced TB medical record sections description.

Medical record sections	Section description
Patient registration and socio-demographic information.	All the patients are registered, also patients without clear TB symptoms. The registration also includes the attribution of a univocal patient number that will follow him/her throughout the clinical course. Socio-demographics data are collected.
Patient classification and clinical information.	Patient classification (new, retreatment, transferred) and related information is recorded, together with main TB symptoms, signs, risk factors (contact with a TB case, MDR-TB cases among the relatives, HIV infection and therapy, diabetes, pregnancy, smoke, alcohol) and body weight.
First medical consultation outcome.	Based on the clinical assessment and the evaluation of risk factors during the first visit, patients could be defined as ≪suspect TB case≫ and referred for diagnostic confirmation or hospitalization. If the patient is not a TB suspect, the diagnosis and therapy are reported in the medical record, that is subsequently closed.
Diagnostic information (laboratory and radiology).	Results of bacilloscopy, GeneXpert, culture, antibiogram, RX, biopsy, HIV test, clinical biochemistry are reported. For the bacilloscopy, reasons for not performing the test need to be specified.
Case classification.	Following the diagnostic process, the TB diagnosis is confirmed or excluded. The TB case is further classified according to the pulmonary or extrapulmonary location and to the presence of HIV co-infection. Contacts of people living with the patient are recorded, to promote active case finding.
Treatment plan.	Type of treatment according to the national guidelines, dosage, starting and end date and observations are recorded.
Therapy follow-up.	Date, type and quantity of medications delivered to the patient along the course of treatment are recorded. Also, patient's eventual delay and reason, and treatment compliance are recorded, in order to determine the next date for the delivery of medications (this will be automatically calculated in the EMR system).
Follow-up consultations.	During follow-up consultations (2, 5, 6 months for drug-sensitive TB and every month for 20 months for MDR-TB), therapy compliance, symptoms, side effects, weight monitoring and observations are recorded.
Diagnostic follow-up (laboratory and radiology).	Follow-up results of diagnostic tests (bacilloscopy, GeneXpert, culture, antibiogram, RX, biopsy, HIV test, clinical biochemistry) are recorded.
Treatment outcome.	Treatment outcomes according to national guidelines are reported.

the process while improving the quality of the data reported. In addition, the stakeholders agreed to the fact that the time spent by the HCWs recording data on paper-based forms and registries, could have been better employed for the management of the patients and for improving the quality of care.

The stakeholders were engaged during the whole process and were consulted at each step, to consult with them about the best strategy to meet their needs. This allowed to enhance the medical record with the information they needed to improve the management of the patients. The patient socio-economic and clinical data were enriched, and even if this may increase the duration of the first visit, the information collected will enable a better care of the patient. The pilot of the system should take this aspect into consideration to find an operational balance.

Mainstream the "Think Digital" Transition

Digital health is a cultural transformation, mostly in low- and middle-income countries, where technology is not yet fully exploited. Local stakeholders endorsed the digital transition and "think digital" promoters in the two health facilities were asked to endorse the digital health cause and to provide evidence of the benefits to the other HCWs (4). These promoters started to support HCWs of the two health facilities few months before the EMR system piloting, in order to guide them to a smooth transition to the digital system and highlight the gaps that the EMR system could fill.

Challenges to the "think digital" transition were mostly identified in the poor digital skills of the HCWs and resistance to the new system due to previous negative experiences. To address these challenges, the EMR system was developed as an easy-to-use system, with a simple interface to reduce complexity. Standard desktop computers with large screens were bought and a basic IT training has been planned at the beginning of the piloting phase to uniform digital skills of the HCWs. Continuous training on the job activities and a stepwise rollout of the EMR system during the piloting stage was planned to allow the HCWs to adapt to the transition from a paper-based system, without causing any disruption to the daily activities.

The development of the EMR system had to be gradual, to have all the stakeholders on board and feed all the recommendation in the process. The organizational leadership of the two health facilities supported the development of the system and addressed critical issues that arose during the process.

Promotion of an M&E Culture

The situation analysis showed the importance of strengthening the monitoring and evaluation system and culture, particularly the quality and the regular evaluation of the data collected. Moreover, it highlighted the necessity to define roles and responsibilities for M&E activities. From the meetings with local stakeholders and HCWs of the two health facilities it was evident that awareness-raising activities about the importance of data quality for TB surveillance and patients' care, should be regularly performed.

Highlighting the practical advantages of the EMR system for data accuracy and timeliness during the recording and reporting

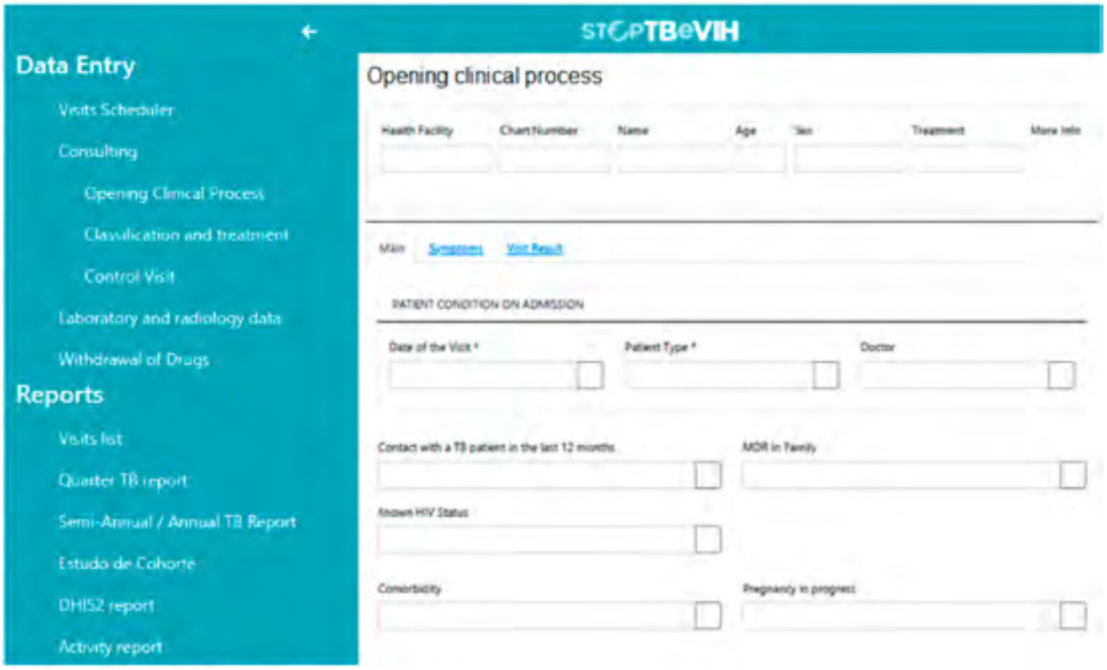

FIGURE 1 | EMR system print screen.

to the National TB Program, was a strong argument that allowed to sow the seeds for an M&E and accountability culture to grow among the stakeholders. Another opportunity to promote M&E culture was to identify M&E champions among local stakeholders and in the two health facilities, to encourage their peers to effective data collection, monitoring and evaluation. The M&E champions were seen by the staff of the two health facilities as a valuable support to improve their M&E and data quality skills. Linking the concept of data quality to a better management of patients, to a reduced time in reporting and to an improved functionality of the facility allowed the HCWs to consider data quality as a priority. The M&E culture promotion will continue to be strengthen during the planned training on the job activities during the the piloting stage of the EMR system.

During the formative workshop in January 2020 in the two health facilities, HCWs were introduced to the importance of accuracy, transparency and accountability of data collected and reported to improve TB surveillance, programmatic decisions and clinical management of patients.

Plan for Sustainability

Stakeholders' engagement was the first step toward the EMR system sustainability, in order for them to endorse the ownership and the buy in of the system (18). After the piloting and evaluation phases of the EMR system, the local stakeholders would need to endorse the system running cost that consist in the hardware and software maintenance and possibly in capacity building activities, like training on the job to increase uptake and utilization of the system by the HCWs.

The involvement of local software programmers in the development of the EMR system will allow system improvement and maintenance beyond the project, without the need to involve foreign consultants, and therefore decreasing the costs. As a matter of fact, looking for in-country expertise can promote initiatives that are more likely to be sustainable than those depending heavily on external support (4).

The possibility for the EMR system to be integrated with the DHIS-2 software, conferred to the EMR system the possibility to be extended to other health units in the country. Also, the flexible features of the system, the user-friendly interface and the easy programming language, will allow it to adapt to different needs and skills, therefore increasing its chance of scalability and sustainability.

LIMITATIONS

The situation analysis was done only in two health facilities. Other relevant needs of other health facilities of the Angolan TB Network might not have been considered.

However, the enhanced medical record and the EMR system were developed considering comprehensive needs of all the stakeholders involved, related to the enhancement of data collection and management, in order to allow replicability in other TB services in Angola.

CONCLUSION

This study was a first attempt to promote a digital health intervention in the context of the TB National Program in Angola. The study was a three-stage process. The first stage allowed the identification of gaps and needs in the data collection systems of the two health facilities. The second stage included the development of the enhanced medical record, based on the findings of the situation analysis. The third stage supported the development of the EMR system. The EMR system developed in the two health facilities in Luanda owns all the features to improve data collection, data quality and finally patients' management and could be exported to the other health facilities across the country.

The main lessons learned in the process were to engage all the involved stakeholders since the beginning and during all the stages; to promote the "think digital" cultural revolution; to support the development of an M&E system through all the steps of the data collection flow; to include sustainability of the system among the priorities areas to be discussed before starting the process. The lessons learned were similar to other studies in similar context (10), thus reinforcing their relevance.

Covid-19 pandemic caused severe disruption in the planned activities for the piloting of the EMR system in the two health facilities. Nevertheless, once the health emergency situation will decrease, the system will be piloted, evaluated and refined. According to other similar studies, during the piloting stage of the EMR system, particular care needs to be focused on enhancing the accuracy of the data recorded (19, 20). The evaluation of the EMR system will target the actual impact of the system on data quality and quality of care. Weaknesses related to data collection that were highlighted during the situation analysis, and the compliance to the EMR system requirements, will be assessed. This will also include an analysis on how well the EMR system matches the actual workflow of patients, and if this could be improved to enhance patient's care.

The TB EMR system would be an important tool to be scaled up to other TB services of the Angolan network, allowing to improve data collection and management and finally to strengthen national TB surveillance, programmatic decision-making and patients' quality of care.

DATA AVAILABILITY STATEMENT

The data were retrieved from patients' registries. Requests to access these datasets should be directed to c.robbiati@cuamm.org.

AUTHOR CONTRIBUTIONS

CR, MD, MT, and GM contributed to conception and study design, data acquisition, and interpretation of results and drafting the manuscript. GP and FD contributed to study conception and interpretation of results and revised the manuscript critically for important intellectual content. PS, OL, and JN contributed to data acquisition and revised the manuscript critically for important intellectual content. MS contributed to study conception and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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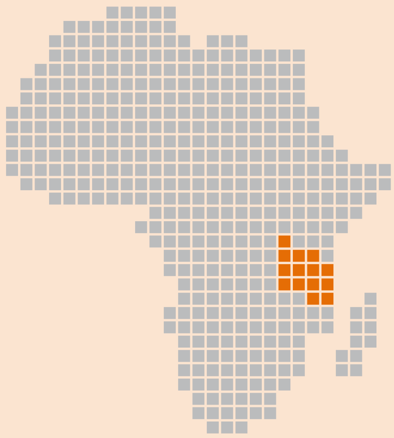
Quality of care in a differentiated HIV service delivery intervention in Tanzania: A mixed-methods study

PAPER



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Quality of care in a differentiated HIV service delivery intervention in Tanzania: A mixed-methods study

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Abstract

Background

Differentiated service delivery (DSD) offers benefits to people living with HIV (improved access, peer support), and the health system (clinic decongestion, efficient service delivery). ART clubs, 15–30 clients who usually meet within the community, are one of the most common DSD options. However, evidence about the quality of care (QoC) delivered in ART clubs is still limited.

Materials and methods

We conducted a concurrent triangulation mixed-methods study as part of the Test & Treat project in northwest Tanzania. We surveyed QoC among stable clients and health care workers (HCW) comparing between clinics and clubs. Using a Donabedian framework we structured the analysis into three levels of assessment: structure (staff, equipment, supplies, venue), processes (time-spent, screenings, information, HCW-attitude), and outcomes (viral load, CD4 count, retention, self-worth).

Results

We surveyed 629 clients (40% in club) and conducted eight focus group discussions, while 24 HCW (25% in club) were surveyed and 22 individual interviews were conducted. Quantitative results revealed that in terms of structure, clubs fared better than clinics except for perceived adequacy of service delivery venue (94.4% vs 50.0%, p = 0.013). For processes, time spent receiving care was significantly more in clinics than clubs (119.9 vs 49.9 minutes). Regarding outcomes, retention was higher in the clubs (97.6% vs 100%), while the

interviews and focus group discussions) contained potentially identifying participants' information and were not included in the dryad dataset. The qualitative data can be accessed upon reasonable request from the Shinyanga T & T project scientific committee through secretariat@aighd.org.

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Competing interests: The Shinyanga and Simiyu Test & Treat program in Tanzania is funded by Gilead Sciences (USA). This does not alter our adherence to PLOS ONE policies on sharing data and materials. [GBG is currently employed by Sanofi Pasteur. Sanofi Pasteur was not involved in any way and did not provide funding for this study]. All other authors declare that they have no competing interests.

proportion of clients with recent viral load <50 copies/ml was higher in clinics (100% vs 94.4%). Qualitative results indicated that quality care was perceived similarly among clients in clinics and clubs but for different reasons. Clinics were generally perceived as places with expertise and clubs as efficient places with peer support and empathy. In describing QoC, HCW emphasized structure-related attributes while clients focused on processes. Outcomes-related themes such as improved client health status, self-worth, and confidentiality were similarly perceived across clients and HCW.

Conclusion

We found better structure and process of care in clubs than clinics with comparable outcomes. While QoC was perceived similarly in clinics and clubs, its meaning was understood differently between clients. DSD catered to the individual needs of clients, either technical care in the clinic or proximate and social care in the club. Our findings highlight that both clinic and DSD care are required as many elements of QoC were individually perceived.

Introduction

Quality of care is at the heart of the differentiated care strategy currently endorsed by WHO for HIV programs. The core principles underlying the approach include client-centeredness and health system efficiency [1], both of which constitute important dimensions of quality [2]. The design of many differentiated service delivery (DSD) interventions reflects these values by prioritizing the needs of clients while considering the health system characteristics. DSD interventions are conducted both within health facilities and the community and rely on formally trained health care workers (HCW), peers, and community health workers (CHW). The involvement of peers and CHW with varying degrees of formal training as an essential part of DSD warrants further investigation to ensure that quality is not compromised.

Community health workers (CHW) have been involved in various HIV interventions before DSD roll-out [3–6]. Their role in DSD varies depending on whether they are supporting or coordinating the specific intervention. In a supportive role, they assist other HCW to provide adherence counseling, distribute pre-packaged antiretrovirals (ARVs), client tracking, documentation, and home visits. As coordinators, they are responsible for facilitating antiretroviral therapy (ART) "clubs" (i.e., small groups of 15 to 30 stable clients who meet at the clinic or community), screening and identifying symptoms of common opportunistic infections e.g., tuberculosis (TB) for upward referral, following up clients who miss appointments, collecting and distributing ARVs to clients. Though good outcomes have been reported with CHW playing these expanded roles, evidence is sparse on the quality of care (QoC) provided in these CHW-led DSD interventions [7–9].

In Tanzania, CHW are involved in health promotional, educational, and rehabilitative interventions but their role beyond these activities, in particular in providing basic curative services, is yet to be formalized. Several studies show promise for expanding CHW roles, but more evidence is warranted [6, 10]. Since DSD limits the frequency of clinical encounters for clients, it becomes pertinent to assure the QoC provided by these lay providers in order not to compromise client outcomes.

Generally, quality underscores the goal of many health systems. However, the complex, subjective and multi-dimensional nature of quality care makes it a difficult concept to define and therefore measure [11]. The Donabedian framework is arguably the most widely used to assess QoC [11, 12]. It promotes a three-pronged approach to assessing QoC encompassing **structure** (characteristics of the care setting and resources available e.g., staff, equipment, supplies, venue), **process** (activities conducted in care provision e.g. time-spent, health screenings, HCW attitude, information), and **outcome** (the effects of care on care recipients e.g. viral load, CD4 count, improved self-worth/confidence and health status) [12, 13].

CHW-led DSD clubs for clients stable on ART (see definition below) have been piloted at the Test and Treat (T&T) project sites in the Shinyanga region, north-western Tanzania, since July 2018. Details of the implementation and research projects have been published elsewhere [14]. This study sought to assess QoC in terms of the sub-themes of structure, process, and outcome of care as outlined by the Donabedian framework. Primarily, we aimed to describe the structures supporting services delivery and the processes of care, to assess some objective client-related outcomes as well as gain the perspectives of clients and HCW, comparing between the DSD clubs and standard clinic care. Our study contributes evidence to the quality and effectiveness of these CHW-led interventions with implications for the scale-up of the DSD strategy.

Materials and methods

Study design and outcomes

A concurrent triangulation mixed-method study design was employed to facilitate the simultaneous assessment of the quality of HIV care employing client-related outcomes and exploring perspectives of both clients and HCW [15–17]. The quantitative part entailed cross-sectional surveys of stable ART clients and HCW in the clinics and clubs. The qualitative part entailed focus group discussions among clients and individual interviews among HCW.

We organized our findings according to the three domains of the Donabedian framework i.e., Structure, Process, and Outcome. Within each domain, we first reported clients' experience of care in the clinic and club, and then the HCW's experience in a similar fashion. In each section, we presented the quantitative, followed by the qualitative findings, as the latter triangulated and provided a deepened understanding of the former. Finally, we summarized the main findings in a joint display table [18].

Study sites

The study was conducted at two HIV care and treatment centers (CTC) owned by the Catholic diocese in the Shinyanga region, Tanzania. Bugisi CTC serves a large widely dispersed population in rural Shinyanga district while Ngokolo CTC serves a peri-urban population in Shinyanga municipality. Both health centers coordinate ART clubs in proximal communities within distances ranging from 3 to 35km. As of June 2019, the time of study commencement and about a year since the commencement of the clubs, there were 46 clubs in total, 25 of which were considered eligible for our study as they had existed for at least 6 months and had a club meeting scheduled within the data collection period (see Table 1).

Study sampling procedure

Stable ART clients were sampled from both clinics and eligible clubs and all HCW providing care at the clinics and clubs. Stable ART clients were defined per the Tanzanian HIV care and treatment guideline as those above five years of age, having received ART for at least six months with $>$95% adherence and no adverse drug reaction or current illnesses [19]. For our study, we included only adults$\geq$18 years old. Sample size calculation for the quantitative part

Table 1. Numbers of interviewed participants per location and data collection method.

	Clinic	Club	Total
Location			
• Bugisi (Rural)	1	16	
• Ngokolo (Peri-urban)	1	9	
Quantitative			
Survey—Clients	378	251	629
Survey—Healthcare workers (HCW)	18	6	24
Qualitative			
Focus Group Discussion (FGD) participants	**23**	**18**	41
• Female	12	9	
• Male	11	9	
Number of FGD with clients	4	4	8
Individual Interviews with HCW	16	6	22

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of the study estimated a total of 334 participants (167 per group), assuming an effect difference of 14% between clinics and clubs using retention in care as a proxy for QoC and an alpha of 0.05 and 80% power [20]. In the absence of an accepted quantitative measurement of QoC, we used retention as a measure for QoC assuming that clients are more likely retained in care when the QoC was acceptable. We defined retention as attendance to the last three clinic appointments/club meetings within the past 9–12 months, given that clubs held quarterly, and the oldest clubs were just about one year old and it was too soon to measure one-year retention across all clubs. Clients were recruited as they attended clinics and clubs for the survey and focus group discussions. At the clinics, a random list of eligible clients scheduled for an appointment was generated on every clinic day. Clients were approached as their number appeared on the random list and those who gave written consent participated. At eligible clubs, all clients were approached during the routine club meetings and those who gave written consent participated. Similarly, all HCW were approached and those who consented were recruited to participate in the survey and individual interviews.

Description of ART club intervention

ART clubs were commenced at the two CTC study sites in July 2018. Stable ART clients living within the same community are invited to constitute clubs. Details of the club model have been described elsewhere [14]. Briefly, under the supervision of the designated nurse, a CHW from the CTC liaises with the existing home-based care worker (HBC) of the community to coordinate club meetings. Club meetings hold every 3 months in community venues selected by members which could be homes, school classrooms, and community halls. At the meetings, the CHW conducts a health talk followed by adherence counseling, weight taking, TB/other infections screening, and drug distribution. Any member with symptoms requiring further investigation was referred to the CTC and the referral was documented appropriately in the club register and client folder.

Description of clinic-based care for stable clients

Stable ART clients who received care in the clinics were seen every 2–3 months at the discretion of the clinician. On clinic days, they go through group counseling/health talk, triage, clinical consultation, and lastly drug pick-up.

Quantitative data collection and analysis

For clients, we adapted an existing instrument, the QoC from the clients' perspective—QUOTE-HIV [21]. The 27-item QUOTE-HIV instrument covers clients' perspectives on generic and HIV-specific aspects of the quality-of-service delivery. Seventeen items were retained as is, four items were combined to make two, four items were rephrased and four items were added to make it more contextually relevant (see S1 Appendix: QoC questionnaire-English & S2 Appendix: QoC questionnaire II-Swahili). For HCW, appropriate questions exploring the structure of care were developed. The Donabedian framework served as a general guide for developing all study questions. Additional data to assess processes and outcomes of care were extracted from client records for the three most recent visits/club meetings e.g., visit attendance, weight measurement, infections/TB screening, referrals, ARV dispensed, adherence assessment, CD4 count, and viral load test and results. Other process-related factors collected in the survey included respectful service and time spent during service.

Clients and HCW participants were characterized and compared between clinics and clubs using the Mann-Whitney test. In terms of the structure of care, the availability of resources for the provision of services was described i.e., human, physical, and financial resources as well as organization and information management. We assigned a value of 0 and 1 to every negative and positive response respectively and summarized percentage scores between clinic and club in the sub-categories. The items in the adapted QUOTE-HIV were categorized in terms of structure, process, and outcome of care as per the Donabedian framework [11]. Proportions of clients reporting their experience of care as "always", "mostly", "occasionally" or "never" across the adapted QUOTE-HIV items were compared between clinic and club according to the Donabedian framework using the Chi-squared test. Main outcomes of care were compared between clinic and club i.e., proportions with suspected opportunistic infection or TB, most recent CD4 count (cells/mm3), and viral load $>$ 50 copies/ml (defined as $<$12 months). To reduce the probability of ascribing an association as significant when, in fact, it was not (i.e., Type 1 error) due to the multiple comparisons made, we lowered the significance level appropriately using the Bonferroni correction. Therefore, considering the 30 variables used in our study and alpha of 0.05, only p values $\leq$ 0.002 were considered significant. All quantitative data were doubly entered, validated, and managed using EpiData software and analyzed using STATA 16 and MS Excel.

Qualitative data collection and analysis

We employed three data collection methods for the qualitative part of the study: focus group discussions (FGD) with clients, in-depth interviews (IDI) with HCW using a semi-structured guide, and a structured observation tool of club meetings. The interview/discussion guide queried participants' perceptions of QoC (structure, process, and outcome), the benefits, and suggestions for improving and sustaining the clubs. The observation guide enabled the detailed articulation of activities in clinics and clubs such as the venue, client characteristics, topics discussed, and interactions among clients and facilitators. Among clients, eight FGD were conducted in Swahili by two trained research assistants with one facilitator and the other taking notes. Participants were sampled from among clinic and club clients who consented to participate in the survey. To facilitate communication, FGD were conducted segregated by sex, four with men alone (two among clinic participants and two among club participants) and the other four similarly with women alone. To make the abstract concept of quality understandable, discussions started asking for participants' preference between two different African textile fabrics "Kitenge", one of which was regarded as highly valuable. Discussions around the reason for preferring one fabric over the other made it easier to introduce the topic of QoC.

Interviews were conducted in either Swahili or English by trained research assistants (see Table 1). Thematic analysis was employed to analyze the qualitative data. An iterative process of reading, transcription, and translation of FGD and IDI memos was used to inductively develop a codebook using the NVIVO 12 Plus software version. In the results inductively derived themes were grouped under the broader Donabedian framework of structure, process, and outcome of care to facilitate comparison between quantitative and qualitative results. Differences in perspective between participants in the clinic and clubs were explored.

Ethical consideration

This study was approved by National Institute for Medical Research, Tanzania (Reference Number NIMR/HQ/R.8c/Vol. 1/674). All participating clients and HCW provided written informed consent for the survey, interview, and audio recording.

Results

Characteristics of study participants

Details of the socio-demographic characteristic of participants comparing between clinic and club in the clients and HCW survey are presented in Table 2. All results will be presented in the order of clinic vs club. Of 629 participants among consenting clients in the survey, 251 (40%) were accessing care in clubs. While females constituted 62.9% of all participants, there were significantly more male participants in clinics than in clubs (41 vs 32%). Over 80% of participants were aged between 25 and 54 years, with the mean age being older in the club. Educational level was generally low with only 5% above primary. The majority were either married or widowed, separated and divorced.

Characteristics of 24 HCW surveyed are provided in Table 2. All HCW who provided care in the clubs accepted to participate in the survey. Across all HCW cadre and on average, clinic staff were older (43.2 vs 32.8 years) and had worked longer in HIV service delivery compared to club staff. All HCW participants had basic primary level education with about half having above secondary level. The number of clients attended to by each HCW at the clinics and clubs varied with an average of 53 vs 27, respectively.

Forty-one stable ART clients consented to participate in focus group discussions, among these, 23 (56%) were clinic participants and 49% were male. Conversely, 22 HCW consented to be interviewed individually, among these, 72% were clinic staff and 50% were male.

Structure of care

Clients. *Quantitative*. Clients agreed that HCW have basic HIV knowledge by affirming the ability of HCW to answer any questions they had about HIV in both club and clinic (75% vs 76%—Table 3). Club participants however had more access, when necessary, via phone to their HCW compared to clinic participants. Only 70% of clients each in both clinic and club confirm always receiving their supply of ARVs, while the rest report receiving ARVs most of the time. Similarly, despite the inadequate space reported in some clubs, more club clients affirmed that there was adequate space in which to discuss confidentially with HCW. Clients in clubs conceded that HCW who deliver services to them have a good relationship with each other (70.9 vs 73.3%).

Qualitative. Related to the structure of care, clients described quality of care in terms of the following themes.

The provision of expertise and support: For clients who attended the clinic, the availability of medicine was considered quality care. This group of clients also described the clinic as a

Table 2. Characteristics of study participants (clients and healthcare workers).

Characteristics	Clients			Health care workers (HCW)			
a. Sociodemographic and clinical profile of Clients				**b. Sociodemographic profile of HCW**			
	Clinic	**Club**	**p-value**		**Clinic**	**Club**	**p value**
Location n, %			<0.001				1.000
• Bugisi	324, 65.8	168, 34.1			10, 55.6	4, 66.7	
• Ngokolo	54, 39.4	83, 60.6			8, 44.4	2, 33.3	
Sex n, %			0.018				0.640
• Female	224, 59.3	172, 68.5			8, 44.4	4, 66.7	
• male	154, 40,7	79, 31.5			10, 55.6	2, 33.3	
Age in years Mean (SD) Age-groups n, %	41.0 (11.2)	46.0 (11.4)	<0.001	Age in years Mean (SD)	43.2 (10.8)	32.8 (9.2)	0.048
• <25	25, 6.6	6, 2.4	<0.001	Age-group n, %	0	2, 33.3	
• ≥25–34	96, 25.1	35, 13.9					
• ≥35–44	137, 36.2	91, 36.3					
• ≥45–54	75, 19.8	62, 24.7		• <25	16, 88.9	4, 66.7	
• ≥55–65	33, 8.7	40, 15.9		• ≥25–55	2, 11.1	0	
• >65	13, 3.4	17, 6.8		• >55			
Educational level n, %			0.801	Educational level n, %			0.514
• No education	97, 25.7	60, 23.9		• *Primary	6, 33.3	0	
• Primary	261, 69.1	180, 71.7		• Secondary	3, 16.7	3, 50.0	
• ≥Secondary	20, 5.3	11, 4.4		• Certificate/Diploma/Degree	9, 50.0	3, 50.0	
Marital status n, %			0.321	HCW cadre n, %			0.410
• Single	94, 24.9	80, 31.9‘		• CHW/HBC/DC	10, 55.6	4, 66.7	
• Married	144, 38.1	78, 31.1		• Nurse/NA	3, 16.7	2, 33.3	
• Separated/Divorced/Widowed	140, 37.0	93, 37.1		• Laboratory Technician	1, 5.6	0	
				• Pharmacy Technician	2, 11.1	0	
Employment status n, %			0.002	• Doctor/MO	2, 11.1	0	
• Unemployed	53, 14.0	60, 23.9					
• Employed	325, 86.0	191,					
Years on ART Median (IQR) Years on ART	3.4 (2.1–5.8)	4.2 (2.2–7.3)	0.001	^Years in HIV service			0.007
• >2 years	90, 24.4	47, 19.3	0.162	• Median (IQR)	6 (3–8.5)	1 (1–2)	
• ≤ 2 years	279, 75.6	197, 80.7					
Time spent during last 3 visits/meeting	119.9 (75.0-	49.9 (33.3-	<0.001	Patients attended daily			0.026
• Median (IQR)	180.0)	76.6)		• Median (IQR)	50 (25–80)	27 (15–30)	

SD—Standard deviation; IQR—Interquartile range; CHW—Community Health Workers; HBC—Home-based Care worker; DC—Data Clerk; NA—Nursing Assistant.
*HCW with Primary education were HBC and CHW;
^The HCW with longer years in service were mostly Doctors and Nurses.

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technical space where laboratory tests for HIV and specialized knowledge on other illnesses were available. In contrast, club participants did not consider the availability of HCW, medicines, and lab tests to define quality care. Amongst both Clinic and Club participants, the provision of adjunct non-medical services such as free breakfast and the prospect of receiving food items and monetary aids had an overwhelmingly positive influence on the perception of quality. Though such services were provided only at the T&T project clinic sites (in some sites to all clients and others only to selected poor clients) and not in the clubs, they were still mentioned as part of quality care by club participants.

Table 3. Structure of care: Clients' perspective on care experience.

	Clinic (N = 378)	Club N = 251	p value
Care experience with HCW from clients' perspective—Clients' survey n, %			
Ensures I get my ARV supply regularly and conveniently (ARV supply)	276, 73.0	179, 71.3	0.640
Can answer any questions I have about HIV (HIV education)	283, 74.9	190, 76.0	0.814
Works well with other health workers (Interprofessional relationship)	268, 70.9	184, 73.3	0.511
I can talk undisturbed during consultation (Confidential space)	297, 78.6	196, 78.1	0.885
Easily accessible by telephone (HCW availability)	162, 42.9	158, 62.9	<0.001
The meeting space is arranged in such a way that no one can hear when I am talking with her in confidence (Confidential space)	272, 71,9	185, 74.1	0.554

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"Service (in the club) is good but if they will have a chance, they can give us nutritional support like flour, sugar, and cooking oil. Because for other people it is difficult to have all of these needs, it is a great problem, because of economic status although we are different in the ability to working."

Male club participant

Clinic decongestion: The decongestion of the clinic was mentioned by club participants as the motivation for club preference, but club members also choose the club because it saved travel time and therefore allowed time for other activities and also saved travel costs

"First the congestion, we also get time in the morning to do all the work then come to the club in the evening, you get good services, there are no congestion issues like before (in the clinic)"

Female club participant

The role of venue: While no specific reference was made to aspects of physical space as an issue in the clinic, it was important for clients to have a venue that was permanent and could assure confidentiality. Club clients mentioned that the venue can be a place in the community but could also be a room in the clinic that does not arouse suspicion when clients visit. The infrastructure of the clinic was seen as safeguarding privacy, where clients were not known to other community members and for clinic clients, this was a reason not to transfer to clubs. We found that more male participants opted to continue clinic-based care than ART clubs (40.7 vs 31.5% see Table 2) because they did not feel assured of confidentiality in the venues used for club meetings within their community.

"I will not join a club because in the street [village] is not good, I'm receiving good service here. In villages, it will be like an advertisement"

—Male clinic participant

The same value of privacy pertained to club participants but was solved by selecting a venue in the village where it is 'normal' to see people going in and out, such as the HBC's house which is a regular meeting space for many groups.

"We are taking/picking drugs inside the house [of the HBC], a venue [like this] is good it looks like we are coming to this family for normal issues"

—Female club participant

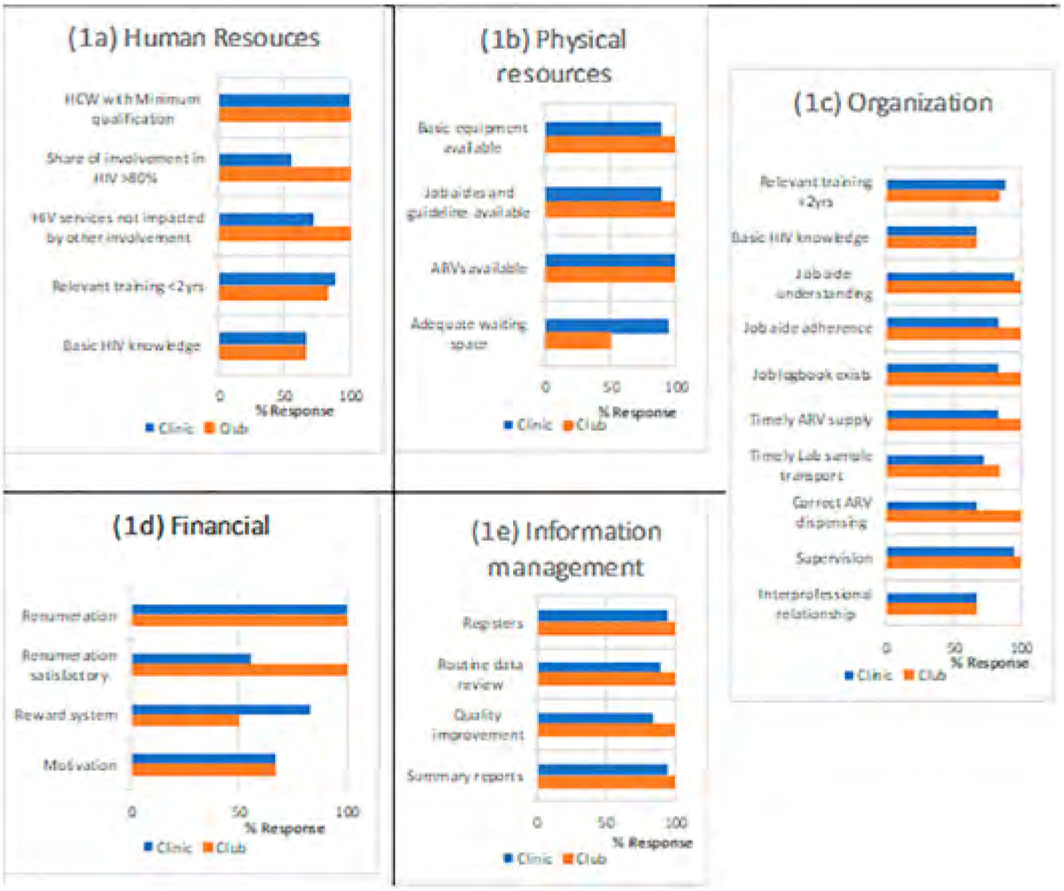

Fig 1. a-e: Structure of care: Health Care workers perception.

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Healthcare workers. *Quantitative.* The possession of minimum job qualification required was comparable between clinic and club staff. Over 80.0% of participants received some form of training in the past 2 years equipping them for their duties, many of which were on-the-job. While all club staff reported maximum involvement in HIV services, 56% of clinic staff reported >80% involvement in HIV services with 72% of those affirming that involvement in other departments did not affect the quality of HIV services they provide. Basic HIV knowledge as well as receiving relevant training within the last two years was similar across clinic and club (see Fig 1a).

All club staff affirmed the availability of basic equipment, materials, job aids, and guidelines required to do their jobs while only 89% among clinic staff affirmed comparably. Adequate ARV availability was reported in clinic and club alike. While sitting and waiting space was reported as adequate in the clinic, in about half of the clubs (94.4 vs 50%), staff reported inadequate space for club meetings (see Fig 1b).

All club staff affirmed understanding, adhering to guidelines, and documenting job done, compared to a slightly lower percentage of clinic staff (all $p > 0.05$). A similar trend was observed in the timely supply and correct dispensing of ARV, timely transportation of laboratory samples, and periodic supervision for job support. Satisfactory inter-professional relation with a clear understanding of the system in place for conflict resolution was comparable between clinic and club though reported by only two-thirds of HCW (see Fig 1c).

While all HCW reported receiving regular remuneration (see Fig 1d), only about half of clinic staff admitted to being satisfied with their pay. Club staff, who were mostly project staff and likely receiving higher remuneration than their clinic counterpart still gave figures much higher than their current pay as their ideal salary expectations. Though reporting satisfaction with their pay, motivation to continue performing on their job among club staff was similar with clinic staff at only 67%. A higher percentage of clinic staff were aware of a reward system to motivate high-performing staff.

The data management system was largely paper based for both the clinic and club. HCW admitted to documenting client information in registers and making summary reports which are shared usually quarterly with the regional authorities. Routine data review by all HCW to identify areas for quality improvement was also comparable between clinic and club (see Fig 1e.–all $p > 0.05$).

Qualitative. Related to structure of care, HCW described quality of care in terms of the following themes:

Specialized skills: The clinic had different cadres of health care workers (nurses, clinicians, etc., while the clubs had only community health workers overseen by a club nurse. Quality HIV care was described in terms of having different HCW with specific specialized skills to attend to clients in the clinic, and having HCW tasked to provide tailored care in the club:

> "First, I think I can say a person may come sick and get served concerning what problem he mentioned like for example he says he has a stomach ache, this and this, but then the doctor sees that according to the explanations, then he will have to check this and this, you then go to the laboratory, then later you get the results and according to those results, the doctor writes down the medicines to be taken for that problem and you go to the pharmacist and you get the medicine then that is quality service. . .as such excellent service is the one when you reach and explain yourself is what you go and test and then get the right results, get the right dose, I think that is excellent service"
>
> —*Male clinic HCW*

Clinic decongestion, and venue: HCW in the clinic noted the decongestion of the clinic since the roll-out of clubs as good for facilitating quality care. In the clubs however, HCW mentioned the need for more permanent venues spacious enough to ensure confidentiality.

Training, collaboration & inter-professional relationship: Clinic and club staff felt they had enough supervision and support to perform their duties and had good working relations and mutual respect irrespective of cadre.

> "Everyone performs his/her duty as per her/his level, if my level is the nurse or the client I will treat them depending to their levels, I cannot do what is out of my order/level, maybe if I go and give the client medicines that is impossible, the order must be followed, when he reaches and is sick I will look for his file then take him to the doctor and the doctor will do her/his responsibilities so we collaborate and work together"
>
> *Male clinic HCW*

At the same time, both clinic and club participants felt that continuous training was important. HCW said the quality of their care would improve with increased salary and more off-site training opportunities

"First of all, of course, a satisfactory salary is important. The second one we must have a lot of training seminars yes because for six eight-nine months [we were] without any training"

Male clinic HCW

Real-time documenting: Documenting the services rendered in appropriate registers or client folders was part of routine service delivery for HCW. Real-time documentation, meant to curtail the cycle of missing or invalid documentation was cited as an important part of providing quality service, as was having a structured and organized filing system. This was however lacking sometimes.

"The filing system, for example currently you can go look for a file but won't get it, it doesn't have any label, they are just there for a new person to get a file it takes a long time"

Female clinic HCW

Process of care

Clients. *Quantitative*. From the clients' perspective (see Fig 2a), regarding the practice of care, more clients confirmed the care process in clubs to be both time-saving—clinic vs club (65 vs 79%) while making enough time for personalized caregiving (72 vs 80%).

Most clients in clubs admitted getting referrals when necessary and data extracted from the records also confirm that most clients (93%) of club clients screened eligible received appropriate referrals to the hub. This is excluding women who became pregnant while in the club, who were all referred back to the hub.

Clinic participants see the clinician during a visit while club participants are referred to the clinic.

On average, time spent in the clinic was over double that spent in the club (119.9 vs 49.9 minutes), thus affirming the time-saving manner of service provision in clubs (see Table 4).

Information related activities were perceived comparably by clients e.g., while more clinic clients agreed that their HCW tell them anything they want to know about their health (67.9 vs 64.5%), more club clients stated that their HCW explained benefits, side effects, and prevention strategies (71.2 vs 73.3%—see Fig 2a).

Health monitoring screenings e.g., the proportion of clients who had weight measurements and adherence assessment were comparable in clinic and club. A shortfall was seen in the proportion of clients documented as screened for OI or TB in the club (85.4 vs 78.5% $p = 0.024$). The proportion of clients who had a recent viral load test done (99.2 vs 97.6% $p = 0.081$) was similar in clinic and club (Table 4).

More club participants acknowledged having enough individualized attention talking about any issue of personal importance (70.4 vs 79.6%). Interestingly, all clients admit to being served respectfully in the survey—see Table 4. Club clients more readily admit that HCW uses simple terms in explaining things like side effects (see Fig 2a).

Qualitative. From both the qualitative interviews, themes related to processes of care commonly used by clients and HCW to describe QoC can be summed into; the practice of care (referrals, time-efficient service, teamwork, reminders); content of care (counseling/

Fig 2. **a**: Process of care: Clients' perspective. **b**: Outcome of care: Clients' perspective.

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Table 4. Process of care: Clients perspective and HCW care delivery.

	Clinic (N = 378)	Club N = 251	p value
Activity completed during all last 3 visits/meetings- Extracted data from client folder n,%			
Weight taken	339, 89.7	213, 84.9	0.071
Screened for OI and TB	323, 85.4	197, 78.5	0.024
*Referrals for O1 or TB documented as done	N/A	63/68, 92.6	
ARV dispensed	370, 97.9	236, 94.0	0.012
Adherence assessed	344, 91.0	236, 94.0	0.167
Client survey			
Respectful service	376, 99.5	251, 100	0.248
Recent VL test done (i.e., ≤12 months)	375, 99.2	245, 97.6	0.081
Time spent during visit in minutes–*(Median, IQR)*	119.9, 75.0–180	49.9, 33.3–76.6	<0.001

ARV—Antiretroviral drug; IQR—Interquartile range; OI—Opportunistic Infections; TB—Tuberculosis; VL—Viral load

*Clinic participants see the clinician during visit while DSD participants are referred to the clinic; Club % is among those referred

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information sharing, health monitoring screening); and manner of care provision (individual attention, non-discriminatory service, respect).

Practice of care: Clients associated reduced waiting time for services with quality of care. The club model reduced waiting time both in the clinics and clubs, but clients felt that sufficient time is spent to attend to sick clients.

> "quality service is when we come here we don't even spend an hour if there are some sick people then we get divided by the doctor that for those with no problem should go there get the medicines and leave but for those with problems have to see the doctor go to the laboratory maybe but it's not the same for us who just come and leave after half an hour so I am happy for that, some other places you can stay for a long time, even losing hope to get service"
>
> —*Male clinic participant*

Content of care: Clients considered the counseling, health information, and screenings they received as crucial in defining QoC, but they emphasized that showing empathy on other life issues, not necessarily HIV-related also shapes their perception of care received.

> "On average, their talks are good. They are using convincing words which strengthen us, also their deeds are good"
>
> —*Male clinic participant*

Manner of care provision: Relatedly, clients also expressed being served respectfully, non-discriminatory service, flexible services, and receiving reminders for appointments including laboratory tests, via call or text message from HCW or through fellow club members as important attributes of quality care. While all clients admitted to receiving respectful service, Club participants in retrospect emphasized a difference between just doing the assigned tasks and actual care.

"Also, when I was going to [clinic name] there were some HCW. they were not polite/humble they seemed as they are fulfilling their responsibilities, which is different from these people who are coming to us nowadays."

Male club participant

Healthcare workers. *Quantitative*. The routine practice of care by HCW as extracted from the documentation in client folders revealed that ARVS were dispensed for more clinic clients i.e. 98 vs 94% during the last 3 clinic visits/ club meetings, while >90% of clients in clubs got a referral to the clinic who needed (see Table 4).

There were no differences in weight measurements or assessment of adherence. Routine screening for opportunistic infections and TB was documented for more clinic clients i.e.85 vs 79% (see Table 4).

There were no indicators routinely collected for assessing how care was provided by HCW at the time of data collection, therefore, we present only results obtained through interviews in the section below.

Qualitative. Practice of care: Time-efficient care provision—HCW reported more time to spend on providing care and conducting daily routines due to reduced client numbers in the clinic. Less work pressure also meant making fewer mistakes with medication.

"It is good. It helps to reduce the population to the clinic, reduce the population you know so make it easier for the workers to work well because sometimes previously it was full, full of clients at the clinic maybe people would start working from morning to six pm. They have worked tiredly; they can't give the right doses they lie to medication sometimes they become unclear they didn't work well. But now they are working well. They enjoy working at the clinic"

Female club HCW about the clinic.

Teamwork:—Both clinic and club staff considered the availability of different HCW cadres equipped with basic tools (equipment, tests, medicines) who work as a team as essential for providing quality care.

"If they work like a team then they will provide quality services because when working in team there is cooperation starting with the HBC to the doctor, nurses and the pharmacist if the services are done on time then the patient will be happy and will be of quality"

Male clinic HCW

Club staff additionally mentioned that fewer clients miss appointments due to time-efficient services in the clubs.

Non-discriminatory service—HCW in the clinic emphasized the need to talk without using abusive or judgmental words. HCW also emphasized the importance of the environment of the client and tailoring services accordingly.

"The way they welcome him [the client], talk to him. . .. without being abused, stigmatized. What we say maybe can make the service to be of quality. And the way I welcome people because you are not to punish them nor say something that may annoy him, [like] Where were you? What happened? No, you are to use friendly language and read the environment of the person you want to serve because if you know what the person wants, then he will give you a chance to serve him the way he wants or likes"

Male clinic HCW

Outcome of care

Clients. *Quantitative*. The proportion of participants suspected to have TB, or another opportunistic infection revealed no difference between the clinics and clubs (Table 5). Similarly, no difference was seen in the most recent CD4 count between the groups. Time on ART was significantly longer among club participants (3.45 vs 4.27yrs). The proportion of participants with a recent viral load <50 cells/mm was high in both groups but statistically lower among club participants—see details in Table 5.

The majority of clients were confident about the level of confidentiality of their interactions with their HCW. In the clinic and club alike (94.6 vs 92.8% p = 0.60), participants were sure that their HCW would keep their confidence and so expressed little fear about confiding in their HCW -**see** Fig 2b. In both club and clinic, though only a minority reported that HCW were aware of their situation at home and work (14.2 vs 38.7% p = 0.00), most participants were unanimous in the opinion that HCW were friendly and approachable. Compared to clinic participants, more club participants expressed being taken seriously (78.7 vs 81.3% p = 0.05), their opinion being regarded as serious (73.7 vs 79.2% p = 0.06) in managing their health and to being treated well.

Qualitative. Peer support and client satisfaction: Both clinic and club clients as did HCW reiterated the value of peer connection.

"But also, I managed to meet a lot of friends that I didn't know but just met them in the services, so the service connects different people and friends"

Male clinic participant

"When you sit here you advise each other and leave happy while everyone with her secrets knowing that we talked so and so even if you leave home with stress when you come to the club and sit with your fellows and discuss other things, you forget about home issues and leave in peace"

Female club participant

Table 5. Outcome of care: Client folder review.

	Clinic (N = 378)	Club N = 251	p value
Extracted data (Documented in folder during last 3 visits/meetings n,%			
OI or TB suspected–*n, %*	103, 27.3	68, 27.1	0.96
Visit/Meeting attended *(proxy for retention in care)*	369, 97.6	251, 100	0.014
Time on ART—*Median, IQR (years)*	3.45, 2.08–6.06	4.27, 2.24–7.61	0.002
Most recent CD4 count—*Median, IQR (cells/mm3)*	500, 334–500	515, 359–747	0.332
Most recent VL <50 cells/mm–*Median, IQR*	0, 0–0	0, 0–0	0.888
Proportion with recent VL <50cells/mm–*n, %*	375 (99.2)	237 (94.4)	<0.001

ARV—Antiretroviral drug; HCW—Health Care Workers; IQR—Interquartile range; OI—Opportunistic Infections; TB—Tuberculosis; VL—Viral load

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Cost-saving and keeping appointments: Club participants emphasized that saving money due to not having to travel to access care is important for quality care. Additionally, no club members had missed any meetings for the three most recent appointments which is a boost for clients' retention in care (see Table 5).

> "Here (club) is very near, there is no cost but there (clinic) we were using money, sometimes you can find that I don't have money"
>
> —*Female club participant*

Improved self-worth due to confidentiality: An overwhelming majority (>90% in both clinic and club) of clients described keeping their status confidential as an essential element of quality care. Generally, clients associated keeping their status confidential with a sense of self-worth and confidence to face life

> "The secrets are kept so that the community won't discriminate us and we to feel like other people and that it shouldn't discriminate us, we live a good life like others"
>
> —*Female club participant*

Individual perception of discrimination: Both clinic and club participants felt that the service models they were engaged in ensured secrecy and therefore prevented discrimination. Interestingly clinic and club participants differed in their assessment of which service-delivery model ensured confidentiality the best. While for clinic participants the clubs represented a risk of unintentional disclosure, Club participants choose the clubs because they felt at risk of unintentionally disclosing their status due to frequent clinic visits as described below:

> "I think I will not join a club because in villages they are advertising to other people that is why I'm fearful about this. I will be here at [the clinic] because I like the services I'm receiving here. In villages there is no secret, people will talk more about me.
>
> —*Male clinic participant*

> "There is no person who is talking in the street about what takes place here. There are many advantages [to the club] for keeping [your status] secret because when we were going to the clinic people were often talking. They said: "Do you see those people? They are going to take drugs". But now they think we are attending a normal meeting because this is an HBC's [Home Based Care worker's] house. And the HBC is a street leader, so they think we are having a normal meeting.
>
> —*Female club participant*

Healthcare workers. As outcomes of care are only applicable to clients, we only present the results of the interviews with HCW expressing their perspective about the outcomes of care they provided below.

Qualitative. HCW and clients defined quality care by the direct outcome and/or effect of care provided or perceived care they received. The main outcomes used to describe quality care fell in those two broad themes, namely client-related outcomes (laboratory indices, client satisfaction, cost-saving) and confidence/ improved self-worth (due to feeling safe, seen, and valued, the confidentiality of service delivery).

Laboratory indices: HCW stated that they assess the health and progress of clients and use that as a measure of the QoC they provide i.e., good progress equates to good care and vice versa. In doing so they use measures such as CD4 count and VL.

"If I take all the tests required if it's the CD4 and find them high I will be happy and know that I provide quality service and they understand my health training and properly take their medicines or if I test for HVL and find them low if they were 20 and I find are undetectable then I know that I provide quality services"

Female club HCW

Client satisfaction: HCW also named subjective outcomes such as client satisfaction revealed by the outward expression of happiness.

Confidentiality/Improved self-worth: HCW also emphasized confidentiality as a core part of what entailed quality care and had strong ideas about how confidentiality should be ensured. This included strict compliance with professional work ethics which binds them to maintain client confidentiality, which they all emphasized they adhered to. They described ways to accomplish this which included not discussing client information with others, attending to clients one by one in a confidential space to allow privacy. Also, in documenting information in registers and client folders, HCW emphasized the necessity to store these in secure places accessible to HCW alone. Documenting such information using codes that are only understandable to HCW to further ensure confidentiality and for client information entered into the electronic data platform restricted by passwords known only to authorized HCW.

"the client's information remains confidential because we always do the same work, not everyone is able and that's why we use codes or something that for the ones not involved may not understand that's why if you look at this paper or medical prescription, we don't write the names we write numbers, yes the names are there but when registering these we use codes so I as the professional it makes me secretive"

Male clinic HCW

The main quantitative and qualitative findings comparing the quality of care between the clinic and club from the perspective of clients and HCW are summarized in the joint display table (Table 6).

Discussion

This study evaluated the QoC in ART clubs compared with standard clinic care employing the Donabedian classic framework as a guide. We enabled in-depth understanding by eliciting the perspectives of clients and HCW on the subject. Our results revealed the non-inferiority of QoC provided in clubs when compared with standard care in clinics. Relatedly, clients and HCW alike considered HIV treatment services of good quality irrespective of the service delivery model. Among clients, process-related themes e.g., time spent, confidentiality, and respect were the most important emphasized for describing quality care in both clinic and club. HCW perspectives, on the other hand, emphasized structure-related themes such as availability of resources, decongestion of the clinic, and hence more time for other duties. Both clients and HCW describe quality in terms of outcomes using similar themes such as costs saved (time and money), client's health progress, and expressed satisfaction. No large contradictions were found between quantitative and qualitative findings, qualitative findings added depth and understanding to the quantitative picture.

Table 6. Joint display table summarizing quantitative and qualitative results by structure, process, and outcome.

lients		HCW	
Quantitative	**Qualitative**	**Quantitative**	**Qualitative**
Structure of care			
• No difference in care experience, except club HCW were better reachable by mobile phone • In both clinic and club, only 70% reported HCW ensured regular ART supply • The service delivery venue was perceived to be inadequate in half of clubs versus almost none in clinics	• Clients defined QoC, differently for clubs (ease of access) and for clinics (centers of expertise). • QoC was associated with adjunct non-medical services. • Clubs led to improved QoC via perceived decongestion of clinic • Choice of club venue was crucial in maintaining confidentiality and to prevent unwanted disclosure. Clubs could be hosted in clinic-spaces or in a village space where it was normal for groups to meet. • Majority of male clients preferred clinic to club-based care.	• Half of club staff found the location to be inadequate, versus 94% of the clinic staff • High proportion of staff in both clinic and club were adequately trained for their tasks • Clinic staff often had other tasks than HIV care, but did not think QoC was affected • Suitable provisions and ART availability were the same in clinics and clubs, half of club HCWs reported inadequate locations for meetings • No differences in logistical, organisational or data managerial aspects between clubs and clinics • Half of clinic staff was unhappy with remuneration versus none of club HCW	• Clinic staff were perceived to have more specialised skills than club HCW • Club and clinic HCW had equal ability to ascertain eligibility criteria, follow guidelines. QoC was seen as ability to maintain ordered documentation. • Clinics were decongested by the clubs, in clubs however need for more permanent location • Both clinic and club HCW perceived support to be adequate, increased pay and training opportunities would lead to better motivation.
Process of care			
• Care in clubs was considered more timesaving than in clinics • Time spent in the clinic was over double the time spent in the club • HCW in clubs had more time for clients than in clinics • There was no difference in information provision or required procedures performed during a visit	• Both clients in clubs and clinics felt they were given enough time for consultation • Enquiries into broader life areas than just HIV were considered QoC • clients valued flexibility, respect and reminders by HCW or fellow club members as central to QoC. Club participants perceived care in clubs as more emphatic than in the clinic	• A slightly lower proportion was dispensed ART in clubs than clinics • Over 90% of club participants who needed a clinic referral based on guidelines were actually referred • Less routine screening for opportunistic infections was performed in clubs compared to clinics	• HCW reported more time for consultations and lower work-pressure, therefore less mistakes. • Time-efficiency led to fewer missed appointments in clubs. • HCW felt smooth teamwork between different cadres of staff ensured QoC • -HCW perceived QoC as looking at the broader life circumstances of clients.
Outcome of care			
• There was very high retention in care in both clubs and clinics • Participants in clubs had been on ART for longer than in clinics • Viral suppression proportions were high, although lower among club than clinic participants • Clients had high confidence in confidentiality of HCW in both clinics and clubs • Clients felt HCW in clubs were more aware of clients' home situation than HCW in clinics, and they felt taken more seriously in clubs	• Both clinic and club participants valued the peer networks that had emerged. • Club members emphasized reduction of travel costs and time as QoC. • Clubs facilitated adherence. • Keeping status confidential was a core aspect of QoC and led to improved self-worth. • Both the clinic and the club model ensured confidentiality but in different ways. This perception shaped participant's choices for clinic or club.	• Not applicable	• HCW use measures such as CD4 and VL as indicators of whether they provide QoC • HCW strongly associated QoC to ensuring client's confidentiality. This pertained to all practices from not discussing a client, to seeing clients in a private space to secure storage and coding of documents.

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In terms of the structure of care, our finding that the availability of resources was similarly important for clinic and club participants and led to a positive perception of quality among clients and HCW alike is intuitive and aligns with the literature [22, 23]. HCW emphasized structure-related attributes e.g., equipment, information management systems, more than clients. Even with reasonable support structures in our study setting, irrespective of delivery model, the suggestions for more training opportunities, and better remuneration among HCW were seen as improving QoC even with other DSD types [24–26]. The availability of HCW as a measure of quality care was cited mainly by clinic participants, non-mention among club participants likely reflects that these were taken for granted rather than are not important. The shortage of HCW leading to long waiting times in facilities is an identified reason for client disengagement from service and motivation for DSD [24]. Similarly, the reliable supply of basic commodities e.g., ARVs, laboratory tests, etc. considered essential by other DSD studies for the provision of quality care, was also found in our study [27–29].

While some studies report the reluctance of clients to participate in DSD due to perceived higher quality of clinic-based care, others support our finding that clients considered DSD desirable and convenient [27, 28]. Our finding that the provision of adjunct non-medical services such as breakfast, food items, and monetary aid was a major influence on the perception of quality is likely associated with the prevailing poverty in our study setting. While this suggests adjunct interventions that can be considered alongside DSD, it raises concerns about sustainability. Additionally, having a conducive and confidential space for service delivery was echoed in our study as an important aspect of quality which is consistent with other studies where clients cited the fear of unintentional disclosure as a reason for not keeping clinic appointments [8, 24]. Our study revealed that what constitutes a confidential space is individually perceived e.g., for clinic participants, it referred to receiving care outside of the social control in the village, whereas for club participants not having to go to a place known as dispensing drugs for HIV was a way to maintain quality care. Moreover, venues selected by clients for ART club were normal meeting places for several groups in order not to arouse any suspicions which could fuel stigma. This alludes to the minimal impact of DSD on HIV-related stigma, in agreement with current evidence in the literature [30–32]. The better funding of the study sites, when compared to public facilities in terms of staff, equipment, and commodities being owned by the Catholic mission and supported by the T&T project, may partly explain our findings. Moreover, clubs were perceived as extensions of the clinics and very much connected.

Whereas HCW focused more on structure as a key aspect of QoC, clients were more concerned with processes. Key care processes were similarly conducted between clinic and club, with clubs revealing better time efficiency. Timely service delivery as a key aspect of quality care resonated throughout our study and is corroborated across many DSD studies as a core part of quality care for clients and HCW [28, 29, 33, 34]. While club clients spent the least amount of time, both club and clinic participants agreed that timely service had improved with the introduction of the DSD model. Our finding that information sharing and counseling from HCW and also from peers was considered a measure of good quality is coherent with the literature [31]. Interpersonal relations with HCW and personable services delivered in a culturally acceptable way and with attention to broader life circumstances of the client, were major influences shaping the perspectives of clients e.g., respectful service delivery ranked highly in the consideration of quality and is consistent with findings from other studies [31, 35]. Our study observed a particular coherence in views of clients and HCW around respect as part of quality, a finding that differs from another related study [36]. This may be related to the prevailing cultural environment which extols politeness and respect as a way of life [24]. It is noteworthy that studies are showing poor HCW attitude as contributing to client drop-out from ART care [37–39]. The optimal attendance we found supports this and therefore suggests? that the club model may facilitate retention among clients who would otherwise be lost-to-follow-up if extended to clients not considered stable. Relatedly, our finding that improved individualized and non-discriminatory care was perceived favorably aligns with a core motivation for DSD namely, client-centered care [31].

Expectedly, core outcomes of QoC such as the most recent CD4 count, and viral load results were similar as our comparison was only among stable clients. Similarities in recent viral load and CD4 count between clinic and club affirms findings from other studies that DSD does not threaten the attainment of desired treatment outcomes [6, 40]. While we found no difference between clinic and club in the proportion of clients with a recent viral load test (<12 months, according to national guidelines), the lower proportion of club clients with results <50 copies/ml may be explained by the few clients who were allowed to participate in clubs with good adherence and a VL result between 50–200 copies/ml (considered as virologic blips) [41]. It may also reflect the early phase of club implementation which requires a period of familiarization with the protocol. Continuous mentoring and monitoring of adherence to procedures by HCW is advocated as in other DSD interventions [29, 42].

While HCW emphasized improved client status, clients emphasized improved social standing and peer support as outcomes of care. Regaining a sense of self-worth and a more positive outlook on life was an important outcome influencing perceptions of HIV care quality in our study and was also seen in other studies [30, 43]. This is closely linked to improved health status, to which ART no doubt contributes to a large extent. Evidence shows that stigma remains an issue in our study setting as in many others. The fear of unintentional disclosure may likely account for the import placed on the assurance of status confidentiality as a measure of quality [43–46]. Additionally, our finding that valuing clients' opinions empowers them to self-manage and feel like allies align with the literature [47, 48]. Beyond psychosocial support, initiatives to support financial wellbeing ranked high, especially among club participants. The prevailing socio-economic conditions in our setting i.e., poverty, illiteracy, and dependence on subsistence farming as major income earners likely explain this finding. The literature shows that DSD offers convenience while saving costs (time and money) which underlies its acceptability across settings [8, 28, 34, 48, 49]. Not surprisingly, savings in terms of reduced access cost (transportation) was mentioned mainly among club participants.

Strength & limitations

The Donabedian framework facilitated the vigorous assessment of QoC taking into consideration that while some aspects of quality care are easy to measure, others are not so. The interpersonal process which drives interaction between care recipients and providers complicates the assessment of QoC. Utilizing the three-dimensional framework enabled the broad exploration of QoC in our study, especially as the relationship between structure, process, and outcome are considered non-linear [13, 36]. We employed a mixed-method study design triangulating quantitative and qualitative data to provide more valid evidence. Our findings must be interpreted in the face of some limitations. The study was conducted one year following the implementation of clubs in the study clinics to provide the intervention with data to improve the model. This means that we were not able to measure the long-term impact of the DSD model on QoC. Our findings however mostly align with the literature even for similar interventions that have been implemented for longer [9, 29, 32, 50]. Moreover, our study sites were mission-owned facilities that are generally better funded and may likely not represent the situation in publicly owned hospitals. It is also possible that some participants gave socially desirable responses. The tendency of clients to refrain from saying disagreeable statements may have influenced responses. We countered this by training research assistants to assure participants that their responses would be anonymized and have no effect on the services they receive but rather provide ways for improving services. There may have been selection bias i.e., those who opted to join clubs may have had different attitudes, status geographic considerations, etc., to those happy to stay at the clinic. By allowing clients' preferences to determine which service delivery model they receive, we believe our findings are relevant to what can be expected in real life.

Conclusion

Our study revealed that QoC was comparable between the ART club and the clinic in our setting in Shinyanga, Tanzania. The perspectives of clients and HCW complemented quantitative results consistently across the sub-dimensions of structure, process, and outcome of care. While HCW emphasizes structure in defining QoC, clients focus on process. The need for both clinic-based care and DSD was apparent as many elements of quality care were individually perceived. Regardless of the model/type of care, QoC will benefit from other interventions addressing socio-economic situations of widespread poverty such as we have in our study setting. Ultimately, contextually relevant adaptations informed by the perspectives of clients and HCW alike will be important for achieving acceptable QoC in DSD interventions across settings. Future research can investigate the longitudinal evaluation of outcomes of care and explore employing ethnographic studies to delve deeper into how the DSD model is perceived over time to inform relevant adaptations in service delivery.

Supporting information

S1 Appendix. Quality of care questionnaire for patients-English.
(PDF)

S2 Appendix. Quality of care questionnaire for patients-Swahili.
(PDF)

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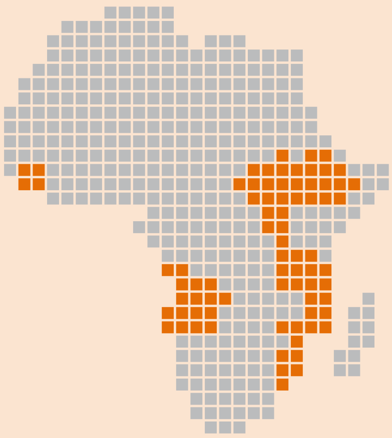

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Exploring the mechanisms behind HIV drug resistance in sub-Saharan Africa: conceptual mapping of a complex adaptive system based on multi-disciplinary expert insights

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Abstract

Background: HIV drug resistance (HIVDR) continues to threaten the effectiveness of worldwide antiretroviral therapy (ART). Emergence and transmission of HIVDR are driven by several interconnected factors. Though much has been done to uncover factors influencing HIVDR, overall interconnectedness between these factors remains unclear and African policy makers encounter difficulties setting priorities combating HIVDR. By viewing HIVDR as a complex adaptive system, through the eyes of multi-disciplinary HIVDR experts, we aimed to make a first attempt to linking different influencing factors and gaining a deeper understanding of the complexity of the system.

Methods: We designed a detailed systems map of factors influencing HIVDR based on semi-structured interviews with 15 international HIVDR experts from or with experience in sub-Saharan Africa, from different disciplinary backgrounds and affiliated with different types of institutions. The resulting detailed system map was conceptualized into three main HIVDR feedback loops and further strengthened with literature evidence.

Results: Factors influencing HIVDR in sub-Saharan Africa and their interactions were sorted in five categories: biology, individual, social context, healthcare system and 'overarching'. We identified three causal loops cross-cutting these layers, which relate to three interconnected subsystems of mechanisms influencing HIVDR. The 'adherence motivation' subsystem concerns the interplay of factors influencing people living with HIV to alternate between adherence and non-adherence. The 'healthcare burden' subsystem is a reinforcing loop leading to an increase in HIVDR at local population level. The 'ART overreliance' subsystem is a balancing feedback loop leading to complacency among program managers when there is overreliance on ART with a perceived low risk to drug resistance. The three subsystems are interconnected at different levels.

Conclusions: Interconnectedness of the three subsystems underlines the need to act on the entire system of factors surrounding HIVDR in sub-Saharan Africa in order to target interventions and to prevent unwanted effects on other

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parts of the system. The three theories that emerged while studying HIVDR as a complex adaptive system form a starting point for further qualitative and quantitative investigation.

Background

HIV drug resistance

HIV drug resistance (HIVDR) remains a threat to the effectiveness of antiretroviral therapy (ART). Over the last decade, major efforts have been made to achieve global 90-90-90 goals by 2020 and to end the HIV epidemic as a public health threat by 2030 [1]. However, levels of HIVDR are rising, compromising the effectiveness of ART and potentially also the efforts to attain the last 90 goal [2]. In 2017, mathematical modeling predicted that if left unchecked, excess levels of pretreatment HIVDR to the NNRTI drug class could directly lead to 890 000 AIDS deaths, 450 000 new infections, and 6.5 billion USD extra ART costs by 2030 in sub-Saharan Africa (SSA) [3]. Recently several cases of multi-drug class resistant HIV have been reported [4, 5].

Several causes of both pre-treatment HIVDR and acquired HIVDR have been described in the literature. Due to the high genetic variability of the virus, selective pressure stemming from a combination of incomplete adherence (defined here in the broader sense of not taking ART as prescribed, which can be influenced by a multitude of factors which are both within and out of the control of the clients themselves) and a low genetic barrier of ART may lead to the emergence of HIVDR [6]. In addition to biological and pharmacokinetic factors influencing the selection and emergence of HIVDR lie other, indirectly related factors. In a meta-analysis Shubber et al. identified diverse barriers to adherence such as forgetfulness, traveling, medication toxicity, stigmatization, food insecurity, alcohol or substance misuse [7]. Other crucial aspects to prevent HIVDR are for example sufficient ART availability and a well-functioning ART supply system [8]. These and other factors described in literature relate to several fields of science and in some cases also to other complex problems. For example, ART drugs have been reported to be used in a mixture of recreational drugs called whoonga in South Africa [9–11]. The complex problem of drug abuse, is therefore linked to HIVDR as this exposure to ART may have consequences for pretreatment drug resistance.

Despite the fact that most of the factors contributing to HIVDR are presumed to be known, and that models to mitigate these causes have been built, pre-treatment HIVDR, especially in SSA, is still increasing [12].

HIVDR as a complex adaptive system

As the factors influencing the emergence of HIVDR are numerous, have roots in different fields of science and are interconnected with other complex problems, we argue that HIVDR should be approached as a complex adaptive system (CAS), combining knowledge of diverse experts and stakeholders. Such systems have been defined by Plsek et al. as 'a collection of individual agents with the freedom to act in ways that are not always totally predictable, and whose actions are interconnected so that one agent's actions changes the context for other agents' [13]. A successful intervention on one element of the system does not guarantee resolving the core problem. Rather, interventions should be planned keeping in mind the entire system, its particular dynamics and possible feedback loops and with the aim of reshaping the system in a favorable way [13, 14]. Feedback loops can be reinforcing or balancing, meaning that a change in a certain direction will either evolve into more change or balance itself out by propagating an opposite effect. CAS have been studied in several other contexts such as ecosystem management, healthcare management and obesity [15–17]. Moreover, the importance of using systems thinking in health care has been widely described in the literature [13, 14, 18–20]. In 2017, Rutter et al. described the need of approaching public health problems as complex systems in order to identify, implement and evaluate effective interventions [14]. Such interventions should be done at leverage points in the systems. These are points where a small intervention can have a large impact on the system [21]. Identifying leverage points is difficult and sometimes counterintuitive. Gaining insights in subsystems or feedback loops may therefore facilitate the identification of leverage points [22].

With this study, we aimed to make a first attempt at understanding the complexity behind HIVDR by combining the expertise and viewpoints from different HIVDR experts. In this article we describe how we identified three interconnected feedback loops influencing HIVDR by developing a systems map that represents the CAS of HIVDR in SSA based on the insights of international HIVDR experts from different disciplines. We discuss the insights gained from these feedback loops and possible applications for quantitative modelling, complexity-informed intervention design and policy development [23, 24].

Methods

Recruitment, inclusion criteria and setting

The systems map was designed based on semi-structured interviews with international experts from or with experience in SSA. For the purpose of this study, international experts were defined as stakeholders from diverse disciplines and institutions, working at an international level on HIVDR related to SSA and with a minimum of five years of experience. The participants were selected based on their expertise concerning HIVDR and with the aim of creating a mix of backgrounds and institutions covering all aspects of HIVDR. Purposive sampling was done starting from the expertise and connections of the Rega Institute and the Institute for the Future in Leuven, Belgium. This was supplemented with snowball sampling, using the expertise and connections of participants, and theoretical sampling, looking for the missing perspectives based on the emergent findings. They were contacted through email or in person when an opportunity presented itself, for example at international conferences. The interviews were held face to face ($n=6$) or online over Skype or Zoom ($n=9$) and were conducted in English. Semi-structured interviews of approximately 60 min were conducted until data saturation was reached, aiming to cover all possible factors influencing HIVDR in SSA. For the purpose of this study we describe data saturation as the point at which no new elements were uncovered in new interviews and no new connections which significantly changed the final conceptual model, were uncovered.

Semi-structured interview guide

An interview guide was designed with the input of several HIVDR and social science experts and was adapted according to insights developed through analysis (Additional file 2). The guide contained three sections: the first section entailed sociodemographic questions concerning the interviewees gender, age and educational background. The questions of section two related to the interviewees professional and personal experience with HIV or HIVDR in SSA. The third and main section covered their perspectives on the factors influencing HIVDR. All experts were asked what, in their experience, were the main causes of HIVDR. As a general guideline, the interviewer aimed to cover the following four areas: causes related to 1) availability of ART at the healthcare centre, 2) PLHIV's ability to fetch ART, 3) PLHIV taking ART as prescribed and 4) ART suppressing the viral load. Additionally, when causes outside these four areas came up, they were also further discussed. Subsequently, depending on the expertise of the participant, follow-up questions such as "What do you think is causing the situation you just mentioned?" aimed to clarify the deeper reasons behind some of those initially indicated causes.

Data analysis

Analysis of the semi-structured interviews was inspired by the QUAGOL method and done simultaneously with the data collection [25]. After each interview a technical report was written describing relevant characteristics of the participant and interview context, helpful for understanding the data in their specific context. The interviews were transcribed verbatim by an external firm and the quality of each transcription was verified by listening to the audio tapes and correcting possible errors in the transcripts. Each transcript was (re-)read until a list of factors influencing HIVDR as well as connections between those factors, mentioned either explicitly or implicitly by the interviewee, was extracted. Connections were assigned a positive, negative or dual polarity. A positive connection indicates that the influencing and influenced element evolve both in the same direction (e.g. A—> B: when factor A increases, B increases too). A negative connection indicates that both elements evolve in the opposite direction (e.g. A- > B: when factor A increases, B decreases and vice versa). A dual connection indicates that both effects are possible. Take the following paraphrased quote as an example: "You know, sometimes people form peer support groups so that each month someone will pick up the medication for the whole group. This way people have to go only once every six months instead of on a monthly basis." This would be translated into a negative arrow from "peer support group" to "required frequency of hospital visits". Subsequently for each of the first six interviews separately, these factors were visualized in a small systems map while re-reading the interview again in order to visualize all the mentioned connections between these factors. Afterwards the separate systems maps of the first six interviews were merged together into one and from that point onwards data from the following interviews was added to the map. Throughout the analysis newly discovered insights were constantly compared with previous findings resulting in an iterative process of re-reading interviews and reviewing the detailed systems map.

The model was designed in Kumu, an online mapping tool which enables the user to save data such as interview quotes and memos for each element and connection [26]. In the first, confidential, version of the systems map, all interview quotes which mention a certain element or connection, are collected in the comment fields associated with the element or connection in the KUMU tool, facilitating our analysis. From this first draft systems map causal loops were identified manually as series of

Table 1 Participant characteristics: different backgrounds and institution types of the interview participants. Note that some participants had a background in several fields of science or were working for more than one institution

Scientific background	N	Institution type	N
Medicine (public health/tropical medicine)	5	Global policy-making institution	3
Virology	4	Local policy-making institution	2
Epidemiology and public health	4	Hospital	2
Psychology	2	NGO	5
Finance	1	Pharmaceutical company	1
Human rights law	1	Insurance company	1
Engineering	1	University	3
Nursing science	1		
Economy	1		
Business	1		
Anthropology	1		

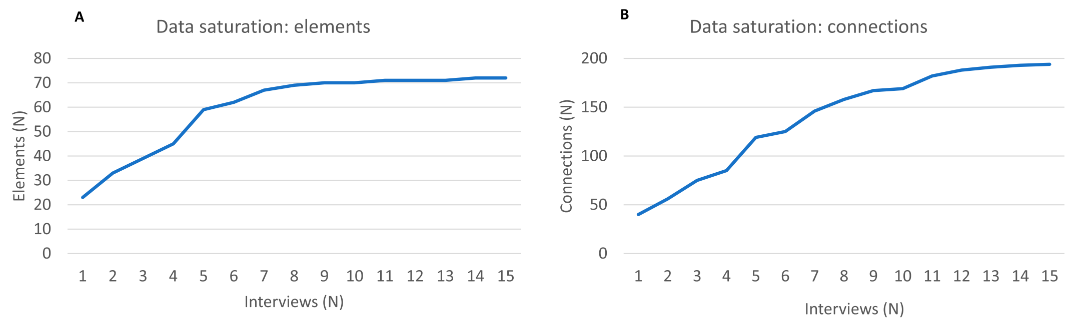

Fig. 1 Data saturation curves. **A**) Number of elements in the systems map after each consecutive interview. **B**) Number of connections in the systems map after each consecutive interview

elements connected to each other in a circular way. Causal loops which contributed to the same mechanism were identified as a subsystem (this can be compared with a road map: all possible routs you could take to go from Brussels to Amsterdam would be classified together as the subsystem "routs from Brussels to Amsterdam"). Because the subsystems consisted of many elements and connections, they were conceptualized into one overall mechanism per subsystem which reflected the overall messages of interviews as well as possible. While each separate element and connection was mentioned in one or several interviews, the resulting feedback loops are based on the combination of knowledge from the different experts. The conceptualization of the subsystems was linked back to the original interviews, discussed with several stakeholders and strengthened with literature evidence.

Results

Systems map of factors influencing HIVDR as informed by the expertise of different HIVDR experts

In total 15 international experts were interviewed. Table 1 summarizes the scientific and institutional background of the interviewees. A diverse sample of experts with different expertise and institutional affiliation was reached, permitting us to gain insights in the various aspects of the CAS. Out of the 15 participants, 13 were researchers or had previous research experience in the field of HIVDR.

Data saturation for elements (factors influencing HIVDR) was reached after about nine interviews and for connections (pathways of influence between two elements) after 12 interviews (Fig. 1).

The subsystems behind HIVDR

All elements and connections identified from the semi-structured interviews are represented in Table 2, Table 3 and Additional file 3. Based on this data, we

Table 2 Connections as presented in Fig. 2 and Additional file 1. The connection type represents the polarity of the connection. A positive connection type indicates that both elements evolve in the same direction (when element A increases, element B will increase too, and vice versa). A negative connection type indicates that both elements will evolve in the opposite direction (when element A increases, element B will decrease, and vice versa)

From	To	Type
Acceptance of HIV status	Adherence	+
Acceptance of HIV status	Engagement and retention in care	+
Acceptance of HIV status	Priority given to treatment	+
Acceptance of HIV status	HIV status disclosure	+
Accessibility of health centre (including safety)	Engagement and retention in care	+
Adherence	Drug levels in body	+
Adherence counselling	Understanding of HIV infection and treatment	+
Adherence counselling	Readiness to start taking ART	+
Administrative and political barriers	Individual and community empowerment	-
Administrative and political barriers	Timely acting on unsuppressed viral load	-
Administrative and political barriers	Well-functioning supply chain	-
ART treatment approach / policy	Timely acting on unsuppressed viral load	±
ART treatment approach / policy	Healthcare system workload	±
ART treatment approach / policy	Correct prescribing practices	±
ART treatment approach / policy	Required frequency of hospital visits	±
ART treatment approach / policy	Competence of healthcare workers	±
Assuring quality of ART	Efficiency of drug combination	+
Availability and quality of equipment	Timely acting on unsuppressed viral load	+
Availability of better drugs	Global effort to tackle HIVDR	-
Availability of better drugs	HIVDR selection	-
Community stigma and gossip	Engagement and retention in care	-
Community stigma and gossip	Distance to the healthcare centre	+
Community stigma and gossip	Self-stigmatisation	+
Community stigma and gossip	Healthcare provider stigma	+
Community stigma and gossip	Adherence	-
Community stigma and gossip	HIV status disclosure	-
Competence of healthcare workers	Timely acting on unsuppressed viral load	+
Competence of healthcare workers	Correct prescribing practices	+
Competence of healthcare workers	Adherence counselling	+
Competence of healthcare workers	Patient-provider relationship	+
Concerns about side effects of ART	Adherence	-
Concurrent disease and opportunistic infections	Feeling and looking ill	+
Concurrent disease and opportunistic infections	Pill burden	+
Concurrent disease and opportunistic infections	Drug-drug interactions	+
Concurrent disease and opportunistic infections	Healthcare system workload	+
Concurrent disease and opportunistic infections	Optimal absorption of drug	-
Correct prescribing practices	Efficiency of drug combination	+
Depression	Adherence	-
Depression	Priority given to treatment	-
Depression	Substance abuse	+
Distance to the healthcare centre	Accessibility of health centre (including safety)	-
Distance to the healthcare centre	Engagement and retention in care	±
Drug levels in body	Viral load suppression	+
Drug levels in body	Side effects of ART	+
Drug prices	Resource allocation with focus on population	-
Drug-drug interactions	Optimal absorption of drug	-
Efficiency of drug combination	Viral load suppression	+

Table 2 (continued)

From	To	Type
Engagement and retention in care	Adherence	+
Engagement and retention in care	Financial situation	-
Engagement in alternative care	Engagement and retention in care	±
Engagement in alternative care	Optimal absorption of drug	-
Engagement in alternative care	Misinformation	±
Engagement in alternative care	Adherence	±
Engagement in risk behaviour	Transmission of HIV(DR)	+
Feeling and looking ill	Community stigma and gossip	+
Feeling and looking ill	Engagement and retention in care	±
Feeling and looking ill	Priority given to treatment	+
Feeling and looking ill	HIV status disclosure	+
Feeling and looking ill	Concerns about side effects of ART	+
Financial situation	Accessibility of health centre (including safety)	+
Financial situation	Timely acting on unsuppressed viral load	+
Financial situation	Migration	-
Financial situation	Food insecurity	-
Financial situation	Priority given to treatment	+
Food insecurity	Adherence	-
Food insecurity	Optimal absorption of drug	-
Forgetfulness	Adherence	-
Gender inequality	HIV status disclosure	-
Gender inequality	Adherence	-
Gender inequality	Engagement and retention in care	-
Gender inequality	Lower social status	+
Gender inequality	Engagement in risk behaviour	+
Global effort to tackle HIVDR	HIVDR Funding	+
Global effort to tackle HIVDR	ART treatment approach / policy	+
Having examples of well-functioning ART	Community stigma and gossip	-
Having examples of well-functioning ART	Acceptance of HIV status	+
Healthcare provider stigma	Engagement and retention in care	-
Healthcare provider stigma	Adherence counselling	-
Healthcare system workload	Adherence counselling	-
Healthcare system workload	Tracing of PLHIV	-
Healthcare system workload	Correct prescribing practices	-
Healthcare system workload	Timely acting on unsuppressed viral load	-
Healthcare system workload	Well-functioning supply chain	-
Healthcare system workload	Competence of healthcare workers	-
Healthcare system workload	Patient-provider relationship	-
Healthcare system workload	Job satisfaction and motivation of healthcare workers	-
HIV status disclosure	Social support	±
HIV status disclosure	Community stigma and gossip	+
HIV status disclosure	Engagement in risk behaviour	-
HIV status disclosure	Adherence	±
HIV status disclosure	Engagement and retention in care	+
HIVDR Funding	HIVDR Research focus	+
HIVDR Funding	Stock availability of ART and reagents	+
HIVDR Funding	Availability and quality of equipment	+
HIVDR Funding	Resource allocation with focus on population	±
HIVDR Funding	Need to show success of the ART programme	+

Table 2 (continued)

From	To	Type
HIVDR Funding	Resistance (and subtype) testing	+
HIVDR Research focus	Availability of better drugs	+
HIVDR Research focus	ART treatment approach / policy	+
HIVDR Research focus	Required frequency of hospital visits	-
HIVDR Research focus	Resource allocation with focus on population	+
HIVDR selection	Global effort to tackle HIVDR	+
HIVDR selection	Viral load suppression	-
HIVDR selection	Transmission of HIV(DR)	+
HIVDR selection	Healthcare system workload	+
Hospital design	Community stigma and gossip	±
Hospital design	HIV status disclosure	±
Incentive to search for information	Understanding of HIV infection and treatment	+
Incentive to search for information	Misinformation	+
Individual and community empowerment	Timely acting on unsuppressed viral load	+
Individual education level	Understanding of HIV infection and treatment	+
Job satisfaction and motivation of healthcare workers	Well-functioning supply chain	+
Job satisfaction and motivation of healthcare workers	Timely acting on unsuppressed viral load	+
Linguistic issues	Adherence counselling	-
Lower social status	Engagement and retention in care	-
Lower social status	Community stigma and gossip	+
Lower social status	Healthcare provider stigma	+
Migration	Healthcare system workload	+
Migration	Well-functioning supply chain	-
Migration	Engagement and retention in care	-
Misinformation	Understanding of HIV infection and treatment	-
Misinformation	Community stigma and gossip	+
Misinformation	Engagement in alternative care	+
Misinformation	Engagement in risk behaviour	+
Need to show success of the ART programme	HIVDR Funding	+
Need to show success of the ART programme	Administrative and political barriers	+
Optimal absorption of drug	Drug levels in body	+
Patient-provider relationship	Understanding of HIV infection and treatment	+
Patient-provider relationship	Engagement and retention in care	+
Patient-provider relationship	Adherence counselling	+
Patient-provider relationship	HIV status disclosure	+
Peer support group	Required frequency of hospital visits	-
Peer support group	Understanding of HIV infection and treatment	+
Pill burden	Pill fatigue	+
Pill burden	Side effects of ART	+
Pill fatigue	Adherence	-
Priority given to treatment	Adherence	+
Priority given to treatment	Engagement and retention in care	+
Punitive laws for MSM and sex workers	Engagement and retention in care	-
Punitive laws for MSM and sex workers	Transmission of HIV(DR)	+
Punitive laws for MSM and sex workers	Community stigma and gossip	+
Punitive laws for MSM and sex workers	ART treatment approach / policy	-
Quality of data systems	Tracing of PLHIV	+
Quality of data systems	Well-functioning supply chain	+
Quality of data systems	Timely acting on unsuppressed viral load	+

Table 2 (continued)

From	To	Type
Readiness to start taking ART	Adherence	+
Religious beliefs	Self-stigmatisation	+
Religious beliefs	Engagement in alternative care	+
Required frequency of hospital visits	Engagement and retention in care	-
Required frequency of hospital visits	Healthcare system workload	+
Resistance (and subtype) testing	Correct prescribing practices	+
Resource allocation with focus on population	ART treatment approach / policy	+
Resource allocation with focus on population	Adherence	+
Self-stigmatisation	Acceptance of HIV status	-
Self-stigmatisation	HIV status disclosure	-
Self-stigmatisation	Depression	+
Side effects of ART	Feeling and looking ill	+
Side effects of ART	Adherence	-
Side effects of ART	HIV status disclosure	+
Social obligations	Financial situation	-
Social obligations	Priority given to treatment	-
Social support	Adherence	+
Stock availability of ART and reagents	ART treatment approach / policy	+
Stock availability of ART and reagents	Timely acting on unsuppressed viral load	+
Stock availability of ART and reagents	Job satisfaction and motivation of healthcare workers	+
Stock availability of ART and reagents	Required frequency of hospital visits	-
Stock availability of ART and reagents	Adherence	+
Substance abuse	Forgetfulness	+
Timely acting on unsuppressed viral load	Efficiency of drug combination	+
Tracing of PLHIV	Engagement and retention in care	+
Tracing of PLHIV	Timely acting on unsuppressed viral load	+
Transmission of HIV(DR)	Efficiency of drug combination	-
Transmission of HIV(DR)	Healthcare system workload	+
Understanding of HIV infection and treatment	Self-stigmatisation	-
Understanding of HIV infection and treatment	Engagement in risk behaviour	-
Understanding of HIV infection and treatment	Incentive to search for information	-
Understanding of HIV infection and treatment	Engagement and retention in care	+
Understanding of HIV infection and treatment	Adherence	+
Understanding of HIV infection and treatment	Acceptance of HIV status	+
Understanding of HIV infection and treatment	Individual and community empowerment	+
Understanding of HIV infection and treatment	Priority given to treatment	+
Understanding of HIV infection and treatment	Community stigma and gossip	-
Understanding of HIV infection and treatment	Engagement in alternative care	-
Viral load suppression	HIVDR selection	-
Viral load suppression	Concurrent disease and opportunistic infections	-
Viral load suppression	Required frequency of hospital visits	-
Viral load suppression	Healthcare system workload	-
Viral load suppression	Transmission of HIV(DR)	-
War and disease outbreaks	Accessibility of health centre (including safety)	-
War and disease outbreaks	Timely acting on unsuppressed viral load	-
War and disease outbreaks	Well-functioning supply chain	-
War and disease outbreaks	Migration	+
Well-functioning supply chain	Peer support group	+
Well-functioning supply chain	Stock availability of ART and reagents	+

Table 3 Overview of elements included in each factor of Fig. 2

Adherence motivation subsystem		Healthcare system burden		ART overreliance subsystem	Interconnected wicked problems
Psychosocial	Social support	**Quality of care**	Timely acting on unsuppressed viral load	**Global effort to tackle HIVDR**	Food insecurity
Acceptance of HIV status	Substance abuse	Accessibility of health centre (including safety)	Tracing of PLHIV	Drug prices	Gender inequality
Community stigma and gossip	**Adherence and retention**	Adherence counselling	Well-functioning supply chain	Global effort to tackle HIVDR	Lower social status
Concerns about side effects of ART	Adherence	Administrative and political barriers	**Health literacy and empowerment**	HIVDR funding	Migration
Depression	Engagement and retention in care	ART treatment approach / policy	Individual and community empowerment	Need to show success of the ART programme	Punitive laws for MSM and sex workers
Engagement in risk behaviour	Engagement in alternative care	Assuring quality of ART	Individual education level	Research focus	War and disease outbreaks
Financial situation	**Clinical manifestations**	Availability and quality of equipment	Incentive to search for information	Resource allocation with focus on population	
Forgetfulness	Concurrent disease and opportunistic infections	Patient-provider relationship	Misinformation	**Availability of ART with a higher genetic barrier**	
Having examples of well-functioning ART	Feeling and looking healthy	Competence of healthcare workers	Religious beliefs	Availability of better drugs	
HIV status disclosure	Side effects of ART	Correct prescribing practices	Understanding of HIV infection and treatment		
Hospital design	**Biology**	Distance to the healthcare centre	**Health system resources**		
Linguistic issues	Drug levels in body	Healthcare provider stigma	Healthcare system workload		
Pill burden	Drug-drug interactions	Job satisfaction and motivation of healthcare workers			
Pill fatigue	Efficiency of drug combination	Peer support group			
Priority given to treatment	HIVDR selection	Quality of data systems			
Readiness to start taking ART	Optimal absorption of drug	Required frequency of hospital visits			
Self-stigmatisation	Transmission of HIV(DR)	Resistance (and subtype) testing			
Social obligations	VL suppression	Stock availability of ART and reagents			

visualized the system in two ways [27]. The first visualization divides the elements in five layers according to their relation to biology (elements and processes happening inside the body), individual factors (psychology, personal factors and behavior of adherence), social context (personal characteristics as a member of the community and baseline conditions in the community), healthcare system (treatment plan and healthcare organization), and 'overarching' factors (such as international policy, research and funding) (Additional file 1).

For the second visualization we grouped the same elements and connections in ten different thematic clusters (Fig. 2) ([27], page 1). The clusters represent elements belonging to the same themes identified in the interview data, being adherence and retention in care, biology, clinical manifestations, complex problems, genetic barrier of the medication, global effort to tackle HIVDR, health literacy and empowerment, health system resources, psychosocial factors and quality of care. The elements included in each cluster are presented in Table 3. When visualizing these clusters and the connections between

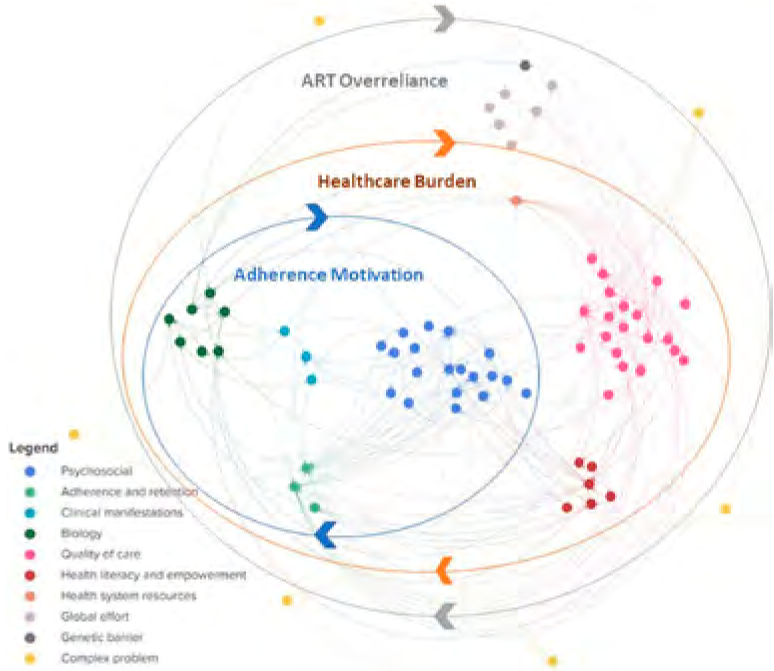

Fig. 2 Clustered systems map visualizing three interconnected subsystems. Each cluster of elements is represented in a different colour, corresponding to the colours used in Fig. 3 and connects elements related to a certain theme. Note that all elements and connections represented here are the same as the ones presented in Additional file 1 but organized in clusters instead of in layers. Three main subsystems are indicated in the blue, orange and grey overlaying circles. An interactive overview this map, can be found in Additional file 3 ([27], page 1])

them, three major feedback loops or sub-systems emerge, indicated by the three circles in Fig. 2.

Adherence motivation subsystem

The first subsystem suggests a mechanism at the personal level through which people living with HIV (PLHIV) may alternate between periods of optimal and suboptimal adherence. In different periods of their lives, PLHIV may give more or less priority to their treatment depending on several factors. When less priority is given to the ART and doses are missed, the viral load will not be suppressed and HIV related illness may develop. When feeling physically unwell, treatment may again be prioritized over other activities leading to a better adherence. When the viral load is suppressed and the individual feels better, other activities may take precedent and doses of ART may be skipped. When studying this subsystem, it is important to keep in mind that this alternating behavior can occur only a limited number of times before HIVDR emerges, after which optimal adherence will not lead to a better physical condition anymore.

We also note that not all individuals follow the pathways of this subsystem. PLHIV may fail to adhere even when feeling physically ill, or on the contrary, may have a continuous optimal adherence. This interplay between factors influencing an individual's adherence has recently been described in a qualitative systematic review [28]. The authors describe how a combination of factors can lead to the decision of PLHIV to either adhere to ART or not and how this is a dynamic process of switching between adherence and non-adherence.

Healthcare burden subsystem

The second subsystem is situated at the programme level and relates to the burden on the healthcare system which, when too high, may jeopardize the quality of service delivery. Services provided at the healthcare center, such as adherence counseling, viral load testing or pill pick-up are essential to sustain viral load suppression but may be compromised when the healthcare system is overburdened. This may lead to delayed acting on a detectable viral load which on its turn leads to emergence of HIVDR and/or transmission of HIV(DR), requiring additional counseling and viral load tests. This, on its turn, increases the healthcare system workload. In short, this loop represents a sequence of events through which a high burden on the healthcare system amplifies itself. On the programme level, a high burden on the healthcare system may lead to delays in acting on non-suppressed viral load as the testing itself may be delayed due to insufficient laboratory and sample transport capacity or the healthcare workers may not have time to file reports or to return test results. HIVDR emergence resulting from a delay in acting on unsuppressed viral load in turn contributes to an increase in overall HIVDR burden at the personal and programme level. The World Health Organization reports that, though the African region carries the highest disease burden, they have the highest population/provider ratios [29]. In line with our findings, a study in Cameroon identified high health system workload as a possible risk factor for emerging HIVDR [30].

ART overreliance subsystem

At the population level, the availability of ART with a high potency and a high genetic barrier for resistance such as combinations including second generation integrase inhibitors offers a new and promising line of therapy. However, several interviewees expressed the concern that resistance against second generation integrase inhibitors such as Dolutegravir will eventually arise given that the first cases of resistance have already been reported [31–33]. With the introduction of integrase inhibitor-based ART in SSA, highly active treatment with a low risk to emergence of drug resistance, policy makers and in particular doctors, risk to overly rely on the effectiveness of the treatment. This shifts the healthcare focus to increasing the numbers of PLHIV on treatment at the cost of assuring high quality care for all. However, when adherence issues are left unsolved, the possibility of developing resistance against new ART regimens, despite their high genetic barrier, remains. This finding is supported by the review of Hamers et al. and by the findings of the ADVANCE trial that pre-treatment HIVDR to NRTIs and/or NNRTIs predicts virologic failure for regimens containing Dolutegravir [34, 35]. Altogether, this subsystem suggests that the use of ART with a higher genetic barrier to resistance alone may not be sufficient to prevent HIVDR and should always be supported by high quality service delivery. We currently see an interest in long-acting drugs with a high genetic barrier to drug resistance, which may facilitate adherence, but may again result in overconfidence, thereby increasing the risk of HIVDR in the long run if not implemented in the context of a systems approach. A similar reasoning has been made by Inzaule et al., who point out the challenges associated with the roll-out of dolutegravir such as reduced effectiveness of the therapy due to NRTI resistance and uncertainty about dolutegravir resistance due to insufficient access to viral load testing [36].

When interpreting the subsystems described above it is important to keep in mind that they are constantly influenced by each other and by other complex problems such as food insecurity, gender inequality or war and disease outbreaks. Figure 3 represents a summarized version of the three subsystems as presented in Fig. 2.

Subsystem interactions

The three subsystems described above exist on different societal levels (personal, programme and population level) and are intrinsically linked with each other. The alternating adherence subsystem takes place on the personal level until HIVDR emerges, at which point the individual will add to the burden of the healthcare system. The increased burden on the healthcare system may then impact the overall quality of care, which in turn may impact the adherence of PLHIV through a delayed switch in ART after detection of viral non-suppression, thus increasing the chances of personal- and population-level HIVDR emergence. Diminished quality of ART service delivery may also impact adherence counselling and support, thereby directly impacting the alternating adherence subsystem at the personal level. Both pathways will eventually lead to an increase in HIVDR, which is reacted upon at the population level by researching and developing new drugs that are more forgiving with respect to adherence (e.g. long-acting drugs) and that have higher genetic barriers to resistance. Policy makers overly relying on these new ART regimens may shift focus away from high quality service delivery and HIVDR prevention measures. As described above, decreased quality of care may then impact the healthcare system burden at the population level and/or alter personal-level adherence.

The HIVDR system is influenced by several other complex problems at different points in the three subsystems. Food insecurity for example, may negatively affect adherence considering PLHIV have to take the ART with a meal each day. Other examples are political instability and disease outbreaks (such as the COVID-19 pandemic), which may destabilize the healthcare system, increase the burden on healthcare personnel and may cause PLHIV to have priorities other than adherence to ART.

Discussion

In this paper we approached HIVDR, by our knowledge for the first time as a CAS by combining the perspectives of experts from diverse disciplines. We visualized the CAS of factors influencing HIVDR in two ways: a layered and a clustered view. We then summarized this detailed systems map into three interconnected subsystems

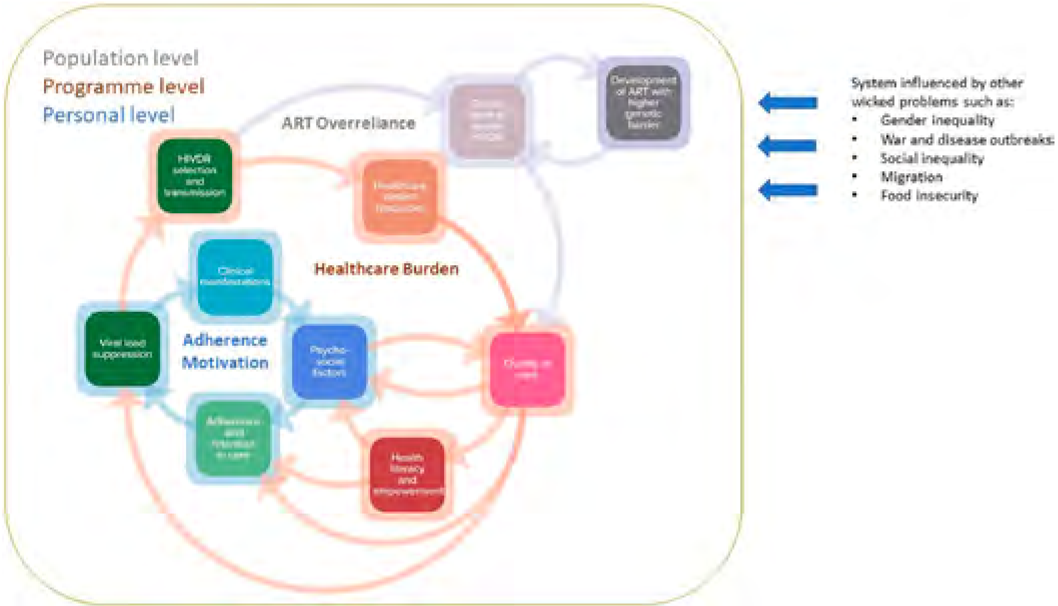

Fig. 3 Three identified interconnected subsystems driving HIVDR. The adherence motivation subsystem at the personal level, the healthcare burden subsystem at programme level and the ART overreliance subsystem at the population level. Each square in this map represents a cluster of Fig. 2, indicated by the corresponding colours.

influencing HIVDR emergence. We want to highlight that other ways of summarizing the detailed systems map are possible, but the three subsystems presented here were identified by the researchers as the most prominent ones throughout a process of analysis and stakeholder feedback.

The designed systems map provides insight in some properties of CASs such as emergence, adaptation and feedback and allowed to visualize the three interconnected subsystems [37]. The interplay between factors influencing adherence is an example of emergence, which indicates a phenomenon that cannot be predicted purely based on the elements related to it but which rather emerges from a complex interplay between the factors. Adherence is influenced by factors stemming from each of the five layers and is influenced at both personal, programme and population level. Whether PLHIV adhere to treatment or not depends on the interplay between those surrounding factors which are constantly changing over time. Adaptation describes how interventions in the system can lead to behavioral changes. Our systems map shows that the implementation of second-generation integrase inhibitors could lead to a change in adherence as a result of the overreliance of policy makers and doctors and depending on how the new therapy is introduced to the community and whether education and other support is provided. The feedback loops summarized here in the three subsystems reveal the interconnectedness between subsystems at different population levels and between factors of different layers and disciplines. This also underlines the need to reflect on the entire system surrounding HIVDR when planning an intervention.

An important shortcoming of this study is that only expert viewpoints were included. To make up for this, we aimed to include experts who have close contact with PLHIV and thus have insights in their perspectives. However, in order to design locally tailored interventions, the systems maps should be strengthened with insights from PLHIV and local actors. In follow-up work that has in the meantime been published, the adapted systems map based on the perspectives of local actors and PLHIV provided us with a better understanding of the personal and context dependent factors such as stigmatization or food insecurity [38]. This shifted the focus of the map with perspectives of local actors and PLHIV towards the "adherence motivation loop", compared to the work presented here. For other study sites, perspectives of PLHIV and other local stakeholders such as local doctors or politicians, religious leaders, and other people of local influence could also help us better understand the differences in perspectives between those groups and identify possible gaps between science and practice. We also need to acknowledge that the mapping was done based on facts but also viewpoints and experiences of international experts. Combining the expertise of multidisciplinary HIVDR experts in a systems map has allowed us to identify the three potentially interesting theories, represented by the three subsystems above, which may not have surfaced through disciplinary or purely quantitative research. This qualitative approach was important to deepen our understanding of the CAS, before future quantitative efforts on specific parts of the system can be done [39].

Applications

Our study illustrates the added value of qualitative methodology to visualize the complexity and dynamics of a system. This may help decision makers to gain insight into the systems complexity and to identify leverage points in order to design targeted and complexity-informed interventions. This methodology can be transferred to study HIVDR in specific settings or could be used to gain insights into other complex problems. Moreover, the content of the model presented in this study may (partially) be extrapolated to other chronic diseases such as diabetes or obesity in order to understand their drivers and feedback loops.

The conceptual model presented here also lays the basis for quantitative mathematical modelling of the factors influencing HIVDR. This will allow quantitative modelers to collect data on relevant parameters in the system to monitor any changes, desired or not, in the entire system. An important advantage of basing a quantitative model on this conceptual map lies in the multidisciplinary manner this map was developed, therefore identifying mechanisms which might not have been identified using a monodisciplinary approach.

Conclusion

We successfully visualized the CAS surrounding HIVDR which is influenced by a complex and interconnected system of factors, transcending disciplines and population levels. This allows us for the first time to study the emergent and adaptive properties of the CAS and to distinguish feedback loops. The model suggests that i) overreliance on ART with a low risk to HIVDR emergence may be a driver for future HIVDR against those same ART; ii) when exceeding a certain threshold, the burden on the healthcare system amplifies itself; and iii) adherence tends to vary given that it is very individual- and context-dependent and might therefore be difficult to influence directly. A deeper understanding of the different aspects of this system will help decision makers to identify leverage points in order to design targeted and effective interventions in line with the complexity of the system.

Abbreviations

ART: Antiretroviral therapy; CAS: Complex adaptive system; HIVDR: HIV drug resistance; PLHIV: People living with HIV; SSA: sub-Saharan Africa.

Supplementary Information

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Additional file 1. HIVDR as a CAS, visualized in layers. Each element represents a factor influencing HIVDR and each line represents a connection between two factors. Factors are organized in five layers according to their connection with biology, the individual, the social context, the healthcare system and 'overarching'. A detailed and interactive version of this map is included in Additional file 1 ([27], page 2).

Additional file 2. Interview guide.

Additional file 3. Interactive systems map and data set Excel file. Additional file 3 contains a weblink to an online interactive version of the systems maps included in the manuscript as Fig. 2 and Additional file 1. The second and third tab contain the data on the elements, connections, descriptions, connection type, layer category, subsystem category and cluster category necessary to recreate the interactive systems maps in Kumu. Moreover, the code for recreating both the layered view and the subsystem view are provided on tab 4 and 5.

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Disclaimer

The study sponsors had no role in the study design, the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Authors' contributions

AK: Study design, conduction of interviews, data analysis and interpretation, systems mapping, writing the manuscript. BDdC: study design, data analysis and interpretation, regular feedback, writing manuscript. GP: study design, regular feedback, data interpretation, editing manuscript. IM: data interpretation, editing manuscript. FM: regular feedback, editing manuscript. TRW: regular feedback, editing manuscript. RZS: data interpretation, editing manuscript. AS: design of interview guide, regular feedback, editing manuscript. NV: regular feedback, editing manuscript. LV: study design, regular feedback, editing manuscript. JK: data interpretation, editing manuscript. MJ: study design, data interpretation, regular feedback, writing the manuscript. AMV: Study design, study supervision, data interpretation, regular feedback, writing the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate

This project is not within the scope of the Belgian Law regarding research on human subjects of 7/5/2004 [40]. This study did not involve patients and the interview did not contain personal questions, but rather involved questions about expert opinions on an international scientific problem, therefore, ethics approval was not required. Before the interviews began, all experts were informed about study's aim and methods and provided informed verbal consent for participation in the study. Participation was voluntary and the experts were free to terminate the interview at any time. Data was collected between October 2018 and February 2020. Face to face interviews were done in Italy and South Africa. We obtained a statement of a local ethical committee confirming that ethical approval in Italy was not necessary. We also refer to the Italian law of 5 June 2019 "garante per la protezione dei dati personali". None of the four experts interviewed during a conference in South Africa, had the South African nationality. Ethical approval was not needed for this research as the South African Health Act of 2003 covers only research done on South African citizens. The interviewees were not study subjects but rather provided their professional opinion about a complex public health problem. Moreover, both the researcher who conducted the interviews and the principal investigator followed a South African good clinical practice course.

Consent for publication

Not applicable.

Competing interests

AV declares consultancy fee from Gilead.

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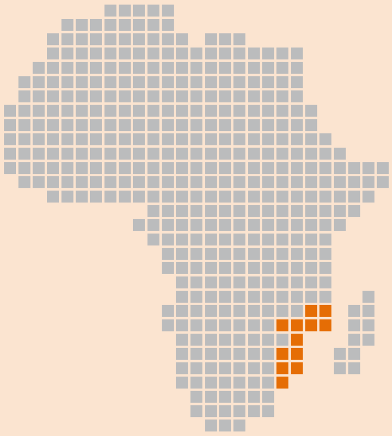
High Prevalence of Mental Health Disorders in Adolescents and Youth Living with HIV: An Observational Study from Eight Health Services in Sofala Province, Mozambique

PAPER



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CLINICAL AND EPIDEMIOLOGIC RESEARCH

High Prevalence of Mental Health Disorders in Adolescents and Youth Living with HIV: An Observational Study from Eight Health Services in Sofala Province, Mozambique

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Abstract

Adolescent mental health (MH) is a significant global health concern, which is extremely relevant when referring to adolescents and youth living with HIV (AYHIV). In Mozambique, ~52% of the population is <18 years and the country has the world's eighth highest HIV prevalence (insert citation). We performed an observational study to evaluate anxiety, depression, post-traumatic stress disorder (PTSD) and alcohol–drug abuse in adolescents and youth assessing health services in Sofala Province, Mozambique. From November 20, 2019, to November 20, 2021, all adolescents and youth (10–24 years) accessing one of the psychological services offered at 8 Servicios Amigos dos Adolescentes (SAAJ) of the Sofala Province were screened by a psychologist using the following standardized tools: Generalized Anxiety Disorder-7 (GAD-7) for anxiety, Patient Health Questionnaire-9 (PHQ-9) for depression, Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) for PTSD, and Cut down, Annoyed, Guilty, and Eye-opener Adapted to Include Drugs (CAGE-AID) for alcohol–drug abuse. Overall, 2108 adolescents and youth were included in the study (63% female, median age: 19 years). Of them, 1096 (52%) were HIV positive. AYHIV had higher scores at the four tools tested and for concomitant MH disorders (GAD-7, PHQ-9, PTSD-5, and CAGE). The multivariable logistic regressions showed a greater probability to be GAD-7 > 10 for women, [adjusting odds ratio (AOR): 1.46, 95% confidence interval (CI): 1.01–2.10], for workers (AOR: 2.18, 95% CI: 1.12–4.23) and people living with HIV (AOR: 1.78, 95% CI: 1.25–2.54). Higher values of CAGE (≥2) and PTSD (≥3) seemed to be associated only with HIV-positive status (AOR: 4.87, 95% CI: 3.72–6.38 and AOR: 1.73, 95% CI: 1.28–237). These data further reinforce the urgent need for a global health policy action with focused intervention on MH in AYHIV patients.

Keywords: adolescent, mental health, HIV, Mozambique, youth, SAAJ

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Introduction

Adolescent mental health (MH) is a significant public health concern that became extremely relevant when referring to adolescents and youth living with HIV (AYHIV).[1] Adolescence is a critical period of physical, emotional, and social development, characterized by increased vulnerability and challenges that may impact on adherence to HIV care and antiretroviral therapy (ART).[2] MH disorders constitute a major burden of disease for adolescents and youth, with suicide being the third leading cause of death for adolescents aged 15–19 years.[3] Half of all MH disorders begin by the age of 14 years and three-quarters by the 20 years.[4]

An estimated one in five adolescents experience a form of MH disorder before entering adult age. MH disorders can be severe and disabling and are associated with disrupting social and economic impacts.[3,4] Stigma, lack of awareness, and low resource allocation for MH programs contribute to making MH conditions one of the most debilitating and neglected challenges for individuals as well as for their families and communities.[4]

Children's and adolescents' MH research lags far behind research focusing on the adult population, especially in resource-limited settings.[5] When other comorbidities complicate MH assessment and treatment, the need for a better understanding of MH becomes even more critical. Children and adolescents living with HIV (ALHIV) may face an increased burden of mental and behavioral health disorders.[6] People living with HIV (PLWH) who also have MH diagnoses or symptoms are less likely to achieve viral suppression than those without the additional comorbidity.[7]

Mozambique rates eighth worldwide for HIV prevalence with 150,000 people infected per year. HIV/AIDS is the second leading cause of death in the country, accounting for 27% of all deaths.[8] In 2020, Mozambique HIV prevalence was 13.2% in adults aged 15–49 years, whereas epidemiological models estimate that 120,000 adolescents in the country currently live with HIV, of whom 80,000 are girls.[8]

Also, Mozambique is a vulnerable and fragile country with economic and political instability, a human development index among the lowest in the world (181/188), affected by several natural disasters such as Cyclone Idai and Kenneth and more recently also by the COVID-19 pandemic.[9–11] In a context that presents such multiple levels of complexity, MH becomes a priority that is as fundamental as it is dangerously neglected. In fact, in Mozambique, both the prevalence of MH disorders and the health coverage of mental patients at the local health unit level are not yet known.

Moreover, in Mozambique, 52% of the population are <18 years with a median age in the adolescent range (17.2 years).[8] To better understand the interventions to be delivered in this setting, we performed an observational study to evaluate anxiety, depression, post-traumatic stress disorder (PTSD), and alcohol–drug abuse in adolescents and youth assessing health services in Beira district, Mozambique.

Methods

This study aimed to evaluate the MH profile of a sample of Mozambican adolescents and youth accessing health services in Beira district with a focus on ALHIV.

To this purpose, psychological support was offered to all patients accessing the health adolescent service—[Servicios Amigos dos Adolescentes (SAAJ) (Friendly Services for Adolescents)]—of eight local health facilities (LHFs) of the Sofala Province. United Nations International Children's Emergency Fund (UNICEF) was also part of this activity involving specific HIV service delivery to adolescent girls and young women (AGYW).

These are defined as specific SAAJs because they provide an integrated health care service from counseling, testing, antiretroviral drugs dispensing, sexually transmitted infections (STIs) screening and treatment, psychological support, antenatal consultation, and for the first pregnancy of HIV-positive AGYW.

All patients who agreed to have a psychological consultation underwent a comprehensive evaluation including four standardized screening tools. The tools aimed to evaluate anxiety, depression, PTSD, and alcohol–drug abuse.

Study setting

Eight LHFs were enrolled in the study: seven located in Beira district: Ponta Gêa, Munhava, Macurungo, Nhaconjo, Mascarenha, Inhamizua, and Hospital Central da Beira, serving a population of ~300,000 people, and one outside Beira district, Nhamatanda,. All of these are in Sofala Province. Within each of these LHFs is incorporated a SAAJ supported by doctor with Africa Colleggio Universitario Aspiranti Medici Missionari (CUAMM), an Italian nongovernmental organization (NGO). SAAJs have been supported by CUAMM since 2013, and were initially established to improve the provision of sexual and reproductive health (SRH) services for adolescents, although they do provide the same services also for women.

The services offered include counseling in SRH, which incorporates contraception, ante- and postnatal care, as well as HIV and STIs prevention and treatment. All the services were established in collaboration with local and national health authorities. From November 1, 2019, a psychological support service was included in the activities of the SAAJ.

Each SAAJ is organized in different sections to ensure that individuals receive services respecting their privacy. No restrictions are in place for adolescents to access these sections. Notably, the SAAJ staff neither request nor require evidence of parental or caregiver consent from an adolescent to obtain the services.

Study design

From November 20, 2019, to November 20, 2021, the psychological support offered at SAAJs has been standardized using the following screening tools:

1. Generalized Anxiety Disorder-7 (GAD-7) for anxiety
2. Patient Health Questionnaire-9 (PHQ-9) for depression
3. Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) for PTSD
4. Cut down, Annoyed, Guilty, and Eye-opener Adapted to Include Drugs (CAGE-AID) for alcohol–drug abuse.

The mentioned tools were administered by a trained psychologist to all adolescents and youth (10–24 years) accessing one of the eight SAAJs for any health problem that spontaneously or invited performed the psychological consultation. The psychologist was available at each SAAJ once a week and his presence was scheduled and advertised through the local associations. Adolescents testing positive to one or more of the tools were taken in care at SAAJ or referred to the upper level of care.

Data from the psychological consultation have been recorded on an open-source online data collection tool (Kobo ToolBox) together with demographic characteristics (age, gender, occupation, education) and HIV status. For HIV-positive individuals' information about ART, knowledge of their HIV status and beliefs on their condition and MH implication were registered. All patients provided written informed consent and ethical approval of the protocol was obtained from the District Health Service, Ministry of Health of Mozambique (approved on November 9, 2019).

Statistical analysis

Data collection included patients' sociodemographic characteristics (i.e., gender, age, occupational status, and education). For PLWH, the information recorded also included duration of the disease, ART status, and reported effects of the impact of the disease on their lives and social relationships. In addition, questionnaires were administered to the whole sample to assess anxiety (using GAD-7), depression (using PHQ-9), PTSD (using PTSD-5), and substance abuse (using CAGE).

Data were summarized using counts and percentages for categorical variables; medians and interquartile ranges (IQRs) were utilized for continuous variables. Data were also stratified by gender and by HIV status (positive vs. negative) and differences between the groups were assessed using the Mann–Whitney test for continuous measures and the Fisher's exact test for categorical data.

Further, we evaluated characteristics potentially associated with anxiety status (GAD-7 > 10),[12] depression (PHQ-9 ≥ 11),[13] PTSD (PTSD-5 ≥ 3),[14] and substance abuse (CAGE ≥2)[15] using a multivariable logistic regression model.

Data were analyzed using Stata software, release 16.0. (Stata Corp, College Station, TX).

Results

The research was conducted on 2108 people including 1096 (52%) with HIV. Among the whole population (both HIV positive and negative), 63% were female, and the median age was 19 years (IQR: 13–24). Overall, 74% ($n = 1568$) were students, 16% unemployed, and 10% workers, no differences in occupational profile were detected according to HIV status. The HIV-negative adolescents and young resulted to have a higher education level: 82% of them declared to be attending or have attended university or secondary schools versus 66% of the HIV positive group ($p < 0.01$; Table 1).

Table 2 shows the characteristics of the HIV-positive patients, related to their diseases and their beliefs and feelings. The median duration of the disease was 24 months (IQR: 7–36) and 98.7% declared to be on ART first line. When exploring their beliefs and feelings, 94% declared ''to believe in antiretroviral treatment''; 38.3% ''to lose confidence in myself''; 16.2% ''to lose self-esteem''; 28.8% ''to feel stigma and discrimination''; 10.8% ''to have difficulties in family relationship, marriage, or sexual relationship''; and 12.5% ''to have many physical complaints without a specific disease,'' and there were no differences between male and female in these answers. Only the ''suicidal ideation'' seems to be more present in women (7.2% vs. 3.5%, $p = 0.047$; Table 2).

Table 3 gives the results of the MH screening tools for all adolescents and young tested, compared with their HIV status. Overall, GAD-7 resulted to be ≥10 in 9% ($n = 189$) of the sample, PHQ-9 depression was ≥11 in 7.3% of the sample ($n = 154$), PTSD-5 ≥ 3 in 12% of the sample ($n = 255$), and CAGE was ≥2 in 23% ($n = 491$) of all the adolescents and young tested. HIV-positive patients had higher scores at the three tools tested (GAD-7, PHQ-9, PTSD-5, and CAGE). Concomitant MH disorders (>1) are reported in 11.4% of the sample ($n = 240$).

Table 1. Demographic Characteristics of the Sample by HIV Status

	HIV⁻		*HIV⁺*		*Total*		
	N = *1012 (48%)*		N = *1096 (52%)*		N = *2108*		p*
Age, years (median and IQR)	20	13–24	18.5	12–24	19	13–24	<0.01
Gender (*n* and %)							
Male	381	37.7	398	36.3	780	37.0	
Female	631	62.3	698	63.7	1328	63.0	0.527
Occupation (*n* and %)							
Student	751	74.2	816	74.5	1568	74.4	
Worker	114	11.3	94	8.6	209	9.9	
Unemployed	147	14.5	186	16.9	331	15.7	0.078
Education (*n* and %)							
None	9	0.9	13	1.2	21	1	
Technical education	24	2.3	2	0.1	23	1.2	
Primary	148	14.7	360	32.8	508	24.1	
Secondary	679	67.1	676	61.7	1355	64.3	
University	148	14.7	45	4.1	194	9.2	
Missing	4	0.3	2	0.1	7	0.2	<0.01

*Fisher exact test or Mann–Whitney test, as appropriated.
IQR, interquartile range.

TABLE 2. ANSWERS OF HIV-POSITIVE PARTICIPANTS RELATED TO THEIR DISEASE

	Male		*Female*		*Total*		
	N = *398*		N = *698*		N = *1096*		p*
How long have you known about your HIV status? (months; median and IQR)	32	8–36	24	7–36	24	7–36	0.189
Mother-to-child HIV transmission	54	12.6	89	12.8	143	13	0.435
In ART (*n* and %)							
First line	396	99.4	686	98.3	1082	98.7	
Second line	2	0.6	12	1.7	14	1.3	0.229
I believe in ART treatment (*n* and %)	373	93.8	662	94.8	1035	94.4	0.505
I thought about suicide (*n* and %)	14	3.5	50	7.2	61	5.9	0.047
I lost confidence in myself (*n* and %)	142	35.7	278	39.8	420	38.3	0.557
Loss of self-esteem, yes (*n* and %)	55	13.9	122	17.5	178	16.2	0.284
Stigma or discrimination, yes (*n* and %)	112	28.3	203	29.1	315	28.8	0.948
Lack of family support, yes (*n* and %)	40	10.0	79	11.3	118	10.8	0.865
I have difficulties in my family relationship, marriage or sexual relationship (*n* and %)	49	12.4	83	11.9	133	12.1	0.978
I have many physical complaints without a specific disease (*n* and %)	52	13.0	86	12.3	137	12.5	0.759

*Fisher exact test or Mann–Whitney test, as appropriated.
ART, antiretroviral therapy; IQR, interquartile range.

For HIV-positive people compared with HIV-negative people, the median values were 6 (IQR: 4–9) versus 3 (IQR: 1–6) for GAD-7, $p < 0.01$; 5 (IQR: 3–7) versus 3 (IQR: 1–5) for PHQ-9, $p < 0.01$; 1 (IQR: 1–2) versus 0 (IQR: 0–1) for PTSD-5, $p < 0.01$; and 1 (IQR: 1–2) versus 0 (IQR: 0–1) for CAGE, $p < 0.01$.

The multivariable logistic regressions show a greater probability to be GAD-7 > 10 for women [adjusting odds ratio (AOR): 1.46, 95% confidence interval (CI): 1.01–2.10, $p = 0.042$], for worker versus unemployed (AOR: 2.18, 95% CI: 1.12–4.23, $p = 0.022$), and for HIV positive (AOR: 1.78, 95% CI: 1.25–2.54, $p < 0.01$). Also, for PHQ-9 ≥ 11, women and workers resulted to have greater probability (AOR: 1.67, 95% CI: 1.11–2.50, $p = 0.013$ and AOR: 2.80, 95% CI: 1.33–5.92, $p = 0.007$, respectively). Finally, higher values of CAGE (≥2) and PTSD (≥3) seemed to be associated with HIV-positive status (AOR: 4.87, 95% CI: 3.72–6.38, $p < 0.01$ and AOR: 1.73, 95% CI: 1.28–237, $p < 0.01$, respectively; Table 4).

Discussion

To the best of our knowledge, this is the first study investigating mental health in adolescents and youth—both HIV positive and HIV negative—in Mozambique.

In our study population, among 2108 adolescents and youth of whom 52% (1096) were living with HIV, we have found a high prevalence of MH disorders, even higher in the AYHIV. Specifically, the differences among the two groups were reported for anxiety 10.3% versus 7.6%, for depression 11.4% versus 7.6%, for PTSD 14.7% versus 9.3%, and alcohol and drug abuse 36% versus 10%, underlining a great burden and need for mental health support in young and especially in AYHIV. Our data are in line with previous studies that have reported higher rates of depression and anxiety in youth living with HIV,[16–18] while we reported higher prevalence compared with very recent data coming from South Africa.[19]

TABLE 3. RESULTS AT MENTAL HEALTH SCREENING TOOLS BY HIV STATUS

	HIV⁻		*HIV⁺*		*Total*		
	N = *1012* (*48%*)		N = *1096* (*52%*)		N = *2108*		p*
GAD-7 (median and IQR)	3	1–6	6	4–9	5	2–8	<0.01
GAD-7 ≥ 10 (*n* and %)	76	7.6	113	10.3	189	9	0.059
PHQ-9 depression (median and IQR)	3	1–5	5	3–7	4	2–6	<0.01
PHQ-9 depression ≥11 (*n* and %)	76	7.6	78	7.1	154	7.3	0.023
PTSD-5 (median and IQR)	0	0–1	1	1–2	1	0–2	<0.01
PTSD-5 ≥ 3 (*n* and %)	94	9.4	161	14.7	255	12.1	0.001
CAGE substance abuse (alcohol and drugs; median and IQR)	0	0–1	1	1–2	1	0–1	<0.01
CAGE ≥2 (*n* and %)	99	10.0	392	35.8	491	23.3	<0.01
Concomitant mental health disorders (>1)	74	7.3	166	15.1	240	11.4	<0.01

*Fisher exact test or Mann–Whitney test, as appropriated.
CAGE, Cut down, Annoyed, Guilty, and Eye-opener Adapted to Include Drugs; GAD-7, Generalized Anxiety Disorder-7; IQR, interquartile range; PHQ-9, Patient Health Questionnaire-9; PTSD, post-traumatic stress disorder.

TABLE 4. FACTORS ASSOCIATED WITH SCREENING TOOLS SCORES

	GAD-7 ≥10			PHQ-9 ≥11			CAGE ≥2			PTSD-5 ≥3		
	AOR	p > z	[95% CI]	AOR	p > z	[95% CI]	AOR	p > z	[95% CI]	AOR	p > z	[95% CI]
Age (years)												
10–14	1.03	0.357	0.97–1.09	0.98	0.569	0.92–1.05	1.00	0.878	0.96–1.04	1.01	0.552	0.97–1.06
15–18	1.23	0.157	1.07–1.49	0.88	0.449	0.78–1.55	1.30	0.238	1.26–1.84	1.05	0.522	0.83–1.12
19–24	1.43	0.204	1.27–1.89	1.20	0.301	1.02–1.85	1.18	0.202	1.06–1.34	1.41	0.152	1.25–1.86
Gender: female vs. male	1.46	0.042	1.01–2.10	1.67	0.013	1.11–2.50	0.80	0.065	0.62–1.01	1.28	0.122	0.94–1.75
Student vs. unemployed	1.37	0.270	0.78–2.39	1.43	0.282	0.75–2.73	0.88	0.474	0.61–1.26	0.96	0.836	0.62–1.47
Worker vs. unemployed	2.18	0.022	1.12–4.23	2.80	0.007	1.33–5.92	1.51	0.078	0.96–2.39	0.77	0.419	0.42–1.44
Primary vs. technical education	0.42	0.201	0.11–1.59	1.22	0.852	0.15–9.98	1.49	0.605	0.33–6.81	0.82	0.852	0.10–6.73
Secondary vs. technical education	0.45	0.213	0.13–1.59	1.64	0.636	0.21–12.55	1.15	0.852	0.26–5.14	1.03	0.972	0.22–4.73
None vs. technical education	0.30	0.328	0.03–3.34	Omitted			1.13	0.899	0.18–7.25	0.99	0.989	0.22–4.37
University vs. technical education	1.26	0.726	0.35–4.58	3.02	0.294	0.38–23.76	0.84	0.826	0.18–3.99	1.12	0.884	0.24–5.20
HIV^+ vs. HIV^-	1.78	0.001	1.25–2.54	1.05	0.792	0.72–1.53	4.87	0.000	3.72–6.38	1.73	0.000	1.28–2.35

AOR, adjusting odds ratio; CAGE, Cut down, Annoyed, Guilty, and Eye-opener Adapted to Include Drugs; CI, confidence interval; GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; PTSD, post-traumatic stress disorder.

This study aimed to evaluate the mental health profile of a sample of Mozambican adolescents and youth accessing health services in Beira district with a focus on the HIV population.

In our study population, ~54% of all young people and adolescents were found to be positive at least to one screening tool for anxiety, depression, PTSD, or drug–alcohol abuse. This was more evident in the young HIV-positive population. When comparing the screening results by HIV status, it resulted that 73% of the HIV-positive group had one or more pathological scores versus ~35% of non-HIV-positive young people. Differences among the two groups were found for anxiety 10.3% versus 7.6%, for depression 11.4% versus 7.6%, for PTSD 14.7% versus 9.3%, and alcohol and drug abuse 36% versus 10%, underlining the great burden and need for mental health in young people and especially in Mozambican HIV-positive young people.

As reported in Table 2, ~30% of adolescents and youth experience stigma or discrimination. As shown in other reports, HIV-related stigma is a key issue that impacts ALHIV across country-income settings by affecting the quality of life, health care access, and health outcomes. Stigma and discrimination experienced by HIV-infected youth through the broader community, as well as in clinical encounters, are significant barriers to HIV treatment, often leading to negative consequences and poor health outcomes.[4,20]

Our data show a strong need for mental services targeted to Mozambican youth and adolescents, especially if they are HIV positive. However, this is in contrast with recent estimates, where mental health services for youth and adolescents in resource-limited countries are rare with difficulties in both accessing and using mental health services.[21,22] It is estimated that there is one psychiatrist per 4–5 million adolescents in low-setting countries and only 1% of schools have mental health professionals as staff members.[22]

The importance of mental health services among young PLWH is a world-wide concern.[23] Mental services are necessary to prevent and treat MH disorders, but also psychological support is crucial to reduce stigma, increase the acceptability of the disease with all its positive effects (greater adherence to treatment, better quality of life), etc., which we have not investigated in this study and deserves future research. It is essential, in our opinion, that NGOs and governments initiate strategies that include mental health integration in HIV services within their health cooperation programs, especially in low-income countries where adolescents are already under severe stress due to future, political, and life perspective instability.

The risk of MH disorders and psychiatric illnesses of HIV-infected adolescents and youth, the specific needs of adolescents and the key issues of HIV-related stigma, disclosure of HIV to others, adherence issues, and the range of factors that may increase or decrease resilience in the face of transitions in care need to be considered in cooperation programs.[24–26]

In our study, we recognize some limitations. First of all, the sample included only adolescents accessing the health services and this could have left behind the most fragile part of this population, those not accessing care, where the burden of mental health could be even higher. Concerning the HIV-positive adolescents, it would have been interesting to investigate also their clinical status with particular reference to HIV RNA measurement to correlate it with the mental health profile. Unfortunately to date in Sofala Province, it is not possible to monitor viral load and not being able to tell young patients that they are no longer infectious can be an additional factor for stigma and substrate for MH disorders. Further, this was a cross-sectional study and no follow-up data were collected, but this could be implemented in future studies.

Our findings clearly showed that developing mental health programs for youth—especially HIV-positive patients—should be a priority for governments and policymakers to (1) reduce stigma, increase treatment adherence, and improve quality of life of these patients; (2) promote awareness and education activities on mental health and HIV in schools, communities, etc.; (3) extend mental health services through alternative delivery modalities such as teleconsultations and telepsychiatry, which may offer particular benefits to adolescents in need of mental health screening and treatment. Given the higher prevalence of disorders among HIV patients, an integrated mental health approach within the primary HIV care setting to address gaps in mental health service access and treatment should be implemented.

Authors' Contributions

Conceptualization of the study was carried out by F.Di.G., C.M., and E.N. Methodology was done by C.M. and F.T. Validation was taken care of F.Di.G., G.P., E.O., A.P., and I.C. Formal writing—original draft preparation—was by F.Di.G. Writing—review and editing—was by L.R., V.C., D.F.B., D.C.M., M.L., G.D.M., M.T., F.Del.G., G.P., and A.S. All authors have read and agreed to the published version of the article.

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Community- and facility-based HIV testing interventions in northern Tanzania: Midterm results of Test & Treat Project

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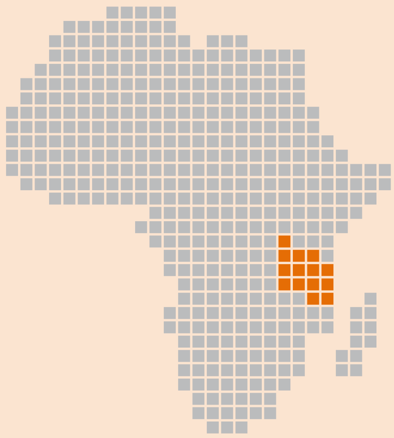

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Community- and facility-based HIV testing interventions in northern Tanzania: Midterm results of Test & Treat Project

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Abstract

Test & Treat Project offers universal HIV testing and access to antiretroviral treatment in Northern Tanzania. The current cross-sectional study provides midterm results on HIV testing and counseling activities through community outreaches and facility-based services. A total 255,329 HIV tests were performed: 198,451 (77.7%) during testing campaigns in the villages, 12,592 (4.9%) during special events outreach and 44,286 (17.4%) in the health facilities. Females represented 53.8% (23,809) among those tested in the health facilities, while males were the majority in the community (54.4%, 114,835). Over one third of tests (n = 104,605, 41%) were performed among first-time testers. The overall HIV positivity rate was 1.2%, ranging from 0.7% in the community to 3.8% in the health facilities and decreased over time. Using a multivariable analysis, a positive test result was associated with age $\geq$ 50 years (PR 1.22, 95% CI 1.11 to 1.34), with female gender (PR 1.61, 95% CI 1.50 to 1.73), being tested in health facilities (PR 5.00, 95% CI 4.65 to 5.36) and for the first time (PR 1.86, 95% CI 1.73 to 2.00). The estimated proportion of PLHIV who knew their status of the project area increased by 28.6% (from 35.7% to 64.3%) and 11.1% (from 57.7% to 68.8%) in the project areas of Shinyanga and Simiyu regions respectively. Reaching the first UNAIDS 90 target by the end of this project seems possible. Future strategies should focus on improving PITC coverage, implementing more targeted testing modalities, together with current universal community-based approach.

Introduction

The global HIV epidemic, despite progressive decline since the introduction of antiretroviral therapy (ART), still resulted in 1.7 million new infections in 2018, which means that the UNAIDS target of fewer than 500,000 new infections yearly by 2020 will not be met [1]. About

61% of these new infections take place in sub-Saharan Africa (SSA) [1], where awareness of HIV status among people living with HIV (PLHIV) ranges from 60 to 86%, according to Population-HIV-Surveys [2].

Scaling up HIV testing services is essential to reach the UNAIDS 90:90:90 targets [3]. HIV testing services (HTS) can be either conventional facility-based or community-based. Facility-based testing includes all tests performed at health facilities, either requested by the clients (voluntary counselling and testing, VCT) or health care provider-initiated testing and counselling (PITC). Community-based testing includes different modalities: home-, mobile-, venue-, workplace-based or as part of a campaign [4, 5]. Index testing involves tracing of sexual contacts and children of HIV clients who are enrolled in care and can either be performed at facility level or be integrated in community testing. WHO strongly recommends the implementation of community-based testing [6], since it showed higher population coverage and identified PLHIV at earlier disease stage compared to the conventional HTS in facilities [5]. Moreover, community testing may overcome barriers between clients and the health facilities (distances, costs, long waiting times) [5]. Since contexts vary depending on local HIV epidemics and cultural factors, UNAIDS suggests to tailor testing modalities according to specific regional policies and needs [7]. Previous universal test and treat trials showed that intensive community testing campaigns can have a strong impact on reaching the UNAIDS first 90 target. However, in light of the relatively lower yield of this universal approach, it could be questioned whether more targeted community testing strategies would be preferred [8, 9].

In Tanzania an estimated 78% of PLHIV were aware of their status in 2018; while in the same year 72,000 new HIV infections were estimated to have occurred in the country, with an overall prevalence of 5% [1]. In 2019 Tanzanian Government has introduced HIV testing guidelines, recommending PITC for all patients who access health facilities and community testing for those who have limited access to health care [10]. Despite these efforts, still many PLHIV remain undiagnosed: approximately 22% of Tanzanian women and 46% of men reported to have never been tested in their life [11].

Test & Treat Project (T&TP), a five-year programme which started in 2016, aims at implementing and supporting HTS and HIV care in Shinyanga and Simiyu regions in northern Tanzania.

The main objective of this paper is to describe midterm results of T&TP, displaying the different HIV testing modalities, their testing yields and the socio-demographic characteristics of the population reached. Secondary objectives are: i) to investigate socio-demographic factors and testing modalities associated with being tested for the first time and with being HIV positive; ii) to analyze the number of performed tests and the testing yields over time; iii) to estimate the impact of T&TP in contributing to the first 90 in the project catchment areas.

Methods

Study design

This is a cross sectional study, providing results of all testing services implemented and supported by T&TP between May 2017 and June 2019.

Study settings and population

The project supports four health facilities located in four districts: Shinyanga District Council, Shinyanga Municipal Council in Shinyanga region and Bariadi District Council and Itilima in Simiyu region. The estimated HIV prevalence is 5.9% and 3.9% in Shinyanga and Simiyu regions, respectively [12]. All facilities host a Care and Treatment Clinic (CTC) for HIV clients and hold some inpatient care capacity.

The catchment area is mostly rural and has a population of 461,932 inhabitants [13]. The study population includes all subjects who underwent HIV testing during the study period, performed by any of the T&TP supported testing activities.

Testing activities

T&TP implements community-based testing in the form of universal mobile outreach campaigns and testing during special events, and supports HTS within the supported health facilities. Testing and counseling procedures for all modalities are conducted in accordance with Tanzania National HTS Guidelines [10, 14].

Community-based testing is carried out by testing teams (one per health facility), composed by four trained nurses and a driver, who offer voluntary testing and counseling. The campaigns take place on normal weekdays, systematically visiting all villages of the catchment area on an approximately yearly basis. Special events are integrated in already existing community activities, such as festivities or other health preventive campaigns. The two modalities offer the same service, but the addressed population might be quite different.

After counseling all clients provide their consent and they are individually screened to assess their eligibility for HTS: clients are considered eligible if they were previously never tested for HIV or tested negative more than 3 months before. The testing algorithm is followed using finger-prick whole blood samples for serial rapid tests: SD BIOLINE HIV I/2-3.0 (Standard Diagnostics, Inc., Gyeonggi, Republic of Korea), followed by Uni-Gold HIV (Trinity Biotech Manufacturing Ltd., Bray, Ireland) only when the first one is reactive. The result is considered positive only when both tests are reactive [10, 14]. In case of discordant results between the two assays another health care worker should repeat the tests; and if the results remain discordant, the client is asked to repeat testing (following the same algorithm) after 14 days. Each newly identified positive client is counselled and offered to immediately go to the nearest CTC for enrollment using the project transportation (motorbike or car), or either accompanied later by a community health worker of the village or autonomously with the referral letter.

T&TP supports facility-based testing by appointing a designated and trained health care worker in each of the facilities, who is involved in HTS at all inpatient and outpatient departments.

Data collection

After each test performed, both for community- and facility-based testing, individual data are entered in the designated government testing registers of the National AIDS Control Program (NACP). Based on these, testing reports are compiled on daily basis for community-based testing, and on monthly basis for facility-based testing. These include the number of tests performed and of positive tests, aggregated by gender and age categories. At the facility, reports contain results of all tests performed, at all departments and by any modality. From these reports, aggregated data were collected in a dedicated project database.

A de-identified, anonymized and aggregated data set file is provided in the (S1 File).

Data analysis

All data were categorical and were reported as numbers and percentages. HIV testing yields were defined as the number of positive HIV tests divided by the number of tests performed. HIV tests and testing yields were stratified by age, sex, previous testing history (first-time tester or not) and testing modalities.

Associations between categorical variables were assessed using the Chi Square test. Factors associated with being tested for the first time were investigated using a log-link binomial generalized linear model. Factors associated with HIV positivity were investigated using a log-link binomial generalized linear model. Effect sizes were expressed as prevalence ratio (PR) with 95% confidence interval (CI).

Joinpoint regression analysis was performed to explore trends in number of tests and testing yield, and to identify possible points in time with a significant change. The best-fitting model and the number of joinpoints were estimated by means of a Monte Carlo Permutation method. The trends were expressed as monthly percentage change (MPC), which were estimated using log-linear regression models. Special events were excluded from trend analysis due to their episodic occurrence.

All tests were 2-sided and a p-value less than 0.05 was considered statistically significant. Statistical analysis was performed using the Joinpoint Regression Program, version 4.1.1 [15] and R 3.5 [16]. Based on previous reports of the regional HIV prevalence, demographics and testing cascade [12, 13], the contribution of T&TP to the first 90 was estimated. Details of methodology and results are shown in S1 and S2 Tables.

Ethical considerations

A specific Memorandum of Understanding was signed in 2016 between Doctors with Africa CUAMM and the Regional Medical Officers (RMO) of Shinyanga and Simiyu Regions before starting the implementation of the activities. The study was approved by the Institutional Review Board of National Institute for Medical Research (NIMR) of Tanzania (NIMR/HQ/R.8c/Vol.I/1447). Data clerks employed by the project transferred the data entry from governmental reports to a project electronical database. All managed data were aggregated and, therefore, anonymous. All data were stored in a password-protected server, which only the researchers, the project manager and coordinators had access to. On monthly basis, the testing activities in the community were reported at district level in order to inform the authorities about the results achieved and to avoid overlap with other stakeholders' projects.

Results

Test conducted by modalities and demographics

A total 255,329 HIV tests were performed: 198,451 (77.7%) during testing campaigns, 12,592 (4.9%) during special events and 44,286 (17.4%) in the health facilities. More than one third of the individuals accessing the health facilities for any reason (38.2%, 44,286 out of 115,979) were offered testing and counselling for HIV. Characteristics of tests performed are shown in Tables 1 and 2. Gender distribution varied among testing modalities: females represented 53.8% (23,809) among those who tested in the health facilities, while males were the majority in the community (54.4%, 114,835 among testing campaigns and special events; $p<0.0001$). Testing in the community involved younger participants (median 15–24 years) compared to health facility-based testing (median 25–49 years; $p<0.0001$). Comparing the two modalities for community-based testing, the proportion of males was higher in the special events than in the testing campaigns (64.1% versus 53.8%), and the special events attracted less children (2.5% vs 22.6% in the testing campaigns).

First-time testers and associated factors

Among the testers, 41.0% (104,605) declared it was their first in a life-time test, with a higher proportion among those younger than 25 years (59.2% versus 22.4%, $p<0.0001$). At

Table 1. Socio-demographic characteristics of performed tests according to testing sites and modalities.

	Community-based		Facility-based	p-value
	Testing campaign	Special events		
	N (% by column)	N (% by column)	N (% by column)	-
Overall	198,451	12,592	44,286	-
Females	91,684 (46.2)	4,524 (35.9)	23,809 (53.8)	<0.0001
Males	106,767 (53.8)	8,068 (64.1)	20,477 (46.2)	
Age:				<0.0001
≤14 years	44,847 (22.6)	312 (2.5)	6,712 (15.2)	
15–24 years	59,352 (29.9)	4,118 (32.7)	13,335 (30.1)	
25–49 years	77,302 (39.0)	6,829 (54.2)	19,369 (43.7)	
≥ 50 years	16,950 (8.5)	1,333 (10.6)	4,870 (11.0)	
First-time testers	84,034 (42.3)	3,600 (28.6)	16,971 (38.3)	<0.0001
Re-testers	111,417 (57.7)	8,992 (71.4)	27,315 (61.7)	

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multivariable analysis, first-time tests were more likely to occur during community-based testing (PR 1.02; 95% CI 1.01 to 1.04), among males (PR 1.05, 95% CI 1.04 to 1.07) and participants aged < 25 (≤14 years: PR 7.31, 95% CI 7.19 to 7.43; 15–24 years: PR 2.13 95% CI 2.10 to 2.17) and ≥ 50 years (PR 1.33, 95% CI 1.29 to 1.37) (S3 Table).

Testing yields, associated factors and trends over time

Overall, the HIV positivity rate was 1.2% (3,114 positives out of 255,329 tests performed), ranging from 0.7% in the community (0.6% in testing campaign and 1.2% in special events) to 3.8% in the health facilities. Summary of testing yields is shown in Tables 3 and 4.

HIV-positivity rate was higher in females compared to males both in the community (0.9% vs. 0.5%, p<0.0001) and in the health facilities (4.2% vs. 3.4%, p<0.0001) and varied among age categories (p<0.0001), with highest rate among those ≥ 50 years both in the community (1.4%) and in the health facilities (6.1%).

At multivariable analysis, being HIV positive was associated with age ≥ 50 years (PR 1.22, 95% CI 1.11 to 1.34), being female (PR 1.61, 95% CI 1.50 to 1.73), being tested for the first time (PR 1.86, 95% CI 1.73 to 2.00) and being tested in health facilities (PR 5.00, 95% CI 4.65 to 5.36). On the other hand, lower HIV positivity rate was associated with age ≤ 24 (age ≤14

Table 2. Characteristics of HIV tests performed among first-time testers and re-testers.

	All	Re-testers	First-time testers	p-value
	N (% by column)	N (% by column)	N (% by column)	-
Overall	255,329	150,724 (59.0)	104,605 (41.0)	-
Testing campaigns	198,451 (77.7)	114,417 (75.9)	84,034 (80.4)	<0.0001
Special events	12,592 (4.9)	8,992 (6.0)	3,600 (3.4)	
Facility-based	44,286 (17.4)	27,315 (18.1)	16,971 (16.2)	
Females	120,017 (47.0)	70,479 (46.8)	49.538 (47.4)	0.003
Males	135,312 (53.0)	80,245 (53.2)	55,067 (52.6)	
Age:				<0.0001
≤14 years	51,871 (20.3)	6,482 (4.3)	45,389 (43.4)	
15–24 years	76,805 (30.1)	46,062 (30.6)	30,743 (29.4)	
25–49 years	103,500 (40.5)	81,359 (54.0)	22,141 (21.2)	
≥ 50 years	23,513 (9.1)	16,821 (11.1)	6,332 (6.0)	

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Table 3. Positivity rates among first-time testers and re-testers.

	Positivity rate among all testers	Positivity rate among re- testers	Positivity rate among first-time testers
	N (% on all testers)	N (% on re-testers)	N (% on first-time testers)
Overall	3,114 (1.2)	1,781 (1.2)	1,333 (1.3)
Testing campaigns	1,267 (0.6)	791 (0.7)	476 (0.6)
Special events	156 (1.2)	121 (1.3)	35 (1.0)
Health facility-based	1,691 (3.8)	869 (3.2)	822 (4.8)
Females	1,871 (1.6)	1,105 (1.6)	766 (1.5)
Males	1,243 (0.9)	676 (0.8)	567 (1.0)
Age:			
≤14 years	147 (0.3)	19 (0.3)	128 (0.3)
15–24 years	520 (0.7)	306 (0.7)	214 (0.7)
25–49 years	1,888 (1.8)	1,175 (1.4)	713 (3.2)
≥ 50 years	559 (2.4)	281 (1.7)	278 (4.4)

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years: PR 0.12, 95% CI 0.10 to 0.14; age in 15–24 years: PR 0.33, 95% CI 0.30 to 0.37) (S4 Table). Comparing the two community modalities, individuals tested during special events were more likely to test HIV positive compared to those accessing the campaigns (PR 1.67, 95% CI 1.41–1.97).

The proportion of clients found HIV positive decreased over time from 2.0% in May 2017 to 1.0% in June 2019, with different slopes among the testing campaigns and the health facilities, as displayed in Fig 1. Estimated testing yield decreased in the first 14 months (MPC -9.69%, p<0.0001) then levelled (MPC –1.94%, p = 0.33) among testing campaigns, while it decreased over study period (MPC -1.26%, p = 0.04) within the health facilities, but with a more irregular curve.

Impact on the first 90

The estimation shows that during the study period, the proportion of PLHIV who knew their status increased by 28.6% (from 35.7% to 64.3%) and 11.1% (from 57.7% to 68.8%), in the project areas of Shinyanga and Simiyu regions respectively (see S1 Table).

The S2 Table shows that the estimated proportion of PLHIV in the area who did not know their status before the project started was 1.6%.

Discussion

Over a two-year period, T&TP has performed more than a quarter million HIV tests, identifying 3,114 positives. Furthermore, 41% of the tests were conducted among individuals who reported to have never been tested before in their lifetime. The positivity rate was slightly

Table 4. Positivity rates stratified by testing modalities, gender and age.

	HIV-positives / tested (%)					
	Campaigns		Special events		Health facilities	
Age classes	Females	Males	Females	Males	Females	Males
≤14 years	25/23,053 (0.1)	19/21,794 (0.1)	0/180 (0.0)	1/132 (0.8)	51/3,483 (1.5)	51/3,229 (1.6)
15–24 years	174/26,182 (0.7)	65/33,179 (0.2)	20/1,434 (1.4)	7/2,684. (0.3)	203/7,918 (2.6)	51/5,417 (0.9)
25–49 years	442/34,900 (1.3)	303/42,402 (0.7)	52/2,423 (2.1)	53/4,406 (1.2)	595/10,228 (5.8)	443/9,141 (4.8)
≥ 50 years	144/7,549 (1.9)	95/9,401 (1.0)	15/487 (3.1)	8/846 (0.9)	150/2,180 (6.9)	147/2,690 (5.5)

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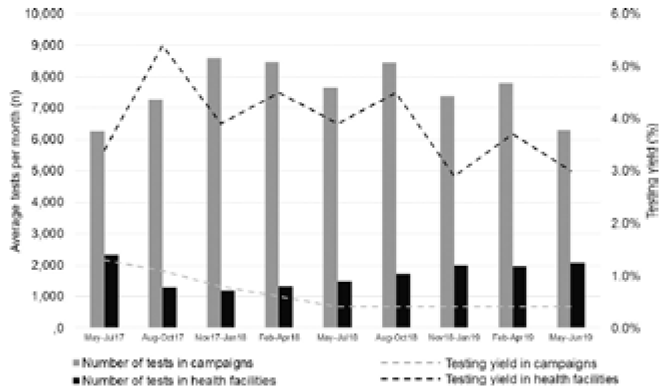

Fig 1. Number of tests performed and testing yields of HIV positives over time among the testing campaigns and within the health facilities. Number of tests is shown as average number per month in y-axis due the duration of the last sub-period (May-June 2019; 2 months) with respect to the duration of the other sub-periods (3 months). Data from special events were excluded from this model due to their episodic occurrence.

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lower than expected and decreased over time. We estimated that the project made a significant contribution towards UNAIDS first 90, aiming to reach the target by the end of the project.

Among the 255,329 HIV tests performed in the first phase of T&TP, the majority took place at community level (82.6%, 211,043), where a higher proportion of males and young adults were observed. This is in line with other reports in SSA [4, 17, 18], with the exception of home testing (not applied in our testing activities), which is more accepted among women [5, 19]. Males might be reluctant to access health facilities for many reasons, among which perceived lack of confidentiality in medical structures, fear of stigma and a feeling of masculinity translated as being strong and healthy and therefore avoiding to seek care [17]. On the other hand, women might feel more comfortable accessing facility-based HTS, given the major role played by routine HIV testing at antenatal clinics [11, 20]. Additionally, women who recently underwent testing at the health facility might be less inclined to participate at community campaigns.

PITC remains probably the greatest and most cost-effective contributor to the first 90 [3, 4, 21]; aiming ideally at 100% PITC coverage should therefore be a primary goal [10, 22]. However, in practice, coverage is often low as a result of multiple challenges, among which understaffing, lack of trained counselors, overcrowding of wards and clinics, and reagents stockouts [5]. Despite the provided support, the coverage of 38.1% at the T&TP facilities is lower than previously described in other research settings [23].

Across the different modalities, 41% of the tests were performed among participants who reported to be first-time testers, which is similar to observations made in a national survey in Kenya (43.1% of 16–64 years participants) [20], and a home-based testing intervention in Zambia (35.2%) [24]. This information could be obtained only by client's self-reporting and is therefore difficult to verify. Nevertheless, despite universal access to HTS being already recommended in Tanzania since several years [14], the high proportion of first-time testers indicates that this service continues to reduce a significant gap in people's knowledge of their HIV status.

Among our population the first-time testers were more likely to be males, below 25 years and to be tested in the community. These findings were also reflected in a large Tanzanian survey, where, among others, men, young adults (18–24) and people living in rural areas more often reported to never have been tested for HIV [11]. The higher proportion of first-time testers in the community-based approach might be explained by the fact that community HTS brings the service closer to healthier individuals, who otherwise might not have reasons to access conventional facility-based HTS. That is also why community HTS identifies HIV individuals at an earlier, mostly asymptomatic stage [18, 25]. During interviews with clients who participated to the testing campaign, it was indeed confirmed that the possibility to test nearby home was among the reasons to get tested (Josien de Klerk, personal communication).

The overall HIV positivity rate was 1.2%, which is slightly lower than the estimated proportion of PLHIV in the area who did not know their status before the project started (1.6%, see S2 Table). However, to note, an unknown number of PLHIV who were tested positive in our HTS might have already known their status, thus falsely increasing the positivity rate.

The yield was considerably higher in the health facilities (3.8%) than in the community-based approaches (0.6%). This contrast has been extensively described previously [4, 25, 26] and is explained by the higher proportion of symptomatic individuals being tested at facility level [25].

The relatively lower yields observed in the community might be related to many factors: i) universal community testing might not be able to target key populations, due to stigma; ii) some HIV negative individuals are likely to be retested over time; iii) the majority of individuals who are HIV positive in the community might be already identified and linked to care, due to interventions of other stakeholders; iv) HIV prevalence in these specific, mostly rural geographic areas might be lower than in previous regional reports, in which the urban positivity rates might have skewed the overall estimation.

As compared to the mobile outreach campaigns, the special events showed a higher positivity rate, as well as higher participation of men. Similar observations were made in a testing intervention in Northern Tanzania where event-based testing was compared with home-based universal testing [4].

Those who tested for the first time showed significantly higher yields compared to re-testers: Sharma et al reported this trend, defining the first-time testers among the target group which mostly benefit from HTS implementation [5] due to their lack of perception of risks [18].

Higher positivity rates found among females and individuals above 25 years old reflect the characteristics of HIV epidemics in SSA [1, 19]. However, we found the highest proportion of HIV positivity among the age category above 50 years, which slightly diverges from the country scenario described by the Population-based HIV Impact Assessment (PHIA), where prevalence among this category is lower than the age group 35–50 [12]. Other authors described higher prevalence among older adults in Tanzania [27, 28], suggesting that, against the perception that HIV/AIDS is mainly a disease of the young, interventions targeting older populations might be implemented in parallel with other strategies.

Finally, the positivity rate significantly decreased over the analyzed time frame and this was more evident among the tests performed in the community through testing campaigns. Despite the relatively short timeframe, this could reflect a general reduction of HIV incidence in Tanzania, as described for SSA [1]. On the other hand, as the project revisited each vicinity over time, individuals who are more concerned about their health status could have been more likely to get retested; leading to an overrepresentation of what could be considered a lower risk population. Social research showed that concerns about one's health status were indeed among the reasons for retesting. However, some re-testers were driven by mistrust of the sexual partner(s) and can therefore hardly be considered to be part of a lower-risk population (Josien de Klerk, personal communication).

The relatively low yield and perceived higher costs could be arguments to shift from universal community testing to more targeted approaches, such as index testing, self-testing and hot spot testing [22]. Also, a focus on increasing ART coverage for those populations with higher transmission risk could have more impact on incidence [9].

However, while implementing these focused strategies, there are many arguments in favor of continuing universal community-based testing modalities. First of all, targeted strategies are more laborious and time consuming, therefore, higher yield does not necessarily result in a higher absolute number of positives found [3, 8]. Secondly, the community testing activities, more than merely finding new positives, promote an extensive process of sensitization and counselling at community level, the value of which cannot be underestimated [19]. Furthermore, social researchers of T&TP reported that the community-based universal testing offers the ability to keep monitoring one's health status, to reassure oneself when felt at risk, or even to confirm a previously positive but doubtfully perceived test (Josien de Klerk, personal communication). Finally, in the effort to reach universal health coverage, outreach campaigns are an opportunity to offer integrated prevention and screening services for many diseases [8, 29].

This work has some strengths: i) its specificity to the context of Shinyanga and Simiyu regions, described among those with highest HIV prevalence in the country [12], ii) a very large sample size, which allows to draw important observations, iii) the comparison between community versus facility-based HTS.

The main limitation of this study was the use of aggregated data, which restricted the statistical analysis, precludes the identification of individuals who got retested over time and did not allow for linkage to individual clinical patient data.

Secondly, the proportion of newly identified cases was not measured since accurate data on PLHIV who already knew their status was lacking.

Thirdly, data on population testing coverage in the catchment areas of the outreach campaign are not available.

This midterm analysis was a useful tool for reviewing the implementation of HTS of T&TP. Its approach managed to reach and sensitize a large population, among which substantial proportions of men, young individuals and first-time testers. In order to be able to reach the first 90 by the end of the project, future strategies should focus on improving PITC coverage, continuing universal community-based testing, while expanding and optimising more targeted modalities, such as special events, key population approaches and index testing.

Supporting information

S1 File. Dataset.
(XLSX)

S1 Table. Calculation of contribution of first 90 in the catchment area of T&TP [30].
(DOCX)

S2 Table. Calculation of expected proportion of PLHIV still to be identified in the catchment area of T&TP.
(DOCX)

S3 Table. Multivariable analysis of factors associated with first-time test.
(DOCX)

S4 Table. Multivariable analysis of factors associated with HIV positivity.
(DOCX)

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Mental health needs of adolescents with HIV in Africa

PAPER

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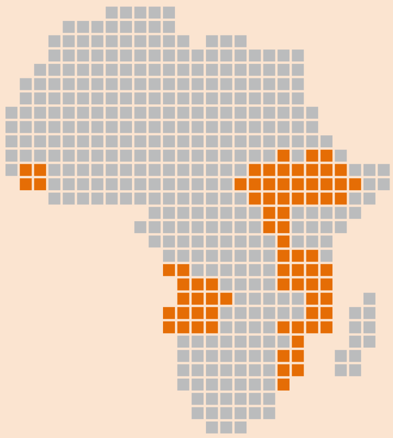

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Mental health needs of adolescents with HIV in Africa

The recent Article on the mental health burden of people living with HIV by Tiffany Gooden and colleagues is very inspiring.[1] The comprehensive study shows how people living with HIV have an increased risk of developing composite mental illness, depression, anxiety, and severe mental illness compared with people without HIV.

We want to bring attention to an often neglected topic that we believe will influence global mental health epidemiology in the coming decades—mental disorders in adolescents and youth living with HIV in sub-Saharan Africa.[2] We particularly want to share our experience from field research in Mozambique, a country with the world's eighth highest HIV prevalence, and where 52% of the population is younger than 18 years.[3] We did an observational study to evaluate anxiety, depression, post-traumatic stress disorder, and alcohol and drug abuse in adolescents and youth accessing health services in Sofala Province, Mozambique.

Data on 2108 adolescents and youths showed that people living with HIV had higher scores than people without HIV for all the four tools tested, with a prevalence of 7·5% anxiety, 10% depression, 12% post-traumatic stress disorder, and 23% alcohol and drug abuse.[4]

Unfortunately, mental health services for adolescents in low-income countries are rare, and there are difficulties in both accessing and using such services: it is estimated that there is one psychiatrist per 4–5 million adolescents, and only 1% of schools have mental health professionals as staff members.[5] In our opinion, it is time for governments and policy makers to invest in mental health programmes for adolescents living with HIV to reduce stigma, to increase adherence to treatment, and to improve quality of life. Mental health programmes should promote awareness and include educational activities on mental health and HIV in schools and communities, and they should pilot the efficacy of alternative delivery modalities such as teleconsultations and telepsychiatry for screening and care. Given the higher prevalence of disorders among people living with HIV, when drafting the mental health international research agenda, solutions for prevention and care of these individuals should be prioritised in the hope of a trend reversal in the coming years.

Our call is directed to the scientific, academic, and policy-making communities. Let us not forget the mental health needs of this population. Please—we are asking loudly for them.

We declare no competing interests.

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Authors' reply

We thank Francesco Di Gennaro and colleagues for raising an important point that the mental health of adolescents living with HIV must not be forgotten. Although we did not include adolescents in our analysis, our findings revealed that mental illness is an issue irrespective of age, with both younger (aged 18–39 years) and older (aged >40 years) people living with HIV at a higher risk than their counterparts without HIV.[1] In 2020, only 395 adolescents (aged 15–19 years) and 226 children (aged <15 years) were receiving HIV care in the UK.[2] However, using the same data source, study period (2000–20) and outcomes as our previous study,[1] we calculated a prevalence of 2·5% (5 of 199) for any mental illness in adolescents living with HIV (aged 13–19 years). Of adolescents aged 11–19 years in the UK, 10·4% have diagnosable depression, anxiety, or severe mental illness.[3] Having an HIV diagnosis adds additional psychological burden due to HIV-related stigma, stress related to HIV disclosure, and managing the condition during periods of developmental transitions.[4] Therefore, the low prevalence we present is likely indicative of underdiagnosis; although, the sharing of mental health diagnoses from secondary to primary care might be reduced for adolescents. Although the small numbers are difficult to interpret, these figures reinforce the importance of including adolescents in future research and health-care planning to ensure they too get the mental health care they need. We fully support the call from Di Gennaro and colleagues to ensure the international research agenda includes this group when discussing mental health care for those living with HIV.

We declare no competing interests.

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Neurocysticercosis in Low- and Middle-Income Countries, a Diagnostic Challenge from Oyam District, Uganda

PAPER

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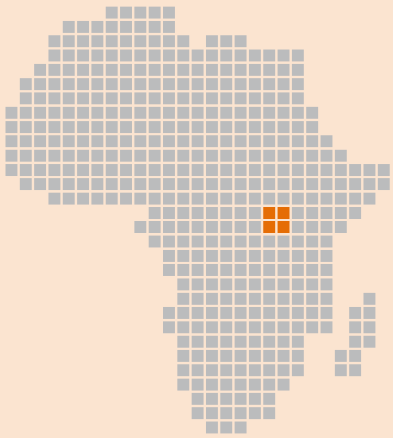

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MDPI

Case Report

Neurocysticercosis in Low- and Middle-Income Countries, a Diagnostic Challenge from Oyam District, Uganda

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Abstract: Background: In countries where *Taenia solium* is endemic, neurocysticercosis (NCC) is the leading identified cause of seizures, accounting for nearly 30% of all epilepsy cases and up to 2.8 million of Disability Adjusted Life Years. Diagnosis of this condition, however, is strictly reliant on either MRI or CT scan, which are poorly available in low- and middle-income countries (LMICs), creating challenges for proper case management and the acquisition of precise neuroepidemiologic data that may guide program and policy development. Methods: Here, we report the case of a 73-year-old woman admitted in a rural hospital in Northern Uganda, who presented with seizures and a progressive inability to walk. She was then diagnosed with NCC after a brain CT scan. Conclusions: This case study represents a rare example of the detection of NCC in a rural district hospital, thus suggesting the potential feasibility of a CT-scan guided diagnostic approach in low resource settings.

Keywords: Uganda; neurocysticercosis; zoonosis; LMIC; *Tenia solium*; computed tomography

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1. Introduction

Cysticercosis is a parasitic zoonosis of both humans and pigs caused by the larval stages of the cestode, a pig tapeworm, *Taenia solium.* [1]. NCC is listed by the World Health Organization (WHO) as one of the neglected tropical diseases, a group of pathologies that affect more than 1 billion people living in tropical areas [1].

In the life cycle of *T. solium*, humans are the definitive host, while swine are the intermediate host [2]. However, after ingesting infected eggs, humans can also act as intermediate hosts. More specifically, cysticercosis is acquired by humans after the ingestion of eggs by the fecal-oral route, e.g., caused by poor hand hygiene, not by eating undercooked pork that contains cysticerci, which is linked to intestinal taeniasis. Autoinfection may occur in humans if proglottids pass from the intestine to the stomach via reverse peristalsis [2]. In these cases, oncospheres hatch in the colon, infiltrate the intestinal wall, enter the blood circulation, and move to different tissues and organs where they mature into cysticerci within 3 months (typically 60–70 days) after the infection [2,3].

The lungs, liver, skin, subcutaneous tissues, heart muscle and other tissues, including the oral mucosa, can be invaded by cysticerci. Some cysticerci will migrate to the brain, causing NCC with potentially fatal consequences [3]. NCC represents the greatest burden of *T. solium*-induced disease, which is estimated to contribute to approximately 30% of epilepsy cases in areas where the parasite is endemic.

In 2010, worldwide, NCC resulted in more than 370,000 NCC-associated epilepsy cases, 28,000 deaths and 2.79 million Disability Adjusted Life Years (DALYs), a loss of the equivalent of one year of full health [4]. In eastern Africa, the disease has been reported in Tanzania, Kenya, Uganda, Burundi and Rwanda, and it is believed to be largely underestimated [5]. In Uganda, since the civil war, the establishment of piggeries and increased pig production by rural farmers has been encouraged as part of central government agricultural planning [6]. Pigs are considered low-input livestock, which can easily grow with minimal feeds, and local governments supply piglets to rural families to promote an alternative source of income. In a study conducted in 2009 in the Kamuli and Kaliro districts on 480 pigs, 8.5% were seropositive for the parasite of *Taenia solium* by B158/B60 Ag-ELISA [7].

2. Case Presentation

Here, we report the case of a 73-year-old woman suffering from high blood pressure and living in the Oyam district of Uganda, who presented in April 2022 to Anyeke level III Health Center with fever, tonic-clonic seizures and the progressive inability to walk, which started one day before. Anti-hypertensive and broad-spectrum antibiotic therapy were started and, three days later, the patient was referred to St. John XIII Hospital of Aber for further management. Here, she presented with severe headache, altered mentation and urine incontinence. On neurological examination, she showed neck stiffness, generalized hyperreflexia and lower limbs hypotonia, with preserved sensory function. She did not present focal neurological deficit and the pupils were hysochoric and normoreactive to light. A routine laboratory test showed no significant abnormalities, while HIV test and thick blood smears for malaria were negative. At hospital admission, lumbar puncture was performed, but cerebrospinal fluid analysis was inconclusive, with normal cell count, glucose, and protein levels. Therefore, a brain CT scan was conducted, which showed signs of multiple round heterodense cystic lesions with white dots, ranging from 4 mm to 8 mm in diameter (Figure 1). Lesions were randomly distributed in the entire supratentorial brain parenchyma, with no associated mass effect or perilesional edema.

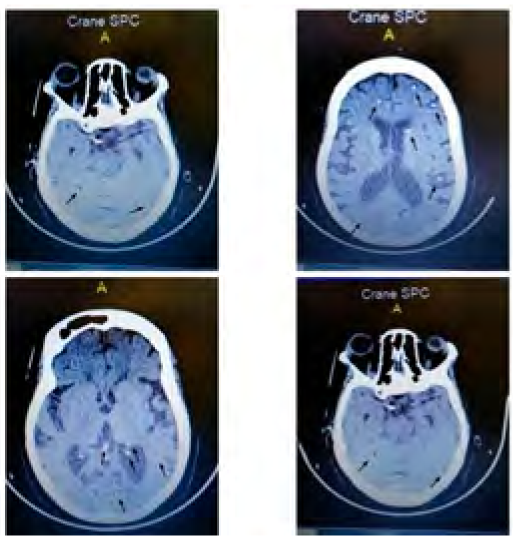

Figure 1. Brain CT scan showing multiple, randomly distributed, round cystic lesions with white dot sign of 4–8 mm in diameter.

A serological test for *T. solium* was not performed due to a lack of equipment at the hospital.

Based on the radiological features, a presumptive diagnosis of NCC was conducted and the patient was treated with albendazole 15 mg/kg/day and Desamethasone 0.1 mg/kg/day for 10 days. Due to a lack of supplies, Praziquantel 50 mg/kg was added on the third day after diagnosis and administered only for four days. Shortly after treatment was started, the patient showed signs of improvement, re-acquiring alertness and orientation on day 2 and the ability to walk on day 5. She did not develop new episodes of seizures. She was discharged seven days after treatment initiation.

3. Discussion

In LMICs (Low- and Middle-Income Countries), while there has been a significant improvement in diagnostic support for HIV/AIDS, tuberculosis, and malaria, significant gaps persists in the availability and quality of diagnostic services for several tropical diseases, even in the case of conditions of public health priority. In LMICs where *T. solium* is endemic, NCC is the leading identified cause of seizures [8], while in Uganda, only in 2010, NCC was estimated to be the cause of 9000 new cases of epilepsy and nearly 3000 deaths, leading to an economic burden as high as 8000 USD per NCC case [9]. However, in LMICs, diagnostic tools and technical skills to diagnose this condition are largely unavailable, and only a minimum share of infections are properly identified.

Neuroimaging with either computed tomography scan (CT) or magnetic resonance imaging (MRI) is considered the gold standard for the diagnosis of NCC [10]. Although a CT scan is less sensitive than MRI in identifying ventricular or cisternal cysts [11], its diagnostic performance for intraparenchymal lesions is comparable to that of MRI and is even superior in the presence of calcified lesions [12], with the additional advantage of requiring less technical skills in both interpretations and maintenance, being less expensive to run and generally more available in low resource settings [13]. Moreover, when combined with physical examination and clinical history, the specificity and sensitivity of CT-scans may rise up to, respectively, 99.5% and 98.9% for a single enhancing lesion [14].

In high income countries, where the socio-economic burden of the disease is incomparably lower than that estimated for LMICs, the use and availability of neuroimaging is widespread, and this inequality is further exacerbated by the lack of low-cost, point-of-care diagnostic tests. In a survey conducted by Yadav et al. [15], the most available diagnostic tools were determined to be point-of-care testing for HIV, malaria, viral hepatitis and syphilis, whereas radiologic imaging was among the least available.

In particular, neuroimaging ranks as one of the most unavailable diagnostic tools in LMICs, creating challenges for the proper recognition of several neurologic conditions and impeding the acquisition of precise neuroepidemiologic data for program and policy development [16]. In a study conducted in 10 LMIC in 2021, Uganda was shown to have the third lowest country-level availability of laboratory medicine and imaging diagnostics, with an overall availability of 34.4% [10]. However, in this study, the in-hospital availability of a CT scan was below 20% in all included countries. New perspectives on diagnosis came from a very recent paper defining the role of recombinant monoclonal-based *Taenia* antigen. From this study, the effectiveness of therapy may be monitored in the cerebrospinal fluid (CSF), serum/plasma, and urine using a recently created recombinant monoclonal antibody-based Ts Ag detection ELISA, with high sensitivity in the detection of extraparenchymal NCC. This method could be crucial in NCC control and diagnosis, especially in low resource settings where the possibility of CT scan or MRI is rare [17].

4. Conclusions

Data are lacking regarding the exact incidence of NCC, but our case represents a rare example of the detection of this condition in a rural district Hospital, thus suggesting the potential feasibility of a CT-scan guided diagnostic approach in low resource settings.

High quality, longitudinal studies are needed to explore the cost-effectiveness of such an approach in patients with a high index of suspicion for NCC.

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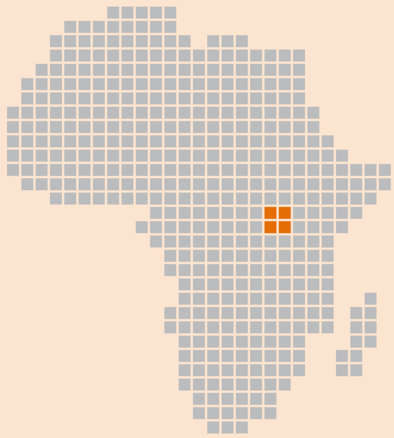

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STUDY PROTOCOL **Open Access**

Impact of antimalarial resistance and COVID-19 pandemic on malaria care among pregnant women in Northern Uganda (ERASE): protocol of a prospective observational study

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Abstract

Background: Uganda accounts for 5% of all malaria cases and deaths reported globally and, in endemic countries, pregnancy is a risk factor for both acquisition of *P. falciparum* infection and development of severe malaria. In recent years, malaria control has been threatened by COVID-19 pandemic and by the emergence, in Northern Uganda, of both resistance to artemisinin derivatives and to sulfadoxine-pyrimethamine.

Methods: In this facility-based, prospective, observational study, pregnant women will be recruited at antenatal-care visits and followed-up until delivery. Collected data will explore the incidence of asymptomatic parasitemia and malaria-related outcomes, as well as the attitudes towards malaria prevention, administration of intermittent preventive treatment, healthcare seeking behavior and use of insecticide-treated nets. A subpopulation of women diagnosed with malaria will be recruited and their blood samples will be analyzed for detection of genetic markers of resistance to artemisinin derivatives and sulfadoxine-pyrimethamine. Also, to investigate the impact of COVID-19 on malaria care among pregnant women, a retrospective, interrupted-time series will be conducted on at the study sites for the period January 2018 to December 2021.

Discussion: The present study will explore the impact of COVID-19 pandemic on incidence of malaria and malaria-related adverse outcomes, along with the prevalence of resistance to artemisinin derivatives and to sulfadoxine-pyrimethamine. To our knowledge, this is the first study aiming to explore the combined effect of these factors on a cohort of pregnant women.

Trial registration: This study has been registered on the ClinicalTrials.gov public website on 26th April, 2022. ClinicalTrials.gov Identifier: NCT05348746.

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Keywords: Malaria in pregnancy, COVID-19, Antimalarial resistance, Sulfadoxine-pyrimethamine, Artemisinin derivatives

Background

Malaria epidemiology and COVID-19

Over the last twenty years, tremendous progress has been made on malaria control, averting an estimate of 1.5 billion cases and saving 7.6 million lives. However, despite the astonishing results achieved in the last two decades, COVID-19 pandemic added a crucial challenge to the fight against the disease. On one side, malaria control relies heavily on individual choice to seek care, and early messaging targeted on reducing SARS-CoV2 transmission advised people to stay home in case of fever. On the other side, supply chains that allow the delivery of malaria commodities, such as insecticide-treated nets or antimalarial drugs, have been disrupted, and healthcare workforce constrained. All these factors contributed to a reverse of the reducing trend in malaria cases and deaths that shifted, respectively, from 227 million and 534,000 in 2019 to 241 million and 602,000 in 2020 [1].

According to the latest WHO World Malaria Report [1], Uganda accounts for 5% of all malaria cases reported globally. Oyam and Kole districts, selected for the study, are among the most affected areas in the country with, respectively, 407 and 361 new cases per 1000 inhabitants in 2019 [2]. In this context, particularly affected are children under five years of age (U5) and pregnant women. In the area where the project will operate, the rate of pregnant women that receives 3 or more doses of intermittent preventive treatment (IPTp) is less than 48% [2].

Concerning the impact of COVID-19 on malaria care in Uganda, a study conducted by Namuganga et al. [3]—except for a modest decrease in the proportion of malaria cases treated with ACT—documented no major effects on malaria disease burden. However, the study did not evaluate the impact of COVID-19 on antenatal care and malaria-related maternal outcomes. At this regard, in the pre-pandemic period (years 2018–2019) the mean antenatal care (ANC) attendance in the district of Oyam was of 1721 first visits per month, while an average of 472 women per month received at least 3 doses of IPTp.

Pregnancy associated malaria

Intermittent preventive treatment

In hyperendemic areas, pregnancy is a risk factor for both acquisition [4] of *P. falciparum* infection and for development of severe malaria [5]. Younger women, primi- or secundigravidae and HIV + women are particularly at risk [6]. Adverse outcomes for mothers and their infants include maternal anemia, low birthweight, prematurity, placental malaria, infant malaria, infant anemia and congenital malaria. Furthermore, adverse events are exacerbated by poor maternal nutritional status [7] and HIV coinfection [8].

Apart from consistent use of ITN, malaria control in this population is based on two pillars: intermittent preventive treatment of asymptomatic women and appropriate management in case of illness [9]. IPTp with sulfadoxine-pyrimethamine (SP) is still highly cost-effective in preventing the adverse consequences of malaria on maternal and foetal outcomes, even in areas with a high prevalence of quintuple mutant parasites [10], but coverage remains unacceptably low in several African countries [11]. For HIV-negative pregnant women, IPTp consists in the administration of at least three doses of SP (1500 mg sulfadoxine/75 mg pyrimethamine), in three antenatal care visits, starting early in the second trimester and at least four weeks apart [9].

In HIV negative women, a promising alternative to SP for IPTp is dihydroartemisinin-piperaquine (DHA-PPQ, 3 full strength tabs, 40 mg/320 mg, given once a day for 3 consecutive days), that showed to be more efficacious in reducing maternal malaria parasitemia and anemia at delivery, stillbirths and early infant mortality. In fact, SP efficacy may be decreased in areas with very high drug resistance and consistent presence of sextuple mutant haplotypes of *P. falciparum* [12]. However, there is no consensus as to the level of resistance at which SP-IPTp should be discontinued and an alternative regimen substituted.

For HIV positive patients, the current WHO guidelines recommend daily co-trimossazole prophylaxis.

Diagnosis and treatment

In most endemic countries, diagnosis heavily relies on the use of rapid diagnostic tests (RDT) which, however, are insufficiently sensitive in detecting the so-called subpatent infections—asymptomatic infections with low parasite densities—and infections due to parasites carrying the pfhrp2 and pfhrp3 gene deletions [13]. These limitations are partly overcome by microscopy and PCR-based tests, that can detect also low parasitemia [14], but the clinical impact of such infections is still matter of debate [15].

Treatment of malaria differs according to gestational age. For women in their first trimester with uncomplicated *P. falciparum* malaria, WHO recommends 7 days of quinine + clindamycin. From the second trimester on, experience with artemisinin derivatives is increasingly reassuring: no adverse effects on the mother or foetus have been reported. Thus, treatment of uncomplicated *P. falciparum* malaria consists of three-day course of oral artemisinin-based combination therapy (ACT). On the other side, treatment of severe malaria does not differ from the one prescribed to non-pregnant women. Parenteral artesunate is the treatment of choice in all trimesters.

Resistance to sulfadoxine-pyrimethamine and artemisinin derivatives

Another substantial challenge for malaria case-management is resistance to first line drugs, namely artesunate and ACT. A recent paper published by Balikagala et al. documented, for the first time in African history, the presence of artemisinin resistance in a longitudinal study conducted in Gulu, Uganda [16]. According to this study, single-nucleotide polymorphisms haplotypes associated with artemisinin resistance (i.e., mutations involving the gene locus *kelch13*) clearly showed the substantial difference of haplotypes between A675V isolates in Uganda and in Southeast Asia, which suggested that the mutation probably emerged independently in Africa and Southeast Asia. In Africa, potential factors that may contribute to a delayed emergence and spread of artemisinin resistance are the extent of acquired immunity, the rate of polyclonal infections and of chronic asymptomatic infections [17]. However, the constant selective pressure exerted by the widespread use of ACT pose a substantial threat for the emergence of clinically relevant forms of resistance.

Furthermore, a study conducted by Mbonye et al. [18] in 2015 documented a baseline prevalence of *Pfdhfr* and *Pfdhps* mutations—conferring resistance to SP in *P. falciparum*—to be 89% for the quintuple mutated haplotype and 3.9% for the sextuple mutated haplotype, reaching 16.7% after one dose of SP. Today's prevalence of the sextuple mutated haplotypes, potentially impairing the effectiveness of SP-IPTp is not known. Conceptual framework of the study is provided in Fig. 1.

Methods

Study design

This will be a facility-based, prospective observational study, using quantitative methods of data collection. Semi-structured questionnaires will be administered to collect the data. The study will be conducted on three separate populations, that is: "Cohort of pregnant women", "Antimalarial resistance sub-population", and "COVID-19 impact population" for which study methods are described separately.

Cohort of pregnant women

The data will be collected following a cohort of pregnant women presenting to antenatal care visits. We shall have both a retrospective cohort for the period January 2018 to December 2021 to determine the Impact of COVID-19 pandemic on malaria control and a prospective cohort for the period July 2022 to June 2024 to determine the incidence of malaria related adverse maternal and foetal outcomes. For the prospective cohort, recruitment will take place at ANC clinic. Collected data will explore the practices towards malaria prevention during the COVID-19 pandemic, malaria and COVID risk-perception and use of insecticide-treated nets, while and follow up will investigate access to antenatal care visits, administration of IPTp, healthcare seeking behaviour in case of fever. Follow-up will end at delivery, when maternal and foetal outcomes will be collected.

Antimalarial resistance population

To estimate the epidemiological burden of resistance to first-line drugs for treatment and prevention of malaria in pregnant women, a separate sub-population of women diagnosed with positive malaria parasitaemia will be recruited. Prevalence of antimalaria resistance will be evaluated with a cross-sectional analysis of genetic polymorphisms in plasmodium parasites isolated from blood samples collected for the period July 2022 to June 2024. Individuals eligible for this subpopulation will be all pregnant women presenting with microscopically confirmed *P. falciparum* malaria in the study sites. For individuals included in this population, clinical data will be collected, and blood samples to be sent to Italian National Institute of Health, Rome, for detection of genetic markers of resistance to artemisinin derivatives and sulfadoxine-pyrimethamine.

COVID-19 impact population

To investigate the impact of COVID-19 pandemic on malaria care, we will conduct a retrospective time-interrupted series. Data will be collected at multiple and equally spaced time points (monthly) comparing trends in two different time periods: "pre-pandemic", from January 2018 to December 2019, and "during pandemic", from January 2020 to December 2021. Facility-based aggregate data will be extracted about the following indicators: total admissions in maternity ward, total deliveries in maternity unit, women presenting to first ANC contact, women presenting to fourth ANC contact, administration of at least one dose of IPTp, administration of at least three doses of IPTp, number of pregnant women presenting to outpatient visits, number of pregnant women

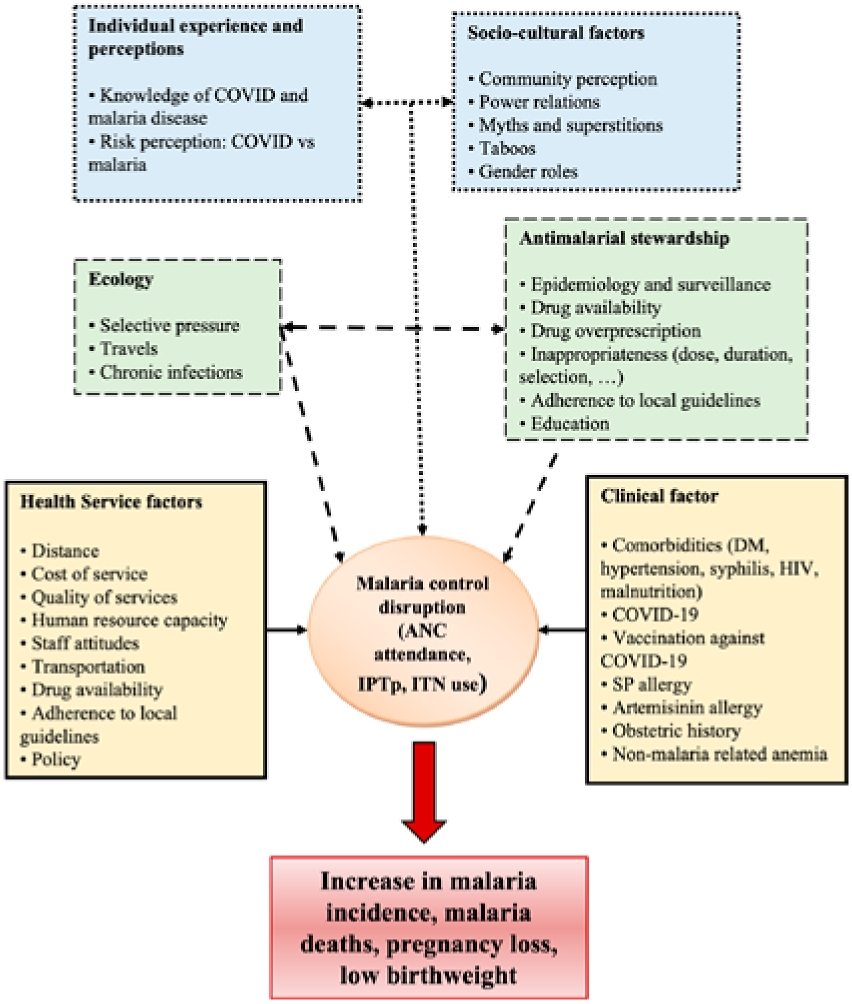

Fig. 1 Conceptual framework showing the possible impact of COVID-19 and antimalarial resistance on malaria care among pregnant women. Dashed line (green): antimalarial resistance; Dotted line (blue): COVID-19; Continuous line (yellow): both COVID-19 and antimalarial resistance

diagnosed of malaria during outpatient clinic, number of pregnant women diagnosed of severe malaria, total number of stillbirths.

Eligibility criteria

Cohort of pregnant women

Inclusion criteria:

All pregnant women at any gestational age presenting to the study sites, both at the emergency department, outpatient or ANC clinic will be eligible to participate in this study. Inclusion criteria will be:

(a) Pregnancy confirmed by obstetrical visit, positive urine pregnancy test or intrauterine pregnancy by ultrasound
(b) Provision of informed consent
(c) Plan to deliver in the hospital

Exclusion criteria:

a. Ongoing labor or delivery

Antimalarial resistance population

All pregnant women presenting to Aber Hospital and selected healthcare facilities with microbiologically confirmed malaria will be eligible for recruitment.

Inclusion criteria:

a. Microscopically-confirmed diagnosis of malaria
b. Pregnancy confirmed by obstetrical visit, positive urine pregnancy test or intrauterine pregnancy by ultrasound
c. Provision of informed consent
d. Agreement to avoid antimalarial medications given outside the Uganda Clinical Guidelines [19]

Exclusion criteria:

a. Too ill to participate in the study according to clinician judgment
b. Intake of any antimalarial medication before recruitment

Sample size estimation

Sample size estimation

- COVID-19 impact population

For the retrospective cohort investigating the impact of COVID-19, we shall use a *facility-based census* to include all pregnant mothers who sought care at the study sites for the period January 2018 to December 2021.

- Prospective çohort of pregnant women

For the prospective cohort, the sample size was estimated using the sample size estimation function in STATA12 for two-sample comparison of proportions. Null hypothesis: p1 = p2, (no difference in preterm birth rates), where p1 is the preterm birth rate among pregnant mothers diagnosed with malaria (exposed group) and p2 is the preterm birth rate among pregnant mothers with no diagnosis of malaria (non-exposed group). Assuming a type I error, alpha, of 0.050 for two-sided hypothesis, power of the study at 0.80, p1 = 0.075 and p2 = 0.039 based on the preterm birth rates reported in the Uganda Birth Cohort Study conducted from 2014–2016 in 12 districts in rural northern and southwestern Uganda [20]. Assuming equal number of participants in both groups, the required sample sizes in each of the two groups is 705. And after factoring in 10% for non-response in both groups, the total minimum required sample size is 1552 pregnant women (776 in each of the 2 groups).

- Antimalarial resistance population

Given the total population of 779,600 in Oyam and Kole districts. Given that, based on Uganda bureau of statistics (UBOS), the total number of pregnant women in the two districts is expected to be 5% of the total population (n = 38,980); the expected rate of parasitemia among pregnant mother is expected to be 27% (n = 10,525) [21]; the expected resistance to sulfadoxine-pirimethamine and artemisinin-derivatives are, respectively, 16% and 20% [16, 18]; using the sample size calculation formula developed by Daniel and colleagues [22] and a margin of error, alpha = 5% the minimum required number of pregnant women diagnosed with malaria is 203. Applying 10% correction factor and assuming an increasing trend the required minimum sample size for this population is 224 cases of microscopically confirmed malaria among pregnant women.

Sampling procedure and selection of participants

Sampling of health Units: The study will use purposive sampling to include Aber Hospital, Aboke HCIV and Atipe HCIII as the site for enrollment. This is based on the following criteria:

- Already existent good laboratory capacity for diagnosis of malaria.
- Presence of an experienced microscopist.
- Antenatal care visit volumes of at least 50 visits per month.
- Good quality of routine service offered to patients with malaria as per periodic quality of care assessment.

Participants coming to the sampled in healthcare facilities that will meet the eligibility criteria will be included in the study. Consecutive enrollment of participants will be undertaken up to when the minimum sample size required for the study will be met.

Study procedures

Microscopy

Thick and thin blood smears will be stained with 2% Giemsa and read by experienced laboratory technologists. Parasite densities will be calculated by counting the number of asexual parasites per 200 leukocytes (or per 500 leukocytes, if the count is < 10 asexual parasites/200 leukocytes), assuming a leukocyte count of 8000/µl. A blood smear will be considered negative when the examination of 100 high power fields does not reveal asexual parasites. Gametocytemia will also be determined from thick smears. Thin smears will be used for parasite species identification. At the time of delivery, recruited women will be screened for parasitemia on placental blood. This will be done by microscopy, with the same methods described above.

Molecular diagnosis and Plasmodium species confirmation

The blood samples of the patients will be collected using filter paper (Whatman 3 MM) during admission to the healthcare facility. The dried blood spots (DBSs) will be collected through a finger prick (three drops of blood per participant) on filter papers which will be dried and kept in plastic bags with desiccant and stored in boxes in a cool dry place at room temperature before being transferred at the ISS for molecular diagnosis and drug resistance analysis.

Shipment of the blood samples

The collected blood samples will be shipped to Italy for advanced polymorphism analysis. During shipment, all the samples will be stored in a dry, cool place at room temperature to the Italian National Institute of Health (Istituto Superiore di Sanità, ISS). To enhance local capacity building, one laboratory person from Aber hospital will attend a two weeks exposure at the reference laboratory in Italy.

Advanced analysis of polymorphism

Total genomic DNA will be extracted from filter blots (3MM Whatman) using the PureLink Genomic DNA Kits-Invitrogen, according to the manufacturer's recommendation. Parasite identification is based on nested PCR assay targeting the 18S rRNA gene [23]. The 18S rRNA gene is used as a target since it contains both highly conserved and variable regions for each *Plasmodium* species. The genus-specific PCR will be followed by *Plasmodium* species-specific PCR amplification. Amplicons from the second PCR will be separated by electrophoresis on a 2% agarose gel and stained with ethidium bromide for visualization using ultraviolet trans-illumination. The presence of parasitaemia will be confirmed when the expected band size corresponding to *P. falciparum*, *P. vivax, P. malariae and or P. ovale* will be identified.

Assessment of Plasmodium falciparum drug resistance.

Target *P. falciparum* drug resistance genes: *Pfk13* propeller, *Pfdhfr* and *Pfdhps*.

The polymorphisms analysis of the propeller domain of the *Pfk13* gene will be performed by PCR amplifications and subsequent sequencing. Analysis of *Pfdhfr* gene at codons 51, 59, 108 and *Pfdhps* gene at codon positions 436, 437, 540, 581, 613 will be done by means of amplifications and subsequent Sanger sequencing. Commercial oligonucleotide primer pairs for *Pfk13* will be obtained based on the published article by Taylor et al. [24], whereas for the analysis of *dhfr* and *dhps* genes primer pairs will be obtained based on the published article by Menegon et al. [25]. The obtained sequences will be compiled and analyzed by Accelrys DS Gene software. PlasmoDB gene identification no. PF3D7_1343700 (*P. falciparum* 3D7 strain) will be used as reference in the numbering of nucleotide and amino acid positions. Molecular studies will be performed only for research purposes and will have no impact on the clinical management of study patients.

HIV and syphilis screening

HIV and Syphilis will be measured according to the Uganda National Guidelines [19]

Blood glucose

Blood glucose will be measured by Glucometer "Accu-Chek Active", Narang Medical LTD.

Hemoglobin levels

Blood haemoglobin levels will be measured by Hemoglobin Testing System "Mission Ultra Hb", Narang Medical LTD.

Data analysis

For descriptive purposes continuous and ordinal variables data will be expressed as median with interquartile range. For categorical variables, percentages are calculated. Student's t-test or analysis of variance (ANOVA) will be used to compare normally distributed numerical variables. Mann Whitney U-tests and Kruskal–Wallis tests will be used to compare numerical variables when normality cannot be assumed, while chi-squared tests will be used to compare categorical variables.

Association analysis will be carried out to identify risk factors for Plasmodium infection and adverse maternal or foetal outcomes. We will compare behavioural factors and adherence to IPTp (and type of IPTp regimen) to the incidence of symptomatic/severe malaria and adverse neonatal or foetal outcomes (miscarriage, stillbirth, low birthweight). Multivariable logistic regression models will be used to identify independent risk factors for the same clinical outcomes. A forward and backwards stepwise approach will used to include variables into the models, with a limit of $P < 0.2$.

A P-value of < 0.05 will be considered statistically significant. Final analyses will be conducted after the end of patient recruitment while interim analyses are planned at half 7 months from the incipit. Statistical analysis will be performed with R-software (R Foundation for Statistical Computing, Vienna, Austria).

Discussion

According to the 2021 Essential Maternal and Newborn Clinical Care Guidelines for Uganda, for a woman with a normally progressing pregnancy the standard recommendation is a minimum of eight antenatal visits [26].

- Contact 1: Anytime ≤ 12 weeks.
- Contact 2: 13–20 weeks of gestation.
- Contact 3: 21–28 weeks of gestation.
- Contact 4: 30 weeks of gestation.
- Contact 5: 34 weeks of gestation.
- Contact 6: 36 weeks of gestation.
- Contact 7: 38 weeks of gestation.
- Contact 8: 40 weeks of gestation.

In addition, participants will be instructed to come to the clinic every time they are ill and will be evaluated at this point too. Outcomes will be assessed at the delivery or/and at the discharge if admitted to the hospital for any other causes related with the pregnancy or malaria (Table 1).

Data will be collected using semi-structured questioners and managed using REDCap electronic data capture tools hosted at "Catholic University of the Sacred Heart", Rome, Italy [28], and will be recorded on standard study data collection forms and will be reviewed for accuracy and completion. Upon resolution of data forms errors/missing values, the form will be ready for data entry. The obtained results will be entered into a database. A database will be developed to accommodate data entry and management of the study's data. The database will be created with a standard data management software package, such as Microsoft Office. A file for each study form will be created.

Ethical considerations

Pregnant women will be asked for written informed consent to participation to the study. In line with the Ugandan National Guidelines for Research involving Humans as Research Participants [29], women below the age of 18 will be considered emancipated minors. Every clinical outcome will be managed as per National Clinical Guidelines for the care of pregnant mothers. Counselling and related clinical support will be offered to participants who get pregnancy losses. This study will not introduce any clinical management strategies outside the national clinical guidelines.

We shall administer consent at two levels; first we shall administer and obtain consent for participation in the study and publication of future results and thereafter consent for collection and transportation of blood samples to Italy. The blood samples collected will be used only for the purpose of this study and will not be stored beyond the current study project. All unprocessed blood samples will be destroyed from the department of infectious disease, Italian National Institute of Health as biological sanitary waste, at the end of the project. The same standard of care will be guaranteed to all individuals irrespectively of participation. The dignity of study participants will be guaranteed by the investigators, as well as data confidentiality and the right to withdraw data and/or biological samples at any time. Consent to pregnant women and to mature and emancipated minors will be obtained according to Uganda Human Subjects Protection Guidelines [29].

For all malaria positive samples processed for molecular analysis in the present study, identifying information will be removed to provide appropriate protection of medical confidentiality and privacy. In this way, sensitive data cannot be linked or re-linked with identifiable human subjects, making anonymous each sample processed.

The polymorphisms analysis of the propeller domain of the *Pfk13*, *Pfdhfr* and *Pfdhps* genes will be performed by advanced amplifications techniques and subsequent Sanger sequencing in a highly specialized scientific laboratory. The blood samples collected in this study will be sent to a laboratory in the Italian National Institute of Health, Italy, in order to have access to the latest gene amplification techniques. To enhance local capacity building, one laboratory staff from Aber Hospital will be supported to attend a two weeks exposure at the reference laboratory in Italy.

The present study has been approved by the Lacor Hospital Institutional Research and Ethics Committee (prot. no LACOR-2022-95).

Dissemination of results

Results from this research will be disseminated at various fora, including local and international scientific conferences, the Ministry of Health, technical working groups and meetings at district offices in Lango region

Table 1 Study time points

Time point	Study procedures and data collection
Recruitment (ANC visit)	– *Full questionnaire* administered by a trained healthcare worker to collect information on demographic (eg. age, area of residence), socioeconomic factors (eg. education, occupation), number of previous pregnancies,, bed net ownership and use, adherence to malaria chemoprevention, barriers to administration of IPTp, use of ITNs, risk perception of COVID-19 and Malaria will be administered – *Clinical examination* assessing the general wellbeing and nutritional status of the woman, along with routine measurements (including weight, height, auscultation, blood pressure and temperature). Gestational age will be assessed, when available, by obstretic ultrasound and, if unavailable, by pelvis examination performed by experienced midwives – *Collection of blood sample* that will be analyzed as follows: oMalaria diagnostic test with microscopy and, when positive, parasite count. Positive samples will be sent to the ISS. Molecular diagnosis will be performed to confirm microscopy results and to discriminate between *Plasmodium* species. *Plasmodium falciparum* positive samples will be analyzed for detection of single nucleotide polymorphisms in *P. falciparum* genes associated with artemisinin and SP resistance. Women diagnosed with malaria will be treated and followed according to Uganda Clinical Guidelines o HIV diagnostic test o Hemoglobin levels o Blood glucose levels o Syphilis testing (RPR) All women found to be HIV+at study entry will be referred for further evaluation and treatment
ANC visits	– Physical examination – Tests to be performed as per study procedure: – HB estimation at first contact and at 26 weeks with every pregnant woman: – HIV testing: first contact and 36w contact – Malaria screening: each ANC visit (maximum 8 times). Malaria diagnostic test with microscopy and, when positive, parasite count. Positive samples will be sent to the ISS. Molecular diagnosis will be performed to confirm microscopy results and to discriminate between *Plasmodium* species. *Plasmodium falciparum* Positive samples will be analyzed for detection of single nucleotide polymorphisms in P. falciparum genes associated with artemisinin and SP resistance. Women diagnosed with malaria will be treated and followed according to Uganda Clinical Guidelines
Any spontaneous visits to the hospital related with pregnancy and/or malaria	– Standardized history – Physical exam including temperature, pulse, and blood pressure measurement – Patients who are febrile (tympanic temperature > 38.0°C) or report history of fever in the past 24 h will have blood obtained by finger prick for a thick blood smear. If the thick blood smear is positive, the patient will be diagnosed with malaria. If the thick blood smear is negative, the patient will be managed by study physicians for a non-malarial febrile illness. If the patient is afebrile and does not report a recent fever, a thick blood smear will not be obtained, except when following routine testing schedules – In patients with positive microscopy for *P. falciparum*, the first, pre-therapy blood sample collected as DBS will be sent for molecular diagnosis confirmation and for genetic analysis of antimalarial resistance to ISS. Furthermore, for hospitalized patients, parasitemia will be reassessed at day 3, as per WHO protocol [27] – Recruitment of the subpopulation of non-pregnant individuals will be undertaken at this time point
Delivery	– *Delivery information*: study staff will document details of the delivery, including date and time, type of delivery, estimated blood loss and any maternal, obstetrical or neonatal complications – *Fetal outcomes:* stillbirths, low birth weight, preterm birth – *Infant information:* Apgar score and birth weight with calibrated scales. At the time of delivery, women will undergo repeat rapid HIV testing based on national guidelines. If women are found to have become HIV-infected during pregnancy, both the mother and their newborn will be referred for care following local prevention of mother-to-child transmission guidelines [26] – Analyses of the Placenta Blood by microscopy to detect placental parasitemia

involving participation of local leaders (Cultural, technical, and Political leaders). To better reach enrolled communities, the findings of the study will also be disseminated in places of worship and community health service points using the community outreaches being organized by CUAMM and the district local governments in Oyam and Kole districts. Findings will also be published in a peer reviewed journal.

Abbreviations

ACT: Artemisinin combination therapy; ANC: Antenatal care; CI: Confidence interval; COVID-19: Corona Virus Disease 2019; HIV: Human Immunodeficiency Virus; IPTp: Intermittent preventive treatment in pregnancy; LMICs: Low- and middle-income countries; MOH: Ministry of Health; NGO: Non-Governmental Organization; PNFP: Private not for profit; Pfdhfr: P. falciparum dihydrofolate reductase; Pfdhps: P. falciparum dihydropteroate synthase; Pfk13: P. falciparum kelch 13; RDT: Rapid diagnostic test; SP: Sulfadoxine-pyrimetamine; UDHS: Uganda Demographic and Health Survey; UNCST: Uganda national council of science and technology; WHO: World Health Organization.

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Author contributions
FVS, FdG, JI, CM, GP, PL and AS conceived the study; FVS, FdG, JI, MIE, EO, EdV JA, VI, GdO, GP, CS, PL and AS contributed to study design; FVS, JI, EdV, VI, JO, BN and LO drafted the manuscript; FdG, RM, MF, SO, GP, PL and AS critically revised the manuscript All authors have approved the submitted version of the manuscript and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Availability of data and materials
All data that will be generated or analysed during this study will be either included in the published article (and its supplementary information files) or will be made freely available to scientists wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Declarations

Ethics approval and consent to participate
Study protocol has been approved by Lacor Hospital research Research and Ethics Committee (prot. no LACOR-2022-95). Enrolled subjects will be asked for written informed consent for participation to the study, publication of results and sample shipment to Italy.

Consent for publication
Consent for publication will be asked along with the consent to participate to the study.

Competing interests
The authors declare that they do not have any competing interests.

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Successful management of generalized tetanus in a 12-year old girl without anti-tetanus immunoglobulins: a case report

PAPER

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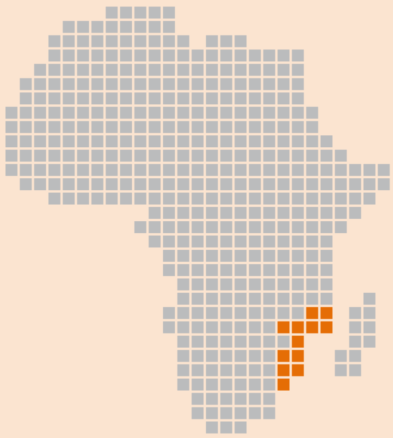

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Case Report

Successful management of generalized tetanus in a 12-year old girl without anti-tetanus immunoglobulins: a case report

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Abstract

In low-income countries tetanus is a major public health concern owing to a low immunization coverage and unclean birth practices. Although it is a vaccine-preventable disease, tetanus can be contracted across the life course. The disease is prevalent and harmful in newborn babies and their mothers when the mothers' are unvaccinated against tetanus. We report on a case of a 12-year-old girl who presented with general malaise, anorexia, dysphagia, trismus and dehydration, which rapidly developed into severe generalized tetanus and was successfully managed in a low-resource setting without the availability of human anti-tetanus immunoglobulins.

INTRODUCTION

Exposure to spores of the bacterium, *Clostridium tetani*, found in soil, saliva, dust and manure is the cause of the illness tetanus. The bacteria may enter the body through deep cuts, wounds or burns and subsequently affect the nervous system [1]. Although it is a vaccine-preventable disease, tetanus can be contracted across the lifecourse. The disease is prevalent and harmful among newborn babies and their mothers when the mothers are unvaccinated against tetanus (the vaccine being tetanus toxoid) [1]. In low-income countries, tetanus is a major public health concern owing to low immunization coverage and common unclean birth practices. Owing to limited surveillance systems in low- and middle-income countries, it is difficult to estimate the true burden of tetanus. It is estimated that in 2015, 79% of deaths are due to tetanus, ~44 612 globally occurred in south Asia and sub-Saharan Africa [2]. More accurate data are available on neonatal tetanus and WHO estimates that in 2018, 25 000 newborns died from neonatal tetanus [1].

The clinical presentation can include jaw and neck cramping commonly known as 'lockjaw' or 'trismus', muscle spasms often in the back, abdomen and extremities, as well as painful muscle spasms that are often triggered by noise, dysphagia, seizures, headache, fever and sweating and changes in blood pressure or tachycardia [3]. However, the onset of a generalized tetanus infection is not always associated with above described symptoms and its presentation with isolated oropharyngeal symptoms should also be considered in differential diagnosis with more common oropharyngeal infection as peritonsillar abscess [3]. Thus, a rapid correct diagnosis is mandatory as those with tetanus may deteriorate and become critical with symptoms including severe muscle spasms, autonomic dysfunction and/or respiratory failure [4]. Patients with suspected tetanus require wound care, tetanus immunoglobulins and antimicrobials. They should also be placed on an intensive care unit for treatment and monitoring. We report a case on a 12-year-old girl who presented with general malaise, anorexia, dysphagia, trismus and dehydration, which rapidly developed into severe generalized tetanus and was successfully managed in a low-resource setting without the availability of human anti-tetanus immunoglobulins.

CASE REPORT

A 12-year-old girl presented with 3 days history of body stiffness at a regional hospital in Mozambique (Fig. 1**A** and **B**). Ten days before she wounded her left thumb with a katana and was treated at a local Health Centre. Three days after the injury, she developed fever and irritability and a week later she developed dysphagia, very painful temporary muscle spasms associated with muscle stiffness, gait changes, asthenia, loss of appetite and increased sweating. The left thumb was oedematous and hyperaemic.

The neurological assessment showed uncontrolled trigeminal, facial and glossopharyngeal nerves with negative Babinski and meningeal signs. The biochemical test performed at admission, after 15 and 30 days are reported in Table 1.

Based on clinical history, examination and test results, the diagnosis of generalized tetanus was made. The girl was isolated and supported with oxygen (0.3 L/min). To control muscle spasms, a combined therapy was started including Diazepam 3 mg/kg per day three times per day and Baclofen 5 mg twice per day. As anti-tetanus immunoglobulins were not available, a

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312 | *Oxford Medical Case Reports*, 2022, Vol. 9, No. 9

Table 1. Biochemical results performed at admission, after 15 and 30 days

Parameter	Admission	15 days after	30 days after
WBC	$5.7 \times 10^3/\mu l$	$6.3 \times 10^3/\mu l$	$5.85 \times 10^3/\mu L$
LYM%	40.1%	30.5%	48.0%
NEUT	53.2%	NRA	42.6%
HGB	11.8 g/dl	11.7 g/dl	12.0 g/dL
HTC	39.0%	37.5%	39.4%
MCV	76.3 fL	77.0 fL	78.6 fL
MCH	23.1 pg	24.0 pg	24.0 pg
MCHC	30.3 g/dL	31.2 g/dL	30.5 g/dL
PLT	$343 \times 10^3/\mu L$	$339 \times 10^3/\mu L$	$290 \times 10^3/\mu L$
MBS	Negative	NR	NR
HIV	Negative	NR	NR
Stool parasites	Negative	NR	NR
Urea	5.18 mmol/L	NR	NRA
Creatinine	48.47 μ/L	NR	NRA
Uric acid	154.2 mmol/L	NR	191.0 mmol/L
AST	63.40 IU/L	NR	9.55 IU/L
ALT	51.31 IU/L	NR	8.52 IU/L
Proteins	64.51 g/L	NR	NRA
Albumin	35.0 g/L	NR	35.5 g/L
TB	NRA	NRA	6.81 mmol/L
DB	NRA	NRA	1.30mmo/L
ESR	NRA	NRA	21.00 mm/h

ALT: alanine aminotransferase; AST: aspartate aminotransferase; DB: direct bilirubin; ESR: erythrocyte sedimentation rate; HGB: haemoglobin; HTC: haematocrit; LYM: lymphocytes; MBS: malaria blood smear; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean cell haemoglobin concentration; NEUT: neutrophils; NR: not required; NRA: not reagents available; PLT: platelets; TB: total bilirubin;WBC: white blood cells

Figure 1. Generalized tetanus in a 12-year-old girl at presentation (**A** and **B**) and at discharge (**C**).

combined treatment, including Ceftriaxone 100 mg/kg twice per day, Metronidazole 30 mg/kg three times per day, hydrocortisone 8 mg/kg four times per day and Ranitidine 8 mg/kg twice per day, was administered.

The wound was also cleaned daily and medicated. Finally, two doses of Diphtheria, Tetanus, Pertussis Vaccine were administered, the first dose after 10 days from admission and the second after 30 days from the first dose.

The conditions improved slowly but constantly and she was discharged after 42 days (Fig. 1**C**).

DISCUSSION

Tetanus still remains a substantial problem, also in adults, in many low- and middle-income countries due to the lack or the disruption of vaccination programmes [5]. As most cases occur in low-income and middle-income countries where surveillance systems are limited, it is difficult to estimate the true burden of tetanus. The appropriate management of generalized tetanus includes prevention of toxin uptake, control of muscle spasms, wound cleaning and debridement and supportive care. The most recognized treatment for the neutralization of tetanospasmin is the human anti-tetanus immunoglobulins [6]. Moreover, the possibility to have a mechanical ventilation support is associated with improved outcomes as it allows spasms to be controlled by high doses of sedatives and, when available, neuromuscular blocking agents [7]. The particularity of this case is the successful management and follow-up of a late stage of generalized tetanus in a low-resource setting with lack or limited tests and treatment availability. Importantly, it was not possible to confirm the diagnosis by any laboratory tests and also routine tests were limited due to the shortage of reagents. Moreover, both the human anti-tetanus immunoglobulins and magnesium sulphate, that are considered a good option in order to reduce the need for other pharmacological agents, were not available [8]. In general, in low-resource settings, the scarcity of resources and appropriately trained staff leads this disease to have a high mortality [9]. In addition to the present case, this is an opportunity to highlight the necessity of rapid and innovative interventions particularly suited to low-resource settings.

It is now mandatory to strengthen and improve health systems both in terms of equipment and public health policies to promote vaccine campaigns and to achieve a vaccine coverage for all preventable diseases aiming to provide adequate health care to all individuals.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

FUNDING

None.

ETHICAL APPROVAL

No approval is required.

CONSENT

Written informed consent was obtained from the parents of the child for publication of this case report and any accompanying images.

GUARANTOR

Arlindo Muhelo.

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Subacute Cardiac Tamponade Due to Tuberculous Pericarditis Diagnosed by Urine Lipoarabinomannan Assay in a Immunocompetent Patient in Oyam District, Uganda: A Case Report

PAPER

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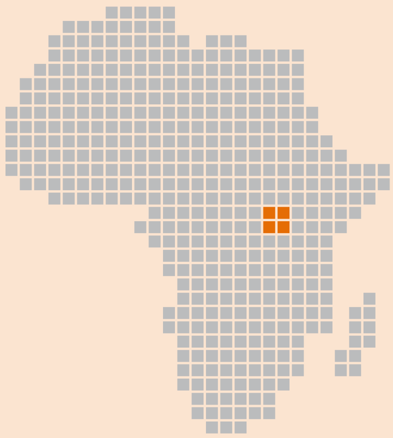

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Case Report

Subacute Cardiac Tamponade Due to Tuberculous Pericarditis Diagnosed by Urine Lipoarabinomannan Assay in a Immunocompetent Patient in Oyam District, Uganda: A Case Report

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Abstract: Background: Uganda ranks among the countries with the highest burden of TB the world and tuberculous pericarditis (TBP) affects up to 2% of people diagnosed with pulmonary tuberculosis worldwide. In Africa, it represents the most common cause of pericardial disease. Here, we present the case of a 21-year-old male patient who was diagnosed of cardiac tamponade due to tuberculous pericarditis with a positive urine LF-LAM. Case report: We report a case of a 21-year-old male living in Oyam district, Uganda, who presented to the emergency department with difficulty in breathing, easy fatigability, general body weakness, and abdominal pain. A chest X-ray showed the presence of right pleural effusion and massive cardiomegaly. Thus, percutaneous pericardiocentesis was performed immediately and pericardial fluid resulted negative both for gram staining and real-time PCR test Xpert MTB/RIF. The following day's urine LF-LAM test resulted positive, and antitubercular therapy started with gradual improvement. During the follow-up visits, the patient remained asymptomatic, reporting good compliance to the antitubercular therapy. Conclusion: Our case highlights the potential usefulness of a LF-LAM-based diagnostic approach, suggesting that, in low-resource settings, this test might be used as part of routine diagnostic workup in patients with pericardial disease or suspected extra-pulmonary tuberculosis.

Keywords: tuberculosis; LF-LAM; Uganda; cardiac tamponade; tuberculous pericarditis (TBP)

1. Introduction

Despite being a preventable and curable disease, tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. Before the emergence of the SARS-CoV2 pandemic, it was the leading cause of death due to an infectious disease and, globally, it is estimated that approximately 1,7 billion people (22% of the world population) are infected with *M. tuberculosis*, while in 2020, a total of 215,000 people died of TB [1].

In resource-limited settings, this number is likely to be underestimated, especially in TB-HIV coinfected patients, in which post-mortem studies estimate that TB may go undiagnosed in up to 45.8% of cases [2]. Uganda ranks among the countries with the highest burden of TB the world, with an estimated incidence rate of 200 cases per 100,000 population and a mortality rate of 35 per 100,000 population only in 2019. However, according to the 2015 Uganda National Tuberculosis Prevalence Survey, only 16% of patients with suggestive symptoms were investigated for TB [3], diagnosis being challenged by factors such as lack of training, low staff motivation, poor health literacy, and stigma [4]. This situation is likely to have deteriorated since the emergence of the COVID-19 pandemic [1], when Uganda was among the countries with the greatest shortfall in TB notifications and had a global impact on increasing TB diagnosis delays and poor outcomes [5].

Tuberculosis is transmitted by inhalation of aerosol droplets and most commonly affects the lungs. However, due to post-primary dissemination of *M. tuberculosis* bacilli through the lymphatic and cardiovascular systems, in 20–25% of cases the disease spreads to tissues and organs outside the pulmonary parenchyma, leading to the development of extra-pulmonary TB (EPTB). In the case of tuberculous pericarditis (TBP), the pericardium may be involved either by hematogenous spread or by contiguous inoculation from lung lesions [6]. Even though it was classically believed that rather than from the direct insult of acid-fast bacilli, pericardial effusion is the result of Th1 initiated inflammatory cascade [1], recent reports suggest that, in patients with culture-positive pericardial fluid, *M. tuberculosis* load as high as 3.91 log10 CFU/mL (range 0.58.96) [6].

Classically, four pathological stages of tuberculous pericarditis are recognized: (1) the dry stage, characterized by fibrinous exudation, abundant mycobacteria, early granuloma formation, and patients presenting with manifestations of acute pericarditis with chest pain and diffuse ST elevation; (2) the effusive stage, most commonly seen, in which serosanguineous effusion gathers within the pericardial space and patient presents with features of heart failure and/or cardiac tamponade; (3) the adsorptive stage, characterized by a volumetric reduction in the effusion, organization of granulomatous lesions pericardial thickening, and symptoms of constrictive pericarditis start to appear; (4) and finally, the constrictive stage, in which the formation of scarring tissue leads to diastolic impairment and no evidence of effusion is demonstrable in the pericardium.

Tuberculous pericarditis occurs in up to 2% of people diagnosed with pulmonary tuberculosis worldwide [7] and in Africa it represents the most common cause of pericardial disease [8,9]. However, in part because of the need of implementing invasive diagnostics, in low-resource settings, the demonstration of *M. tuberculosis* into the pericardial fluid is rarely obtained [9]. Lateral flow lipoarabinomannan (LF-LAM) assay is a simple, point-of-care test that detects a component of *M. tuberculosis* cell envelope on patient's urine. LF-LAM is endorsed by the WHO for the detection of TB in HIV-positive patients living in low resource settings, but its role in identifying disseminated tuberculosis in non-HIV-infected, immunocompetent patients is still a matter of debate [10].

Here, we present the case of a 21-year-old male patient who was diagnosed of cardiac tamponade due to tuberculous pericarditis with a positive urine LF-LAM.

2. Case Report

A 21-year-old man living in Oyam district, Uganda, presented to the emergency department of St. John XIII Hospital of Aber with difficulty in breathing, easy fatigability, general body weakness, and abdominal pain. At admission, he showed signs of severe dyspnea and hemodynamic instability, with blood pressure levels of 80/60 mmHg, 145 heart beats per minute, 30 respiratory acts per minute, and a peripheral oxygen saturation of 93% in room air. While taking clinical history, he reported that he attended to a burial two weeks before admission where he suspected to have ingested poisoned tea. Upon general physical examination, he presented as afebrile, poorly hydrated, and pale, with signs of increased external jugular vein pressure, muffled heart sounds, and moderate lower limb swelling. At abdominal examination, he manifested moderate distention with tender hepatomegaly, complaining of diffuse discomfort during palpation. Thus, abdominal US was performed, which detected congestive hepathopathy, mild ascites, gross right pleural effusion, and massive pericardial effusion. Chest X-ray (Figure 1) confirmed the presence of right pleural effusion and massive cardiomegaly. Thus, percutaneous pericardiocentesis was performed immediately through subxiphoid approach, and 100 cc of serosanguineous pericardial fluid was aspirated from the patient. The laboratory test showed HbsAg-negative, AST elevation, normal kidney function, and presence of pus cells at the stool analysis. Testing for human immunodeficiency virus (HIV) was negative. Pericardial fluid resulted negative both for gram staining and real-time PCR test Xpert MTB/RIF.

Figure 1. Chest X-ray postero-anterior view showing massive cardiomegaly due to pericardial effusion.

Therapy with intravenous furosemide and oral prednisolone 1 mg/kg was started. The following day, we collected 10 mL of urine and urine LF-LAM (Abbott Determine™ TB LAM Ag test) resulted positive, and antitubercular therapy with isoniazid 5 mg/kg/day, rifampin 10 mg/kg/day, pyrazinamide 25 mg/kg/day and ethambutol 15–20 mg/kg/day was added. After therapy initiation, the patient stabilized, difficulty in breathing resolved, and tolerance to exercise gradually improved. The patient was discharged on day 5. We were not able to perform the cultural examination due to lack of reagents in the setting where we were operating.

During the successive three follow-up visits, at 1, 2, and 3 weeks, the patient remained stable, asymptomatic, reporting general wellbeing, and good compliance with antitubercular and steroid therapy.

3. Discussion

After stabilization, identification of the etiologic agent leading to massive pericardial effusion is a challenging step for clinicians working in low-resource settings, as proper recognition of the underlying cause is critical for patient survival. In the effusive stage of tubercular pericarditis, ultrasonography may detect signs of serosanguineous pericardial effusion, while pericardial thickening, calcifications, and septal flattening are more frequent in the absorptive and constrictive stages [11].

On the opposite, cardiac tamponade with no radiologic inflammatory signs is more suggestive of malignant effusions. In low-resource countries, other etiologies of subacute cardiac tamponade due to effusive pericarditis are estimated to be rare [9,12].

For TB with extra-pulmonary organ involvement, diagnosis is challenged by the low sensitivity of conventional, sputum-based diagnostic approaches, since only a minority of those cases have traceable M. tuberculosis in their respiratory secretions. Furthermore, sputum samples are often difficult to obtain, and more sensitive techniques such as the automated real-time PCR test Xpert MTB/RIF (Cepheid Inc., Sunnyvale, CA, USA, and Foundation for Innovative New Diagnostics, Geneva, Switzerland) are expensive and require a reliable source of electricity [12].

Furthermore, in EPTB, both Xpert MTB/RIF and LF-LAM tests show very high NPV and specificity but suboptimal sensitivities, with performances varying in relation to the involved organs [12,13], while culture, although more sensitive, is limited by the fact that results are available only after several weeks and is thus of little or no help in clinical decision-making.

In the specific case of TBP, when combined with PCR- and culture-based tests, measurement of adenosine deaminase (ADA) on the pericardial fluid might be a valuable help in increase the sensitivity of etiologic diagnosis [14]. Moreover, when available, clinician can differentiate between exudative and transudative effusions by the Light's criteria [15]; a protein-rich, lymphocytic exudate is the most typical finding of PTB. In cases when a definitive microbiological diagnosis is not obtained despite extensive pericardial fluid analysis, or when pericardial fluid is difficult to obtain, pericardial biopsy might be warranted. However, apart from the limitations described above, the large-scale feasibility of those tests is further challenged by the inherent invasivity of the sampling technique; while histology, even in the few centers in low-resource settings where it is available [16,17], is strictly operator-dependent, scarcely reproducible, and has a sensitivity that does not exceed 10–64% [6]. Therefore, the ability to perform a rapid rule-in test using an easily obtainable biological sample represents an attractive option.

The glycolipid lipoarabinomannan (LAM), found in the outer cell wall of M. tuberculosis and mycobacterial species, is released from metabolically active or degrading bacterial cells during TB infection. During infection, LAM acts an important immune modulator, by inhibiting phagosome maturation and acting as a down-regulator of the secretion of interferon-gamma and interleukin-12 [17,18]. Its' structure is composed of a mannan "core" decorated by a single branched arabinan chain that have attached to them short oligosaccharides called "mannose capping motifs". It is considered a virulence factor associated with the pathogenesis of M. tuberculosis infection [19].

The first report on the use of LAM was published in 2001 by Hamasur et al., nevertheless it did not reach the sensitivity required for a diagnostic test; thereafter, a lateral flow test, the Determine TB-LAM Ag (Determine TB-LAM; Alere Inc., Waltham, MA, USA), was produced as a point of care (POC) test. Although easier to perform compared with the "Mtb ELISA" test, an employing polyclonal antibody preparation, first marketed by Chemogen Inc. (South Portland, ME, USA), the sensitivity of that test remained low, as demonstrated in numerous clinical studies [20].

To our knowledge, LF-LAM diagnostic accuracy was investigated in only one study, conducted by Pandie et al. on a cohort of 151 patients in South Africa. In this study, in which 31.5% of patients were HIV-negative, both urine LAM ELISA and LAM strip testing had high specificities, but sensitivity ranged between 17.4% and 27.6%. Moreover, both tests performed better in HIV-positive patients with a CD4 count below or equal to 100 cell/mm^3, while performing the same tests on pericardial fluid offered no additional diagnostic accuracy with reported sensitivity and specificity values of, respectively, 17% and 93% [19].

In low-income countries, a multisite study conducted in 2019 [20] showed that implementing the LF-LAM test is easily achievable and requires minimal logistical input and little extra workload for the healthcare workers. Moreover, the speed with which it provides results may improve patient outcomes by making it possible to start antitubercular therapy right away, especially in patients with severe forms of the disease [2,21]. This is especially true for patients with severe forms of the disease. However, despite its low cost and implementation barriers, evidence is still lacking on the usefulness of this test in non-HIV-infected patients with suspected extra-pulmonary tuberculosis, and clinicians are forced to rely on local epidemiology and presumptive treatments.

In HIV-negative TB patients the concentration of LAM in urine is very low, Neves et al. found that the true concentration of LAM in urine is in the range of 15 pg·mL^{-1} to several hundred ng·mL^{-1} [20,21] so urine concentration renders LAM detectable for most "ordinary" TB patients [22,23], for this reason a method based on very efficient monoclonal anti-LAM antibodies in combination with a concentration step using gold-coated nanoparticles [23,24] has been developed, reaching a sensitivity of 82% and a specificity of 100% in

HIV-negative patients with active TB. However, this method has some limitations such as a shelf life of the test of about 3 months and the presence of the matrix components due to the different composition of human urine that may mask and/or change the conformation of either antibodies or LAM epitopes in the assay, as well as the type of assay used [25]. The urine TB-LAM test is performed by applying 60 µL of fresh urine to the sample using a micro-pipette [26], there is a lack of information in the literature about the use of LF-LAM in end-stage renal disease. The use of serum antilipoarabinomannan (anti-LAM) antibody detection for the diagnosis of latent TB in a dialysis population has been evaluated in association with the tuberculin skin test [27].

4. Conclusions

In sub-Saharan Africa, tuberculosis is the leading cause of pericardial disease, the cause of effusive pericarditis remains unknown in most cases, with few centers adopting standardized diagnostic algorithms [9]. Our case highlights the potential usefulness of a LF-LAM-based diagnostic approach, suggesting that, in low-resource settings, this test might be used as part of routine diagnostic workup in patients with pericardial disease or suspected extra-pulmonary tuberculosis.

There is an increasing interest in point of care especially in low- and middle-income countries, such as ultrasound [28,29] and LF-LAM. These tools have a relatively steep learning curve, reasonable costs, and good sensitive profile, thus making it an attractive option in resource-limited settings with high incidence of TB. Our case report showed an important role for urine LF-LAM that was cost-effective, sustainable, and applicable, especially in countries with a high incidence of tuberculosis. Future perspectives may include standardized interpretation of LF-LAM and Xpert MTB/RIF combined results or the development and distribution of new generation, more sensitive LAM tests, and their integration with ultrasonography which is another very useful tool for the diagnosis of tuberculosis especially in resource-limited settings, as well as their integration into TB diagnosis algorithms in low-resource settings.

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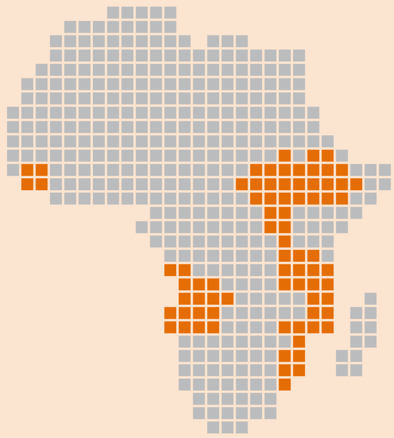
Guinea Worm Disease: A Neglected Diseases on the Verge of Eradication



PAPER

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Review

Guinea Worm Disease: A Neglected Diseases on the Verge of Eradication

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Abstract: Background: Dracunculiasis, also known as Guinea worm disease (GWD), is a neglected tropical disease (NTD) caused by a parasite (*Dracunculus medinensis*). In the past, dracunculiasis was known as "the disease of the empty granary" because of the difficulties patients had in going to work in fields or to school when affected by this disease. In tropical areas, the condition has been widespread in economically disadvantaged communities, and has been associated with reduced economic status and low levels of education. Methods: we searched PubMed, Scopus, Google Scholar, EMBASE, Cochrane Library, and WHO websites for literature addressing dracunculiasis published in the last 50 years. Results: by development and optimization of multi-layered control measures, transmission by the vector has been interrupted, but there are foci in several African countries with a high risk of compromising the results obtained in the control of this neglected disease. Conclusion: this review features state-of-the-art data on the infection prevalence, geographical distribution, diagnostics, parasite–host interactions, and the pathology of dracunculiasis. Also described are the current state and future perspectives for vector control and elimination strategies.

Keywords: dracunculiasis; Guinea worm disease; NTDs; Africa; Spirurida; neglected diseases

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1. Introduction

Dracunculiasis, also known as Guinea worm disease (GWD), is a neglected tropical disease (NTD) caused by a parasite (*Dracunculus medinensis*). The name of the disease comes from its prevalence in the Gulf of Guinea. In the past, dracunculiasis was known as "the disease of the empty granary" because of the difficulties patients faced in going to work in fields or to school when affected by this disease [1,2]. *Dracunculus medinensis* (DM) is a nematode and belongs to the order of Spirurida, tissue parasites that produce eggs containing larvae and spread free larvae in the water. The life cycle of this parasite requires arthropods as intermediate hosts. GWD is listed among the common filariases, and it has been widespread in economically disadvantaged communities in tropical regions, including Africa and South Asia, where it has been associated with reduced economic status and low levels of education [3]. Dracunculiasis was targeted for eradication several decades ago, because of its limited geographical distribution, predictable seasonality, and straightforward diagnosis [4]. In the past, it was thought that humans were the unique host, but recent studies have shown that larvae can also infect dogs, which complicates the success of eradication within the time frame foreseen by the Guinea Worm Eradication

Program (GWEP) [5]. In this review, we aim to summarize the current knowledge on epidemiology, clinical manifestation, transmission, life cycle, management, and control strategies. Table 1 shows the parasite species, their geographical distribution, and their location within the human host.

Table 1. Filarial parasites and Guinea worm.

Species	Distribution	Vectors	Adult Form Location	Microfilariae Location
Wuchereriabancrofti	Tropical countries	*Mosquito* spp.	Lymphatics	Blood
Brugia malayi and *B. timori*	East Asia (timori in Indonesia)	*Mosquito* spp.	Lymphatics	Blood
Loa loa	Central and West Africa	*Chrysops* spp.	Connective tissue	Blood
Dracunculus medinensis	Africa and India	Copepods	Connective tissue and Skin	
Onchocercavolvulus	Central Africa and South America	*Simulium* spp.	Skin	Skin
Mansonella perstans	Central Africa and South America	*Culicoides* spp.	Skin	Skin
Mansonella streptocerca	Central and West Africa	*Culicoides* spp.	Skin	Skin
Mansonella ozzardi	America (Central and South)	*Culicoides* spp.	Serous membranes	Blood and skin

2. Materials and Methods

We searched PubMed, Scopus, Google Scholar, EMBASE, Cochrane Library, and WHO websites (http://www.who.int (accessed on 2 October 2022) for literature addressing dracunculiasis, published in the last 50 years. We searched for the literature using the following search strategy: "Dracunculiasis [tiab] OR Guinea worm disease [mh] OR Dracunculus medinensisis [tiab] OR Spirurida, [tiab] OR GWD [tiab] OR water flies [tiab] OR Copepods [tiab])". All studies dealing with epidemiology, physiopathology, clinical characteristics, screening and diagnosis, therapy, management and eradication programs were included.

3. Epidemiology

The disease is typical of rural communities in low-income countries, whose survival depends on the presence of open surface water. For this reason, disease prevalence highly depends on rain patterns and climate. In arid areas, transmission occurs mainly in the rainy season, when surface water is more easily available [6]. In wet areas, on the other hand, the disease strikes more intensely in the dry season, when drinking water sources are few, as stagnant water collection points, such as wells and cisterns, are well-known parasite reservoirs [7].

GWD can affect people of all ages but is more common in young adults aged 15 to 45, with no difference in prevalence between males and females. In the 1940s, an estimated 48 million people were affected by GWD in Africa, the Middle East, and India, while in the 1980s, only 3.5 million cases per year were reported in 20 countries worldwide, including 17 in Africa. In the same period, the GWEP was initiated, and this led to a sharp reduction in cases in the following years. The number of reported cases dropped below 10,000 for the first time in 2007, falling further to 542 cases in 2012, 54 cases in 2019, and 27 cases in 2020 (of these cases, 1 in Angola, 12 in Chad, 11 in Ethiopia, 1 in Mali, 1 in South Sudan, and 1 in Cameroon) [8]. As of 30 October, according to the WHO, 198 countries, territories and areas have been certified free from dracunculiasis transmission. Seven countries remain to be certified, of which one (the Democratic Republic of the Congo) has no recent history of dracunculiasis [9]. The six other countries are either endemic (Angola, Chad, Ethiopia, South Sudan, and Mali) or are in the pre-certification phase (Sudan). According to WHO and CDC data, 15 Guinea worm cases were reported in 2021 [8,9]. Figure 1 shows the GWD human cases in African countries in 2021.

Figure 1. GWD human cases in 2021.

4. Transmission and Life Cycle

Humans contract GWD by drinking unfiltered water from wells and other stagnant water sources infested with copepods, "water fleas" too small to be seen with the naked eye. Guinea worm larvae are ingested by copepods which are ingested, in turn, by people who drink the contaminated water. In the human host, the copepod is dissolved by gastric juice, releasing Guinea worm infective larvae [4,5]. Once in the stomach, the larvae penetrate the gastric or intestinal mucosa and, after a period in the abdominal cavity, migrate up to the connective tissue. Here, *Dracunculus* larvae mature to adult worms and, after mating, the male worms die, and female worms mature and acquire a cylindrical, white and smooth body. The tip of the tail is pointed forming a blunt hook. Female worms take 9 to 14 months to reach adult form, and can measure up to 1 m in length. Approximately one year after infection, female worms migrate through the subcutaneous tissue, reach the surface and emerge from the skin, often at the lower extremities. Before they emerge, they create a painful and itchy blister on the skin site. Affected individuals normally seek pain relief by dipping the lower limbs in cold water, an action that leads to the rupture of the blister and the emergence of the worm from the skin. In this phase, the first stage *larvae* are released into the water and are then ingested by the copepods, reaching the final stage and re-starting their life cycle [10].

Alternatively, infection can occur in humans and dogs after eating aquatic animals, such as fish and frogs, that have ingested infected copepods and may be carriers of Guinea worm *larvae* without presenting signs of infection [11]. If these animals are, in turn, eaten raw or undercooked, they can release the larvae into the digestive tract of the second predator. This alternate cycle has made eradication of GWD more difficult, particularly in

Chad [12,13]. The guinea worm life cycle, adapted from the Centers for Disease Control and Prevention (CDC), is illustrated in Figure 2.

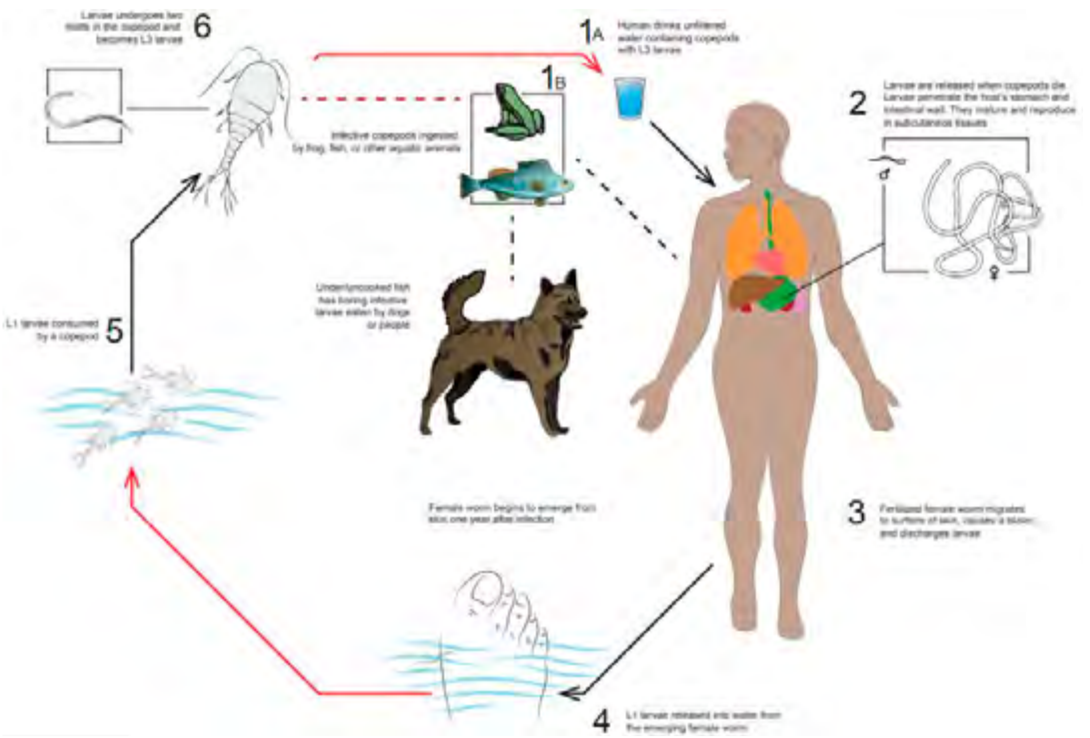

Figure 2. GWD life cycle.

5. Clinical Manifestations

Usually, patients remain asymptomatic for about a year after infection or may experience aspecific symptoms, such as lymphadenitis or hepatomegaly, due to the growth of non-specific granulomas in the liver and lymph nodes resulting from hypersensitivity or foreign-body reactions to dead male worms [14–16]. Concurrently, mature female worms reach the skin, causing a painful papule in the dermis due to the host reaction. Blisters are accompanied by redness and induration and may be preceded by systemic symptoms such as fever, urticarial rash, intense itching, nausea, vomiting, diarrhea and dizziness [15]. More than 90% of worms emerge below the knees, but they can emerge from anywhere in the body. Other common areas of worm surfacing are the head, arms, breasts, back, and scrotum. Usually, infected patients experience one worm emergence per year, but up to 20 (or more) worms may appear at the same time in one individual, and this painful process might last for more than 8 weeks [16].

Generally, patients obtain symptom relief by soaking the affected limb in water or by pouring water over the lesion, which accelerates the sloughing-off of the skin over the blisters [17]. After vesicle rupture, pain and systemic symptoms reduce. Female worms protrude their anterior end from the ulcer and discharge first-stage larvae (640 × 23 µm) into the water. It remains protruding for the following 2–6 weeks, releasing larvae each time the infected body part is immersed in water. After this period, the worm dies [9–11]. Worm protrusion is often exacerbated by secondary bacterial infections. In fact, the lack of adequate medical care usually results in superinfections—with an incidence rate that often exceeds 50% of lesions—leading to different complications: local cellulitis, abscesses, tetanus, septic arthritis or sepsis [18]. Tetanus is a serious complication of GWD. Articular manifestations include acute monoarthritis (due to direct invasion of the worm) or arthralgic syndrome secondary to deposition of calcifications in the joints [19]. Joint infection may lead to deformities or contractures, particularly in the knees, where it can evolve into a destructive arthropathy [20].

During manual extraction (see below), rupture of the Guinea worm can occur, leading to an intense inflammatory reaction, as the remaining part of the dead worm starts to degrade inside the body. This causes more pain, swelling and cellulitis along the worm tract [15].

During their migration, Guinea worms occasionally end up in ectopic sites such as the pancreas, lungs, periorbital tissue, testicles, pericardium and spinal cord, causing dreadful complications such as pleurisy, pancreatitis, compression of the spinal cord, inguinal adenopathy, compression and abscess formation. In pregnant women, larvae migration may also be responsible for placental bleeding and abortion [21]. Clinical manifestations are summarized in Table 2.

Table 2. Clinical manifestations of GWD.

Local	Vesicle, induration, redness
Systemic	Fever, rash, itching, nausea, vomiting, diarrhea, dizziness, hepatomegaly, lymphadenopathy
Joints	Destructive arthropathy
Ectopic sites	Pleurisy, pancreatitis, compression of the spinal cord, inguinal adenopathy, local compression and formation of abscesses, non-specific granulomas
Pregnancy	Placental bleeding, abortion

6. Diagnosis

Diagnosis of GWD is mainly clinical and it consists of observation of the worm emerging from the blister [15]. Epidemiological considerations have an important role, considering the fact that the blisters cannot be distinguished from other common skin lesions, such as bacterial infections or diabetic foot-related conditions [14]. The diagnosis can be formulated only when the female worm emerges, typically wrapping around a stick. During worm spillage, the diameter of the nematode should be assessed, since bodies that are smaller than 2 mm represent a risk factor for worm body rupture [19]. Active larvae can be obtained by immersing the protruding adult female in a small tube or container with water. First-stage larvae, with their characteristic pointed tails, can then be observed under a microscope.

Despite the simplicity of diagnosis, GWD can be misdiagnosed due to the initial symptoms' non-specificity [14]. In addition, in countries where the two parasites are co-endemic, differential diagnosis with *Onchocerca* spp is needed, because of their similar clinical presentation and to inform public health officals in charge of both Guinea worm and onchocerciasis control campaigns. In addition, clinicians should not miss the opportunity to provide correct treatment for *Onchocerca* infections [22–24]. Furthermore, when available, species identification allows for better surveillance. Thanks to genomic analysis, the common origin of animal and human infections has been proven [25,26] and new *Dracunculiasis* species are now under study in Vietnam (WHO-defined GWD-free country) [27,28].

Radiological diagnosis is also possible, even if it generally represents an occasional finding. Case reports of breast location are described during mammogram screening [29–31]. A typical radiological finding of GWD is the calcification sign. Calcification occurs once the gravid female dies inside the soft tissue. Thus, even when the imaging procedure is performed for pain complaints and not for screening, GWD radiological findings indicate only previous contact with parasites, and no active infection [32]. However, radiography can suggest a relation between systemic symptoms and previous Guinea worm infection. In a case report from Chad, X-ray observation of typical calcifications made clinicians aware of a rare form of past GWD infection related to new onset asthma [33]. In addition, a prospective study correlated localized myalgia (55%), chronic monoarthralgia (35%) and chronic knee synovitis with previous dracunculiasis in view of radiological findings (in two cases, eosinophilia was also present in the synovial fluid) [34].

It is still important to consider that GWD is not the only helminthiasis showing radiological signs. Usually, radiography shows a characteristic long, string-like, serpiginous calcified lesion within the soft tissues. Still, morphological differential diagnosis should rule out other parasite infections: much smaller calcifications located into the hands suggest *Loa loa* and *Onchocerca volvulus*; while multiple "rice grain" calcifications along muscle fibers are indicative of cysticercosis. Generally, these radiological features orientate to an etiological diagnosis. Diagnostic problems can occur when the worm has partially disintegrated, and calcifications are amorphous [32–34].

Concerning laboratory values, eosinophil count is often increased [35]. Serological tests can be considered to prove contact with *D. medinensis*. In consideration of possible cross-reactions with other nematodes, ELISA and western blot detection of IgG4 has been observed to obtain the best sensitivity and specificity [35]. A possible confirmation of these findings can be assumed by recent studies by Priest et al. for the realization of multiplex bead assay for seroprevalence assessment among dog populations in endemic areas [36,37]. Nevertheless, serological tests are not included among tools for either seroprevalence assessment or as confirmation tests [38].

7. Treatment and Management

First-line treatment of Guinea worm active infection consists of removing the female worm when it comes out of the skin and pulling it out gently to avoid rupture or returning it inside the wound. Worms must be alive during extraction. Usually, a gauze or a small stick is used to allow the worm to roll around it, continuing to exert some traction to bring it out. This is a long process that can take hours or days, because the worm can be longer than a meter. Two actions facilitate the exit of the worm: dipping the affected body part in a bucket with water (to avoid contaminating drinking water) and squeezing the bump to empty the adult worm from the *larvae*, so that it is thinner and can exit from the wound more easily [39,40].

There is no oral anthelmintic medication available for dracunculiasis. Support therapies such as anti-inflammatory drugs and painkillers can be used to reduce edema and pain. Along with frequent dressings with antiseptic solutions, antibiotic ointments may be applied to blisters to avoid wound superinfections. Until the whole worm body has been pulled out, the wound must be covered with medicated gauze and, until successful eradication, an infected person is not allowed to enter drinking water sources [40]. Tetanus vaccination is recommended. GWD-specific vaccines are not available [41].

8. Eradication Program and Intervention

Dracunculiasis eradication was a goal set out in 1980 in the USA by the Centers for Disease Control and Prevention (CDC) with the GWEP [42]. Eradication can be considered achieved when in one state there are no more cases for at least 12 consecutive months.

In the 1980s, GWD was present in 20 countries, with more than 3 million people infected every year, 90% of whom were living in Africa. There has been a reduction in the overall number of cases, from 3 million to 27 cases at the end of 2020. At this time, the last disease outbreaks were localized in only few sub-Saharan countries. Due to the absence of effective drugs or vaccines, eradication programs are based on simple public health measures [43]. Deadlines for eradication have been progressively shifted from 1991 to 2009, 2015 and 2020. Considering the previously unknown new routes of transmission, the World Health Organization (WHO) has further postponed the target date for the eradication of the disease from 2020 to 2030. Unfortunately, the 2020 goal has been hampered by an increase of dog infections in Chad; the emergence of the first known cases in Angola; infections in baboons in Ethiopia; and conflicts that broke out in Mali, Sudan and South Sudan [44].

In Chad in 2010, after 10 years of no reports, new GWD cases were documented in people who lived along the Chari River [45], with suboptimal surveillance being the likely cause of disease recurrence. Indeed, the country also reported its first cases among dogs in 2012. Dogs became infected by eating aquatic animals. Since then, there have been several reports of infections in animals such as dogs, cats, and baboons. Smaller outbreaks of GWD in dogs have previously been reported in Mali and Ethiopia. The significant number of animals infected with GWD represents a major challenge for global eradication.

The strategies of the global dracunculiasis eradication campaign, a CDC initiative, are based on case reporting (thus identifying all communities with endemic transmission), on water decontamination and hygiene education [46]. Simple filtration systems to purify water are needed to prevent infection spread. Water chlorination or, at home, fine mesh gauze or boiling are useful to kill larvae, making the water safe for home use. In addition, larvicides have been approved to kill the tiny crustaceans infected by the larvae. A population education program was implemented, which recommended cooking food (especially fish) and gave behavior rules in case of infection [47]. The discovery that pets could be a reservoir of infection reinforced the eradication campaign with the offer of a premium to anyone who reported the appearance of infection in their pet, with free dog care and feeding being offered until the worms were removed. Nevertheless, the main challenge remains the maintenance of wells built in recent decades with the aim of providing drinking water, that may often be many kilometers away from the most isolated houses [7]. Further challenges are represented by the need for a constant water supply, difficulty in digging a specific territory, and funding surveillance conservation activities [43].

9. Conclusions

Dracunculiasis is a disease that is still present in some low-economic development areas of the world, where the CDC's global dracunculiasis eradication campaign and the GWEP have been underway for many years [48–51]. The difficulty in eradication derives from the poor control of the sources of infection and the difficulty in reaching the rural areas where it is still present. Nevertheless, the eradication campaign has achieved excellent results over the last twenty years. Only 14 human cases were reported in 2021 in 14 villages. At the end of 2021, there were 187 countries certified free of dracunculiasis [49,50]. The reduction—nearly a 50% drop from the 27 cases reported in 2020—is the result of a nearly 40-year effort by international organizations and national governments to permanently eliminate GWD. If successful, it will join smallpox and rinderpest as the only diseases to have been completely eradicated in human history [48–51]. In response to infection, the WHO coordinates and monitors the surveillance in Guinea worm-free areas as well. The ultimate goal is to reach eradication worldwide by 2030. It is also crucial to maintain the high quality of studies and clinical attention on neglected diseases in Europe as well and especially in Italy [52], the gateway to the Mediterranean, which can make an important contribution to the control and definitive eradication of this disease, and other neglected diseases [53].

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Onchocerciasis: Current knowledge and future goals

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Human Onchocerciasis, caused by infection by the filarial nematode *Onchocerca volvulus*, is a neglected public health disease that affects millions of people in the endemic regions of sub-Saharan Africa and Latin America. It is also called river blindness because the Blackflies that transmit infection breeds in rapidly flowing fresh water streams and rivers. This review features state-of-the-art data on the parasite, its endobacteria *Wolbachia*, the prevalence of the infection and its geographical distribution, its diagnostics, the interaction between the parasite and its host, and the pathology of Onchocerciasis. By development and optimization of the control measures, transmission by the vector has been interrupted in foci of countries in the Americas (Colombia, Ecuador, Mexico, and Guatemala)and inSudan, followed by Onchocerciasis eliminations. The current state and future perspectives for vector control and elimination strategy are described.

KEYWORDS
Onchocerciasis, Ivermectin, Diethylcarbamazine, blindness, microfilariae; NTDs, Africa

Introduction

Human Onchocerciasis is a vector-borne disease, a parasitic infection caused by filarial worms and transmitted by repeated bites of infected blackflies. Because the vectors - blackflies of the genus *Simulium* - are insects that breed as larvae in fast-flowing rivers and streams and bite humans near these sites, the disease is also known as "river blindness" (1).

Onchocerciasis' physical manifestations include troublesome itching, skin rash, visual impairment, and irreversible blindness; these manifestations result from dying and dead microfilariae inciting an immunologic and inflammatory response, ultimately resulting in tissue damage and scarring. The disease is second to trachoma as the leading cause of blindness due to infection in the developing world (2).

Onchocerciasis causes morbidity and disability in affected populations and has a significant psychosocial and economic impact, including the depopulation of arable lands along river valleys. Historically, river blindness has impeded impeding the economic development of countries affected by the desertion of large areas of fertile land adjacent to vector breeding sites (3).

Methods

We searched PubMed, Scopus, Google Scholar, EMBASE, Cochrane Library, and the WHO website (http://www.who.int) for literature addressing Onchocerciasis published in the last 25 years. We used the following search strategy in Human Onchocerciasis [tiab] OR Onchocerca volvulus [mh] OR Onchocerca [tiab] OR river blindness [tiab] OR Simulium [tiab] OR Simulium blackflies [tiab] OR Onchocercomas [tiab]) All of the studies mentioned concern epidemiology, physiopathology, clinical characteristics, screening and diagnosis, therapy, management, and eradication programs.

Epidemiology and transmission

Infections due to *Onchocerca* spp. are found in tropical climates and are currently endemic in 37 countries, of which 30 are in sub-Saharan Africa. The endemic area starts from Senegal in the west to Ethiopia in the east and extends to the south of the equator from Angola in the west to Tanzania in the east. Pockets of Onchocerciasis exist in Sudan and Yemen. The disease was previously endemic in small foci in 6 Latin American countries (Brazil, Colombia, Ecuador, Guatemala, Mexico, and Venezuela) (4).

Despite the adoption of specific plans, the proportion of people affected by the diseases is high, with about 37 million people in tropical Africa and 140,000 in Latin America and an incidence of approximately 40,000 cases per year in low-endemic countries (4).

Onchocerciasis causes 46,000 new cases of blindness annually, resulting in 270,000 individuals being blinded and an additional 500,000 developing visual impairment, making Onchocerciasis the second leading cause of infectious blindness worldwide (5).

The disease is generally more prevalent in males than females and individuals aged between 20 and 30. Men are more affected due to increased exposure to blackfly bites during their occupational activity (farmers, fishermen) (2).

The disease pattern varies considerably between geographical zones, with ocular pathology more common in hyperendemic localities with savanna climates. At the same time, forest communities are more affected by the dermatological manifestations of the disease. One hypothesis to explain this difference is the existence of two parasite strains in West Africa, namely forest and savannah strains (6), which differ significantly in epidemiology and disease severity and are carried by different vectors. The savannah strain found in West Africa is associated with blindness, while the forest strain causes less severe ocular diseases, even in individuals with high parasite load. However, according to a recent study, the evidence for a savannah blinding onchocerciasis strain in simple contrast with a non-blinding forest strain is equivocal. A re-appraisal of the strain hypothesis to explain patterns of ocular disease is needed to improve the understanding of onchocerciasis epidemiology and disease burden estimates (7).

Onchocerciasis was previously the most common filarial infection diagnosed outside the tropics, and it mainly occurs in immigrants and refugees. The incidence of imported infection appears to be decreasing, probably as a result ofvector control and elimination programs. However, it remains common in migrant populations from highly endemic areas of sub-Saharan Africa, among which is likely underdiagnosed (8) but also visitors or migrants from tropical countries and long-term European travelers (9).

For instance, almost 400 cases of onchodermatitis were identified in patients from Equatorial Guinea at a single Spanish center (10). In a multicentre cross-sectional study conducted in five tropical disease units in Italy (11), 9.25% of migrants from sub-Saharan Africa had a positive pan-filarial enzyme-linked immunoassay (ELISA), though only a fraction was likely caused by *O. volvulus*.

The primary vectors of human Onchocerciasis in Africa are blackflies belonging to the *S. damnosum* species complex. Among the 65 species described so far, at least 15 may act as parasite vectors (12). Humans are the only definitive host for *O. volvulus*, the infective larvae transmitted through *Simulium* blackflies' bloodmeal. In Eastern Africa, the disease may also be transmitted by members of the *S. neavei* complex (subgenus *Lewisellum*, 9 species), which have their immature stages developing phoretic relationships with freshwater crabs. For this reason, people at risk of acquiring Onchocerciasis are those who live or work near streams or rivers where *Simulium* blackflies are present. It is assumed that *Simulium* biting rates follow a seasonal pattern (4).

Life cycle

Onchocerca volvulus has a complex life cycle (Figure 1) involving a definitive and intermediate host, respectively humans and Simulium blackflies. Common blackfly hosts include *S. damnosum and S. neavei* in Africa and *S.ochraceum, S. metallicum, S. callidum, and S. exiguum* in the Americas (13).

Blackflies ingest microfilariae during blood meals. After ingestion, microfilariae migrate from the blackfly's midgut through the hemocoel to the thoracic muscles. Here, microfilariae develop from first-stage larvae to third-stage infective larvae, that may be introduced into human skin by a second *Simulium* bloodmeal, where they mature into adult parasites (macrofilariae) over the next 6 to 12 months. Adult filariae reside in subcutaneous nodules connective called "Onchocercomas", where they can survive for approximately 15 years. Each nodule is made of numerous worms. Older nodules often contain necrotic material with calcified remnants of filariae and numerous male and female worms. Nodule location depends on geographical area: most infections in Central America exhibit nodules above the waist (especially on the neck and head), and those in Central Africa exhibit nodules below the waist (especially on the knees and pelvic area). This relationship is based on the biting preferences of the blackfly vector (14).

Clinical manifestations

Clinical manifestation may be influenced by host genetic factors and duration of exposure to infective bites, and begins to occur one to three years after parasite injection. The main clinical findings are dermatological and ophthalmological alterations, in addition to some systemic features (15). Clinical manifestations of 272 Onchocerciasis are summarized in Table 1 and Figure 2.

Onchocercal skin disease

The spectrum of skin pathology manifestation is broad. Dermatitis is variable in appearance, probably in relation to the chronicity of infection, host age, geographic area of acquisition, and relative immune responsiveness. The development of a formal clinical classification and grading system describing the cutaneous changes in Onchocerciasis facilitated formal mapping of the true global burden of onchocercal skin disease (OSD). The categories of Onchocercal skin disease delineated are summarised in Table 1.

A study carried out in the northern Nigeria by skin observation of in 6,790 individuals in endemic communities and 1,343 individuals in nonendemic communities declared the association between Onchocercal Skin disease and markers of infection (16). A population survey of residents in savanna mesoendemic Villages Northern Nigeria showed that the presence of nodules was the most common finding (21.2%), followed by atrophy (6.1% of those <50 years), APOD (3.4%), depigmentation (3.2%), itching (9.5%) (Michele E. M., Trop. Med. Infect. Dis.).

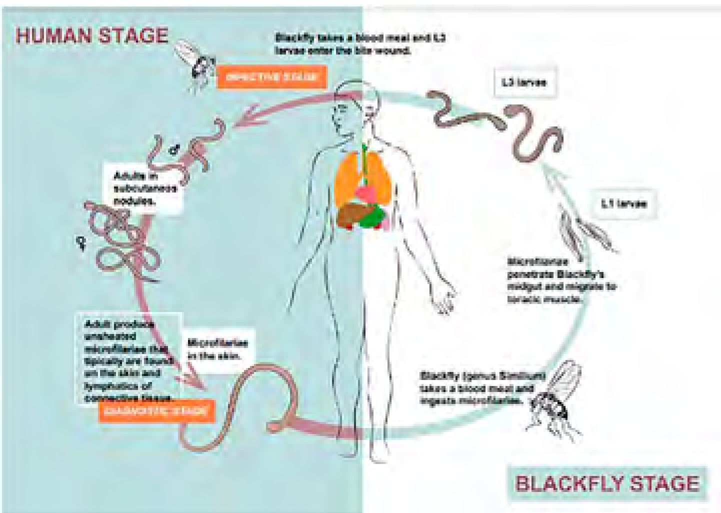

FIGURE 1
Life cycle of Onchocerca volvulus.

TABLE 1 Clinical manifestation of Onchocerciasis.

Clinical manifestation	
Onchocerca skin disease	
Acute Papular Onchodermatitis **(APOD)**	Small, itchy, monomorphic, papular-macular rash in upper trunk and arms
Chronic Papular Onchodermatitis **(CPOD)**	Larger pruritic papules, often after hyperpigmentation in the pelvic area and limb
Lichenified Onchodermatis **(LOD)**	Hyperkeratotic, hyperpigmented plaques associated with lymphadenopathy
Skin Atrophy	Loss of skin elasticity and excessive wrinkling in people aged less than 50 years old
Depigmentation	Extensive and bilateral, in patients with long-standing Oncodermatitis
Onchocercomas	Later cutaneous form, single or multiple palpable nodules between 0.5 and 5 cm overlying bony prominences, especially iliac crest, trochanters, knees, and pelvic girdle
Ocular Onchocerciasis	
Punctate Keratitis	Common, acute, and reversible, snowflakes opacities around dead microfilaria in the cornea
Sclerosing Keratitis	Chronic full-thickness fibrovascular change of the cornea
Uveitis	Flare in absence of an accompanying cell infiltrate
Optic atrophy	Chronic, followed by an episode of optic neuritis
Onchochorioretinitis	Damage to retinal pigment epithelium in the temporal area of the macula, and cases of massive retinal loss can cause atrophy and retinal death.
OAE (Onchocerca associated Epilepsy) criteria:	
Major criteria	A previously healthy person in an onchocerciasis endemic area who develops head-nodding or convulsive epilepsy of unknown etiology between the ages 3 and 18; Plus at least one of the following:
	Other neurological abnormalities (cognitive decline, school dropout due to cognitive/behavioural problems, psychiatric manifestations, other neurological abnormalities)
Minor criteria	At least 3 years of residence in an onchocerciasis-endemic village with high epilepsy prevalence and frequent household clustering of persons with epilepsy
	Stunting or wasting
	Delayed sexual development

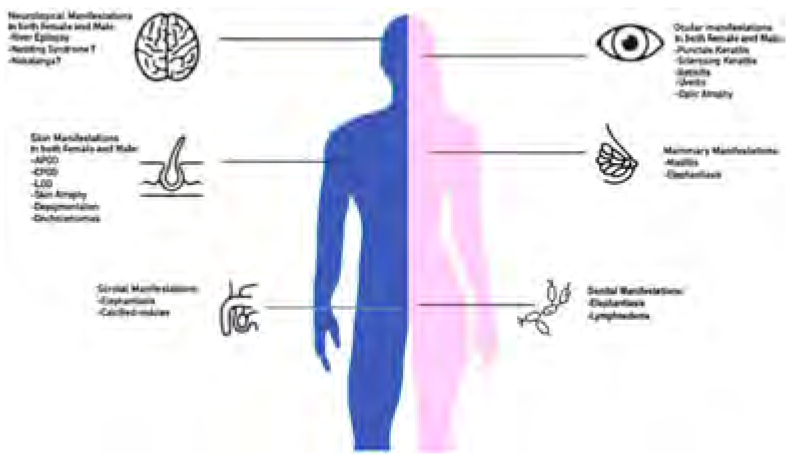

FIGURE 2
Clinical manifestation of Onchocerciasis.

In travelers returning from endemic areas, itchy papular dermatitis may occur early in the course of the infection, often localized to one extremity (17). According to data collected from 1994 to 2014 among expatriates and travellers from non-endemic areas the most frequent clinical manifestations are itching (76.7%), unilateral leg or forearm swelling (43.3%) and rash (40%), minimally (6.9%) two (6.9%) ocular symptoms.

Onchocerciasis is characterised by eosinophilia and IgE production due to the Th2 response mediated by CD4+ T cells and macrophages producing IL-10 and TGF-β, suppressive cytokines. In hyperreactive onchocercomas there is less expression of TGF-β, thus the Th2 response and consequently IL-13 production, resulting in increased IgE synthesis by plasma cells. (Low levels of transforming growth factor-beta (TGF-beta) and reduced suppression of Th2-mediated inflammation (18).

Eosinophilia is very common, with median counts of 2915/μL among migrants and 1960/μL among travellers and expatriates (19).

The more common generalized form presents with subclinical or intermittent dermatitis (acute and chronic papular dermatitis). It may progress to skin hyperpigmentation or depigmentation (leopard skin) and atrophy and elasticity loss, thus resulting in chronic distressing pruritus and disfiguring lesions. After years of repeated exposures, itching reduces, while atrophic and hypopigmented lesions (leopard and lizard skin) and, lastly, subcutaneous nodules appear (Onchocercomas) (20). Generalized onchocerciasis (GE) is characterized by high microfilarial burden and immunological tolerance to the worms. However, in rare cases infection leads to the sowda form of the disease displaying low microfilarial numbers, i.e. microfilarial control a T helper 2, Th helper 17-type immune response and an high immunoglobulin (Ig)E levels. This pathogenetic mechanism could partecipate in the development of severe Onchocercias (18) In this regard Hoerauf et al., suggested that Arg110Gln variant of IL-13 (which confers an IgE-independent risk for asthma and atopy) may lead to increase IL-13, promoting hyper-reactivity against the helmints (21).

Sowda, a lichenified onchodermatitis prevalent in Yemen is an hyperreactive skin condition characterized by intense pruritus and hyperpigmentation of the skin mainly affecting the legs below the knees, but may extend to the thighs and gluteal region, with common secondary suppurative and papular dermatitis (22); [Michele, (23)]. In Central America, another manifestation of acute Onchocerciasis includes facial swelling with itching and erythema, a finding known as erysipelas de la costa. In Zaire and Central America, acute urticarial eruption may be seen, while the association of hyperpigmentation with signs of inflammation is also known as mal morado (24). Secondary to onchocercal skin disease, lymphadenopathy may develop, most commonly in the groin area and in the mammary region, eventually leading to genital elephantiasis or mimicking a metastatic breast mass (25). Calcified nodules are typically seen in the scrotal region and around the hip and elbow but, rarely, similarly to cysticercosis and echinococcosis, they may also be found within the central nervous system (26).

Ocular Onchocerciasis

Ocular damage depends on both mechanical invasion of microfilariae and deposition of immune complexes. Conventionally, anterior chamber lesions had been attributed to a cascade of inflammatory processes triggered by filarial products. In this regard, a pathogenetic hypothesis suggests that the pro-inflammatory events leading to increasing corneal opacity are stimulated not only by the parasite itself but also by its recently discovered endosymbiotic *Wolbachia* bacteria when released by dying microfilariae.

The most common ocular pathology involves the cornea, but other structures of the anterior and posterior segments of the eye can also be affected. Corneal pathology begins with "snow-flake" opacities (punctate keratitis), which later coalesce and may become hyperpigmented (sclerosing keratitis) (3). In addition to the multiple risks to the visual apparatus, as shown by a cross-sectional case-control study, there is a positive association between subclinical onchocerciasis and glaucoma (27). Studies using animal models have shown the essential role of innate immune response in Onchocerca keratitis: toll-like receptors 2 and 6are expressed in the cornea, and activation can induce keratitis as a consequence of activation of keratocytes caused by death and degeneration of microfilariae into the confined environment of the corneal stroma. Activated keratocytes can mature into stromal fibroblasts, which produce pro-inflammatory cytokines and chemokines and can induce the expression of adhesion molecules on vascular endothelial cells. Underlying this pathogenetic mechanism is the role of *Wolbachia*-derived diacyl-lipoproteins, which stimulate molecules required for TLR2/6 ligation and produce pro-inflammatory cytokine and chemokine responses [Turner (28)].

TLR4 role in neutrophil recruitment to the development of corneal haze was denied as number of macrophages in TLR4-deficient animals after intrastromal injection of *O. volvulus* remains comparable to those with no TLR4-deficiency. [Gillette-Ferguson, et al. (29)].

These changes mediate neutrophil recruitment from peripheral, limbal vessels into the avascular corneal stroma, stimulating further neutrophil infiltration, degranulation, and secretion of cytotoxic products such as nitric oxide and myeloperoxidase and oxygen radicals. A cytotoxic effect on keratocytes and corneal endothelial cells will lead to loss of corneal clarity (3, 30).

Neurological manifestation - Onchocerciasis-associated epilepsy

There is increasing epidemiological evidence that Onchocerciasis is associated with a spectrum of epileptic seizures, mainly generalized tonic-clonic seizures, but also atonic neck seizures, myotonic, and absence (31).

This strong association allows the definition of Onchocerciasis-associated epilepsy (OAE), also known as "River epilepsy" which is characterized by recurrent episodes in more than 60% of cases. It has been estimated that approximately 400,000 cases of epilepsy in Africa could be prevented by appropriate onchocerciasis control (32).

Furthermore, onchocerciasis may be implicated in the pathogenesis of Nodding syndrome, a yet unexplained neurologic condition mainly affecting children living in South Sudan, Tanzania and Uganda, characterized by paroxysmal head nodding frequently accompanied by epileptic manifestations and mental decline. In this regard, studies indicate that skin microfilarial density in early childhood is associated with the risk of developing epilepsy later in life, and that this association may be time and dose-dependent (33, 34), the pathological basis for this association being a neuroinflammatory disorder possibly induced by antibodies directed against Leiomodin-1, that may cross-react with a similar protein that is present in the *O. volvulus* parasite (32). Onchocerciasis may also be associated with Nakalanga syndrome, a condition characterized by stunted growth, delayed pubertal development, mental impairment and, in some cases, epileptic manifestations (32). However, for both Nodding and Nakalanga syndromes, along with Onchicerciasis, various infectious, toxic, nutritional, metabolic and genetic causes have been proposed and investigated (35).

From a pathological perspective, the role of *O.volvulus* CNS invasion in the pathophysiology of onchocerciasis-associated neurological manifestations is debated, as recent studies involving subjects with OAE and high skin microfilariae load showed no signs of microfilariae in the cerebrospinal fluid the infected hosts (36).

In 2017, Colebunders et al. suggest an association between ivermectin coverage and reduction of epilepsy and seizer frequency in OAE; this correlation would have major consequences on reducing the burden of epilepsy in onchocerciasis-endemic regions. Another clinical trial postulates that the administration of doxycycline can improve outcomes in Nodding Syndrome by targeting O. volvulus through cross-reaction of doxycycline effects on *Wolbachia* (37).

Diagnosis

The tools for diagnosis of Onchocerciasis in the laboratory include examination of skin snips by microscopy for emergent microfilariae, the Mazzotti test, detection of antibodies to onchocercal antigens, or use of highly sensitive polymerase chain reaction-based (PCR) techniques for detection of microfilariae DNA in skin snips (14).

Currently, the diagnosis of infection with *O.volvulus* is predominantly based on nodule palpation and microscopic detection of microfilariae in superficial skin biopsies (Skin Snips). This technique is the most widely used standardized technique for Onchocerciasis in many endemic regions. Samples are usually collected from the scapula over the iliac crest or calf. Its use is discouraged because of the invasiveness and lack of sensitivity when microfilarial densities are low, as in *O.volvulus*-hypoendemic areas (14, 17).

Obtaining the biopsies is both painful and carries some risk of transmitting blood-borne infections for these reasons WHO does not recommend the use of skin snip-based assays as a primary diagnostic for the verification of elimination (38).

For diagnosis of human infection several approaches have been considered using antibodies, antigens or nucleic acid detection for the development of a diagnostic tool based on a biomarker (39).

Many antibody tests have been identified as candidate tests and as surveillance tools for control programs, but the major drawback is the need for laboratory infrastructure to support the performance of Enzyme-Linked Immunosorbent Assay (ELISA) tests. Serological assessments for human Onchocerciasis are based on IgG4 reactivity against the OV-16 antigen, with sensitivities of 60-80% (39).

Recent studies showed that a combination of rOVOC3261 with OV-16 improved serologic assessment of *O.volvulus* infection (40). The relevance of developing tests that incorporate a wider range of antigens has been highlighted in a study from Yemen that evaluated the diagnostic potentials of OvMCBL02 multiepitope antigen to differentiate between infected individuals and patients who had been undergoing treatment (41).

Therefore, novel diagnostic tests are needed that can be used singly or in combination with the Ov-16 test to improve its sensitivity.

A study by Hotterbeekx et al. made a comparison between the sensitivity of the Ov-16 test alone with the tandem use of OvMANE1 and Ov-16, assuming that the tandem use of OvMANE1 and Ov-16 tests may represent a more appropriate tool for onchocerciasis elimination mapping because of the improved sensitivity (42).

For rapid assessment of O. volvulus infection, it is possible to test a mixture of four recombinantly produced Onchocerca volvulus antigens (Ov-FAR-1, Ov-API-1, Ov-MSA-1, and Ov-CPI-1) using luciferase immunoprecipitation systems (LIPS)

The multi-antigen LIPS assay can be used as a rapid and specific tool not only to diagnose individual Ov infections but also as a sensitive and potentially point-of-care method for early detection of recrudescent infections in areas under control and for mapping new areas of transmission [Burbelo, et al. (43)].

Some studies have already demonstrated that the detection of *O.volvulus* DNA using PCR in such skin biopsies has a higher sensitivity than this classical approach (44). Similar sensitivities can be achieved with the *O.volvulus* cox1 LAMP assay (45). The *cox1* LAMP assay has comparable clinical sensitivity and specificity to those of the O-150 qPCR assay, even though the latter has the advantage of targeting a repeat sequence that is present multiple times in the *O.volvulus* genome. Moreover, the *cox1* LAMP assay is capable of providing results within 30 min (46).

Ophthalmologic evaluations, obtained before treatment of eye lesions, are often necessary to detect microfilariae in the cornea or anterior chamber on slit-lamp examination or find adult worms on a nodule biopsy specimen. The literature describes the development of humanized mouse models that are susceptible to *O.volvulus* infection. These novel mouse models could play an important role in the development of specific and sensitive diagnostic tests for the presence of parasites (47).

Several studies have been performed in West Africa to evaluate the patch test, demonstrating that it constitutes a valuable tool to evaluate the levels of endemicity and to detect recrudescence of transmission in previously controlled areas (48). One exampleis the Mazzotti test, which uses Diethylcarbamazine (DEC) for the detection of skin microfilariae. The Mazzotti reaction is an immunological reaction that can occur within a very short time under anthelmintic therapy, triggered by an exuberant reaction of the immune system due to the death of the worms (49).

Treatment and management

The complex life cycle of Onchocerciasis poses an exceptional challenge to the therapeutic strategy. In addition, several drugs used in the past 70 years have proved to be independently toxic to the host at the same dose levels used to cure the infection, while some others have caused adverse reactions associated with parasite death (50).

Diethylcarbamazine (DEC) has been the mainstay of Treatment for Onchocerciasis for many years. It is a micro and macrofilaricidal molecule, affecting the neuromuscular system of the parasites and promoting cellular cytotoxicity mediated by immune factors. Side effects of DEC include itching and urticaria (reactions to disintegrating microfilariae), facial swelling, headache, nausea, vomiting, fever, joint pain and anorexia. Due to the severity of adverse reactions, DEC is now contraindicated except for diagnostic purposes (see above) (14).

Ivermectin (IVM), the first-line option according to the Center for Disease Control and Prevention (CDC), is a safe and efficacious anthelmintic drug that acts as microfilaricidal, embryostatic (temporary inhibition of microfilarial release from female worms) and modest permanent sterilizing action of *O. volvulus* (4). Ivermectin has been shown to reduce the number of microfilariae in the skin and eyes and to decrease microfilariae production for several months. However, the effect of IVM on the viability of the adult worms (macrofilaricidal effect) is considered moderate, and treatments have to be repeated every year (or at shorter intervals) to maintain skin microfilarial densities at low enough levels not to be associated with clinical manifestations (51).

To this matter, in a trial conducted by Campillo et Al., when compared to annual regimens or higher doses, a 3-monthly IVM regimen appeared to be associated with a significant reduction in the number of new onchocercal nodules (52). Nevertheless, the use of IVM is associated with common dermatologic adverse reactions triggered by the death of the microfilariae: itching, edema, and urticarial rash, while IVM use is not associated with the worsening of eye symptoms (14).

Recently, novel chemotherapeutic approaches focus on the use of antibiotics against the endosymbiotic bacteria *Wolbachia*, as long-term depletion of this endosymbiont impairs worm reproduction and survival (53). Daily treatment with 100 milligrams of doxycycline for six weeks (or 200 milligrams daily for four weeks) leads to an interruption of embryogenesis that lasts for 18 months or more (54).

However, these regimens are difficult to include in mass chemotherapy programs. This is due to the prolonged duration of treatment, the various contraindications to antibiotics, and the risk of inducing resistance in other pathogens. The impact of doxycycline on the duration of therapy has not been studied in nonendemic settings; however, mathematical modeling of clinical trial data from endemic areas estimated a 70–80% decrease in the lifespan of *Wolbachia*-depleted *O. volvulus* worms (54). Ivermectin treatment should be given a few days before Doxycycline. The dosage of doxycycline is 100-200 mg daily for 6 weeks. Several studies showed that administration of Doxycycline 200mg/day for six weeks followed by Ivermectin at 3 and 12 months can induce the sterility of adult female worms and can reduce the number of skin microfilariae over a long period (15). Also, a single dose combination of Ivermectin and Albendazole did not have a greater effect than Ivermectin alone. Rifampicin and azithromycin, despite their activity against *Wolbachia*, are not effective for clinical management of Onchocerciasis (55). Table 2 shows WHO indications for onchocerciasis treatment. Before Treatment with Ivermectin, patients should be evaluated for co-infection with *Loa loa*, another filarial parasite, due to the risk of potentially fatal encephalitic reaction to Ivermectin in *Loa loa* infected patients (56). At this regard, a 'test-and-treat' (TNT) strategy involving the use of a smartphone microscope device (LoaScope) has been introduced for endemic areas to identify individuals with a high risk of post-ivermectin severe adverse events (55). Treatment of co-infected people with doxycycline has only been studied in persons with *Loa loa* counts of <8000 microfilariae per mL. In areas of *O. volvulus* and *Loa loa* co-endemicity, new approaches for onchocerciasis elimination include the combination of test-and-treat strategy with doxycycline andthe spreading in the ground of the organophosphate larvicide temephos (57). (Wanji, et al., Implementation of test-and-treat with doxycycline and temephos ground larviciding as alternative strategies for accelerating onchocerciasis elimination in an area

TABLE 2 Pharmaceuticals indicated or in development for onchocerciasis.

Pharmaceuticals indicated or in development for onchocerciasis

Drug compound	Dosage	Common adverse events	Micro/Macrofilaricida/Anti Wolbachia		MDA	TNT
Ivermectin	150 mcg/Kg	Headache and increased liver-associated enzymes	Microfilaricide	CDTI but risk of SAEs in Loa Loa co-endemic area	YES	YES
Moxidectin	8 mg single dose	Mazzotti reaction, hypertension, edema and worsening and onchodermatitis	Microfilaricide	CDTI but risk of SAEs in Loa Loa co-endemic area	YES	
Doxycycline	100 or 200 mg daily for 4-6 weeks	Nausea, photosensitivity, teeth discolouration	Macrofilaricide			YES
Flubentylosin (TylAMac)*		Not Known	Anti-Wolbachia	Phase I, II		
Emedepside*		Not Known	Anti-Wolbachia	Phase I, II		
CC6166*		Not Known	Potential macrofilaricide	research phase		
AWZ1066*		Not Known	Anti-Wolbachia	Phase I		
Oxfendazole*		Not Known	Beta tubulin polymerisation inhibitor and a potential macrofilaricide	Phase I, II		

of loiasis co-endemicity: the COUNTDOWN consortium multi-disciplinary study protocol, 4 Dec 2019).

Moxidectin is an anthelmintic drug recently approved by the FDA for single-dose treatment of onchocerciasis in persons aged ≥12 years. Moxidectin (8 mg) exerts a potent microfilaricidal effect and leads to prolonged suppression of microfilaraemia, which may be the result of a robust embryostatic effect (temporary inhibition of microfilarial production by adult female worms) (58). According to a recently published, large phase 3 clinical trial conducted in the Democratic Republic of Congo, Ghana and Liberia moxidectin may be superior to Ivermectin in suppressing the presence of parasites (microfilariae) in the skin that cause the disease and that are taken up by blackflies (58). Compared to Ivermectin, Moxidectin is a stronger and longer microfilarial suppressor: its microfilaricidal effect leads to almost complete clearance of skin microfilariae, and it could be used in Loa co-endemic areas excluding people with high Loa loa microfilaremia (4). However, after a single dose, moxidectin is not considered to be curative or macrofilaricidal (killing of adult worms), while these results may be reached by the administration of repeated doses but data on repeated treatments with long follow-up times are lacking (59). A small-scale trial conducted in Ghana evaluated the efficacy, toxicity and safety profile of moxidectin, hinting at the possibility of being used after large-scale evidence for mass treatment (49).

Besides moxidectin, also flubendazole, an inhibitor of tubulin polymerization, has been investigated as a candidate drug, since it has been shown to have the ability to kill adult filarial worms. Despite this promise, flubendazole has several limitations that complicate its use, including limited oral bioavailability and human embryotoxicity (60) because of this, it is not possible to identify a flubendazole treatment regimen that would prove to be safe for humans while keeping its efficacy (61).

1-2 Several studies are paving the way to alternate anti-Wolbachia drugs with promising results. Among these, a notable example is a tylosin analogue ABBV-4083 (TylAMac), now called flubentylosin, a macrolide veterinary antibiotic, an inhibitor of bacterial protein synthesis currently in clinical development. [Taylor et al., (62)]. Flubentylosin is orally available, induces a robust anti-*Wolbachia* effect in several *in vivo* models, demonstrates clear superiority over the current treatment doxycycline, and is effective after a shorter dosing regimen (https://dndi.org/research-development/portfolio/flubentylosin/).

Treatment through Flubentylosin resulted in a >99% elimination of Wolbachia after 1-2 weeks of treatment initiation. Moreover, it has an embryostatic action leading to complete clearance of circulating microfilariae, along with expressing relatively low activity against microfilariae of L. loa (39).

Another candidate in clinical trials is the azaquinazolin AWZ1066S an antiWolbachia agent, has the potential to deliver a novel antifilarial therapy that could be deployed in target populations in a sub–7-day dosing regimen (63) (https://clinicaltrials.gov/ct2/show/NCT05084560?term=AWZ1066S&draw=2&rank=1).

In conclusion, the next years will be key for offering new safe and effective onchocerciasis drug development in an efficient strategy to definitive eradicate it (64–66).

Onchocerciasis elimination strategies and interventions- vector control and policy changes

Onchocerciasis elimination is defined as the reduction of local onchocerciasis infection and transmission to such low levels that transmission can no longer sustain itself and treatment can be safely stopped without risk of recrudescence of infection and transmission (67). In 1974, the WHO established the Onchocerciasis Control Program (OCP), while spraying started in 1975, with the aim of interrupting transmission for twenty years to allow for all existing adult worms to die. The OCP Initially implemented weekly larvicidal administration on vector breeding grounds and, after achieving this, elimination strategies required abolishing vector sources for as long as microfilariae remain in human skin. This duration was deemed to be at least 14 years (considering the life expectancies of both adult worms and microfilariae) (55, 68).

In 1987, the advent of Ivermectin has enhanced prospects for control or elimination of the disease in many areas, including Africa. The medicine is provided free of charge by Merck & Co., Inc. under the Mectizan Donation Program. Mass distribution of Mectizan (to all those aged five years or older, excluding pregnant women and those breastfeeding a child younger than one week old) revolutionized the approach to onchocerciasis control and has, since then, led to the development of similar mass drug administration programs for other neglected tropical diseases (NTDs). Every year, the program reaches more than 300 million people in 35 countries, with more than 3.4 billion treatments. (69, 70).

The first empirical evidence on the feasibility of IVM-based elimination strategies is available from studies conducted in three onchocerciasis foci in Senegal and Mali. These studies showed that after 15 to 17 years of treatment, the prevalence of infection and the intensity of transmission had fallen below postulated threshold values for elimination (71). As stated above, the effectiveness of Ivermectin on microfilarial reproductive capacity and longevity seems to be affected mainly by treatment frequency (72).

In Latin America, the areas affected by onchocerciasis were small and well-circumscribed, with an estimated half a million people infected. Here, the strategy has been based on the treatment of everyone at risk and not taking into account the levels of endemicity. The Onchocerciasis Elimination Program for the Americas (OEPA) started in 1995 and has regional resolutions to recommend periodic treatment for elimination in the WHO Region of the Americas. Eligible populations in countries endemic to the disease in this region have been treated twice or more per year (72). As a result, onchocerciasis has been eliminated from Colombia, Ecuador, Mexico and likely now Guatemala under these strategies. Only Venezuela and Brazil still have some cases, particularly deep in the Amazon forest, on their common border (73).

In sub-Saharan Africa, the African Programme for Onchocerciasis Control (APOC) was launched in 1995 to control Onchocerciasis in the remaining 19 African countries (5). Its main strategy has been the establishment of sustainable Community-Directed Treatment with Ivermectin (CDTI) aiming to obtain a beneficial effect on the incidence of onchocercal optic nerve disease and visual field loss, along with a substantial reduction in other clinical symptoms. Moreover, the APOC carried out successful anti-vector activities using aerial spraying with organophosphate and ground larvicide along thousands of kilometers of rivers in West Africa at very regular intervals during the peak breeding season, often using helicopters to treat inaccessible areas (74). Since then, CDTI strategy has proven to be extremely useful, becoming a community platform for the integration of other interventions, above all the chemotherapeutic and pharmacological ones (i.e., vitamin A supplementation and albendazole for lymphatic filariasis treatment) (5, 75).

However, as mentioned above, ivermectin-based strategies are not applicable to areas of onchocerciasis and loiasis co-endemicity (mainly in central Africa) since IVM treatment may result in severe adverse events (76).

In 2015, APOC was replaced by the Expanded Special Project for Elimination of NTDs (ESPEN), with the aim of alleviating the burden of Onchocerciasis in Africa. ESPEN relies on population-based treatment with Ivermectin, with a minimum requirement of 80% therapeutic coverage which has to go on for about 15 years of yearly treatment corresponding to the lifespan of adult O. volvulus worms (77).

In meso-and hyperendemic onchocerciasis areas (i.e., onchocercal nodule prevalence >20% in adults) in 2017 a test-and-not-treat (TaNT) strategy was launched and successfully piloted in Cameroon (Wanji, Patrick, & Ndongmo, Impact of repeated annual community directed treatment with ivermectin on loiasis parasitological indicators in Cameroon: Implications for onchocerciasis and lymphatic filariasis elimination in areas co-endemic with Loa loa in Africa, 2018).

By this approach, the relatively small proportion of L. loa-infected individuals at risk of SAEs (those with > 30,000 mf/ml) are identified and excluded from treatment with Ivermectin. This could help to prevent severe adverse events (SAEs) post-ivermectin treatment (including neurological sequelae and fatal encephalopathy).

Because polyparasitism is still widespread especially in rural communities, exploring other potential therapeutic strategies is of great interest. Commercially available aspartyl protease inhibitors (APIs) immunodeficiency syndrome (AIDS)) have been shown to have macrofilaricidal effects in *in vitro* studies with L4 stages of O. volvulus (78). Alternative strategies to achieve onchocerciasis elimination is a test-and-treat with the doxycycline and ground larviciding, with a large-scale implementation trial in Cameroon being currently evaluated.

The advantages of this model are a reduction in community prevalence of skin microfilaria by 37% and a superior range of anti-filarial efficacies of Doxycycline in the absence of loiasis-associated SAE [Wanji et al., (57)]. In 2020 despite disruptions caused by the COVID-19 pandemic in endemic countries for Onchocerciasis

WHO Department of Control of Neglected Tropical Diseases continued the prevention of the transmission by distributing ivermectin treatment to more than 112 million people (79).

In order to improve the effectiveness of the control program, OCP has sponsored the development of ONCHOSIM, a computer program that models onchocerciasis transmission and control. According to ONCHOSIM predictions, the outcome of elimination of onchocerciasis depends on pre-control endemicity level, frequency of MDA and treatment coverage (TC) achieved (80).

As a result, in 2016, the WHO recommended stopping mass drug administration (MDA) programs from verifying the interruption of transmission using geostatistical models (69). To accelerate the elimination of Onchocerciasis by 2025, the WHO recommends the Ov-16 serological test for onchocerciasis mapping to determine eligibility for MDA, as this would help to detect a status of infection and parasite transmission at a low level of endemicity. According to the WHO Onchocerciasis Technical Advisory Subgroup's report of 2018, the provisional threshold for commencing mass ivermectin treatment is set at 2% Ov-16 seropositivity (44). Conflicts and civil wars are further obstacles to the monitoring of endemic areas and the widespread distribution of medicines. In such contexts, MDA could be carried out through collaboration with local NGOs or humanitarian organizations, whose volunteers are often present in war zones to achieve an improved geographic coverage of Ivermectin (81). Furthermore, there is an effort run by The Sabin Vaccine Institute Product Development Partnership (Sabin PDP) and other partners to prophylactic or therapeutic onchocerciasis vaccine. Also, a global initiative known as TOVA – The Onchocerciasis Vaccine for Africa – was launched in 2015 to evaluate vaccine development as a complementary control tool (68).

To date, three candidate antigens have proven to be efficacious in three different filarial animal model systems and three independent laboratories. A recently published study showed the feasibility of eliciting significant protective immunity in mice using selected recombinant *Onchocerca volvulus* antigens produced in yeast or bacteria, including Ov-103, Ov-RAL-2, and Ov-CPI-2M (45, 69).

Finally, other strategies are primarily based on vector elimination: the Esperanza Window Trap (EWT) was used for monitoring the transmission of *O. volvulus* in Mexico in elimination programs. The program consisted in positioning a vertical blue and black striped sheet with a sticky surface that attracted black flies. Later, EWT was optimized in Northern Uganda and has resulted in vector biting rates reduction (82). Also, on the Bioko islands, Republic of Guinea, a seasonally adjusted vector control model based on the use of larvicides (temephos) spread by helicopters on riverbeds and areas with high density, led to the successful elimination of the vector (67, 83–89).

Finally, in the Democratic Republic of Congo and South Sudan, the "Slash and Clear" strategy, which involves the removal of vegetation from *S. damnosum* breeding sites considering climatic and seasonal variations, showed also to be able to reduce vector populations (82).

Conclusion

Despite the various control programs implemented in recent decades, river blindness remains a global health problem, a cause of disability and stigma, a disfiguring skin disease and a source of poverty in countries where it is endemic (90–95). Although valuable diagnostic tools are available for individual use, community-based onchocerciasis control needs a reliable, cheap, and more practical technique for rapid epidemiological assessments. Numerous efforts to develop novel diagnostic assays that support the monitoring of current and future control measures are underway (96-100). Future epidemiology-directed control strategies need to take into account challenges such as Loa loa co-infections and environmental sustainability and will likely have to combine vector control, community-directed mass administration programs and future therapeutic perspective i.e. CC6166 an anthelmintic molecules with macrofilaricidal action in phase I development with DNDi (95, 101-103). (https://dndi.org/wp-content/uploads/2021/06/DNDi-RFP-Filarial-PharmaceuticalDevelopment-June2021.pdf).

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Malaria, HIV and Malnutrition among Internally Displaced People in Mozambique During COVID-19 Pandemic: Results from a Community-Based Intervention

PAPER

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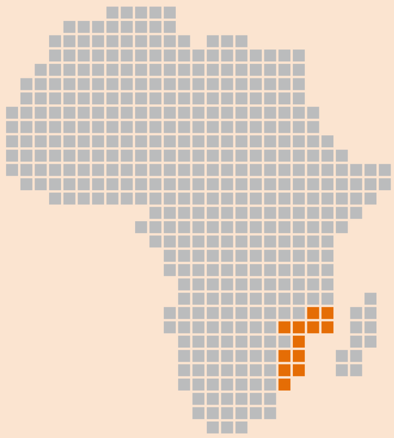

Malaria, HIV and Malnutrition among Internally Displaced People in Mozambique During COVID-19 Pandemic: Results from a Community-Based Intervention

Annals of Global Health

ORIGINAL RESEARCH

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ABSTRACT

Background: The spread of COVID-19 poses an unprecedented challenge to care delivery in post-disaster and conflict situations. In Mozambique, the 2019 cyclone Idai and the violence by Non-State-Armed-Groups devastated the province of Sofala and Cabo Delgado respectively and led to the displacement of thousands of people living in poor and overcrowded conditions. The pandemic has further aggravated the situation. Doctors with Africa CUAMM (University college for aspiring missionary doctors) implemented surveillance activities in these regions between October 2020 and September 2021. The aim of this study is to give an overview of the prevalence of malaria, malnutrition, COVID-19 related symptoms and access to HIV testing.

Methods: Data were collected in targeted internally displaced people (IDP) sites in Sofala and Cabo Delgado province between 31st January and 25th September 2021. The tool used enabled to assess COVID-19 symptoms, risk of HIV infection, malaria cases and malnutrition in children under five.

Results: The project reached 93 503 people. During the study period, 13.6% people reported at least one symptom suggestive of COVID-19 infection. Malaria Rapid Diagnostic Tests (RDT) were administered to 86% of the recruited people (n = ?), with a positive diagnosis in the 4.5% of them (n = ?). Among the recruited Internally Displaced Persons (IDP), 23.1% were considered eligible for HIV screening, but only 1.4% were referred for testing. Acute malnutrition was found in 6.3% of children screened and, among these, a higher prevalence of concurrent COVID-19 symptoms was reported.

Discussion: Our study highlights the importance of mass clinical screening for COVID-19 infection in this target population to enact prevention behavior, although this may not be enough, due to the pivotal role played by asymptomatic transmissions. Considering the overlap of the symptoms of COVID-19 and malaria, a combined diagnostic algorithm is urgently needed to avoid underdiagnosing malaria. Moreover, the high prevalence of respiratory symptoms in malnourished children confirmed the known correlation between malnutrition and respiratory infection. Finally, access to HIV screening needs to be implemented, given the high prevalence of people with HIV risk factors to avoid diagnostic delay.

Conclusions: Population-specific needs make necessary to develop new screening methods that respond to the specific characteristics of the target population.

INTRODUCTION

Internally displaced people (IDP) are among the most vulnerable populations since they struggle to access essential health, water, and sanitation services including clean water [1]. In March 2019, Sofala province was hit by the cyclone Idai, resulting in the displacement of thousands of people [2], while the violence carried out by Non-State Armed Groups in Cabo Delgado province led to the displacement of hundreds of thousands of people. Apart from the insufficient access to proper sanitation and vaccination, internally displaced people (IDP) live in situations of overcrowding, are more vulnerable to HIV infection [3], and routinely face surges in malaria and malnutrition [4, 5]. In times of pandemics, HIV, malnutrition and malaria control in vulnerable populations is further threatened by supply-chain interruptions, health resources overload and decision-making adaptation [6].

In this scenario, the advent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), brought significant disruption. In March 2020, the first cases of the COVID-19 pandemic were reported in Mozambique. Pandemics usually have a major impact on vulnerable communities and, although COVID-19 is well-known in Mozambique, myths about avoidance and cures must be dispelled. As happened in other sub-Saharan countries, the infection rate rose in two peaks, occurring from January to April 2021 and July to September 2021 [7]. The spectrum of clinical manifestations of COVID-19 ranges from pauci- or asymptomatic infections to severe respiratory failure and death [8]. The most common clinical symptoms of COVID-19 include loss of smell, loss of taste, cough, runny nose, fatigue, fever, and chest pain and, in some patients, SARS-CoV2 acute infection resolves in a wide spectrum of long-term signs and symptoms known as “long COVID”. Even though symptom-screening alone is considered unreliable in COVID-19 identification and surveillance [9], symptomatic individuals are significantly more likely to test positive [10].

From October 2020 to September 2021, Doctors with Africa CUAMM (University college for aspiring missionary doctors) implemented a community-based surveillance intervention with support from the United Nations Population Fund (UNFPA) in Mozambique. The initiative was funded by Norway as part of a project that aimed to contribute to Mozambique’s efforts in preparing and responding to the COVID-19 pandemic, with a focus on mitigating its consequences on the lives of women and girls affected by cyclone Idai and Kenneth in Sofala and armed conflicts in Cabo Delgado. CUAMM’s interventions targeted internally displaced people (IDPs) accommodated in 12 resettlement sites established since 2019. In those areas, the project piloted the community surveillance strategy developed by the Mozambican Ministry of Health. The aim of this study is to report test-positivity rate and prevalence of malaria, malnutrition, COVID-19-related symptoms and access to HIV

Di Gennaro et al.
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testing among people living in resettlement camps. Data will be used as baseline assessment for future intervention.

METHODS

STUDY SETTING

In Mozambique, the IDP site is usually composed of a limited number of areas/neighborhoods (bairros), each one accommodating people coming from the same community or neighboring villages, in order to guarantee linguistic and cultural closeness, kinship, cohesion and uniformity.

For the intervention, CUAMM engaged with teams of 15 community-based volunteers, or "activists", in each district (totaling 90 in the 2 provinces). Activists were purposely selected for being part of the target communities and for their proficiency in local languages and willingness to be trained in surveillance, data collection processes, and administration of screening tools for malaria, HIV and malnutrition.

Symptom screening was carried out based on the indications contained in the 2020 "Community Intervention Strategy for the fight against the COVID-19 pandemic" [11] defined by the Ministry of Health and in which CUAMM actively contributed to its design and drafting.

In accordance with local authorities, each activist was assigned to a specific geographical area, thus avoiding overlapping data and duplication. Here, activists screened and interviewed random samples of the population, mapped each household and cross-checked the information with the census data provided by local authorities. Data was then shared with the supervisor on a weekly basis and entered into an electronic Excel database.

The intervention was implemented in IDP communities located in Sofala and Cabo Delgado provinces, Mozambique. In Sofala, 12 resettlement sites distributed in 3 districts were targeted: Nhamatanda (IDP sites of Ndeja and Segredo), Dondo (Mutua and Setembro) and Beira (Macurungo and Munhava). In Cabo Delgado, study intervention took place in the districts of Montepuez (IDPs sites of Mapupulo and Nicuapa), Chiúre (Meculane and Marrupa) and Ancuabe (Nanjua A and Nanjua B).

DATA COLLECTION AND ANALYSIS

Data were collected in targeted IDP sites between 31st January to 25th September 2021, using data collection tools developed by the Ministry of Health. The first sites where outreach activities were implemented were Nhamatanda and Sofala province, where the data collection lasted for up to 34 weeks (see Table 1). The tool enabled the assessment of COVID-19 symptoms, HIV testing, malaria cases and screening for malnutrition in children under 5 years of age. In addition to screening, the intervention included community support in developing hand washing devices from readily available materials. Furthermore, study staff conducted individual and group awareness sessions on the prevention of COVID-19, HIV and malaria.

Recorded COVID-19 symptoms included fever, cough, runny nose and difficulty in breathing. In case of clinical suspicion, malaria rapid diagnostic tests (RDT) were immediately administered. HIV and TB patients were monitored and sensitized on therapy adherence, but follow-up data were not included in this study. The nutritional status of children aged 6 to 59 months was assessed using MUAC (Mid Upper Arm Circumference).

COVID-19 suspected cases were referred to the nearest health facility for further testing and treatment. Once validated by the health facility, data collected in this study were used for the drafting of monthly reports that were shared by the District Health Department and then transferred to the National Health Information System for Monitoring and Evaluation (SISMA), managed by the Ministry of Health. Reports were also shared with District and Provincial Health Departments and UNFPA.

		SOFALA				CABO DELGADO				TOTAL OVERALL
		NHAMATANDA	DONDO	BEIRA	TOTAL SOFALA PROVINCE	MONTEPUEZ	CHIÚRE	ANCUABE	TOTAL CABO DELGADO PROVINCE	
Estimated population in IDP sites		14 126	16 522	23 883	54 531	14 502	13 918	12 654	41 074	**95 605**
Data collection starting date		January 31st, 2021	February 7th, 2021	February 21st, 2021		February 28th, 2021	March 14th, 2021	March 14th, 2021		
Total weeks of data collection		34 weeks (from Epi Week 5 to 38)	33 weeks (from Epi Week 6 to 38)	31 weeks (from Epi Week 8 to 38)		30 weeks (from Epi Week 6 to 38)	28 weeks (from Epi Week 11 to 38)	28 weeks (from Epi Week 11 to 38)		
Total population reached		13 259	16 418	23 882	53 559	14 416	13 068	12 460	39 944	**93 503**
Sex	Male	6 097 (46.0)	7 366 (44.9)	11 080 (46.4)	24 543 (45.8)	6 654 (46.2)	6 168 (47.2)	5 939 (47.7)	18 761 (47.0)	**43 304 (46.3)**
	Female	7 162 (54.0)	9 052 (55.1)	12 802 (53.6)	29 016 (54.2)	7 762 (53.8)	6 900 (52.8)	6 521 (52.3)	21 183 (53.0)	**50 199 (53.7)**
Age	<5	1 986 (15.0)	2 668 (16.3)	2 610 (10.9)	7 264 (13.6)	2 515 (17.4)	2 160 (16.5)	1 606 (12.9)	6 281 (15.7)	**13 545 (14.5)**
	5-24	6 140 (46.3)	8 392 (51.1)	11 441 (47.9)	25 973 (48.5)	6 032 (41.8)	5 074 (38.8)	5 349 (42.9)	16 455 (41.2)	**42 428 (45.4)**
	25-44	3 101 (23.4)	3 623 (22.1)	7 337 (30.7)	14 061 (26.3)	3 345 (23.2)	3 730 (28.5)	3 516 (28.2)	10 591 (26.5)	**24 652 (26.4)**
	>44	2 032 (15.3)	1 735 (10.6)	2 494 (10.4)	6 261 (11.7)	2 524 (17.5)	2 104 (16.1)	1 989 (16.0)	6 617 (16.6)	**12 878 (13.8)**
Covid-19 symptoms	Cough	437 (3.3)	1 031 (6.3)	230 (1.0)	1 698 (3.2)	3 418 (23.7)	3 262 (25.0)	2 389 (19.2)	9 069 (22.7)	**10 767 (11.5)**
	Fever	640 (4.8)	983 (6.0)	142 (0.6)	1 765 (3.3)	3 491 (24.2)	2 792 (21.4)	2 524 (20.3)	8 807 (22.0)	**10 572 (11.3)**
	Running nose	140 (1.1)	406 (2.5)	63 (0.3)	609 (1.1)	1 494 (10.4)	2 340 (17.9)	167 (1.3)	4 001 (10.0)	**4 610 (4.9)**
	Difficulty breathing	96 (0.7)	373 (2.3)	20 (0.1)	489 (0.9)	1 249 (8.7)	2 014 (15.4)	369 (3.0)	3 632 (9.1)	**4 121 (4.4)**
	At least one symptom	882 (6.7)	1 137 (6.9)	355 (1.5)	2 374 (4.4)	3 107 (21.6)	4 272 (32.7)	2 927 (23.5)	10 306 (25.8)	**12 680 (13.6)**
Malaria	Total tested	11 783 (88.9)	15 822 (96.4)	21 993 (92.1)	49 598 (92.6)	9 728 (67.5)	9 320 (71.3)	11 747 (94.3)	30 795 (77.1)	**80 393 (86.0)**
	Positive	416 (3.1)	48 (0.3)	157 (0.7)	621 (1.2)	999 (6.9)	2 071 (15.8)	514 (4.1)	3 584 (9.0)	**4 205 (4.5)**

(Contd.)

		SOFALA				CABO DELGADO				TOTAL OVERALL
		NHAMATANDA	DONDO	BEIRA	TOTAL SOFALA PROVINCE	MONTEPUEZ	CHIÚRE	ANCUABE	TOTAL CABO DELGADO PROVINCE	
HIV	Screened	11 475 (86.5)	7 071 (43.1)	23 882 (100)	42 428 (79.2)	13 908 (96.5)	12 264 (93.8)	12 464 (100)	38 636 (96.7)	**81 064 (86.7)**
	Eligible for testing	1 563 (11.8)	31 (0.2)	18 763 (78.6)	20 357 (38.0)	71 (0.5)	1 139 (8.7)	0 (0.0)	1 210 (3.0)	**21 567 (23.1)**
	Referred for test	30 (0.2)	10 (0.1)	222 (0.9)	262 (0.5)	81 (0.6)	908 (6.9)	65 (0.5)	1 054 (2.6)	**1 316 (1.4)**
	Self-revealed HIV	76 (0.6)	791 (4.8)	465 (1.9)	1 332 (2.5)	277 (1.9)	974 (7.5)	212 (1.7)	1 463 (3.7)	**2 795 (3.0)**
	Self-revealed HIV on ART	66 (0.5)	624 (3.8)	465 (1.9)	1 155 (2.2)	252 (1.7)	918 (7.0)	207 (1.7)	1 377 (3.4)	**2 532 (2.7)**
Malnutrition*	Screened	1 344 (67.7)	2 251 (84.4)	2389 (91.5)	5 984 (82.4)	2 148 (85.4)	1 926 (89.2)	1 424 (88.7)	5 498 (87.5)	**11 482 (84.8)**
	Malnourished	31 (1.6)	100 (3.7)	33 (1.3)	164 (2.3)	109 (4.3)	198 (10.3)	386 (24.0)	693 (11.0)	**857 (6.3)**
	Malnourished with COVID symptoms	27 (1.4)	44 (1 6)	4 (0.2)	75 (1.0)	44 (1.7)	210 (0.1)	345 (21.5)	599 (9.5)	**674 (5.0)**

Table 1 Data collection details and demographic characteristics of people who accessed the service and diseases screening in Sofala and Cabo Delgado.

* As denominator only <5 population reached has been considered.

Di Gennaro et al. 6
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RESULTS

The project reached 93 503 people, including 53 559 (29 016 females and 24 543 males) people living in Sofala and 39 944 (21 183 females and 18 761 males) in Cabo Delgado province. The modal age group was 5–14 years. In total, women represented 53.7% of the population (Table 1).

During the study period, a total of 12 680 (13.6%) people reported at least 1 symptom suggestive of COVID-19 infection, respectively 2 374 (4.4%) and 10 306 (25.8%) living in Sofala and Cabo Delgado. Overall, data shows a higher prevalence of COVID-19 symptoms in Cabo Delgado, peaking in March-April and August-September 2021, especially in Chiure district. The most frequently observed symptoms were cough and fever, both present in 11% (n = 10 767) of the recruited people.

Concerning malaria, a total of 621 out of 2 664 (23.3%) of subjects living in Sofala and 3 584 out of 6 160 (58.2%) in Cabo Delgado tested positive during the study period. Figure 1 shows the temporal trend of malaria testing and incidence in the two provinces.

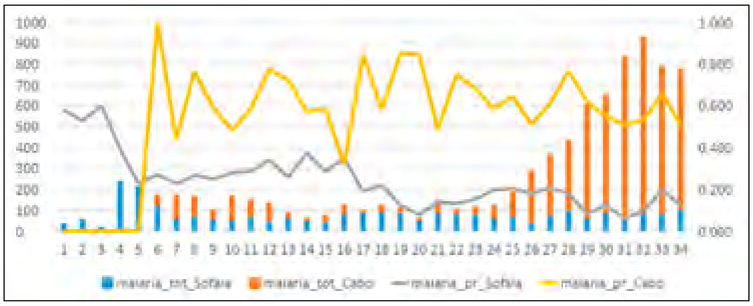

Figure 1 Total number of malaria cases and test positivity rate. Vertical bars show the total number of malaria cases diagnosed among internally-displaced people in Sofala (blue) and Cabo Delgado (orange) provinces. Continuous lines show the test-positivity rate for malaria in Sofala (grey) and Cabo Delgado (yellow) provinces during COVID-19 pandemic.

Among people living in Sofala, 38.0% of recruited subjects (n = 20 357) were considered eligible for an HIV screening, but only 262 people (0.5%) were referred for testing, while in Cabo Delgado, 1 210 (3.0%) were eligible and 1 054 (2.6%) were referred for testing.

Eighty-four percent of the 13 545 children under the age of 5 that were reached by community outreach were screened for malnutrition and, in the Sofala region, 164 (2.7%) were diagnosed with acute malnutrition. Interestingly, in Sofala, 75% of the children with acute malnutrition reported at least 1 concurrent sign or symptom of COVID-19 (45.7%). In the Cabo Delgado region, acute malnutrition was diagnosed in 693 out of 5 498 (12.6%) children under5, with a prevalence of concurrent COVID-19 symptoms as high as 86.4% (n = 599) of the children presenting at least 1sign and symptom of COVID-19. In this study, the malnutrition rate was higher in Cabo Delgado than in Sofala, with the highest incidence between the 5th and 15th Epi week (Figure 2).

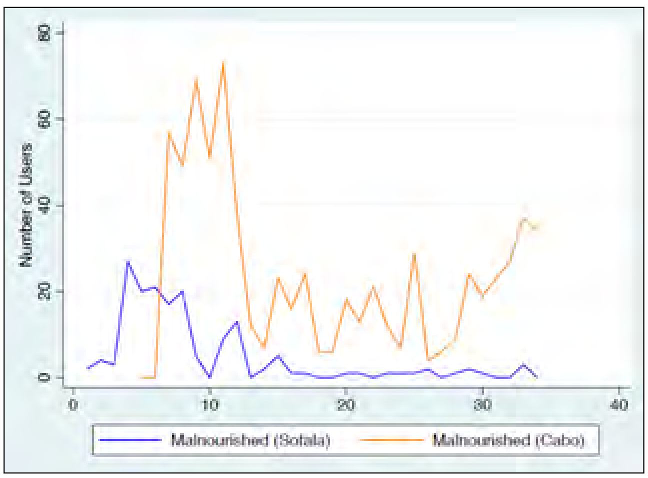

Figure 2 Total number of malnutrition cases. Total number of internally displaced children <5 diagnosed with malnutrition in Sofala (blue line) and Cabo Delgado (orange) provinces during the COVID-19 pandemic. X axis: Epi week; Y axis: number of children diagnosed with malnutrition per week.

DISCUSSION

This study follows the lead of community mobilization to promote health from a wider perspective. During COVID-19 times, among internally displaced people, active community engagement promotes disease awareness and mitigates the lack of healthcare workforce, thereby contrasting the diversion of health expenditure from primary healthcare to COVID-19 treatment [12]. In this context, internally displaced people are particularly vulnerable to COVID-related healthcare disruption, since several factors – such as poor living conditions, societal isolation, and instability of healthcare supply – converge in affecting the delivery of sustained disease control interventions [13]. In terms of infectious diseases, since the beginning of the pandemic, African countries have witnessed a large increase in the disability-adjusted life years (DALY) related to HIV, TB, and malaria, combined with a generalized decrease in case reporting.

Since the beginning of the pandemic, although the high prevalence of hard-to-reach populations, cultural barriers, and diagnostic tool unavailability has been recognized as critical challenges for COVID-19 management in Africa [14–16], the recent experience with Ebola fostered a rapid, diffuse community-based response [17]. In this context, our study highlights the importance of mass clinical screening, as we detected 13% of our population had at least 1 COVID-19 symptom. Although we were not able to report disease incidence, the wavelike trend of people positive for COVID-19 clinical screening may suggest that a prompt adoption of prevention behavior (such as isolation) based exclusively on clinical suspicion could help to reduce infection spread. Nevertheless, since asymptomatic transmission plays a pivotal role in COVID-19 spread [8], relying solely on clinical symptoms may be misleading.

In low resource settings, case management is further complicated by the overlapping of COVID-19 and malaria clinical presentation, as fever, joint pain, fatigue, and headache are well-recognized symptoms of both diseases [9, 18]. A combined diagnostic algorithm allowing healthcare workers to consider malaria and COVID-19 coinfection is urgently needed [19], as well as studies addressing the combined impact of both diseases among vulnerable populations [20]. In our study, we administered malaria RDT to 86% of the recruited people, which led to a positive diagnosis in 4.5% of the total population and, interestingly, about one-third of the people who reported at least one COVID-19 symptom tested positive for malaria. Although the effect of malaria on COVID-related outcomes is still a matter of debate [21, 22], these findings stress the importance of combining mass screening for COVID-19 in malaria service delivery in endemic areas [23].

On the other hand, it is widely confirmed that malnutrition and pneumonia are strictly related, as respiratory infections are one of the major complications of undernutrition, and wasting and stunting increase the mortality from pneumonia by about 15-fold [24]. On its own, pneumonia represents 14% of the overall under 5 mortality [25]. In this context, we understand that the COVID-19 pandemic sheds new light on pneumonia epidemiology and therefore on how we need to approach pneumonia as a disease. For this reason, our study included screening for malnutrition, reaching 84.8% of children under 5 years old in this population.

While evidence is growing that, worldwide, children are less likely to develop severe forms of COVID-19 [26], in African countries a substantially lower rate of disease is observed. Several epidemiological factors (such as the protective effect of other endemic infections or vaccinations) are being studied. Nevertheless, since the beginning of the pandemic, malnutrition proved to be bound to COVID-19 disease both for being a risk factor for severe disease and for being a consequence of the COVID-induced social crisis [27, 28]. In our population, among the 6.5% of under 5 children diagnosed with acute malnutrition, about 80% presented at least one symptom of COVID-19. However, as stated before, we were not able to assess the proportion of those symptoms attributable to SARS-CoV2 and, given the increased risk of pneumonia experienced by malnourished children [24], they may be the manifestation of other respiratory infections due to, for instance, respiratory syncytial virus (RSV), human metapneumovirus, *S. pneumoniae* or *S. aureus*.

Finally, our project included referrals for HIV screening. Access to HIV testing represents a constant challenge, as mistrust and fear often hampered screening initiatives. In our study, we notice that the community mobilization contributed to promoting access to HIV testing, as 86.7% of people were reached and counselled by study interviewers. On the basis of the interview, one-fourth of the enrolled subjects were eligible for the test, as they fit the risk criteria identified by our tool. Nevertheless, just 6% of our population got tested for HIV. This low rate stresses the existence of barriers to accessing HIV testing among IDPs, which, in turn, may be a consequence of the long distance to the first HIV testing facility, which should be prioritized when planning future interventions. In our project, the only possible referral to HIV testing service was the mobile service managed by our team, which visited the camps. In this context, Omam LA et al [29]. describe a similar experience with mobile-clinic among IDPs in Cameroon, and the authors conclude that this approach represents a promising tool to overcome difficulties due to the COVID-related constraints in access to health services.

Nevertheless, a common finding in HIV projects among IDPs is that the absence of a structural service for HIV screening represents a major challenge for test delivery to all eligible people [30]. Thus, a reaction strategy to SARS-CoV2 outbreak, along with the implementation of COVID-19 mitigation initiatives, should entail the adaptation of existing services for delivering care for all the major causes of death and morbidity, including malnutrition and HIV-malaria coinfections [31, 32].

We recognize some limitations in our study. For example, the lack of testing capacity for COVID-19, no consideration can be made to the actual verified case number of COVID-19 resulting from the clinical screening alone.

HIV testing depended on a mobile team without-reach activity. This makes it difficult to understand the real percentage of people who would have actually benefited from the combined screening and would have gone to be tested for HIV.

CONCLUSION

The COVID-19 pandemic in the African context can develop different scenarios in respect of what has been reported in other continents. Population-specific needs make it necessary to develop new screening methods that respond to the specific characteristics of the target population. Thus, non-healthcare personnel can be trained for a first symptom-based screening, but, considering the importance of asymptomatic transmission of SARS-CoV-2, this needs to be associated with proper microbiologic testing.

The use of funds and social resources mobilized for COVID-19 is an important chance to improve healthcare to fight against HIV and other transmissible diseases. In regions where malaria is endemic, the disease should be ruled out in all cases of febrile illness. For this reason, combined point-of-care testing for both COVID-19 and malaria, along with HIV sensitization and screening for malnutrition, play a pivotal role in community-based interventions like the one described here. In low-resource settings, the diversion of financial and human resources to initiatives exclusively focusing on COVID-19 care may, instead of bringing solutions, decrease the overall health status of vulnerable populations such as IDP.

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

All authors had access to the data and a role in writing the manuscript.

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PAPER

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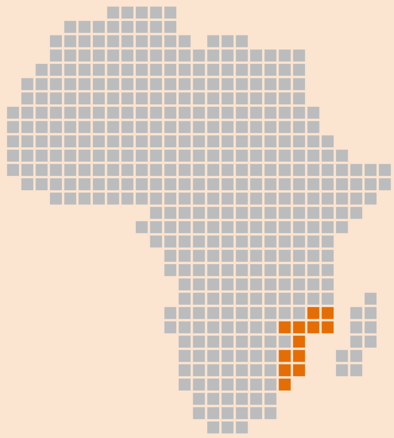

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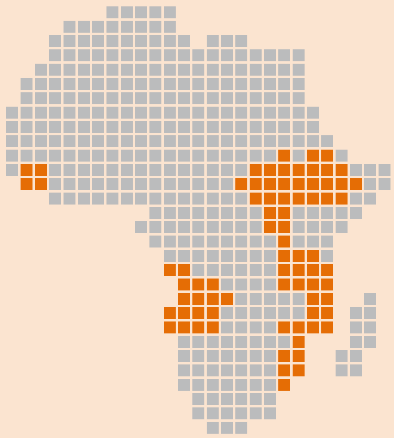
Evaluating Healthcare Performance in Low- and Middle-Income Countries: A Pilot Study on Selected Settings in Ethiopia, Tanzania, and Uganda

PAPER



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Evaluating Healthcare Performance in Low- and Middle-Income Countries: A Pilot Study on Selected Settings in Ethiopia, Tanzania, and Uganda

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Abstract: The literature reports some experiences regarding the design of integrated healthcare Performance Evaluation Systems (PES) applied in Low- and Middle-income Countries (LMIC). This study describes the design of an integrated and bottom-up PES aimed at evaluating healthcare services delivery in rural settings. The analysis involved four hospitals and their relative health districts in Ethiopia, Tanzania, and Uganda. The evaluation process was undertaken for those indicators that could be evaluated using the same reference standard. The evaluation scores were determined through the international standards identified in the literature or through benchmarking assessment. Both administrative and health data were extracted from the hospitals' registers and District Health Information Systems (DHIS) from 2017 to 2020. We defined 128 indicators: 88 were calculated at the hospital level and 40 at the health district level. The evaluation process was undertaken for 48 indicators. The evaluated indicators are represented using effective graphical tools. In settings characterised by multiple healthcare providers, this framework may contribute to achieving good governance through performance evaluation, benchmarking, and accountability. It may promote evidence-based decision-making in the planning and allocation of resources, thus ultimately fostering quality improvement processes and practices, both at the hospital and health district level.

Keywords: performance evaluation system; multidimensional performance evaluation; constructivist approach; health system; healthcare; international benchmarking; low- and middle-income countries

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1. Introduction

Health systems in Low- and Middle-income Countries (LMIC), compared to High-income Countries (HIC), are faced with somewhat different intrinsic challenges, which are, in large part, due to interrelated issues of poverty, education, lack of resources, as well as weak leadership [1].

Nevertheless, health systems in all countries, irrespective of income availability, put in place similar policies that aim to improve accessibility, quality of care and equity of healthcare [2,3].

A wide array of interventions has been implemented so far in order to increase accessibility to healthcare across LMICs, and to guarantee that "individuals that can potentially benefit from effective healthcare do in fact receive it" [4], thus achieving Universal Health Coverage [5]. Moreover, a lot of work has been focused on refining policy interventions to improve quality of healthcare in deprived settings [6].

Despite crucial differences between health systems in HICs and LMICs, the need to ultimately improve similar aspects of these systems implies that a substantial level of complexity is present across all health systems, irrespective of epidemiological, social and economic context [7,8].

The last two decades saw an extensive effort to design, develop and implement Performance Evaluation Systems (PES) in HICs to manage such a high level of complexity and improve the performance of health systems [9,10]. International agencies have designed frameworks to assess health systems performance through the monitoring of different key dimensions [11–14].

The literature reports only a few experiences regarding the design of PES framework applied to LMICs. When available, they refer to specific services or geographical settings [15–17], and they do not compare performance of different settings from a multidimensional perspective [18,19]. Indeed, this approach hinges on the need to take into account multiple indicators (related to efficiency, structure, process, quality of care, appropriateness, and equity) [20], as well as the different interests of several stakeholders in the healthcare system, by embracing a population-based perspective [21,22].

Given this premise, the primary objective of this article is to answer the following research question:

RQ: What are the features and challenges of designing and developing a bottom-up and integrated approach of PESs in LMICs?

For this purpose, the paper describes the development of a PES in four selected settings from three Sub-Saharan African countries, namely Ethiopia, Uganda, and Tanzania. In particular, the PES aims to evaluate and compare the performance of healthcare services delivery of four different healthcare settings, providing policy makers and healthcare managers in LMICs with a specific and scalable framework that can contribute to improving efficacy when assessing performance of healthcare services at hospital and district level.

Theoretical Background

Nowadays, it is common practice for HICs to measure and evaluate the performance of their healthcare systems. Health system assessments have been developed to address the need to face the common challenges of health systems in HICs, such as demographic changes and population aging, limited resources, and rising costs, along with the need to improve quality of care delivery and guarantee equitable access to healthcare services, while ensuring the financial sustainability of the whole system itself [23,24]. Aside from this, in the past few years there has been increased capacity for measurement and analyses, driven by massive advances in information technology and associated progress in measurement methodology [25].

In this scenario, over the last few decades, the international literature on performance measurement proposed several conceptual frameworks and taxonomies. In 1988, Donabedian developed the first model to assess health services and evaluate quality of care by including three domains: structure, process, and outcomes [26]. This framework referred to the impact healthcare has on the health status of patients, stressing that effectiveness is a measure through which "attainable improvements in healthcare are reached" [11].

Partially based on the Donabedian model, a framework developed by the WHO and OECD was created at the beginning of the new century [14,27]. Nevertheless, these frameworks represent the first attempt to evaluate healthcare performance across different countries using a top-down approach and including a broader range of dimensions, as shown in Table 1.

However, it is worth noticing that countries and organisations also adopted different approaches that depend on the specific context, intended use and acceptability [28]. Moreover, their effective adoption and usage often face difficulties that are mainly due to the differences in social and environmental characteristics, as well as the intrinsic complexity of healthcare systems [7,9,24].

Table 1. Theoretical framework analysed, i.e., WHO, OECD, and Italian PES.

Framework	Unit of Analysis	Dimensions	Benchmarking	Approach	Visualization Tool	Comparison
WHO	Country	• Improving health • Expenditure or cost • Efficiency • Equity • Patient centredness	✓	Top-down	Ranking	Between Countries
OECD	Country	• Accessibility • Effectiveness • Expenditure or cost • Efficiency • Equity • Patient centredness	✓	Top-down	-	
Tuscany region IRPES Network	Health DistrictsHospitals Regional Healthcare Systems	• Population health • Efficiency/financial performance • Patient/staff satisfaction • Regional strategy compliance • Quality/appropriateness/continuity of care • Governance and quality of supply • Pharmaceutical care	✓	Bottom-up	Dartboard Stave	Within the reference Country

Embedded in this research field is the experience of the PES developed and implemented in a number of Italian regional healthcare systems [20] and adopted by other countries [10,29,30] and international organizations, e.g., OECD [31,32]. A peculiarity of these evaluation systems, compared to the international frameworks, is that they are based on a bottom-up approach and envisage specific graphical representation tools for the return of multidimensional evaluation data [20,33].

More generally, this generation of "integrated" PESs [34] is characterized by several features, summarized by Nuti et al. [33] in the following six items: multidimensionality, evidence-based data collection, systematic benchmarking of results, shared design, transparent disclosure of data, and timeliness.

To the best of our knowledge, there are few integrated PESs specifically applied to LMICs, and research and publications are limited [35,36]. Moreover, these initiatives are implemented at national level and usually imply top-down approaches aimed at evaluating healthcare systems at macro level or project level [37–40]. Therefore, we based the methodology of this study on the abovementioned PESs to adapt the fundamental evaluation principles to the analysed settings in LIMCs by using a bottom-up approach.

2. Materials and Methods

2.1. Methodological Approach

This paper is based on a constructivist research approach. The approach is widely used in technical sciences, mathematics, operations analysis and clinical medicine, management research [41–43] as well as in building PESs in healthcare [20,44].

This approach highlights the principal issues involved in the measurement and evaluation of performance in African hospitals and healthcare districts. It is based on a continuous interaction between the research team (RT) and healthcare managers and professionals of the hospitals and healthcare districts to build up a PES according to their specific needs and requirements.

The RT includes four experts in healthcare management from the Management and Health Laboratory (MeS Lab) of the Institute of Management of the Sant'Anna School of Advanced Studies and two medical doctors employed by the NGO Doctors with Africa CUAMM (CUAMM). The constructivist approach entailed a series of meetings and workshops, which took place either virtually or in person, and two site visits in the selected African hospitals and healthcare districts between September 2019 and March 2020. Overall, the design and development of the system involved 5 researchers, 3 public health experts, and 15 professionals on the field. In addition, a panel of 20 experts and professionals was involved in the phase of validation of the PES, as better clarified in Table 2.

Table 2. The phases that characterized the development of the PES.

	Activity	Task	Workshops/Meetings	Role of Professionals Involved
1	Selection of the indicators	The RT assessed the most relevant information from existing literature and selected the first set of indicators to be applied in the selected contexts.	Two online meetings and one meeting in person between June and September 2019. One mission on the field (21 days) in the direction office of the St. Luke Hospital—Wolisso (Ethiopia) in September 2019.	The RT was involved in the literature review for the identification of the indicators to be applied in the PES and defined a preliminary list of indicators.
2	Feasibility analysis	In order to understand what indicators could be effectively included into the PES, the RT balanced professionals' opportunities and costs of grabbing data from both digital and paper informative systems that were already in place.	Five online meetings and 11 meetings in person. One mission on the field (21 days) in the direction office of the St. Luke Hospital—Wolisso (Ethiopia) in September 2019. Three missions on the field (40 days) in the direction offices of Tosamaganga Designated Discrict Hospital (Tanzania), St. Kiziko Matany Hospital and Pope John XXIII Aber Hospital (Uganda) from February to March 2020.	This phase included the RT and four medical doctors from all the hospitals involved. Based on the results of the first phase, taking into consideration the available data at the health district and hospital level, the involved professionals tried to understand if the identified indicators were applicable in the PES or how they could be adapted in the selected settings. Four lists of available indicators were defined for each setting.
3	Data collection and data analysis	The RT supported the hospitals and health districts' professionals in extracting aggregated data in a homogeneous way from different health registers and information systems. The RT calculated the indicators and produced the preliminary graphs for evaluation of indicators.	Eight online meetings in March and April 2020.	This phase included 2 experts in healthcare management, 11 experts in public health (statistical staff and medical doctors), 6 experts in monitoring and evaluation, and 1 expert in accounting and finance. The hospitals and health districts staff collected data, computed numerators and denominators, and shared them with the RT. By means of these elements, the RT calculated the indicators for the three years and produced the preliminary bar charts.
4	Standards identification	The RT worked closely with one public-health experts in order to identify standards to be applied to evaluate information collected and to perform graphical representations.	Seven online meetings from April to June 2020.	This phase included the RT and one more expert in public health. The professionals viewed the preliminary graphs produced after the calculation of the indicators and, by comparing the results with the main evidence in the international literature, they chose a set of standards tailored to the specific settings analysed.
5	System validation	The RT shared the preliminary results with a group of experts and professionals to receive their opinions and comments before the dissemination of the results.	Two online meetings in July 2020.	This phase included the RT and a group of experts in hospital management, public health, and infectious diseases. The RT shared the preliminary evaluation results, received opinions and suggestions from the group of experts involved in the first meeting, and validated the PES system in the second meeting.
6	Results dissemination	The RT organized a series of events for disseminating and returning results to healthcare managers of the selected settings to illustrate and eventually discuss how to use them.	A workshop in blended form (October 2020) and two online seminars (November 2020). Additionally, eight other online meetings between December 2020 and October 2021 involved the local staff in results presentation.	The RT organized some workshops for officially presenting the definitive results and two other seminars in Italy. The eight online meetings envisaged the presentation of the results of the PES to the local staff and aimed at raising their awareness of the relevance of this system as a management tool.

2.2. Stages of Development

As previously mentioned, the methodology used here was inspired by the approach adopted for the design, development, and implementation of the PES of Tuscany Region and the Inter-Regional Performance Evaluation System (IRPES) in place in Italy to measure and evaluate the multidimensional performance of public healthcare organizations across Regional Healthcare Systems [20,45]. The MeS Lab launched the PES in the Tuscany Region in 2004. Later, the IRPES network was established in 2008 as a network across the Regional Healthcare Systems that joined the initiative first developed in Tuscany. In practical terms, it represents a voluntary based governance tool to support healthcare managers and policy makers at the regional and local level.

With regard to the development of the PES system in Ethiopia, Uganda, and Tanzania, Table 2 illustrates the activities and tasks undertaken throughout the different stages of development.

2.3. Study Setting

The pilot study involved four hospitals and their respective healthcare districts, which are supported by CUAMM through clinical and administrative activities both at hospital and district level.

The analysed contexts are embedded within three distinct National Health Systems with specific governance, financing, services delivery models, and different levels of per-capita expenditure [46–48]. For further details, see Table 3 below.

Table 3. Governance models, financing schemes, services delivery levels, and health expenditure per capita from domestic sources by country.

Country	Governance	Financing	Services Delivery	Domestic General Government Health Expenditure per Capita (Current USD—Year 2018) *
Ethiopia	Federal system of governance based on mutually agreed resource allocation criteria: • National Government; • Regional States; • Woreda authorities; • Kebele (village) authorities.	Three main sources: • Government budget funded by general tax revenue (including on-budget donor support); • Off-budget donor assistance; • Private out-of-pocket expenditures.	Three main levels of delivery (public and private): 1. Primary hospitals, health centres, and health posts; 2. General hospitals; 3. Specialized hospitals, serving as referrals from general hospitals.	$15.57
Tanzania	Decentralised system: • National Government; • Regional authorities; • Local government authorities (districts).	Three main sources: • Government budget funded by general tax revenues; • Development partners; • Household/out of pocket.	Three main levels of delivery (public and private): 1. Dispensaries and health centres; 2. District designated hospital; 3. Regional hospitals.	$48.30
Uganda	The main administrative levels are: • At the national level (central government); • At the district level and one city (local governments).	Three main sources: • Government funds mainly drawn from taxation, funds collected from decentralized local governments and development partners; • Donor or development partner funding through project support; • Out-of-pocket funds.	Three main levels of delivery (public and private): 1. Health subdistricts composed of village health teams, health centres or hospitals; 2. Regional referral hospitals; 3. National referral hospitals.	$22.06

* Public expenditure on health from domestic sources per capita expressed in international dollars at purchasing power parity (PPP time series based on ICP2011 PPP). Sources: World Health Organization Global Health Expenditure database.

In all these contexts, the four hospitals analysed have the same institutional setting: they are private, faith based, and not for profit. These private hospitals act in the name and on behalf of the public health system according to specific Private Public Partnerships (PPP) with the Local Health Authorities. Indeed, these hospitals are mainly funded by the regional governments that bear some of the recurring expenses, such as costs of personnel, utilities, and drugs and consumables. The other two main sources of funding are represented by out-of-pocket payments from the patients and refunds from insurance companies. Alongside the hospitals, the health districts are managed by the regional government and are characterized by similar organizational models, featuring a wide variety of healthcare providers at different levels. Primary and secondary care is offered at dispensaries and health centres, which are spread within the reference territory and intended to provide mainly outpatient services, e.g., prevention, health promotion, maternity, and some in-patient curative services. Tertiary care is provided by regional hospitals, which offer more specialized services, including consultation, emergency, and surgical services. These hospitals serve as referral hospitals for the districts. The distribution of facilities across levels of care reflects the healthcare needs of the population, with most cases treated at the district level and more complex cases referred to reference hospitals.

Table 4 shows the main information related to the four hospitals and districts participating in this study.

Table 4. List of the analysed hospitals and their relative health districts or catchment area.

Country	Region	Health District [1]	Estimated Population (Year 2020)	Reference Hospital	Hospital Beds (2019)	Area (km^2)	Population Density (Citizens per km^2)
Ethiopia	Oromia region	5 Woredas in Shoa-west Zone (Wolisso Town, Wolisso Rural, Ameya, Wonchi, Goro)	633,359	St. Luke—Wolisso Hospital	208	27,000	22.6
Tanzania	Iringa region	Iringa District Council	308,009	Tosamaganga District Designated Hospital	165	19 256	15.6
Uganda	Northern region	Napak District	166,549	St. Kizito—Matany Hospital	250	4978.4	31.5
Uganda	Northern region	Oyam District	449,700	Pope John XXIII—Aber Hospital	217	2190.8	197.2

[1] With regard to Ethiopia, the information reported in the cell does not refer to an institutional health district, but to the catchment area covered by Wolisso Hospital.

The Wolisso catchment area is in the Southwest Shoa Zone, one of the eighteen zones of Oromia Region in central Ethiopia. The catchment area includes five health districts (referred to as a "woreda" in Ethiopia) inhabited by around 633,000 people. In the reference area, primary care is offered by a total of 22 health centres that refer to the St. Luke Hospital—Wolisso Hospital, a private, not-for-profit institution established in the early 2000s. In Tanzania, the Iringa District Council is one of the 158 health districts of the country [49] and is located in the region of Iringa in South-Western Tanzania. While primary and secondary care is provided by around 90 dispensaries and health centres, Tosamaganga District Designated Hospital serves as reference hospital for the health district, a rural area outside Iringa, the regional capital city. Uganda is divided into 128 health districts [50], which are grouped into four administrative regions. Both the Napak and Oyam Districts are in the northern region. More specifically, the Napak District is in the Karamoja region in North-Eastern Uganda, near the border with Kenya. The district, which is in turn subdivided into 6 sub-counties and 200 villages, comprises 16 health centres providing primary healthcare services to approximately 167,000 people. St. Kizito—Matany Hospital, a private, not-for-profit institution, was built at the beginning of the 1970s and is designed as the referral centre for the Napak district. The Oyam District is in a rural region in the northern part of the country and, in 2020, registered an estimated population of approximately 449,700. In comparison to the Napak District, the Oyam District covers a territory with a higher density of population that is served by 30 health facilities, including the reference Pope John XXIII—Aber Hospital, a private not-for-profit facility.

Although the hospitals and health districts are located in different countries with different environments and epidemiological contexts, they all aim to pursue the three main goals of the healthcare system: better-quality care delivery, guaranteeing equitable access for the entire population, and maintaining the overall financial sustainability of the system [51,52].

2.4. Data Collection and Graphical Representation

To better realize the relevance of some phenomena and the assessment of the performance indicators, the RT collected data for the years 2017, 2018, 2019, and 2020. As recommended by the literature on the multidimensional character of healthcare performance [11,26,34,45,53], the dimensions considered for evaluation in the PES are: Regional Health Strategies, Efficiency and Sustainability, Users Staff and Communication, Emergency Care, Governance and Quality of Supply, Maternal and Childcare, Infectious Diseases, and Chronic Diseases. These dimensions are, in turn, subdivided into 24 areas of evaluation [54]. The consistency of the selection of these dimensions and areas of care was ascertained with regard to the peculiarities of the contexts analysed in the study.

The indicators were calculated both at hospital and district level. Hospital-level indicators were extracted from the registers of hospitals' departments, whilst district-level indicators were retrieved from the District Health Information System (DHIS) of Ethiopia, Uganda, and Tanzania [55]. With reference to hospital registers, the hospitals of Wolisso and Matany had electronic information systems, whereas Tosamaganga and Aber hospitals had paper-based information systems.

Hospitals and health districts datasets were used to collect aggregated data on pre-defined variables (per year of study) and subsequently elaborated into an Excel spreadsheet (Activity 3, Table 2). The RT run data analyses and relative graphical representations in Statistical Analysis System (SAS) version 9.4 (Activity 3, Table 2).

With respect to the final version of the list of defined indicators, some of the indicators were evaluated through the process designed and implemented by the MeS Lab research group in Italy, as inspired by the IRPES [20]. The indicators were evaluated through the identification of five bands, considering the statistical distribution of the indicators' values [20,54,55]. Evaluation scores were built using an algorithm matching each band with a value between 0 and 5, and a colour spanning from red (a very low score) to dark green (a very high score) [54,55]. The band's construction varies according to the sign of the indicator, which can either show signs of increasing or decreasing (Activity 4, Table 2).

The evaluation was performed for the year 2020 only. The evaluation scores were determined by either using international standards identified in the literature when available, or using the benchmarking assessment of values statistical distribution, as described in Tavoschi et al. [55]. The RT evaluated each indicator by taking into consideration if the identified reference standard could be adopted across all hospitals and health districts included in the study. Moreover, the RT conducted a context analysis to ascertain that the standards and indicator signs applied in the evaluation process were consistent and valid.

To provide an overview of each organization's performance, the RT applied the abovementioned scores to populate a target chart (the "dartboard"), which consists of five coloured strips spanning from red to dark green, each of which corresponds to one of the five evaluation bands. The evaluated indicators are represented in the dartboard as white dots. The closer they are to the centre of the dartboard, the higher the performance of the hospital or the health district is [20].

In order to overcome a static representation and provide an integrated and continuous view of the performance across different settings [33], we also considered the entire patient journey along different care pathways, metaphorically represented by the music stave (the "stave"). The stave illustrates the patients' care pathway, allowing the user to focus on the strengths and weaknesses of the healthcare services delivered to patients along the continuum of care [55]. The previously described process also applies to care pathways, for which the stave, similarly to the dartboard, uses five colour bands (from red to dark green). In this case, however, the bands are now displayed horizontally and framed into different phases of healthcare services delivery.

All indicators that could not be evaluated were included in the final list to observe specific and relevant context-related phenomenon.

3. Results

The work illustrated in the present paper produced a total number of 128 indicators over 8 different dimensions and 24 areas. While a total of 88 indicators were calculated at the hospital level, 40 were calculated at the district level. Among these 128 indicators, 48 were evaluated using the abovementioned process, corresponding to around 38%.

Table 5 describes the evaluated dimensions along with the respective areas and included indicators.

As already mentioned, the indicators selected for evaluation were indicators that the Tuscany Region was considered feasible evaluate using the same reference standard. All sources of evaluation standards, alternative in terms of dimensions of evaluation to the IRPES standards and benchmarking assessment, were identified through a review of the international literature.

Table 5. Overall map of evaluation dimensions, areas, and indicators.

Performance Dimension	Area	Number of Indicators
Regional Health Strategies	Vaccination Coverage	6
	Hospital attraction	2
Efficiency and Sustainability	Economic and financial viability	3
	Per capita cost for health services	7
	Assets and liability analyses	1
	Inpatients efficiency	2
Users, Staff and Communication	Users, staff, and communication	4
Emergency Care	Emergency Care	1
Governance and quality of supply	Hospital-territory integration	2
	Healthcare demand management capability	2
	Care appropriateness of chronic diseases	2
	Diagnostic appropriateness	3
	Quality of process	1
	Surgery variation	1
	Repeated hospital admissions for any causes	4
	Clinical risk	3
Maternal and Childcare	Maternal and Childcare at district level	7
	Maternal and Childcare at hospital care	13
	Maternal and Childcare—Child Malnutrition	10
Infectious Diseases	Infectious Diseases—Malaria	9
	Infectious Diseases—Tuberculosis	14
	Infectious Diseases—Gastroenteritis	14
Chronic Diseases	Chronic Diseases—HIV	14
	Other Chronic Diseases	3

For example, bar charts were used in Figure 1 to report the results from the evaluation of two system indicators. Figure 1 Panel A illustrates the indicator "Proportion of pregnant women who attended ANC4+ during the current pregnancy", which refers to the district level and belongs to the Maternal and Childcare dimension. The standard refers to a specific target defined by WHO and adapted to African contexts [56,57]. Figure 1 Panel B shows the indicator "Percentage of discharged patients for diarrhoea and gastroenteritis", which refers to the hospital level and belongs to the infectious diseases dimension. The standard was defined though the abovementioned benchmarking assessment of the values' statistical distribution.

To provide an overall picture of the multiple dimensions of the healthcare services, the RT used the visualization tool of the dartboard, as seen in other studies conducted in Europe [10,30,33]. Figure 2 displays the dartboard related to the performance of the four health districts analysed in this study.

The dartboard shows the weaknesses and strengths of each catchment area. The dartboard of Wolisso Catchment Area presents a very disperse configuration of indicators, although with a prevalence of indicators scored in the red band as counter to the green and dark green bands. There are very positive performance results relative to all the indicators of vaccination coverage at residence level. On the other hand, there are opportunities for improvement with regard to areas related to Malaria, Tuberculosis, and HIV.

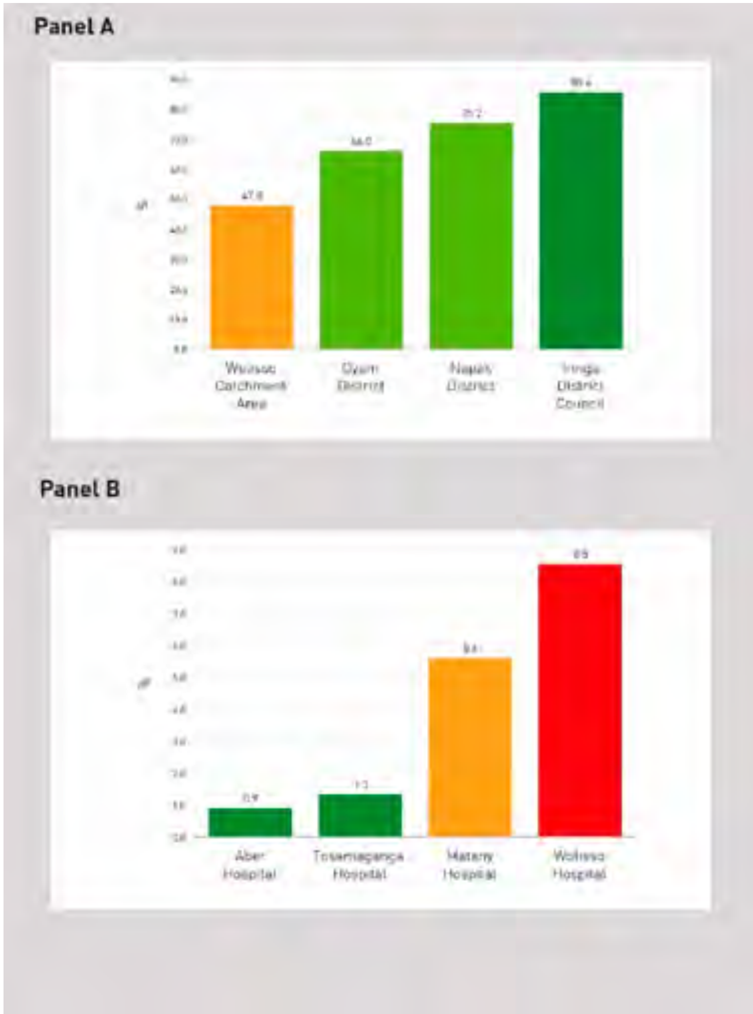

Figure 1. Two examples of evaluated indicators at hospital and district level. (**A**) Proportion of pregnant women who attended ANC4+ during the current pregnancy; (**B**) Percentage of discharged patients for diarrhoea and gastroenteritis.

Concerning the dartboard of Iringa District Council, the observation of data suggests the need to keep the indicators relative to the vaccination coverage of polio under control. In addition, it is possible to observe a certain degree of inefficiency regarding hospital management, showing potential for improvement in both the Average Length of Stay (ALOS) and the Bed Occupancy Rate (BOR).

The dartboard of Napak District shows a high dispersion of performance scores, with a wide prevalence of indicators that fall in the external evaluation bands of the dartboard, and a quite small number of indicators located in the centre of the dartboard. Main criticalities are noteworthy concerning all infectious diseases areas, with particular emphasis on the management of tuberculosis and malaria, while an ups-and-downs trend emerges by observing the areas related to gastroenteritis and HIV.

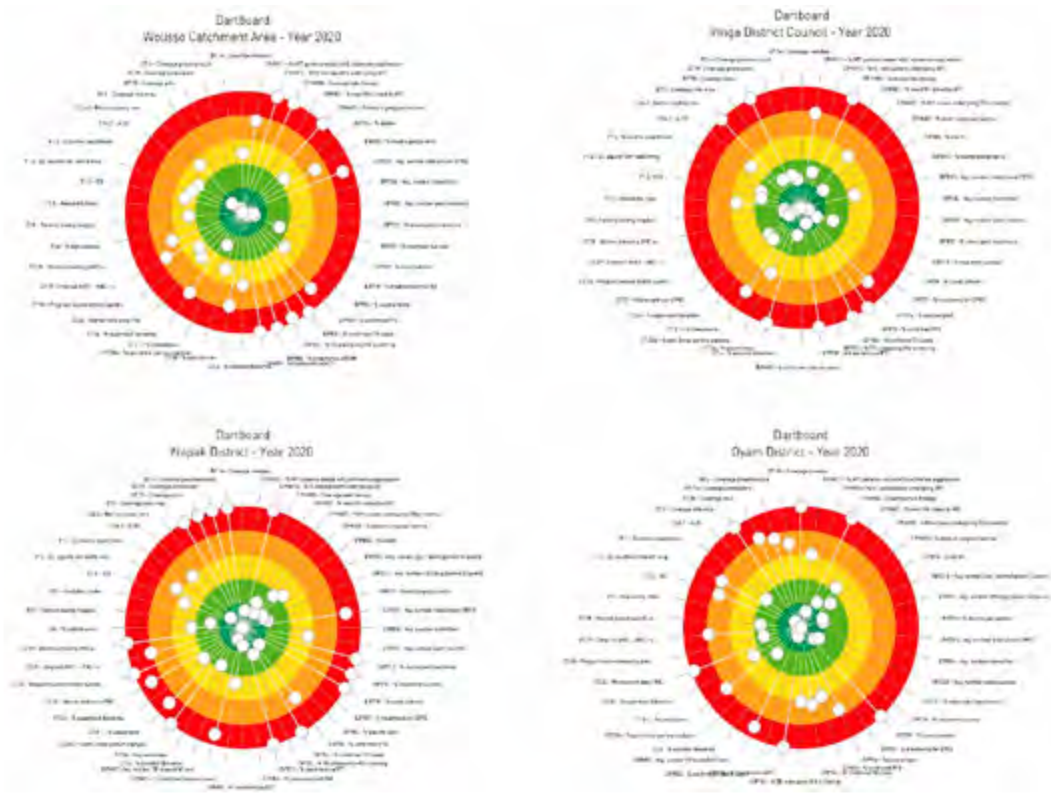

Figure 2. The four dartboards related to the performance of the health districts.

With respect to the dartboard of Oyam District, the graph shows a quite good balance between indicators presenting a good or excellent performance and those presenting poor performance levels. Indicators regarding vaccination coverage reveal poor performance outcomes for all the indicators analysed.

Regarding the care pathways, we selected four care pathways based on the relevance of health-related issues in LMICs: the maternal and childcare pathway; the infectious diseases care pathway for two of the most common infectious diseases in Sub-Saharan Africa (tuberculosis and gastroenteritis); and the chronic diseases (HIV/AIDS) care pathway.

As mentioned above, each care pathway is represented by a stave [33] that consists of specific phases characterizing the patient's journey throughout a particular area of care. The maternal and childcare pathway includes pregnancy, childbirth and first-year-of-life phases. The infectious diseases care pathways include prevention, diagnosis, treatment, and outcome phases. Finally, the chronic diseases care pathway includes screening, diagnosis, treatment, and outcome phases.

Figure 3 shows the care pathway related to maternal and childcare in the four healthcare settings. It displays district and hospital performance along the care pathway and, more specifically, the individual contribution of each provider to the overall care pathway performance.

The stave of Wolisso Catchment Area shows quite poor performance in the pregnancy phase, and average and excellent performance scores in the last phase of the care pathway. Regarding the childbirth phase, the results are hybrid, as positive performance is found with respect to the percentage of caesarean sections and the percentage of peri/intra-partum asphyxia, while a quite poor performance can be observed with regard to the percentages of episiotomies and assisted deliveries performed.

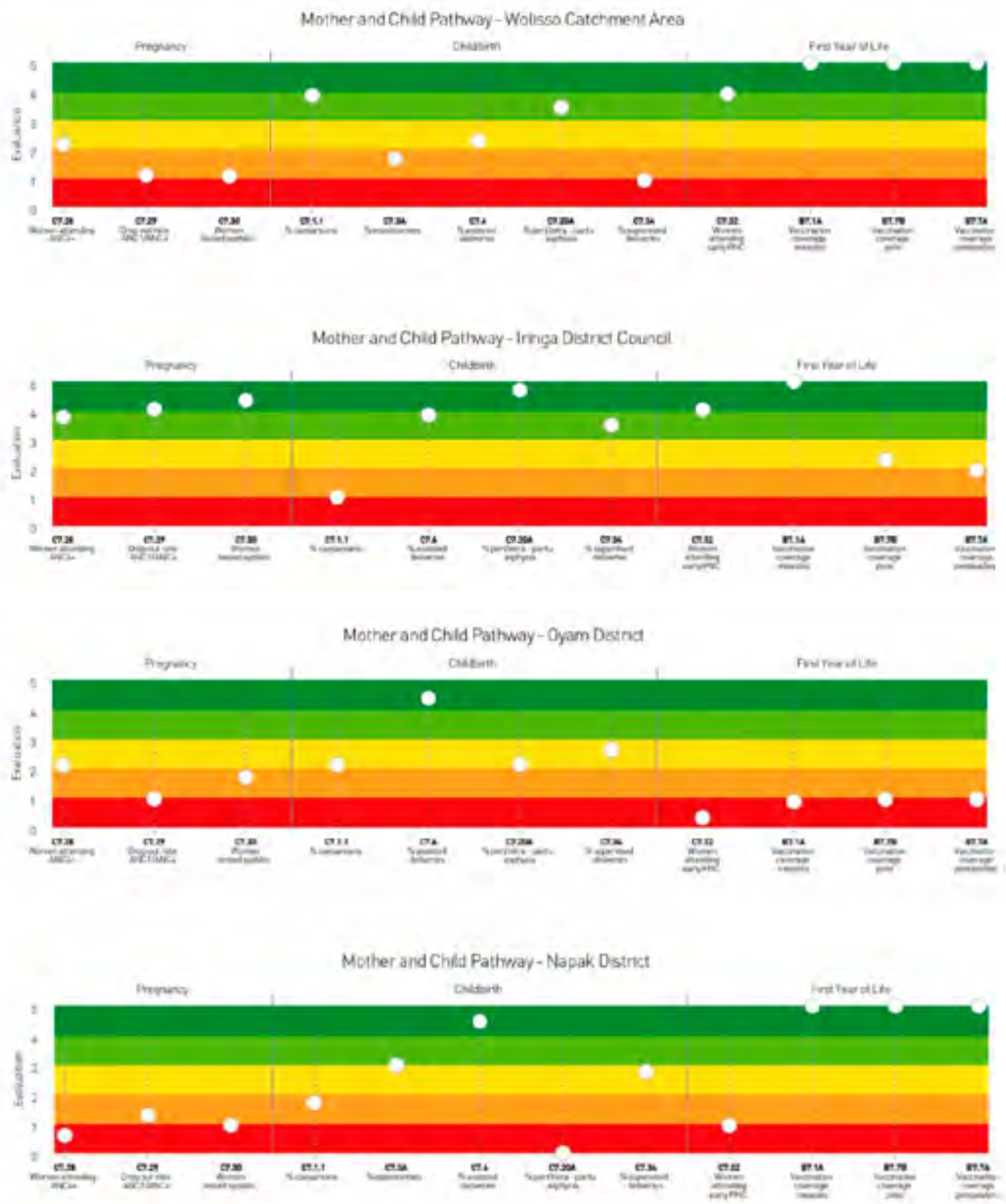

Figure 3. Example of staves related to the performance of the Maternal and Childcare pathway of Iringa District Council (Tanzania), Napak and Oyam Districts (Uganda) and Wolisso Catchment Area (Ethiopia).

The stave of Iringa District Council illustrates a high concentration of indicators with excellent and good performance scores in all phases of the Maternal and Childcare pathway. Contrary to the overall excellent performance reported in the Maternal and Childcare pathway, an element of weakness in the hospital performance is represented by the high percentage of caesarean sections performed.

In the Napak District, there are potential areas for improvement pertaining to the antenatal care and childbirth phases, with the percentages of supervised deliveries and assisted deliveries at residence level and episiotomies at hospital level performing slightly better than the indicator relative to the peri-/intra partum asphyxia and percentage of caesarean sections. Moreover, there is a weak capability of ensuring care continuity in the first year of new-born's life and positive evaluation scores relative to the indicators of vaccination coverage.

Finally, with regard to the Oyam District, the stave shows difficulties, especially during the antenatal care and care in the first year of new-born's life. This represents one of the domains that deserve greater attention from the hospital and district managers. However, the indicators relating to the childbirth phase score slightly better, especially the percentage of assisted deliveries and the percentage of peri-/intra-partum asphyxia.

4. Discussion

This paper is embedded in a stream of the literature which has been enriched by scholars for a long time: healthcare performance evaluation. The contribution of this paper is proposing, with a constructivist approach, a system of hospital and residential indicators for four different African settings. To the best of our knowledge, this is one of the first examples of integrated PES aimed at benchmarking the performance of hospitals and health districts at local level in different LMICs. This PES focuses on the evaluation of the performance of healthcare services delivery within the local health system, which includes several residential health centres and their relative reference hospitals. It also came into existence as the result of a bottom-up and voluntary-based initiative [58]. It was not commissioned and regulated by governments or international agencies with supranational legal attendance, rather it emerged from the needs identified by an NGO, which supports the provision of services at the local level by healthcare institutions owned by third parties. It is worth noticing that the process has been triggered by an international NGO and not by the local health system decision makers. However, this approach was made possible because the hospital managers, in collaboration with health districts managers, favourably welcomed the development of an integrated evaluation system taking into consideration both the healthcare institution itself as well as its collaboration with residential services, thus leading to services integration. This aspect is especially important because the measurement of the integration of different care settings is challenging not only in terms of the identification of appropriate measures, but also in relation to their joint acceptability by all healthcare providers and professionals involved in healthcare delivery [59,60].

The framework developed in this study resembles the core principles and features of performance evaluation that were mentioned in the theoretical background. In addition, the indicators are reported through three peculiar graphical representation tools, i.e., evaluation bands, dartboards, and staves [20,33], which can effectively highlight the multidimensional aspects of performance in healthcare. Indeed, since low-income settings are characterized by many national and international actors that provide different contributions to the health system, the effective use of indicators considering integrated aspects of care is made more difficult by the complexity of ascertaining the isolated contribution of each provider. In this sense, the model of PES presented here may help overcome this issue by combining different aspects in a unique representative solution and highlight the weaknesses and strengths of the system. By means of the effective visual representation of indicators, the PES could facilitate negotiations at different levels and between different providers and organizations that are called on responding to healthcare needs of the population in a specific setting. As emerged from the workshops for the methodological process sharing and evaluation data return organized to involve local healthcare decision makers and professionals (activity 6, Table 2), all participants provided positive feedback on the relevance of having a system with graphical representation tools offering an overview of the multidimensional aspects of healthcare performance and capturing the effective contribution of each provider to the local health system.

If used from a system viewpoint, comparing results in data benchmarking among closer realities may allow the identification of unwarranted geographical variation areas and, in turn, measure horizontal equity at local level [61]. Indeed, this system could help policy makers and managers to achieve a better understanding of the determinants of health inequalities in the delivery of healthcare services and, consequently, to manage variation in a more appropriate way.

In the contexts in which the PES has been already implemented and used, it has proven that the potential use of benchmarking data can be achieved when publicly disclosing performance results, thus making policy makers and managers accountable for their management. Additionally, the experience in using this methodology suggests that the systematic use of benchmarked performance data, paired with effective data-visualization tools, can stimulate local staff motivation by the leverage of reputation. As stated elsewhere, raising professionals' awareness leads to a "reputational competition" that, in turn, contributes to promote change, and hopefully improvement [21,62,63].

Additionally, as emerged from the feedback provided by the group of public health experts working in the field (Activity 5, Table 2), a huge amount of data and indicators are collected on a regular basis but not used for managerial purposes either at hospital or at district level. It is important to mention that this burden of data is usually shared for producing statistics and reporting with national and international agencies, thus implying that there is no effective critical interpretation of these data linked with integrated management approaches. Our experience has proven that the PES system could work as a tool to improve capacity building in the professional environment, and the participative approach can partially temper the problem of data availability. It could promote the development of skills and competencies among professionals in data collection and analysis, thus sharpening their ability to adopt a population-based approach when interpreting the results [21] and improving the quality of data collected. Consequently, the PES could eventually accelerate the transition from a traditional paper-based information system towards a fully digitalized information system.

Limitations

This research comes with some limitations. First, in this specific case, the scalability of the system strongly depends on the commitment and strategic vision of CUAMM and on the effective feasibility of collecting hospitals' and health districts' integrated data. Based on the assumption of the pre-existing network, this tool represents an evaluation model easily scalable to other organizations providing healthcare services in other Sub-Saharan African Countries with the support of CUAMM, irrespective of internal and external factors of influence, i.e., environmental or epidemiological needs, institutional characteristics and features, or organizational frameworks. The prerequisite for this type of scalability is that the other stakeholders do not assume an attitude of distrust or disinterest in being evaluated together with other organizations. Nevertheless, the fact that the PES is scalable in other settings that are supported by CUAMM does not exclude the possibility of adapting such system in other contexts where there is an intermediate party that guarantees the commitment of local professionals or their willingness to voluntarily participate in this kind of initiative. Moreover, the issue of scalability is not necessarily related to the external validity of the method followed, which was developed according to the main indications provided in the international literature on performance evaluation.

Second, the PES does not provide a full view of the health system because the details of indicators computation in some contexts are based on an estimation (e.g., reference population) and the performance results do not consider all providers within the same target territory. Therefore, in the hypothesis of extending the analyses to other realities, estimation errors should be considered while defining and calculating indicators.

Another main limitation of this research is related to data quality, which depends on the level of development and availability of digital recording systems. The reliability of available data can influence the credibility and robustness of the defined indicators. However, the use of data for evaluation purposes may leverage the progressive improvement of data quality and, in general, the digitalization of information systems. Moreover, since the system has been designed and developed for four different environments, the set of indicators defined are necessarily linked to the data available in these specific contexts. Therefore, as already pointed out by the group of experts, the set of indicators defined does not comprehend all aspects and dimensions that could influence the performance of healthcare delivery in LMICs, e.g., the fees become a barrier preventing access to hospitals' services. However, this limitation does not invalidate its underlying innovative approach, which can be adapted and adjusted in a fine-tuning process to fit the hospitals and health providers involved, thus respecting the contextual peculiarities evolving within the system.

5. Conclusions

This study investigates the results of a constructivist research study related to the development of a system aimed at evaluating the performance of healthcare services delivery within the local health system.

The added value of this study resides in the fact that, to the best of the authors' knowledge, this is the first experience of this kind found in the literature concerning the design, development, and implementation of an integrated performance evaluation system, aimed at assessing the performance achieved by either the hospital or the health district in rural areas of Sub-Saharan Africa, with a bottom-up approach, using systematic benchmarking to leverage on professionals' reputation, and by considering the multidimensional nature of healthcare performance.

The performance evaluation system presented in this paper represents a useful framework to be shared with actors and professionals involved in the design, implementation, and use of PESs in LMICs. In settings characterised by multiple healthcare service providers, this framework may contribute to achieve good governance through performance evaluation, benchmarking, and accountability. Additionally, thanks to its great potential to strengthen culture of data collection and monitoring, this framework may promote evidence-based decision making in the planning and allocation of resources, thus ultimately fostering quality improvement processes and practices both at hospital and health-district level.

From this perspective, future research should explore how the developed PES has been adopted by local decision makers and healthcare managers and the impacts of its use with respect to the improvement of healthcare performance in the long run.

There are also opportunities for further research related to the progressive amelioration of the system developed so far. Particularly, there should be systematic and continuous involvement of health professionals in the selection of new and refinement of currently existing indicators. On the other hand, existing indicators should be risk adjusted according to the socio-demographic characteristics of the population and epidemiological and institutional contexts should be observed so as not to neglect possible discrepancies among the analysed settings.

These considerations should be undertaken in managerial as well as strategic terms, to provide hints for cooperation programs and NGOs, to identify specific potential areas for improvement for each setting in addition to the individual view of health professionals and, eventually, to make the system scalable in other LMICs.

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Abbreviations

PES	Performance Evaluation System.
HIC	High Income Country.
LMIC	Low-and-Middle-Income Country.
OECD	Organisation for Economic Co-operation and Development.
WHO	World Health Organization.
DHIS	District Health Information System.
CUAMM	Doctors with Africa CUAMM.
MES	Management and Healthcare Laboratory.
IRPES	Inter-Regional Performance Evaluation System.
RT	Research Team.
SAS	Statistical Analysis System.
ALOS	Average Length of Stay.
BOR	Bed Occupancy Rate.

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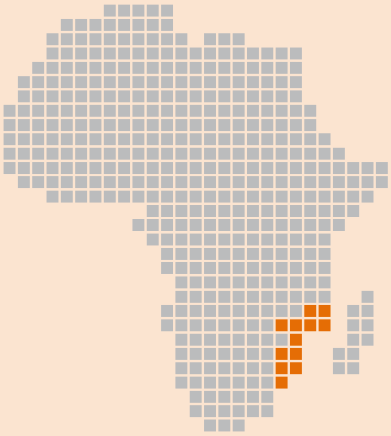
The impact of COVID-19 pandemic on the access to HIV services at urban context-based health facilities supported by CUAMM in collaboration with UNICEF, in Beira Mozambique

POSTER PRESENTATIONS



Conference
14th ICAR, the Italian Conference on AIDS and Antiviral Research

Location
Bergamo, Italy

Presentation date
14-16 June 2022

Authors
Ronzoni N.. et. al.

Focus country
Mozambique

Youth HIV services in the context of COVID-19 pandemic in Sofala province, Mozambique

POSTER PRESENTATIONS

Conference
Congresso Nazionale della Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica (SItI)

Location
Padua, Italy

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28 September - 1 October 2022

Authors
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Focus country
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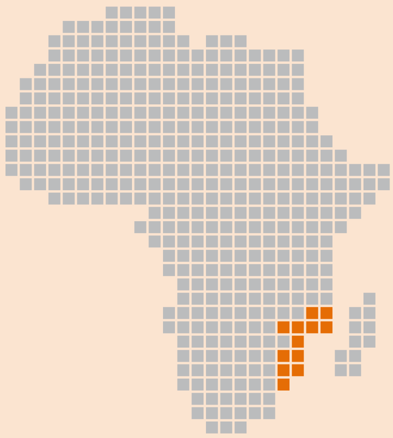

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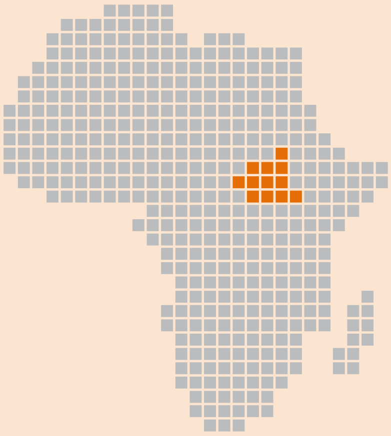

POSTER PRESENTATIONS

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IX Congresso Nazionale della Società Italiana di medicina tropicale e salute globale

Location
Florence, Italy

Presentation date
7-8 November 2022

Authors
Prato M. et al.

Focus country
South Sudan

An outreach intervention against loss to follow-up (LTFU) among HIV-positive adolescent and youths: data from Mozambique

ORAL PRESENTATION

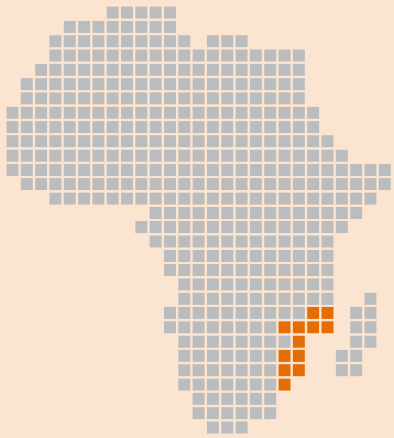
Conference
MSF Scientific Days Southern Africa

Location
Harare, Zimbabwe

Presentation date
25 October 2022

Authors
Di Gennaro F. et. al.

Focus country
Mozambique



Chronic diseases

Association between diabetes and food insecurity in an urban setting in Angola: a case-control study

PAPER

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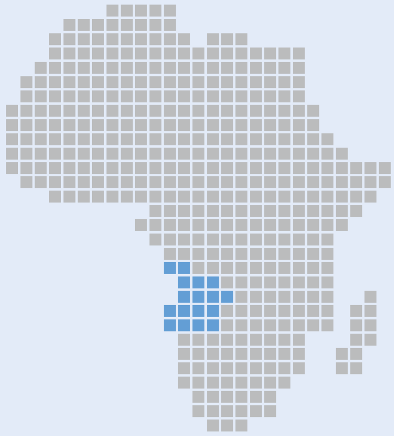

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Association between diabetes and food insecurity in an urban setting in Angola: a case–control study

Claudia Robbiati[1]✉, António Armando[2], Natália da Conceição[2], Giovanni Putoto[3] & Francesco Cavallin[4]

Diabetes is common in urban settings in Sub-Saharan Africa. Household food insecurity has been suggested to increase the chance of developing diabetes among adults. The relationship between diabetes and food insecurity has not been explored in Angolan urban settings so far. This case–control (1:2) study investigated the association between diabetes and food insecurity among adults attending six healthcare facilities in Luanda (Angola) between April 2019 and September 2019. All subjects with fasting blood glucose (FBG) levels ≥ 126 mg/dl were included as cases. For each case, the next two subjects with FBG levels < 110 mg/dl were included as controls, to warrant the achievement of the set 1:2 ratio. Food insecurity was assessed using the Food Insecurity Experience Scale (FIES). A total of 663 participants (221 cases and 442 controls) were enrolled in the study. Median FIES raw score was 7 (IQR 1–8) in cases and 5 (IQR 2–8) in controls ($p = 0.09$). The distribution of FIES levels (0–3; 4–6; 7–8) was different between cases and controls ($p < 0.0001$), with highest FIES scores (7–8) recorded in 53.0% of cases and 38.2% of controls. Our findings revealed an association between diabetes and severe food insecurity among adults attending healthcare facilities in the capital city of Angola.

Diabetes is an increasing public health burden in Sub-Saharan Africa (SSA). In 2019, 4.7% of adults aged 20–79 years were estimated to be living with diabetes in SSA, and this percentage is expected to rise to 5.1% by 2030[1].

Diabetes is common in urban settings in SSA, where lifestyle changes such as unhealthy eating behaviours and adoption of a sedentary lifestyle may lead to obesity and development of non-communicable diseases (NCDs)[2]. As a matter of fact, a healthy diet is fundamental for diabetes prevention and management, but in low-resource settings adherence to an adequate dietary regimen may be hampered by food insecurity[3].

According to the Food and Agriculture Organization (FAO), food security is defined as "everyone, at all times, having physical and economic access to sufficient, safe, nutritious food that meets their dietary needs for an active and healthy life"[4]. Food security has been recognized as a pivotal determinant of health and its role in supporting physical and mental health of individuals is unquestionable[5]. Hence, several indicators have been proposed to measure food insecurity[6,7].

A recent systematic review in high and middle-income countries supported the hypothesis that household food insecurity may increase the chance of developing diabetes among adults, and suggested the following mechanism: food insecure individuals usually adopt unhealthy eating behaviours such as consuming processed foods which are inexpensive and easily accessible[8]. This can lead to an increased total energy intake, accumulation of visceral fat, and subsequent development of chronic disease like diabetes.

Food security is related to all the United Nations Sustainable Development Goals (SDGs) to be reached by 2030, and particularly to #3 (good health) and #11 (sustainable cities)[9]. As a matter of fact, the process of urbanization may hamper the access to food for poor and vulnerable people, which leads to a rise in hunger and fatalities, and limits the development of the community[10].

Luanda is the capital city of Angola and is experiencing an epidemiological transition and a double burden of communicable and non-communicable diseases (as common in SSA urban settings) due to changes in lifestyle, diet and physical activity[11]. A recent cross-sectional study showed a diabetes prevalence of 12% among adults

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During the last 12 MONTHS, was there a time when:

Question	Label
you were worried you would not have enough food to eat because of a lack of money or other resources?	WORRIED
you were unable to eat healthy and nutritious food because of a lack of money or other resources?	HEALTHY
you ate only a few kinds of foods because of a lack of money or other resources?	FEWFOODS
you had to skip a meal because there was not enough money or other resources to get food?	SKIPPED
you ate less than you thought you should because of a lack of money or other resources?	ATELESS
your household ran out of food because of a lack of money or other resources?	RANOUT
you were hungry but did not eat because there was not enough money or other resources for food?	HUNGRY
you went without eating for a whole day because of a lack of money or other resources?	WHLDAY

Number of yes»	Interpretation
0-3	Food security
4-6	Moderate food insecurity
7-8	Severe food insecurity

Figure 1. Food Insecurity Experience Scale (FIES): description and interpretation.

reaching health centres in Luanda, with lifestyle factors such as low consumption of vegetables, high consumption of free-sugars food/beverages and sedentarism associated with diabetes[12]. Moreover, in Luanda as well as other SSA settings, the burden of infectious diseases like tuberculosis, contributes to the burden of diabetes[13]. Food insecurity is also related to tuberculosis resulting in suboptimal adherence to treatment and consequent poor outcomes[14].

Dedicated literature offers few studies on the relationship between food insecurity and diabetes in SSA. A study in Kenya highlighted the high prevalence of food insecurity amongst patients with diabetes in a resource-constrained setting[15]. A study in South Africa suggested that food insecurity hampers glycemic control in patients with diabetes, therefore primary care settings should promote early identification and management of food insecurity in diabetic patients[16]. Finally, food insecurity and medical insecurity were shown to be critical for diabetes patients' clinical presentations and prognoses in Ethiopia[17]. To our knowledge, the relationship between diabetes and food insecurity has not been explored in Angolan urban settings so far. Therefore, this study aimed at investigating the association between diabetes and food insecurity among adults accessing healthcare facilities in the capital city Luanda.

Methods

Study design. This was a case–control (1:2) study that investigated the association between diabetes and food insecurity among people attending healthcare facilities in Luanda (Angola). The study was part of a larger project on the prevention and the management of diabetes in Luanda.

Setting. The study was carried out in Luanda, the capital city of Angola. According to the last edition of the 2014 census[18], about 6,542,944 inhabitants live in the capital. Six health centres, from six different urban districts, were randomly included in the study. Subjects reaching the six health centers between April and September 2019 were appraised for inclusion criteria to be enrolled in the study.

Participants. Eligible subjects were adults (≥ 18 years) of both sexes attending the six health centers between April 2019 and September 2019. Pregnant women, people not fasting for at least 8 h and people with a previous diagnosis of diabetes were not eligible for the study.

Eligible subjects had their fasting blood glucose (FBG) measured by professional nurses using a glucometer (Infopia, South Korea). All subjects with FBG levels ≥ 126 mg/dl were included as cases[19]. For each case, the next two subjects with FBG levels < 110 mg/dl were included as controls, to warrant the achievement of the set 1:2 ratio.

Data collection. Research data were collected by professional nurses using a case-report form. Data included demographics (age and sex), clinical parameters (weight, body mass index BMI, waist circumference, systolic blood pressure SBP, diastolic blood pressure DBP and heart rate) and food insecurity levels.

Food insecurity was assessed using the Food Insecurity Experience Scale (FIES), developed by the Food and Agriculture Organization of the United Nations (FAO)[20]. The FIES is one of the indicators to track progress toward reaching the Sustainable Development Goals (SDGs), particularly for goal 2.1, which aims to end hunger and ensure access to food by all people to safe, nutritious and sufficient food all year. The FIES consists of eight questions about respondent's access to food of adequate quality and quantity over the last 12 months (Fig. 1).

	Cases (diabetes)	Controls (no diabetes)	p-value
N	221	442	–
Age, years[ab]	46 (35–57)	35 (27–46)	< 0.0001
Males	67 (30.3)	149 (33.7)	0.43
Weight, kg[ac]	68 (56–79)	65 (56–74)	0.09
BMI, kg/m^2[ad]	24.9 (21.4–29.0)	23.1 (20.1–26.6)	0.0004
Waist circumference, cm[ae]	86 (77–98)	77 (64–88)	< 0.0001
Systolic blood pressure, mmHg[af]	130 (120–154)	123 (114–136)	< 0.0001
Diastolic blood pressure, mmHg[ag]	80 (71–90)	76 (67–83)	< 0.0001
Heart rate, bpm[ah]	77 (68–88)	73 (65–84)	0.002

Table 1. Participant characteristics. Data expressed as n (%) or [a]median (IQR). Data not available in [b]2, [c]1, [d]10, [e]22, [f]3, [g]9 and [h]17 participants.

	Cases (diabetes)	Controls (no diabetes)
N subjects with available FIES	215/221	432/442
Food security	80 (37.2)	156 (36.1)
Moderate food insecurity	21 (9.8)	111 (25.7)
Severe food insecurity	114 (53.0)	165 (38.2)

Table 2. Food insecurity according to FIES among cases and controls.

Participants were classified into three food insecurity levels according to the respondents scores. Scores 0–3 indicate food security, scores 4–6 indicate moderate food insecurity and scores 7–8 indicate severe food insecurity[20,21].

All data were collected by a professional nurse before participants went into the doctor's consultation room. Data collection was coordinated and supervised by a research assistant.

Statistical analysis. Categorical data were summarized as frequency and percentage, while continuous data as median and interquartile range (IQR). Categorical data were compared between two groups using Chi Square test, while continuous data using Mann–Whitney test. Severe food insecurity (SFI) and moderate-severe food insecurity (MSFI) were compared between cases and controls, and effect sizes were reported as odds ratio (OR) with 95% confidence interval[20,21]. Single items were presented with descriptive purpose and not used in single-item comparisons[21]. All tests were 2-sided and a p-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R 4.0 (R Foundation for Statistical Computing, Vienna, Austria)[22].

Ethics. This study was approved by the National Public Health Directorate of the Ministry of Health of Angola and by the Ethics Committee of the Ministry of Health of Angola (number 21/2018). Each participant signed a full informed consent form. All methods were performed in accordance with the relevant guidelines and regulations. The study used anonymized data and no identifiable data were collected.

Results

A total of 663 participants (221 cases and 442 controls) were enrolled in the study from April to September 2019. There were 216 males and 447 females, with a median age 38 years (IQR 28–51; range 18–88). Participant characteristics are shown in Table 1. Diabetes was associated with older age ($p < 0.0001$), and higher BMI ($p = 0.0004$), waist circumference ($p < 0.0001$), heart rate ($p = 0.002$) and systolic and diastolic blood pressure ($p < 0.0001$).

Food security and food insecurity were calculated according to FIES in 215 cases and 432 controls (Table 2), while the information was incomplete in the other 16 participants. MSFI was found in 135/215 cases (62.8%) and 276/432 controls (63.9%) (OR 0.95, 95% CI 0.68 to 1.34; $p = 0.78$). SFI was found in 114/215 cases (53.0%) and 165/432 controls (38.2%) (OR 1.83, 95% CI 1.31 to 2.54; $p = 0.0004$). Figure 2 displays occurrence of affirmative answers to single items with descriptive purpose.

Discussion

Our findings revealed an association between diabetes and severe food insecurity among adults attending healthcare facilities in the capital city of Angola. To our knowledge, this is the first study on this topic in Angola and it contributes to the investigation of the relationship between diabetes and food insecurity in SSA. In particular, our investigation focused on an urban setting since many SSA countries have been facing a rise in NCDs due to diet and lifestyle changes associated with urbanization[11]. Moreover, food insecurity affects billions of urban poor in low resource settings and growing literature links food insecurity with adverse diabetes outcomes[8].

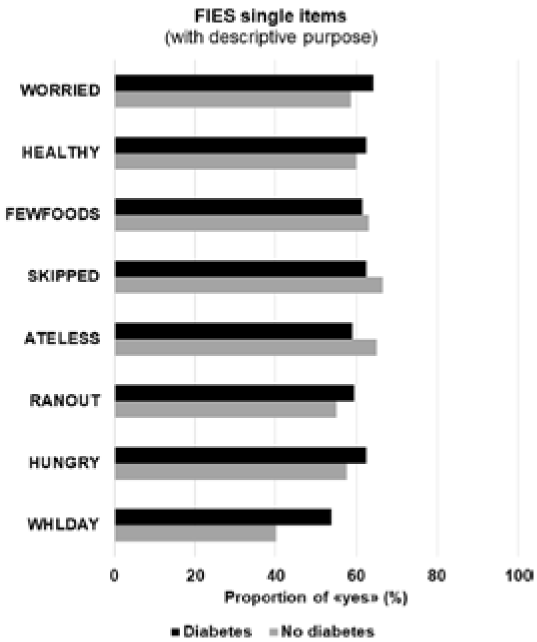

Figure 2. Single items of FIES in cases and controls.

SSA is currently home to 1.1 billion people and its population is predicted to reach 2.4 billion by 2050[23]. Hence, urbanization in SSA should be considered as an opportunity to develop food security strategies to prevent the rise of diabetes and NCDs[11].

In Angolan urban settings, a paucity of studies have explored diabetes and its determinants, and no study investigated the role of food insecurity for diabetes outcomes so far. In the capital city Luanda, a recent study found that some diet and lifestyle factors (such as low consumption of vegetables, daily consumption of free-sugars foods and beverages, and time spent seated) were associated with diabetes and/or Impaired Fasting Glucose[12]. Of note, our data corroborated the previous association between diabetes and some demographic parameters (older age, high BMI and high blood pressure).

Mechanisms for the association between food insecurity and diabetes could be linked to the fact that food insecure people report skipping meals, eating more energy-dense foods and have a lower dietary quality, which is associated with obesity and the increased risk of developing diabetes[3]. Our study confirmed a higher proportion of severe food insecurity among diabetic adults in Angola. Unfortunately, our data did not allow to explore the mechanisms underlying this association. Of note, more diabetic participants reported to have skipped meals for a whole day, but the single items of the FIES should not be used for direct comparisons[18].

Food insecurity is an important target for diabetes prevention and management since it is associated with poor glycaemic control, higher rates of complications and hospitalization, and poor adherence to treatment[24]. Therefore, addressing food insecurity may help tackle the burgeoning challenge of diabetes in SSA, where health systems are already overwhelmed by infectious diseases and are struggling to cope with the burden of non-communicable diseases[23]. Food insecurity screening among individuals with diabetes could help healthcare workers to identify patients' difficulties in adhering to treatment and dietary recommendations[24]. Policies addressing food insecurity should be included into diabetes programs to promote the access to sufficient, safe and nutritious foods[25]. Poverty is one of the root causes of food insecurity, therefore local economy growth and food systems strengthening should be a priority in SSA. Strategies and policies to increase affordability and availability of healthy food like fruits and vegetables, should be promoted by the means of vouchers, investments in agriculture, incentives to healthy low-cost foods retailers and promotion of community initiatives, like urban gardens and farmers markets[3].

The present study has some limitations that should be considered. First, the case–control design precludes any causal association between diabetes and food insecurity, which should be investigated with large prospective studies. Second, the participants were adults attending health facilities in Luanda, thus the generalization of the findings should be limited to similar settings (i.e. adults attending health facilities in urban areas in Sub-Saharan countries) and to newly diagnosed diabetic adults. In addition, sampling bias may have been introduced by the voluntary participation to the FBG measurement. Third, data on socio-economic status of the participants were not collected. Fourth, we relied only on point-of-care testing to classify diabetes, since other diagnostic tests were not available.

This study is a first attempt to explore the relationship between diabetes and food insecurity in an urban setting in Angola and it calls for further longitudinal studies to look into the pathways between diabetes and food insecurity. In future studies, uniformity of indicators to assess food insecurity levels should be adopted, for example by using the FIES at individual level, that is easy to perform and interpret. In addition, the mechanisms underlying the association between diabetes and food insecurity warrant further investigation.

Conclusions

Our findings revealed an association between diabetes and severe food insecurity among adults attending healthcare facilities in the capital city of Angola. Further longitudinal studies are required to assess the pathway linking diabetes and food insecurity in this setting.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

C.R. contributed to conception and study design, data acquisition, interpretation of results and drafting the manuscript. G.P. contributed to study conception and interpretation of results and revised the manuscript critically for important intellectual content. N.d.C. contributed to data acquisition and revised the manuscript critically for important intellectual content. A.A. contributed to data acquisition and revised the manuscript critically for important intellectual content. F.C. contributed to study design, data analysis, interpretation of results and drafting the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare no competing interests.

Additional information
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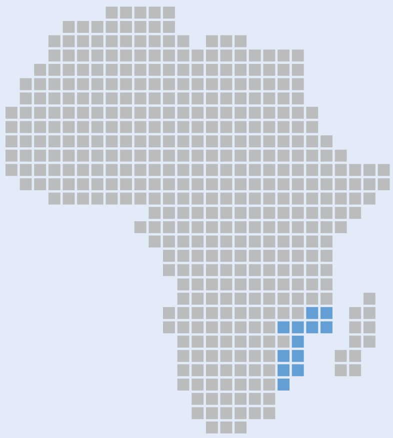
Effectiveness of remote screening for diabetic retinopathy among patients referred to Mozambican Diabetes Association (AMODIA): a retrospective observational study



PAPER

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ORIGINAL ARTICLE

Effectiveness of remote screening for diabetic retinopathy among patients referred to Mozambican Diabetes Association (AMODIA): a retrospective observational study

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Abstract

Aims Diabetes represents a growing public health problem in sub-Saharan Africa, where diabetic retinopathy (DR) is a major cause of permanent visual loss. We reported the results of a remote screening of DR among urbanized Mozambican people with diabetes.

Methods We retrospectively collected retinal images and clinical characteristics from 536 patients screened for DR in Maputo (Mozambique), over a period of 2 years (2018–2019). Retinal photographs were captured, digitally stored, and scored locally and by an expert ophthalmologist in Italy remotely.

Results The overall prevalence of DR was 29% with sight-threatening forms accounting for 8.1% of that number. Inter-reader agreement between the local and the Italian ophthalmologists was poor ($k < 0.2$). Patients with DR were older, had a longer duration of disease, worse glycaemic control, and a higher prevalence of comorbidities. In the multivariate logistic regression analysis, HbA1c, diabetes duration, and coronary heart disease (CHD) were associated with DR.

Conclusion Prevalence of DR among urbanized Mozambican patients was similar to that observed in Western countries. Telediagnosis might partially overcome the paucity of local ophthalmologists with experience in DR.

Keywords Diabetes · Retinopathy · Remote screening · Mozambique

This article belongs to the topical collection Eye Complications of Diabetes, managed by Giuseppe Querques.

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Introduction

The prevalence of diabetes is rapidly growing worldwide, in both developed and developing countries. The International Diabetes Federation (IDF) has estimated that the number of patients with type 2 diabetes in Sub-Saharan Africa (SSA) is expected to increase from 19 million in 2019 to 47 million by 2045 [1]. Despite this dramatic scenario, the needs for diabetes diagnosis and management remain mostly unmet [2]. IDF has estimated that 60% of people with diabetes remain undiagnosed and will be referred to healthcare facilities only when chronic complications have already arisen.

DR represents a common and disabling complication of chronic hyperglycaemia. DR can be divided into two main categories: non-proliferative diabetic retinopathy (NPDR)

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and proliferative diabetic retinopathy (PDR). NPDR is characterized by abnormal permeability of retinal capillaries leading to retinal oedema, vascular occlusion, and ischaemia. PDR occurs when retinal ischaemia leads to neovascularization. In this stage, visual loss occurs when the new abnormal vessels bleed into the vitreous or when tractional retinal detachment is present. It has been estimated that approximately 30% of patients with diabetes experience some degree of DR during their lives [3]. A recent meta-analysis reported that the global prevalence of DR and STDR was 22.3% and 6.2%, respectively. Sub-Saharan Africa had the highest prevalence of DR (36%) and STDR (14.3%) [4]. The Global Burden of Disease Study found that in adults aged 50 years and older, DR was the fifth leading cause of blindness and severe vision impairment [5]. In the period between 1990 and 2020, the prevalence of blindness due to DR arises by 140% in SSA compared to a 35% reduction in Western Europe. These data highlight the need to improve the screening for DR to identify patients that need timely treatment to avoid permanent vision loss.

In 2018, a program focused on the implementation management of diabetes was launched in Mozambique. It was financed by the Italian Agency for Cooperation and Development and implemented by a partnership between Doctors with Africa CUAMM, Mozambican Diabetes Association (AMODIA), and the Mozambican Ministry of Health. Within this project, AMODIA was equipped with a fully automated ophthalmoscope that permits the remote scoring of locally acquired retinal images. The present study was carried out to investigate the prevalence of DR and the clinical characteristics associated with DR in diabetic patients referred to AMODIA for the retinal examination over a period of two years. Furthermore, the agreement between a local and an Italian ophthalmologist was assessed.

Methods

Study design

This is an observational retrospective study. We collected data of urbanized patients with diabetes screened for DR at the headquarters of AMODIA (Hospital Central de Maputo) during the period of January 2018 to December 2019. Retinal images and clinical data were captured, encrypted, and stored in a telemedicine platform for remote consultation. As data were anonymized at the time of extraction, making patient re-identification impossible, no informed consent was required according to national regulations concerning retrospective studies.

Clinical data collection

We recorded the following data: age, sex, weight, body mass index (BMI), type of diabetes, diabetes duration, glycated haemoglobin (HbA1c), serum creatinine, lipid profile, concomitant risk factors, micro- and macrovascular complications of diabetes, and anti-diabetic medications. Concerning the type of diabetes, given the lack of pancreatic autoantibodies determination, we considered type 1 those who required intensive insulin treatment before 30 years with a BMI lower than 25 kg/mq. Hypertension was defined as systolic blood pressure (BP) of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater or the use of antihypertensive medications. Dyslipidaemia was defined as an LDL cholesterol level $\geq$ 3.4 mmol/L or a triglycerides level $\geq$ 1.7 mmol/L or use of lipid-lowering drugs. Smoke was defined as being habitually smoking one or more cigarettes per day. Metabolic syndrome (MS) was defined using International Diabetes Federation (IDF) criteria [6]. Among patients with diabetes, MS was diagnosed in the presence of BMI $\geq$ 30 kg/mq and at least one of the following criteria: systolic or diastolic BP $\geq$ 130/85 mmHg; HDL cholesterol < 1.16 mmol/L in men or < 1.29 mmol/L in women; triglycerides $\geq$ 1.7 mmol/L. The estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease (CKD) Epidemiology Collaboration formula. CKD was defined as an eGFR less than 60 mL/min per 1.73 m^2. Coronary artery disease was defined as a past history of acute coronary syndrome or coronary revascularization; cerebrovascular disease was defined as a past history of cerebral ischaemia or evidence of carotid artery atherosclerosis. According to the International Working Group on the Diabetic Foot (IWGDF), a diabetic foot was defined by the presence of an ulcer or previous minor or major amputation [7].

Grading of DR

DR was defined based on 45-degree non-mydriatic retinal fundus images (Nexy, Next Sight), according to the Early Treatment Diabetic Retinopathy (ETDR) classification [8]. Sight-threatening forms referred to proliferative retinopathy and/or macular oedema. Proliferative DR was defined by the presence of neovascularization or preretinal haemorrhage. Macular oedema was defined as retinal thickening at or around the fovea with or without hard exudates. Digital retinal images were both examined by a local ophthalmologist and scored remotely by an experienced ophthalmologist in Italy to evaluate inter-rater reliability. The scoring by Italian ophthalmologist was considered the gold standard to divide patients with and without DR.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), where appropriate. Categorical variables were reported as a percentage. The normality of the variables was tested by a Kolmogorov–Smirnov test. Non-normal variables were log-transformed before the analysis. Comparison between two groups was performed using unpaired, two-tail Student's t test for continuous variables and Chi-square test for categorical variables. A multiple logistic regression analysis was used to find variables associated with retinopathy among those emerging from univariate analysis with p values of < 0.05. Cohen's kappa coefficient (k) was used to measure inter-rater reliability between retinal fundus images scored locally and remotely by an experienced ophthalmologist. A k value ≥ 0.7 indicated good agreement. The number need to screen (NNS) was calculated to define the number of people with diabetes who needed to be screened by telemedicine to detect one case of visual-threatening DR. It was calculated as the reciprocal of the difference between the prevalence of severe DR scored

Table 1 Characteristics of patients

	Total	NS	S	p value	NDR	DR	p value
N	536	102	434		307	127	
Age, y	56 ± 13	61 ± 13	55 ± 13	**< 0.001**	54 ± 14	57 ± 11	**0.011**
Male sex, %	37	34	38	0.5	37	39	0.7
Weight, Kg	72 ± 14	71 ± 15	72 ± 14	0.4	72 ± 14	73 ± 12	0.4
BMI, Kg/mq	26	25 ± 5.4	26 ± 5.3	0.5	26 ± 5.5	26 ± 4.9	0.7
Obesity, %	22	23	22	0.8	20	27	0.2
T2DM, %	94	93	95	0.6	92	98	**0.026**
DM duration, y	4 (1–9)	5 (2–11)	4 (1–9)	**0.050**	3 (1–7)	6 (2–12)	**< 0.001**
HbA1c, % (mmol/mol)	9.9 ± 3.9 (85 ± 19)	9.9 ± 3.2 (85 ± 11)	9.8 ± 4 (84 ± 20)	0.9	9.4 ± 3 (79 ± 9)	10 ± 5.8 (96 ± 40)	**0.006**
Total-C, mmol/L	4.8 ± 1.1	4.7 ± 1	4.8 ± 1.1	0.6	4.8 ± 1.1	4.8 ± 1.2	0.6
HDL-C, mmol/L	1.2 ± 0.6	1.3 ± 1	1.2 ± 0.3	0.3	1.2 ± 0.4	1.2 ± 0.3	0.8
LDL-C, mmol/L	3.3 ± 1.1	3.1 ± 1.3	3.3 ± 1	0.1	3.3 ± 1	3.3 ± 1.2	0.9
TGL, mmol/L	1.2 ± 0.8	1.2 ± 0.7	1.2 ± .8	0.8	1.2 ± 0.8	1.2 ± 0.8	0.9
Dyslipidemia, %	52	61	50	0.1	49	52	0.5
Hypertension, %	61	72	58	**0.008**	55	67	**0.019**
Smoke, %	0.9	0	1.2	0.3	1.3	0.8	0.6
MS, %	19	20	20	0.8	17	25	0.1
Microangiopathy							
eGFR, ml/min	90 ± 25	83 ± 26	91 ± 24	**0.002**	93 ± 24	87 ± 24	**0.014**
CKD, %	12	22	10	**0.001**	7.8	16	**0.007**
Neuropathy, %	50	52	50	0.6	51	50	0.5
Macroangiopathy							
CHD, %	2.8	2.9	2.8	0.9	1.3	6.3	**0.004**
Stroke, %	0.7	1	0.7	0.7	0.8	0.7	0.9
PAD, %	2.6	2.9	2.5	0.8	2.3	3.1	0.6
Diabetic foot, %	4.7	2.9	5.1	0.4	3.9	7.9	0.9
Diabetes therapy							
Diet only, %	9.9	9.8	9.9	0.9	12	3.9	**0.007**
Metformin, %	72	68	73	0.3	72	77	0.2
Sulphonilureas, %	20	23	19	0.4	19	20	0.8
Insulin, %	27	30	26	0.4	21	37	**0.001**

Significant p-values are bold

NS not suitable for medical reporting; *S* suitable for medical reporting; *NDR* non-diabetic retinopathy; *DR* diabetic retinopathy; *BMI* body mass index; *T2DM* type 2 diabetes mellitus; *MS* metabolic syndrome; *eGFR* estimated glomerular filtration rate; *CKD* chronic kidney disease; *CHD* coronary heart disease; *PAD* peripheral artery disease locally and remotely. Statistical significance was accepted at $p < 0.05$, and SPSS version 21.0 was used.

Results

Overall Patient characteristics

We recorded data on a total of 536 patients. Baseline characteristics of patients are shown in Table 1. Among them, 102 patients (19%) had poor quality fundus images that were unsuitable for medical reporting. The patients with ungradable retinal images were significantly older ($p = 0.05$) with a higher rate of hypertension and chronic kidney disease. The patients suitable for screening of DR ($n = 434$) were 55 ± 13 years old, and 38% were males. The median diabetes duration was 4 years (IQR 1–9) and glycaemic control was poor. Individuals with type 1 diabetes (6.1%) had significantly worse glycaemic control than those with type 2 diabetes (Hb1Ac 12% vs 9.7%, $p = 0.001$). Approximately, 20% of patients were obese and a half had dyslipidaemia or arterial hypertension. The prevalence of MS was 20% according to the IDF criteria. Six per cent of patients had macroangiopathy and 60% had at least one microangiopathic complication. Metformin was the most common anti-hyperglycaemic drug, whilst one-third of patients were on insulin.

Table 2 Prevalence of DR and agreement between Italian (ITA) and Mozambican (MZB) readers. DR: diabetic retinopathy; NPRD: non-proliferative diabetic retinopathy; STDR: sight-threatening diabetic retinopathy, including proliferative retinopathy and/or macular oedema. K Cohen < 0.2 indicated poor inter-rater concordance

	ITA	MZB	Person Chi-square	k Cohen
Total DR, %	29	12	< 0.0001	0.18
NPDR, %	21	12	0.031	0.10
STDR, %	8.1	0.5	0.029	0.05

Prevalence of DR

The overall prevalence of DR scored by the Italian ophthalmologist was 29%, significantly higher than 12% reported locally ($p < 0.0001$). STDR accounted for 8.1%. The value of Cohen's kappa coefficients was lower than 0.2 suggesting a poor inter-rater agreement between Italian and local physicians (Table 2). The NNS was 13 for STDR over two years. Therefore, remote scoring of 100 patients potentially identifies 13 individuals that need timely treatment to avoid permanent vision loss. In Mozambique, where an estimated 337,500 people have diabetes, an extensive two-year remote scoring campaign might preserve more than 40,000 patients from blindness if only a proper treatment were available.

Characteristics of patients with DR

Patients with DR were older, had a longer duration of disease, a worse glycaemic control, and a higher prevalence of comorbidities than those without DR. Insulin therapy was more common among patients with retinal damage compared to those without (Table 1). Clinical characteristics of patients with STDR were similar to those with NPDR, except for lower levels of HDL cholesterol and a higher rate of metformin users (Supp. Table 1).

Clinical variables associated with DR

Variables emerging from univariate analysis with $p < 0.05$ (age, type and duration of diabetes, HbA1c, hypertension, eGFR, CKD and CHD) were included in the multivariate logistic regression analysis (Table 3). In the multivariable analysis, HbA1c, duration of diabetes, and CHD were associated with DR. Notably, the presence of DR led to a fourfold higher odd of CHD (Supp. Table 2).

Table 3 Univariate and multivariable logistic regression analysis for factors associated with the presence of overall DR. The OR refers to 1-unit increase in independent variables

	Univariate analysis				Multivariate analysis			
Variables	p value	OR	LL	UL	p value	OR	LL	UL
T2DM, %	0.036	3.7	1.08	12	0.2	2.72	0.64	11
DM Duration, y	< 0.001	1.08	1.04	1.12	**0.018**	1.05	1.01	1.09
HbA1c, %	0.001	1.12	1.05	1.19	**0.001**	1.13	1.05	1.21
eGFR, ml/min	0.015	0.98	0.98	0.99	0.9	0.99	0.98	1.01
CKD, %	0.008	2.33	1.24	4.37	0.2	1.77	0.76	4.12
Neuropathy, %	0.5	0.85	0.56	1.29	Not included			
Hypertension, %	0.020	1.67	1.08	2.58	0.5	1.21	0.74	1.96
CHD, %	0.009	5.10	1.50	17	**0.044**	3.71	1.04	13

Significant p-values are bold

Discussion

To our knowledge, this is the first study reporting the prevalence of DR in a cohort of urbanized Mozambican outpatients. The overall (29%) and vision-threatening (8.1%) prevalence of DR was similar to that observed in different African countries by Burgess [9], and comparable to that reported in Western countries [10, 11]. A previous meta-analysis by our group found an analogous prevalence of retinopathy (26%) in a wide cohort of African patients with diabetes having foot ulcers [12]. However, the high rate of ungradable retinal images might underestimate the prevalence of DR. Previous reports using ultrawide field imaging indicated that the prevalence of STDR is likely to be at least 10% in patients with ungradable retinal images [13]. Therefore, reducing the rate of unassessable images is pivotal for telemedicine programs. Although we did not evaluate the proportion of any visual impairment due to DR, a population-based study from South Africa identified DR as the cause of 8% of blindness and 11% of severe visual loss in persons $\geq$ 50 years [14]. Moreover, a recent global meta-analysis showed that, in the last twenty years, the prevalence of blindness due to DR increased by 140% in SSA compared to a 35% reduction in Western Europe [5]. Systemic screening for DR is cost-effective in terms of sight years preserved compared with no screening [15]. African countries face a chronic lack of equipment, trained healthcare workers and ophthalmologists. In particular, SSA has one of the lowest numbers of ophthalmologists per million population worldwide, with fewer than three ophthalmologists per million population, compared with the approximately 80 ophthalmologists per million population in high-income countries [16]. Hence, the identification of appropriate and cost-effective strategies to detect and manage DR with less strain on human sources is a compelling need.

Tele-ophthalmology might represent an opportunity to improve screening for DR in resource and specialist limited-countries. The Zimbabwe Retinopathy Telemedicine Project is a positive example of such types of approach [17]. In our study, non-mydriatic retinal images were captured by a trained nurse, evaluated by a local ophthalmologist, and finally graded by an experienced reader in Italy. Approximately, 20% of stored images were of low quality and did not permit fundus oculi exploration. The project funded by the Italian Agency for Cooperation and Development intended to improve the training of the healthcare personnel involved in the acquisition and scoring of retinal images. In particular, the project aims to fund remote teaching and local meetings with Italian experts, but the COVID-19 pandemic had significantly delayed the educational schedule. Furthermore, remote reporting was not real-time, meaning patients had to be recalled at a later date to receive their results. We realized this "stored and forward mode" was difficult to pursue in the Mozambican context, where patients often travel long distances to the hospital and do not have a telephone to be contacted again. Therefore, providing patients with instant feedback is preferred. A strength of our study was the evaluation of inter-rater diagnostic agreement between local and Italian ophthalmologists. The prevalence of overall DR assessed by the Italian reader was three times higher than that reported by the Mozambican ophthalmologist. The disagreement was even higher for the sight-threatening disease. This worrying discrepancy emphasizes the insufficiency of trained specialists for the management of DR that need to be tackled immediately to prevent blindness.

In this context, the emerging technologies based on artificial intelligence (AI), with the use of automated grading software, will provide a beneficial effect on the cost-effectiveness of the screening. This allows non-clinicians to be trained on retinal imaging, obtaining interpretation of the images within minutes and thus giving patients instant feedback. Recently, the accuracy of an AI model using deep learning has been evaluated in a population-based diabetic retinopathy screening program in Zambia [18]. The AI showed a good performance in detecting DR, STDR, and macular oedema, with a sensitivity and specificity similar to human graders. Analogous results were reported by the only other study involving AI and DR in Africa which was done in Nakuru, Kenya [19]. The use of a smartphone's in-built camera for retinal imaging could be another valuable approach to detecting DR due to its portability and ease of use. Images obtained can be graded remotely by trained graders or using smartphone-based automated analysis software [20]. Recent evidence from cost-effectiveness analysis shows that AI, either standalone or used with humans, might be more cost-effective than manual DR screening [21]. Unfortunately, efforts to improve screening programs faced with the lack of treatments such as photocoagulation and intravitreal injections of vascular endothelial growth factor (VEGF) that are unavailable in many parts of Africa.

Few studies evaluated the clinical features of patients with diabetes in Mozambique. In 2005, the cross-sectional study by Silva-Matos et al. reported an average age of 40 years and a body mass index of 23 kg/mq in a cohort of patients with diabetes mainly from rural areas [22]. Over 15 years, we observed a significant increase in life expectations and body mass index as a result of lifestyle changes and urbanization. Notably, the prevalence of MS was around 20%. This demographic transition leads to widespread of detrimental comorbidities such as hypertension, coronary heart disease, and kidney failure. In our study, 70% of patients aged over 50 years had hypertension. Approximately, 3% of subjects had CHD and 12% had CKD. However, the prevalence of coronary and renal disease might be underscored due to the lack of appropriate diagnostics. The metabolic control was extremely poor and more than 70% of patients had HbA1c higher than 7.5% (58 mmol/mol). Similar findings have been reported from other sub-Saharan countries and might reflect both limited access to drugs and poor awareness of long-term diabetes complications [23, 24]. Notably, the duration of diabetes was very short for a predominantly type 2 population. This might be explained by the delay between onset and clinical diagnosis. Because of the gradual and asymptomatic onset, type 2 diabetes may remain undiagnosed for 4–6 years before a clinical diagnosis. Therefore, the real duration of type 2 diabetes might be longer than 10 years.

Several limitations of this study have to be acknowledged. First, we used a single non-mydriatic 45-degree central-field photograph to facilitate the local staff training. However, we are aware that such a method is burdened by a low sensibility (54–78%) and specificity (88–89%) and is not recommended for community-based screening in high-income countries, where two to four-field imaging is preferred [25]. Furthermore, this approach did not permit the grading of non-proliferative forms of DR. Second, outpatients referred to the AMODIA office in Maputo might not be sufficiently representative of rural areas. Third, we considered type 1, patients who required intensive insulin therapy before 30 years. This is a conservative estimate that might not include late-onset autoimmune diabetes. Finally, data on albuminuria were not available, leading to a potential underestimate of diabetic renal impairment.

In conclusion, the prevalence of DR among urbanized Mozambican patients with diabetes was similar to Western countries. Screening programs play a crucial role in the detection of sight-threatening diseases but are uncommon in Africa due to insufficient ophthalmologists and expensive equipment. In such a context, telediagnosis might be cost-effective, providing time and human sparing solutions. However, any diagnostic effort is likely to be useless if a treatment opportunity is not made available. In logistic regression analysis, HbA1c levels, duration of diabetes, and CHD were associated with DR. The improvement of glycaemic control is still an unmet need that requires immediate action to prevent the future development of detrimental healthcare burden complications.

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Author contributions MR study designed, data analysis and manuscript writing. LN, LS and LMCS data collection. GPF, AA, GP and AT manuscript revision. All authors read and approved the final version of the manuscript. MR is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Declarations

Conflict of interest MR received lecture and advisory board fees from AstraZeneca, Boehringer, Lilly, Mundipharma, Novo Nordisk, Sanofi. AA received research grants, lecture or advisory board fees from Merck Sharp-Dome, AstraZeneca, Novartis, Boeringher-Ingelheim, Sanofi, Mediolanum, Janssen, Novo Nordisk. GPF received lecture fees or grant support from Abbott, AstraZeneca, Boehringer, Lilly, Merck-Sharp-Dome, Mundipharma, Novartis, Novo Nordisk, Sanofi, Servier. The other authors declare no conflict of interest.

Human and animal rights The study was conducted in accordance with the Declaration of Helsinki.

Ethical standard The protocol was approved by the local Ethics Committee.

Informed consent In agreement with National regulations retrospective studies and on data protection and privacy, no informed consent was collected because the database was anonymous.

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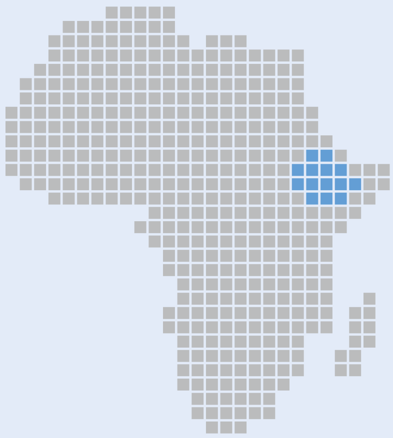

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Epidemiological factors affecting outpatient department service utilization and hospitalization in patients with diabetes: A time-series analysis from an Ethiopian hospital between 2018 and 2021

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Background The burden of diabetes-related deaths reached two million in 2019 globally. Accessibility to health care services and adherence to follow-up and therapy are key to improving outcomes for diabetic patients. We aimed to assess outpatient department (OPD) service utilization and diabetes-related hospitalizations over a period of 44 months.

Methods A retrospective cohort study was conducted on OPD visits and hospitalizations recorded between January 1, 2018, and August 31, 2021, at the St Luke Catholic Hospital (Ethiopia). All diabetic patients were included in the analysis. A linear regression model was used for univariate analysis of OPD visits and hospitalizations and their association with potential predictors. The autoregressive integrated moving average (ARIMA) method was applied to both the time series of OPD visits and hospitalizations. Potential predictors were sociodemographic factors, COVID-19 cases, mean monthly temperature and precipitations.

Results In the time series analysis, OPD visits increased over time ($P<0.01$) while hospitalizations were stable. The time series model was ARIMA (0,1,1) for OPD visits and ARIMA (0,0,0) for hospitalizations. There were 1685 diabetes OPD patients (F=732, 43%). Females had an average of 16% fewer OPD accesses per month ($P<0.01$) and a lower number of hospitalizations per month ($P=0.03$). There were 801 patients missing follow-up (48%). The time between follow-up increased with age ($P<0.01$). OPD visits decreased differently by geographic area as COVID-19 cases increased ($P<0.01$). There were 57 fewer forecast OPD visits per month on average using COVID-19 cases as ARIMA regressor. The odds ratio (OR) of new diagnosis at hospitalization was lower in patients with type 2 diabetes (OR=0.26, 95% CI=0.14-0.49, $P=0.02$).

Conclusions Despite an increase in OPD visits for diabetic patients over the study period, the number of losses at follow-up and diagnoses at hospitalization remains high. Female sex, older age, and COVID-19 were associated with impaired OPD service accessibility. Primary health care should be implemented to achieve better health coverage and improve diabetes management.

Non-communicable diseases (NCDs) are the leading cause of death globally. The four major NCDs are cancer, chronic vascular diseases, diabetes mellitus, and chronic respiratory diseases [1]. The global share of NCD deaths among all deaths grew from 60.8% in 2000 to 73.6% in 2019, reaching 33.2 million. Most NCDs related deaths are concentrated in low- and middle-income countries (LMICs), where 10.5 million deaths are accountable to these four diseases in 2019 only. Currently, Ethiopia has been challenged by the burden of NCDs which are estimated to be liable for 39% of all deaths [2].

Among NCDs, diabetes mellitus is an important cause of morbidity, mortality, and a burden for health systems around the world. Global diabetes deaths grew by 72% since 2000, reaching almost two million in 2019. The International Diabetes Federation estimated that 463 million people had diabetes in 2019, and this number is projected to reach 578 million by 2030, and 700 million by 2045 [3]. The greatest increase in incidence and the highest proportion of undiagnosed diabetes mellitus was observed in the African continent (59,7%) [4].

Management and clinical outcome of diabetic patients are linked to the accessibility of health care facilities, availability of screening, and follow-up visits [5]. In LMICs, barriers to health care access are more numerous and more extreme than in high-income countries (HICs). Gender is the most common demographic barrier, followed by cultural factors. Financial factors combine with geographical; indirect costs due to long travels to health care facilities add to direct prices, often excessively high [6].

Health care access has changed during the COVID-19 pandemic: all over the world, facility utilization decreased by one-third. Service reduction was prominent in LMICs [7]. The impact of COVID-19 on health care systems was linked to insufficient staff availability, fear of becoming infected while accessing hospitals, and lockdown policies [8]. Concerning NCDs, half of the countries worldwide reported disruptions to diabetes mellitus management services [9].

Although adherence to visits is critical in chronic diseases, such as diabetes, few studies have explored factors associated with health care services utilization and accessibility in LMICs. The primary objective of this study was to assess the impact of sociodemographic and environmental factors of patients with diabetes on service utilization (in terms of access per month, losses at follow-up, and readmissions). The secondary objective was to explore the impact of COVID-19 on access to the outpatient department (OPD) service and to hospitalizations. The main hypothesis was that access to health care services was impaired by factors such as female sex and older age and that access decreased during the rainy season.

METHODS

Study design

A retrospective cohort study design was used to analyse the role of sociodemographic and environmental factors on health service utilization by patients with diabetes.

Setting

St Luke Catholic Hospital (SLCH) is based in South-West Shewa Zone (SWSZ), Oromia region (Ethiopia). It has an estimated population of 1 311 406 inhabitants [10]. The SWSZ is divided into twelve districts called "woreda"; these are the third level of the administrative division. SLCH is a general hospital located in Wolisso Town, 114 km from the capital Addis Ababa. Its catchment area includes the woreda of Ameya, Wenchi, Wolisso rural, Wolisso town, Becho, and Goro representing the reference hospital for 743 797 individuals. The hospital has 200 beds with an annual average bed occupation rate of 94.1%.

Data collection

Data on the number of outpatient department (OPD) visits and hospitalizations, age, sex, residence at woreda level, date of hospital access, type of diagnosis, and data on the outcome (only for hospitalized patients) were obtained from the registration software of the SLCH, Open Hospital, from January 1, 2018, to August 31, 2021.

To explore potential determinants in the monthly number of OPD visits and hospitalizations during the study period, the number of monthly newly registered COVID-19 cases in Ethiopia and the mean monthly values of precipitation millimetres and temperature (°C) estimated in the Oromia region between 1991 and 2020 were collected [11,12].

Operational Definitions

According to Ethiopian guidelines, the following criteria were adopted by hospital doctors for the diagnosis of diabetes [13]:

1. A diabetes case was diagnosed if the patient had a fasting blood sugar (FBS) ≥126 mg/dL (at least two tests needed), or random blood sugar (RBS) ≥200 mg/dL plus classic symptoms of hyperglycaemia (i.e., fatigue, polyuria, polydipsia, blurred vision, recurrent skin infections), hyperglycaemic crisis, or symptoms related to chronic complications.
2. When a patient was diagnosed with diabetes and presented with classic symptoms such as excessive urination or thirst, unexplained weight loss, or if the patient had suggestive sociodemographic characteristics (i.e., young age), he/she was diagnosed with type 1 diabetes.
3. When a patient met the criteria for the diabetes diagnosis and presented with other symptoms such as overweight or obese, chronic diabetic complication (i.e., numbness or pain over the lower limbs, visual impairment, foot abnormalities (such as ulcer, ischaemia, deformity), body swelling), had a family history of diabetes, dyslipidaemia, or was aged 45 years old or more, he/she was diagnosed with type 2 diabetes.

Study endpoints

The primary endpoints were the number of OPD service accesses and the number of hospitalizations per month in patients with diabetes. The secondary endpoint was the frequency of patients with diabetes not attending a follow-up visit and requiring hospital readmission.

Statistical analysis

Descriptive analysis

Categorical variables were presented as frequencies and proportions, while continuous variables were presented as means and standard deviations (SDs) or medians and interquartile ranges (IQRs). Sample distribution was tested via $\chi 2$ and Fisher exact test for categorical variables or Mann-Whitney-U non-parametric or ANOVA test for continuous variables, as appropriate. The Shapiro-Wilks test was used to test the normality of the distribution of the included variables. Logistic regression models were fitted for multivariable analyses, where follow-up visit (yes/no), first diagnosis during hospitalization (yes/no), readmission (yes/no), and readmission within 30 days (yes/no) were the response variables, and type of diabetes, age and sex were potential determinants. Results were presented as odds ratio (OR) with 0.95 confidential intervals (CIs).

Time series analysis

Univariate analysis of monthly OPD visits and hospitalizations for diabetes and their association with potential predictors was carried out using a general linear model. Independent variables were the time (in months), sociodemographic factors, precipitations, temperature, and the number of COVID-19 cases newly registered in Ethiopia.

The time series analysis was applied to monthly OPD visits and hospitalizations for diabetes. To identify the trend of the time series, LOcally Weighted Scatterplot Smoothing (LOWESS) function was used to test different smoother spans ($f = 2/3$, $f = 1/3$, and $f = 0.1$). The trend was then subtracted from the time series to isolate the random error (remainder component).

AutoRegressive Integrated Moving Average (ARIMA) model was applied to identify significant predictors as well as to forecast the number of OPD visits and hospitalizations [14].

The p, d, and q of the model were chosen by combining unit root tests, the minimization of the Akaike information criterion (AIC), and Maximum Likelihood Estimation (MLE). To choose the best ARIMA model, an algorithm was applied using a stepwise search to traverse the model space selecting the best model with the smallest AIC. The KPSS test was used to determine the number of differences (d) in the Hyndman-Khandakar algorithm for automatic ARIMA modelling [15,16].

The ARIMA model was applied to the time series of the monthly number of OPD visits and hospitalizations. First, to forecast the number of monthly OPD visits and hospitalizations, an ARIMA model was fitted with the previously registered values. The number of periods (h) was set at six months. Then, the same analysis was repeated with the monthly number of Ethiopian newly registered cases of COVID-19 as a regressor in the ARIMA models to estimate the impact of the COVID-19 pandemic on hospital accessibility. The residuals from the ARIMA models have been tested for no autocorrelation through the Ljung-Box Tests [17].

All analyses were performed using R software (version 4.1.1). A P-value <0.05 was considered significant.

Ethical approval

The inclusion of a patient in this protocol did not require any additional exams besides those normally needed for clinical routine. The research was performed following the ethical standards of the 1964 Declaration of Helsinki and was approved by the Ethical Committee of St Luke Catholic Hospital on May 26, 2021 (protocol number 665/41).

RESULTS

Sample characteristics

In the study period, 93301 patients from the SWSZ were assisted at the OPD of the SLCH and 1685 (1.8%) for diabetes. Sex distribution was 732 females (43.4%) and 953 males (56.6%) (**Table 1**). Females had a mean age of 38.8 years (SD = 19.3) and were younger compared to males (mean = 42.0 years, SD = 19.8, P < 0.01). Of all the patients with diabetes, 467 (28.2%) were diabetes mellitus type 1 (DM1) with a mean age of 18.7 years (SD = 14.3) and 1218 (71.8%) were diabetes mellitus type 2 (DM2) with a mean age of 49.0 years (SD = 14.0). There were no differences in sex distribution between types of diabetes (P = 0.14) (**Table 1**). The first visit at SLCH resulted in a first diagnosis for 1522 patients (90.3%), and 84 (5.5%) of these occurred because of hospitalization.

The median number of visits per patient was 2 (IQR = 1-6); 801 (47.5%) patients attended only one OPD visit with no further follow-up. Considering patients (n = 884, 52.5%) with at least one follow-up visit during the study period, the median number of visits per person increased to 6 (IQR = 3-11). The mean time between follow-up visits was 63.8 days (SD = 84.9). The odds ratio of having at least one follow-up visit increased with age (OR = 1.84; 95% CI = 0.098-0.223, P = 0.03). There were no differences in the time between follow-ups based on patient sex (P = 0.98) or type of diabetes (P = 0.25); the time between visits was longer as the age of the patients increased (P < 0.01).

In the study period, 8619 patients from the SWSZ were admitted to the medical and paediatric wards of the SLCH and 408 (4.7%) had diabetes (**Table 1**). Females had a mean age at admission of 31.4 years (SD = 19.8) and were younger than males (mean = 37.7 years, SD = 20.3; P < 0.01).

There were no differences in mean length of stay based on sex (P = 0.17) or diabetes type (P = 0.37), while it decreased as age increased (P = 0.01). There were 52 (12.7%) patients with more than one hospitalization with a median readmission number of 1.0 (IQR = 1.0-3.0). The median readmission time was 132.2 days (IQR = 50.9-279.8). There were no differences in the odds ratio of readmission based on sex (P = 0.86), age (P = 0.99), or diabetes type (P = 0.11). The odds ratio of receiving a new diagnosis at hospitalization was lower in DM2 (OR = 0.26; 95% CI = 0.14-0.49, P = 0.02) with no differences based on sex (P = 0.45) or age (P = 0.19).

Time series analysis

The total number of OPD visits per month between January 1, 2018, and August 31, 2021, was considered together with the number of COVID-19 cases newly registered in Ethiopia (Table S1 in the **Online Supplementary Document**). The mean rain precipitation millimetres and temperature per month are shown in Table S3 in the **Online Supplementary Document**. Considering the time series of the number of OPD visits, the lowess function with f = 0.1 was found to better fit the trend (Figure S1 in the **Online Supplementary Document**). The decomposition of the time series is shown in Figure S2 in the **Online Supplementary Document**. The trend of diabetes OPD visits is shown in **Figure 1** (panel A).

The number of OPD visits for diabetes increased by 2.8 (standard error (SE) = 0.5) over the months (P < 0.01), while neither the mean monthly temperature (P = 0.21) nor precipitation (P = 0.99) was associated with OPD attendance for diabetes. Males had an average of 16% more OPD visits per month than females (β = 28.4, SE = 4.9; P < 0.01) (**Figure 2**, panel A).

The best-fitting model for OPD visits time series was ARIMA (0,1,1), which is a non-seasonal and non-stationary moving average model. The residuals from the ARIMA model had no autocorrelation (Q = 6.7, degrees of free-

Table 1. Characteristics of diabetic patients attending OPD services and admitted to medical and paediatric wards of the St. Luke Catholic Hospital between January 1, 2018, and August 31, 2021, distinguished by diabetes type

	Type 1 (OPD = 467, H = 188)	Type 2 (OPD = 1218, H = 220)	*P*-value*	Overall (OPD = 1685, H = 48)
Diabetes OPD visits				
Sex				
Female	245 (52.5%)	487 (40.0%)	0.02	732 (43.4%)
Male	268 (57.4%)	685 (56.2%)		953 (56.6%)
Age (years – mean (SD))	18.7 (14.3)	49.0 (14.1)	<0.01	40.6 (19.6)
At least 1 follow-up visit				
Yes	192 (41.1%)	692 (56.8%)	0.10	884 (52.5%)
No	420 (81.9%)	893 (76.2%)		801 (47.5%)
First follow-up <30 days				
Yes	192 (41,1%)	692 (56,8%)	0.51	372 (22.1%)
No	275 (58,9%)	526 (43,2%)		1313 (77.9%)
Time between follow-up (days – mean (SD))	60.3 (87.2)	64.7 (84.4)	0.25	63.8 (84.9)
First diagnosis during hospitalization (N/A = 163)				
Yes	44 (10.1%)	41 (3.7%)	0.02	84 (5.5%)
No	384 (89.9%)	1054 (96.3%)		1437 (94.5%)
Diabetes hospital admissions				
Sex				
Female	88 (46.8%)	89 (40.5%)	0.23	177 (43.4%)
Male	100 (53.2%)	131 (59.5%)		231 (56.6%)
Age (years – mean (SD))	17.8 (12.1)	49.7 (13.0)	<0.01	35.0 (20.3)
Length of stay (days – mean (SD))	6.9 (5.9)	5.9 (5.8)	0.37	6.4 (5.9)
Readmission				
Yes	31 (16.5%)	21 (9.5%)	0.30	52 (12.7%)
No	157 (83.5%)	199 (90.5%)		356 (87.3%)
Readmission within 30 days				
Yes	6 (3.2%)	4 (1.8%)	0.48	10 (2.5%)
No	182 (96.8%)	216 (98.2%)		398 (97.5%)
Outcome				
Death	5 (2.7%)	7 (3.2%)	0.75	12 (2.9%)
Alive	183 (97.3%)	213 (96.8%)		396 (97.1%)

OPD – outpatient department services, H - hospitalizations, SD - standard deviation
*Fisher exact test, χ^2 test, analysis of variance (ANOVA), logistic regression.

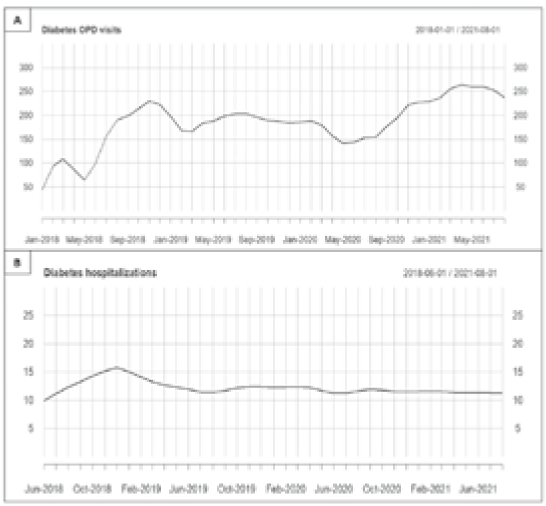

Figure 1. Time trend of diabetes OPD visits (panel A) and hospitalizations (panel B) between January 2018 and August 2021.

dom (df) = 8; P = 0.57, Figure S3 in the **Online Supplementary Document**). The mean forecast number of the OPD visits for the following six months (September 2021 to February 2022) was 243.7 (95% CI = 135.6-351.80) (**Table 2**).

Comparing the monthly number of OPD visits during the first months of the pandemic (March 202 to August 2020) with the same period in 2019, there was a 28% reduction in overall diabetes visits (Table S1 in the **Online Supplementary Document**). The best-fitting model for OPD visits time series, using the monthly number of newly registered COVID-19 cases as a regressor, was ARIMA (1,0,0), which is a non-seasonal, stationary, autoregressive model. The residuals from the ARIMA model had no autocorrelation (Q = 8.8, df = 6; P = 0.184, Figure S4 in the **Online Supplementary Document**). The mean forecast number of the OPD visits for the following six months (September 2021 – February 2022), based on the number of monthly newly registered COVID-19 cases, was 186.7 (95 CI% = 84.7-289.8) (**Table 2**).

In the multivariable analysis with an interaction term between woreda and the monthly number of newly registered

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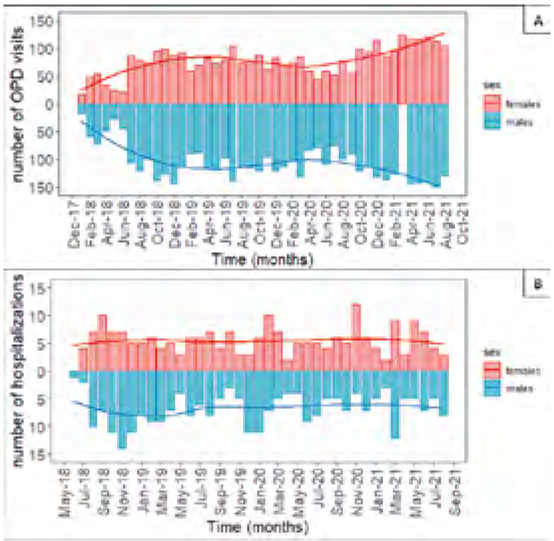

Figure 2. Divergent bar chart and time trend of the number of outpatient department (OPD) visits (panel A) and of hospitalizations (panel B) from 01/01/2018 and 31/08/201) distinguished by sex (females = red coloured and upper part of the graphs; males = blue coloured and lower part of the graphs).

Table 2. Forecast number of diabetes OPD visits fitted without (ARIMA 0,1,1) and with (ARIMA 1,0,0) monthly number of newly registered COVID-19 cases as a regressor

	ARIMA (0,1,1)		ARIMA (1,0,0)	
	Forecast	95% CI	Forecast	95% CI
September 2021	243.7	166.2-321.2	199.6	121.2-278.0
October 2021	243.7	151.9-335.5	192.3	95.1-289.5
November 2021	243.7	139.5-347.9	186.9	81.0-292.9
December 2021	243.7	128.5-358.9	183.1	78.8-293.4
January 2022	243.7	118.4-369.0	180.2	67.6-292.8
February 2022	243.7	109.1-378.4	178.1	64.3-291.9

ARIMA – autoregressive integrated moving average, CI – confidence interval

COVID-19 cases, the number of OPD visits for diabetes was lower for all woredas when compared to Wolisso town as the number of COVID-19 cases increased ($P<0.01$) and was lower for the woreda of Ameya and Becho ($P=0.01$) when compared to Wolisso rural ($P=0.04$) (Figure 3). There were no differences in the number of monthly diabetes hospitalizations in the same analysis (Wolisso town as reference level: Ameya ($P=0.60$), Becho ($P=0.61$), Goro ($P=0.42$), Wolisso rural ($P=0.24$), Wonchi ($P=0.58$)).

Considering the time series of the number of hospitalizations for diabetes, the lowess function with f = 1/3 was found to better fit the trend (Figure S5 in the Online Supplementary Document). The decomposition of the time series was shown in the supplementary file (Figure S6 in the Online Supplementary Document). The trend of diabetes hospitalizations was shown in Figure 1 (panel B).

The number of hospitalizations for diabetes remained stable over the months ($P=0.54$) (Table S3 in the Online Supplementary Document). Males had a higher number of hospitalizations per month than females ($\beta=1.3$, SE = 2.3; $P=0.03$) (Figure 2, panel B). Neither the mean monthly temperature ($P=0.27$) nor precipitation millimetres ($P=0.10$) were associated with the number of hospitalizations for diabetes. There were no differences in the monthly number of hospitalizations based on the number of COVID-19 cases in Ethiopia ($P=0.83$).

DISCUSSION

This study explored the service utilization by patients with diabetes from a rural area of Ethiopia. A gender gap, to the disadvantage of women, was found in OPD service utilization and hospitalizations. Contrary to what was assumed, weather conditions (particularly the rainy season) did not appear to affect access to the hospital.

In the time series analyses, females had 28.4 fewer OPD visits per month than males, showing 16% fewer visits on average. A similar trend was found in the number of hospitalizations per month. Despite this difference in health service utilization, the prevalence of diabetes in Ethiopia was reported to be similar between males and females [18]. Healthcare access may be problematic in African countries, where the gender gap may result in different opportunities and education [19]. The strict connection between health care access inequity and gender is a direct consequence of inequalities suffered by women, such as lower financial resources, lower levels of education, and lower independence within society and family. In many countries, women are discriminated against in terms of access to medical care, leading to higher mortality (the so-called “missing women” concept); this gender gap is particularly evident in Asia and Africa [20].

During the study period, we observed an overall increase in OPD visits, while the number of hospitalizations remained stable. The “Doctors with Africa CUAMM” project in Wolisso existed for several years [21]. This investment in health promotion may have led to higher-than-average health literacy, and consequently, good adherence to screening and follow-up resulting in an increase in OPD access. However, the prevalence of diabetes mellitus is increasing in all countries. Growth in new diagnoses was observed in LMICs and collected data reflect this trend [3].

Many individuals did not return for follow-up after the first diagnosis of diabetes mellitus. The prevalence was higher for DM1 than for DM2 (59% vs 43%). Patient education, perception of risk, and environmental factors such as lack of infrastructure and public transport can influence this loss. Moreover, the time between follow-ups increased with age. This data may suggest fewer health care access possibilities for the elderly and could be explained by difficulties in travelling alone to the health care facilities and arduous support by younger relatives who may need to prioritize providing for their family. Overall, 47.5% of individuals were lost after diagnosis: this data emphasizes the importance of investing in health promotion and infrastructure [22]. This result was also highlighted by the lower 30-day readmission rate in our sample (12.7%) compared with the 20% reported in Western studies [23]. This low readmission rate could be associated with a higher death rate at home due to acute complications, little confidence in the health care system, and difficult transport to the hospital.

The included patients with DM1 had a mean age of 19 years. In sub-Saharan Africa, there was evidence of a spike in diagnoses for DM1 a decade later than in HICs. Prolonged breastfeeding has been proposed to be possibly involved in reducing the incidence and delaying the onset of DM1 [24]. Additionally, diagnosis criteria may differ in LMICs and the lack of clear official guidelines for diabetes screening in resource-limited health systems can lead to delayed diagnosis [25]. This was confirmed by the high number of patients accessing the SLCH and receiving a first diabetes diagnosis and by the higher odds ratio of new diagnosis at hospitalization for patients with DM1. Our results showed a similar epidemiological pattern to those reported in the literature also regarding the peak age of DM2 (40 to 59 years old). Interestingly, 24% of patients with DM2 were found to be in the 20 to 39 years old range. A similar prevalence was estimated in sub-Saharan Africa by the International Diabetes Federation [24]. Considering this last age range group of young adults with a diagnosis of DM2, we must take into account the possibility of a diagnostic misclassification of some of these patients, whose diagnosis could be re-classified in LADA (Latent Autoimmune Diabetes in Adults), if only they were not lost at follow-up.

Then, we analysed the influence of the weather on OPD accesses: even though a reduction of OPD visits was expected during the rainy season, no seasonality was retrieved in the time series analysis. Climate seasonal changes do not seem to be an important factor to discontinue health care access for both OPD visits and hospitalizations. Other studies reported an influence of geographic and environmental factors on health accessibility, but there is a lack of data on the weather and seasonal impact [6].

In March 2020, the first COVID-19 case was detected in Ethiopia. The time-series analysis shows a deflection in OPD visits during the first months of the pandemic (March to August 2020) with a reduction of 28% in OPD visits compared to the same months of 2019. Moreover, in the forecast projection of OPD visits using new COVID-19 cases as a regressor, the number was lower by 57 visits per month on average, compared to the forecast without considering COVID-19 cases. Interestingly, when analysing the interaction between new COVID-19 cases and woredas in terms of distance from SLCH, woredas influenced the decreasing rate of access, showing a higher negative impact on distant woredas (Figure 3). All over the world, essential health services were affected by the COVID-19 pandemic. In Ethiopia, most departments decreased their activity, including outpatient visits. COVID-19 had direct and indirect effects on health care accessibility. While patients may have been hesitant to seek treatment because they may have considered facilities as infected or because of their possible doubts about the expertise of health care providers, lockdown, other restrictions, or poor infrastructures may have made reaching hospitals more difficult for them [26].

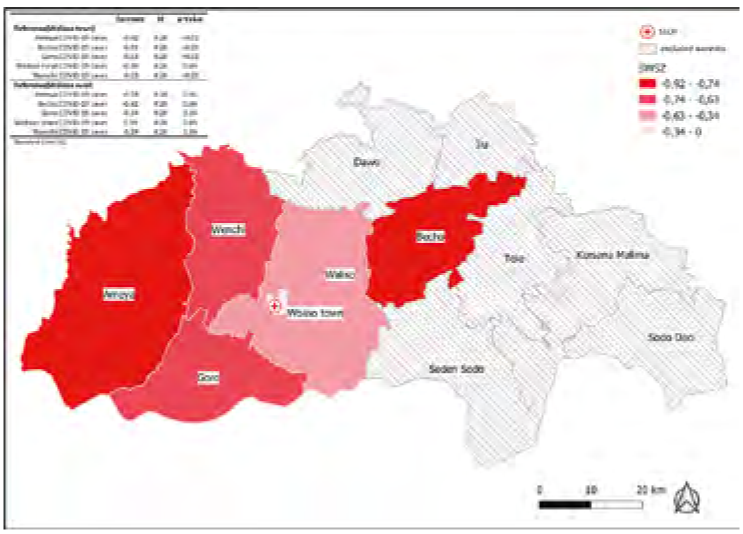

Figure 3. Graphical representation of the coefficients from linear regression model fitted on the number of monthly diabetes outpatient department visits as dependent variable, and months and interaction between the number of monthly newly registered COVID-19 cases and woreda (reference Wolisso town and Wolisso rural) between 01/01/2018 and 31/08/2021. Increasing colour intensity shows lower coefficients (ie, a greater decrease in the number of visits as COVID-19 cases increase). Crossed-out areas show woredas excluded from the analysis because they are out of the catchment area of the St Luke Catholic Hospital (SLCH).

There are several limitations to this study. First, data was limited to a single centre; however, the study focuses on a rural area often underrepresented in scientific literature. Second, the retrospective study design used available medical records, which may not have always been complete and/or correctly compiled. However, the research covered more than three years, reaching a consistent number of individuals. Lastly, the diagnosis of diabetes mellitus was often based on glucose measurement alone, lacking glycated haemoglobin (HbA1c) or an oral glucose tolerance test. This circumstance could have led to some inaccuracy in the estimated prevalence of diabetes. Moreover, the lack of autoantibodies tests and the high rate of losses at follow-up could have misled the diabetes type categorizations, especially for those with DM1 (ie, patients with LADA).

CONCLUSIONS

Factors involved in health care access in the context of this analysis suggest that investment in patient empowerment, gender equality, infrastructures, and travel opportunities in rural areas must be encouraged. Previous studies have proposed diabetes mellitus as a potential tracer for evaluating health care systems [27]. Our findings show that public health is still a challenge in LMICs. Although the number of OPD visits increased during the study period, the high rate of loss to follow-up and of newly diagnosed at hospitalization shows the need for interventions to improve patient health literacy and health services at the local level. We need to consider whether the local health care system is adequate before improving screening programs for diabetes and for all NCDs [28]. Limited accessibility and a health system unable to handle large and growing volumes of NCD-related admissions could jeopardize the achievement of the Sustainable Development Goals set by the World Health Organization for the 2030 Agenda for Sustainable Development.

Ethics statement: This study was approved by the Ethical Committee of St Luke Catholic Hospital on May 26, 2021 (protocol number 665/41).

Data availability: The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Funding: We received no funding for this study.

Authorship contributions: RB and GA conceptualized and designed the study and made substantial contributions to original writing, RB was responsible for the data analysis. AS contributed to the interpretation of data and original writing. MU supervised and contributed to data collection. AB and AP contributed to data collection. HS, AT, and BG reviewed the study critically. FM reviewed the study and contributed to data interpretation.

Disclosure of interest: The authors completed the ICMJE Disclosure of Interest Form (available upon request from the corresponding author) and disclose no relevant interests.

Additional material:
Online Supplementary Document

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Caratteristiche cliniche e rischio di chetoacidosi diabetica nei pazienti dell'Ospedale St. Luke in Etiopia: un'analisi spaziale geografica

POSTER PRESENTATIONS

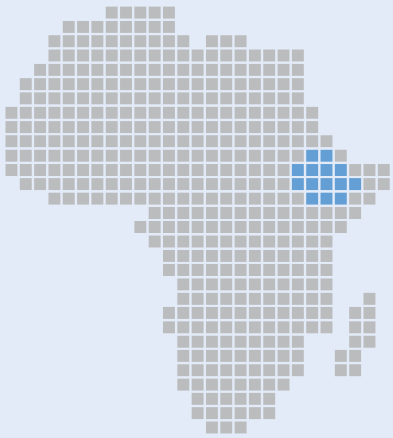
Conference
XLVI Convegno Associazione Italiana di Epidemiologia (AIE)

Location
Padua, Italy

Presentation date
29 June - 1st July 2022

Authors
Paiola E. et al.

Focus country
Ethiopia



Nodding Syndrome Alliance - preliminary data on clinical management from a multi-sectorial initiative addressing nodding syndrome and other forms of epilepsy in Western Equatoria, South Sudan

POSTER PRESENTATIONS

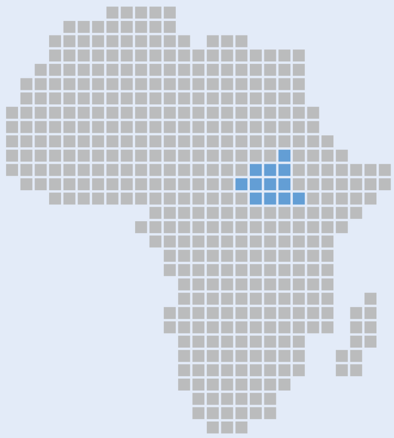
Conference
14th European Epilepsy Congress

Location
Geneva, Switzerland

Presentation date
9-13 July 2022

Authors
Scanagatta C. et al.

Focus country
South Sudan



Epidemiological factors affecting health service utilization in diabetic patients in Ethiopia

POSTER PRESENTATIONS

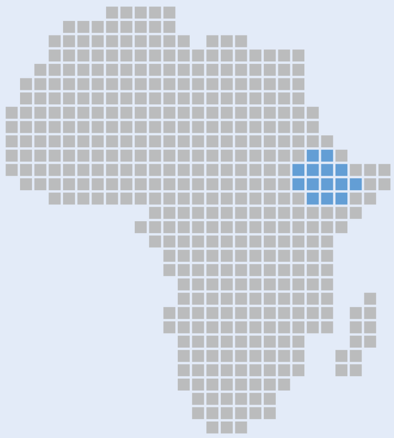
Conference
15th European Public Health Conference

Location
Berlin, Germany

Presentation date
9-12 November 2022

Authors
Benoni R. et al.

Focus country
Ethiopia



An Integrated Management System for the treatment of Noncommunicable Diseases: evidences from a program implementation in Iringa DC

POSTER PRESENTATIONS

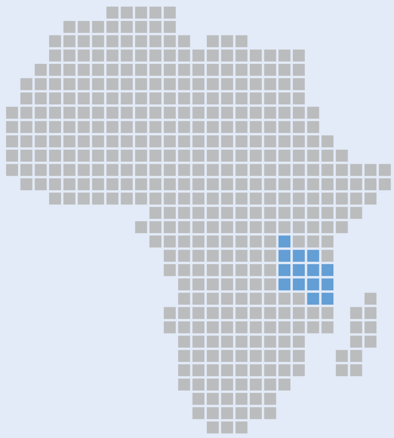
Conference
The 4th National Non-Communicable Diseases Scientific Conference

Location
Mwanza, Tanzania

Presentation date
10-11 November 2022

Authors
Bazzanini et. al.

Focus country
Tanzania



Diabetic ketoacidosis among patients admitted to a general hospital in Ethiopia: a spatial analysis

ORAL PRESENTATIONS

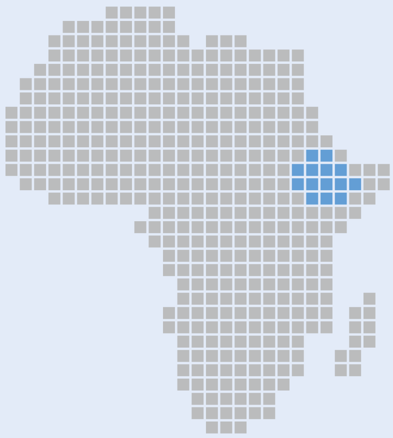
Conference
15th European Public Health Conference

Location
Berlin, Germany

Presentation date
9-12 November 2022

Authors
Paiola E. et al.

Focus country
Ethiopia



Nutrition

Influence of a quality improvement intervention on rehabilitation outcomes of children (6-24 months) with acute malnutrition: a retrospective study in rural Angola

PAPER

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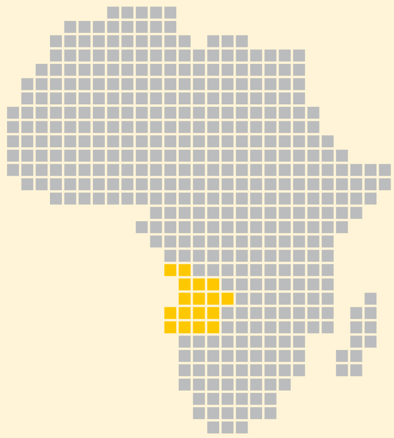

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BMC Pediatrics

RESEARCH Open Access

Influence of a quality improvement intervention on rehabilitation outcomes of children (6–24 months) with acute malnutrition: a retrospective study in rural Angola

Andrea Pietravalle[1*], Alessandro Baraldi[2], Martina Scilipoti[2], Francesco Cavallin[3], Magda Lonardi[2], Ivo Makonga Tshikamb[4], Claudia Robbiati[2], Daniele Trevisanuto[5] and Giovanni Putoto[1]

Abstract

Background: Defaulting is the most frequent cause of Community Management of Acute Malnutrition (CMAM) program failure. Lack of community sensitization, financial/opportunity costs and low quality of care have been recognized as the main driving factors for default in malnutrition programs. The present study aimed to evaluate if a logistic reorganization (generic outpatient department, OPD vs dedicated clinic, NRU) and a change in management (dedicated vs non dedicated staff) of the follow-up of children between 6 and 24 months of age with acute malnutrition, can reduce the default, relapse and readmission rate and increase the recovery rate.

Methods: Retrospective observational study on the impact of quality improvement interventions on rehabilitation outcomes of children (6–24 months) with acute malnutrition, admitted at the Catholic Mission Hospital of Chiulo (Angola) from January 2018 to February 2020. Main outcome measures were recovery rate, the default rate, the relapse rate, and the readmission rate.

Results: The intervention was associated with a decrease in the default rate from 89 to 76% ($p = 0.02$). Recovery rate was 69% in OPD and 88% in NRU ($p = 0.25$). Relapse rate was nil.

Conclusions: The present study supports the hypothesis that an improvement in quality of care can positively influence the rehabilitation outcomes of malnourished children. Further studies are needed to identify children at risk of low adherence to follow-up visits to increase the effectiveness of rehabilitation programs.

Keywords: Acute malnutrition, Nutritional rehabilitation, Default

Introduction

The term malnutrition refers to both under-nutrition and over-nutrition, but it is generally used to indicate under-nutrition, including acute (wasting), chronic (stunting) and composite form depending on the extent and timing of nutritional deprivation. over 45% of all deaths among under-5 children has undernutrition as underlying cause. In addition the impaired development and growth in

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survivors often lead to adverse consequences in later life regarding intellectual ability, school achievement, work productivity and earnings [1]. In 2017, acute malnutrition affected worldwide nearly 51 million of under-5 children, with over 25% of them living in Africa [2]. Undernutrition has multifactorial genesis including environmental degradation, natural disasters, political and civil conflicts, poverty, infectious disease, inadequate access to food and feeding practices [3]. The last national census showed that in Angola, 38% of under-5 children are stunted and 5% are affected by wasting. Exclusive breastfeeding is 62% at 1 month of age and 17% at 4–5 months of age, and usually lasts around 3 months. The WHO minimum acceptable diet standard is met by only 13% of children aged 6–24 months. Under-5 mortality rate ranges from 68 to 98 deaths per 1,000 live births in urban and rural areas, varying by residence, province and household wealth [4].

Community Management of Acute Malnutrition (CMAM) program is the globally endorsed approach for the treatment of moderate and severe acute malnutrition in emergency and non-emergency settings. It works identifying malnourished children at community level and referring them to outpatient or hospital care in accordance with the severity of malnutrition [5]. The key indicators to define CMAM program success are represented by a recovery rate above 75%, a death rate below 10% and a default rate below 15% [6]. Defaulting seems to be the most frequent reason of CMAM program failure and is associated with lack of community sensitization (awareness about the programme and malnutrition), financial/opportunity costs (carer busy or sick, distance, lack of money) and inadequacies associated with the quality of care [7, 8].

The presence of under-resourced, overburdened, not adequately trained and unmotivated staff, necessarily leads to poor quality of care. A limited explanation of the child's condition and its treatment may result in a failure to convey essential information which would encourage mothers to comply with weekly attendance until recovery [7, 8].

The present study aimed to evaluate if a logistic reorganization (generic outpatient department vs dedicated clinic) and a change in management (non dedicated vs dedicated nursing staff) of the follow-up of children between 6 and 24 months of age with acute malnutrition, can reduce the default, relapse and readmission rate and increase the recovery rate.

Materials and methods

This is a retrospective observational study on the impact of quality improvement interventions on rehabilitation outcomes of children (6–24 months) with acute malnutrition, admitted at the Catholic Mission Hospital of Chiulo (Angola) from January 2018 to February 2020. The Ethics Committee of the Angolan Ministry of Health approved the study (ref. number 032020) and waived the requirement for written informed consent because of the retrospective study design and the use of anonymized data from hospital records. All procedures were performed in accordance with the relevant guidelines and regulations.

Community Management of Acute Malnutrition (CMAM) program

CMAM program works identifying malnourished children at community level and referring them to Stabilization Centers (SC) or Outpatient Treatment Programs (OTP) in accordance with the severity of malnutrition. Children with severe (SAM) or moderate (MAM) acute malnutrition and medical complications are admitted to SC and receive F75 and F100 therapeutic milks. After stabilization of their clinical conditions and resolution of the complications (usually four to seven days), the treatment is carried on in the Outpatient Treatment Units (OTU) until nutritional recovery. Relapsed children are referred again to the SC. Children with SAM/MAM without medical complications receive routine medical treatment and nutrition rehabilitation with Ready to Use Therapeutic or Supplementary Foods (RUTF/RUSF) at the OTP. Children attend outpatient care at regular intervals (every one or two weeks) until recovery is achieved (usually two months) [5, 9].

Setting

The Hospital of Catholic Mission of Chiulo (Cunene province, Angola) is a district hospital implementing the CMAM program in a rural area of 12,263 km^2 with 345,490 inhabitants (including 60,392 under-5 children) [9]. As part of a network of 36 healthcare facilities involved in the national nutrition program, Chiulo Hospital acts as SC for the inpatient care of malnourished children with complications, as well as Outpatient Treatment Unit (OTU) for the rehabilitation phase after discharge. The nutritional rehabilitation unit counts 10 beds and is managed by a dedicated staff of doctors, nurses and paramedics. In 2018, 253 admissions were registered at the nutritional rehabilitation unit.

Patients

All children aged 6–24 months with SAM/MAM discharged from SC were eligible for inclusion.

Outcome measures

The outcome measures included the recovery rate, the default rate, the relapse rate, and the readmission rate. Definitions are provided in Sect. 2.6.

Data collection

Children data included sex, age, severe/moderate malnutrition (as defined in Sect. 2.6), distance from Chiulo hospital, discharge information (in-hospital death, self-discharge, discharge) and follow-up data (default, readmission, attendance to follow-up visits, recovery and relapse) All data were retrospectively collected from hospital charts.

Definitions

Malnutrition was defined by the combination of clinical assessment and anthropometric measurements (Weight for Height ratio or Mid-Upper Arm Circumference) according to WHO classification [10]. MAM was indicated by Weight for Height ratio ≥ 3 and < 2 Standard Deviation, or Mid-Upper Arm Circumference > 115 and < 124 m. SAM was indicated by Weight for Height ratio < 3 Standard Deviation and Mid-Upper Arm Circumference ≤ 115 mm. Within the CMAM program, an admission is the first contact with the program; a default designates a beneficiary who is absent for two consecutive weightings; a relapse designates a beneficiary readmitted to the program after having been successfully discharged as recovered within the last two months; a readmission identifies a beneficiary readmitted to the program within two months of leaving it for a reason other than recovery (e.g. defaulting or non-response) [4]; a recovery designates a beneficiary achieving weight-for-height ratio ≥ -2 Standard Deviation at least or Mid-Upper-Arm Circumference ≥ 125 mm and without edema for at least 2 weeks [5].

Comparisons

A comparative analysis was carried out to assess the impact of the quality improvement intervention on rehabilitation outcomes of children (6–24 months) with acute malnutrition. The intervention included the introduction of a dedicated clinic for the rehabilitation follow-up of the malnourished children. This clinic was located within the SC in the Nutritional Rehabilitation Unit (NRU) and was managed by dedicated and adequately trained staff.

In the main analysis, we compared the 6-month period following the introduction of this clinic (June-November 2019) with a previous 6-month period (January-July 2018) when the follow-up was managed in Out Patient Department (OPD), which was not exclusively dedicated to malnourished patients but responsible for evaluating all accesses for pediatric visits (Fig. 1). The choice of comparing these non-consecutive periods was due to ensure that both groups under comparison had received RUTF/RUSF.

In a first sub-analysis, we compared two sub-periods of 4 months (April-July 2018 vs August-November 2019), in which the caregivers had superimposable work

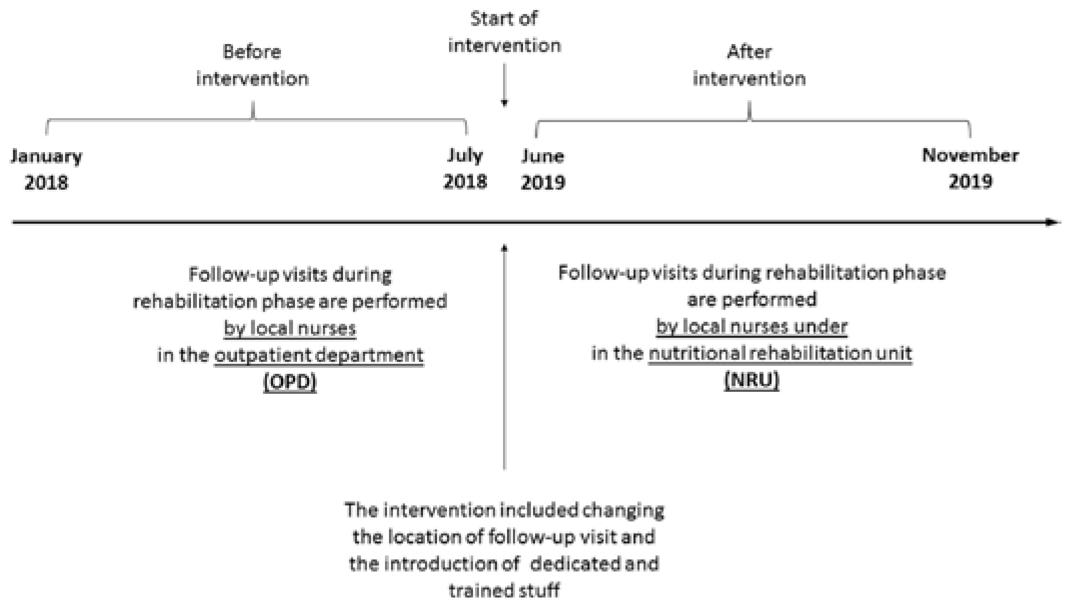

Fig. 1 Scheme of intervention

commitment in agriculture activities. The purpose was to limit the influence of financial/opportunity costs on the default rate.

In a second sub-analysis, we compared the two 6-month periods in the subsets of patients living in the Chiulo area. The purpose was to limit the effect of the distance from the treatment center, which could affect the outcome of interests.

Statistical analysis

Categorical data were summarized as frequency and percentage, and continuous data as median and interquartile range (IQR). Child characteristics were compared between OPD and NRU using Chi Square test and Mann–Whitney test. Outcome measures were compared between OPD and NRU using Chi Square test and Fisher's exact test (unadjusted analysis). The comparison of default between OPD and NRU was also adjusted for unbalanced characteristics at baseline (age and SAM/MAM) and distance from the treatment center using a logistic regression model (adjusted analysis). The small sample size at follow-up visits and in the subset of patients living in Chiulo area did not allow any meaningful multivariable analyses. The association between default rate and distance from Chiulo was evaluated using a Beta regression model using data from 2018–2019. All tests were 2-sided and a p-value below 0.05 was considered statistically significant. Statistical analysis was performed using R 4.0 (R Foundation for Statistical Computing, Vienna, Austria) [11].

Results

Overall, 402 children (128 in Jan-Jul 2018 and 274 in Jun-Nov 2019) were include in the study. Children characteristics are shown in Table 1. Children admitted to NRU (June-November 2019) were older ($p=0.001$) and with a larger proportion of SAM ($p<0.0001$) compared to those admitted to OPD (January-July) (Table 1).

In the main comparison (OPD January-July 2018 vs. NRU June-November 2019), default rate decreased from 89% (104/117) in OPD to 76% (143/189) in NRU ($p=0.02$) (Fig. 2). Multivariable analysis confirmed the reduced default rate in NRU vs. OPD ($p=0.01$) and showed increased default rate with increasing distance from Chiulo ($p=0.0003$) (Table 2). Recovery rate was 69% (9/13) in OPD and 88% (42/48) in NRU ($p=0.25$), while relapse rate was nil (Fig. 2).

In the first sub-comparison (OPD April-July 2018 vs NRU August-November 2019), default rate decreased from 90% (52/58) in OPD to 76% (143/189) in NRU ($p=0.03$) (Fig. 3). Multivariable analysis confirmed the reduced default rate in NRU vs. OPD ($p=0.03$) and showed increased default rate with increasing distance from Chiulo ($p=0.002$) (Table 2). Recovery rate was 83% (5/6) in OPD and 87% (40/46) in NRU ($p=0.99$) (Fig. 3).

In 2018–2019 period, default rate increased with longer distance from Chiulo ($p<0.0001$) (Fig. 4). When restricting the analysis to patients living in Chiulo area, default rate was 80% (8/10) in OPD and 69% (9/13) in NRU, while recovery rate was 100% (2/2) in OPD and 100% (4/4) in NRU (Fig. 5). Statistical testing was not performed due to the small sample size.

Discussion

Our findings showed a significant reduction of default rate after the introduction of a dedicated clinic for the rehabilitation follow-up of the malnourished children. Nonetheless, default rate remains high and limited further improvements in recovery rate and relapse rate.

In the treatment of acute malnutrition, about 24% of the default cases can be ascribed to inadequacies in the quality of care [7]. Given the efforts made by caregivers to access treatment, the environment of care, the communication with health care providers and the information received during the treatment can become a key factor for their continuing attendance [8]. Staff/beneficiary ratios and the corresponding time that staff can allocate to each service user can be targeted by interventions for improving the quality of the interface between SAM treatment services and caregivers. In fact, CMAM program services often rely on overburdened community-based health workers [12]. The service delivery model funnels all SAM cases towards a limited number

Table 1 Child characteristics

	January-July 2018	June-November 2019	*p*-value
N children	128	274	-
Males, n (%) Females, n (%)	58 (45.3) 70 (54.7)	137 (50.0) 137 (50.0)	0.44
Age (months), median (IQR)	12 (9–12)	12 (10–17)	0.001
SAM, n (%) MAM, n (%)	83 (64.8) 45 (35.2)	230 (83.9) 44 (16.1)	< 0.0001
Distance from Chiulo (km), median (IQR)	29 (14–39)	29 (16–58)	0.08

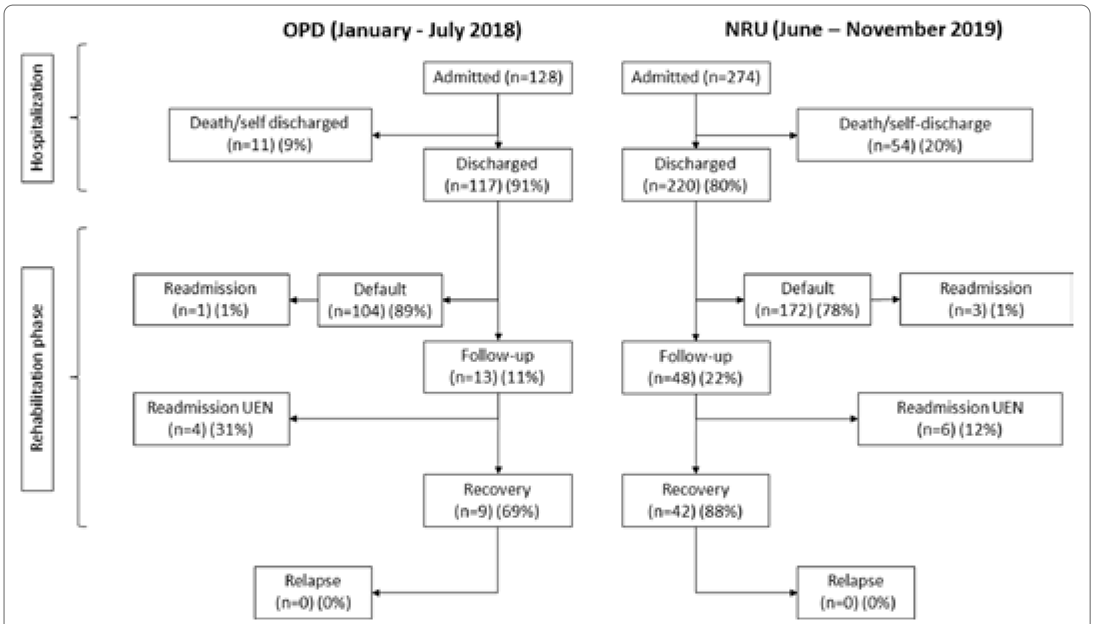

Fig. 2 Flow-chart of patients during follow-up (OPD January-July 2018 vs. NRU June-November 2019)

Table 2 Multivariable analysis of default

Comparison	Variable	Odds ratio (95% confidence interval)	*p*-value
OPD January-July 2018 vs NRU June-November 2019	NRU vs. OPD	0.38 (0.18 to 0.77)	0.01
	Age at admission, days	1.01 (0.96 to 1.07)	0.63
	SAM vs. MAM	0.90 (0.42 to 1.83)	0.92
	Distance from Chiulo, km	1.03 (1.1 to 1.05)	0.0003
OPD April-June 2018 vs NRU August-November 2019	NRU vs. OPD	0.34 (0.12 to 0.81)	0.03
	Age at admission, days	1.00 (0.95 to 1.06)	0.91
	SAM vs. MAM	0.90 (0.38 to 1.97)	0.79
	Distance from Chiulo, km	1.03 (1.01 to 1.05)	0.002

of facilities, forcing these under-resourced, overburdened and often demotivated health workers to deliver treatment to a high number of cases per week [8]. This not only increases the waiting times [13] but also decreases the amount of time available for communicating with each caregiver [8]. The lack of adequate health workers training and homogenization between the referral and admission criteria, result in a high number of case rejections [14]. An inadequately explained rejection results in frustration which in turn prevents future attendance when the child's condition deteriorates [15]. Available literature suggests that rejection and staff/beneficiary interface can be positively influenced by supervision and motivation [16]. Our findings support such consideration confirming the key role of providing dedicated, adequately trained, and motivated staff.

Among the financial/opportunity costs (which may be responsible for about 25% of the default cases), distance from health facility plays an important role [7, 8]. Despite the advantages of the decentralization of SAM management from hospitals to health facilities, the access to treatment still implies travelling significant distances for most caregivers [17]. Early community-based SAM treatment models clearly specified the need to place service delivery points within 3-h walk (one day round-trip) of the targeted populations or within a 15 km threshold

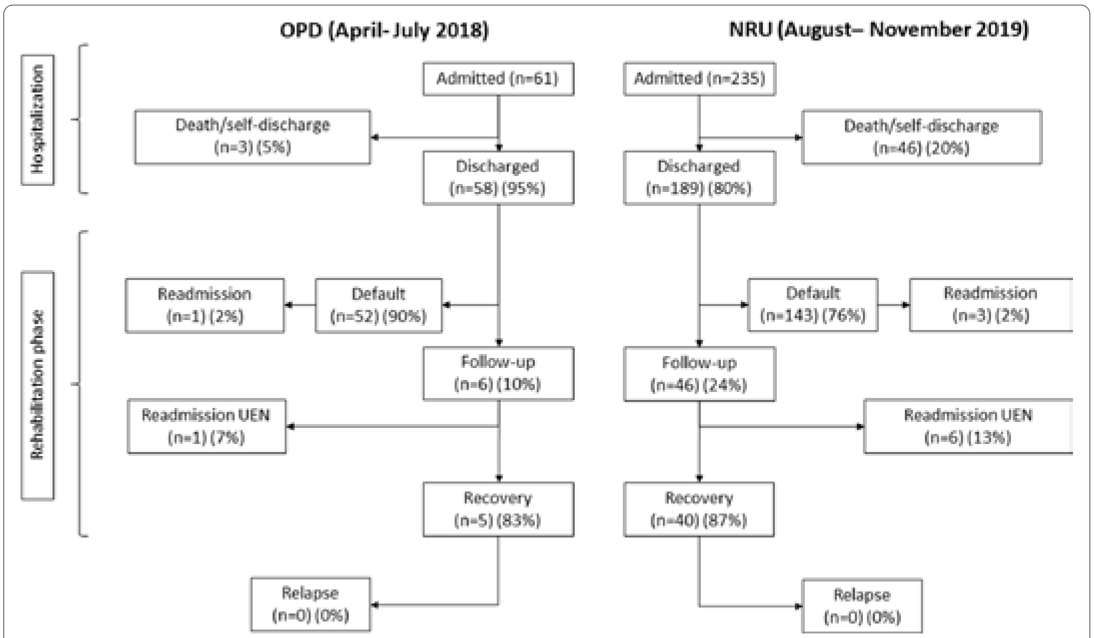

Fig. 3 Flow-chart of patients during follow-up (OPD April-July 2018 vs. NRU August-November 2019)

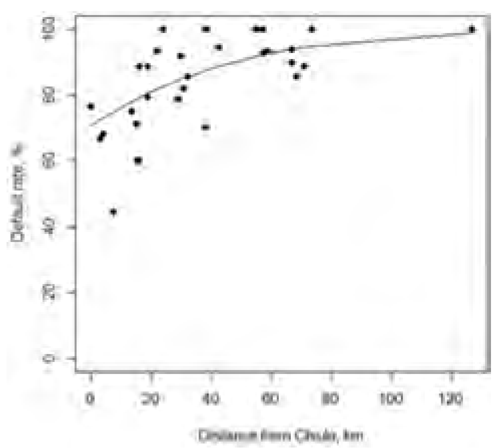

Fig. 4 Association between default rate and distance from Chiulo

[18]. Our data confirmed the association between longer distance and higher default rate. This issue is exacerbated by the actual travel distance, as most caregivers lived over 20 km from the hospital and usually travelled on foot due to economical restrictions. Nonetheless, default rate was very high (around 70–80%) also among children living in Chiulo area, thus implying the effect of other factors such as lack of community sensitization. The awareness about the program and malnutrition has been identified as the most important cause of default (45% of all default cases) [7]. The main strategy to address this problem consists in raising awareness about the condition and the treatment services available, through the involvement of key community figures, including local leaders, Traditional Health Practitioners and community groups [19, 20].

A future intervention to improve community sensitization, may consider the introduction of specific educational sessions in the immunization service, routinely performed by the Public Health Staff of Chiulo Hospital during dedicated outpatient clinic in health centers and outreach sites.

Overall, this study suggests that introducing a dedicated clinic for the rehabilitation follow-up of the malnourished children may reduce the default rate. However, the reader should be aware of the study limitations. The retrospective design limited the availability of potentially important data such as background information, possible confounders, and reasons for not attending follow-up visits. Such data can be retrieved in prospective studies using pre-established data collection forms and including contacts with caregivers of children not compliant to follow-up visits. The identification of children at risk of low

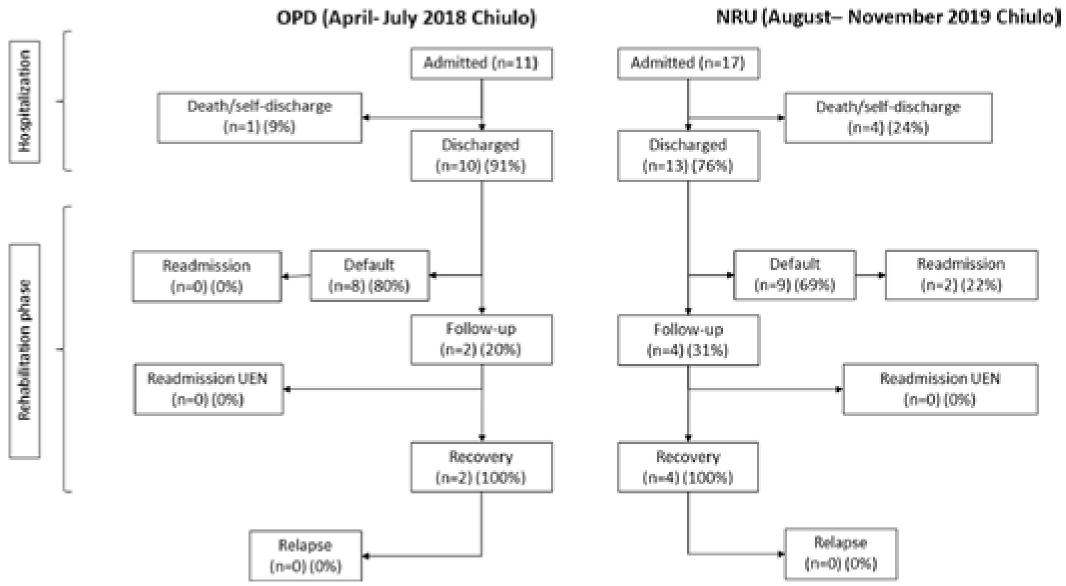

Fig. 5 Flow-chart of patients living in Chiulo area during follow-up (OPD January-June 2018 vs. NRU June-November 2019)

adherence to follow-up may increase the effectiveness of the rehabilitation program. The single-center design limited the available sample size for analysis and the generalizability of the findings to similar settings. Implementing the interventions in multiple sites may help in overcoming such limitations. Lastly, we cannot exclude that the inclusion of different months in before-intervention and after-intervention periods might have introduced some seasonality-related effects on the findings. Unfortunately, the choice of the periods for comparison was influenced by the retrospective design, the timing of the intervention, and the need for ensuring that RUTF/RUSF was available in both periods under comparison. In the analysis, we also considered the impact of seasonality on workload, and we performed a sub-analysis comparing two sub-periods of 4 months (April-July 2018 vs. August-November 2019), in which the caregivers had superimposable work commitment in agriculture activities.

Conclusions

The data emerging from the present study support the hypothesis that an improvement in quality of care can positively influence the rehabilitation outcomes of malnourished children. Further studies are needed to identify children at risk of low adherence to follow-up visits in order to increase the effectiveness of rehabilitation programs.

Abbreviations

RUTF/RUSF: Ready-to-Use Therapeutic /Supplementary Food; CMAM: Community Management of Acute Malnutrition; SAM: Severe Acute Malnutrition; MAM: Moderate Acute Malnutrition; SC: Stabilization Center; OTP: Outpatient Treatment Program; OTU: Outpatient Treatment Unit; OPD: Outpatient Department; NRU: Nutritional Rehabilitation Unit.

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Authors' contributions

Conceptualization: AP; data curation: AP and AB and MS; formal analysis, FC and AP; investigation: AP and AB and MS and ML and IMT; project administration: AP and CR and GP; supervision: FC and DT and GP; visualization: AP and FC; writing—original draft preparation: AP and FC and DT; writing—review and editing: AB and MS and ML and IMT and CR and GP. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Angolan Ministry of Health (ref. number 032020), which waived the need for written informed consent given the retrospective nature of the study and the use of anonymized data from hospital records. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
NA (Not applicable).

Competing interests
The authors declare no conflict of interest.

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Cross-sectional nutrition assessment in a refugee camp in Gambella region, Ethiopia

POSTER PRESENTATIONS

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Presentation date
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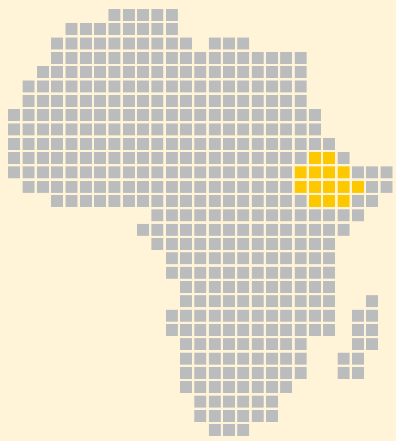

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A critically important part
of caring for patients is caring
for the health workforce.

*Prendersi cura dei pazienti
significa anche e soprattutto prendersi
cura della risorsa umana.*