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A comparative analysis of the different HIV testing techniques used in Zambia: data from a clinical performance study

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Abstract

Background Approximately 40 million people globally are living with HIV (PLWH) and more than 50% of these PLWH reside in Eastern and Southern Africa. Zambia has an adult HIV-1 prevalence (ages 15–49) of 11.1 [10.5–11.6] %, among the highest in the world (UNAIDS, 2021). In 2020, 1.5 million people were estimated living with HIV-1 in Zambia. Despite the success of many HIV preventative strategies, and worldwide sensitization to know one's status, there remains a substantial number of people with HIV who are unaware of their infection and are still infecting others. Globally, about 20% of HIV infections are due to transmissions from recently infected individuals. As Zambia's adult HIV prevalence is about 11.1%, if 3rd generation RDTs are used for first time HIV testing, all the people tested that are within the acute period will be given a false negative result. Hence the need to develop better first line HIV testing techniques.

Method A quantitative descriptive approach was used to analyze samples of 2564 participants, between the ages of 15 to 95 years from two Lusaka sites. The 2564 participants were subjected to OraQuick ADVANCE Rapid HIV-1/2 Antibody Test and Abbot Determine™ HIV-1/2 antibody test, if Reactive on either test, the result was confirmed on Uni-Gold™ Recombigen® HIV-1/2 rapid test as a confirmatory RDT. An EDTA tube of blood for each of the 2564 participants was collected and sent to the central laboratory for further testing on fourth generation Abbot ARCHITECT HIV Ag/Ab Combo and then any discrepancies were confirmed on Genscreen™ ULTRA HIV Ag-Ab. Using a systematic analysis technique, quantitative methods were applied to evaluate different variables and compare them against each other to find relationships. The data were cleaned using Microsoft excel and were analyzed using SPSS version 25.0.

Results The Abbot ARCHITECT HIV Ag/Ab Combo fourth generation assay was used as the gold standard, of the total 2564 tested 267 (10.4%) were reactive tests and 2297(89.6%) non-reactive. OraQuick ADVANCE Rapid HIV-1/2 test detected 245(9.6%) reactive tests and 2319 (90.4%) non-reactive, Abbot Determine™ HIV-1/2 test detected 249(9.7%) true reactive tests and 2315 (90.3%) non-reactive, all reactive tests on the first two RDTs were confirmed on Uni-Gold™ Recombigen® HIV-1/2 rapid test which detected 247 (9.6%) reactive and 2317 (90.4%) non-reactive. These results show that compared to the gold standard the 3 RDTs missed more than 18 (6.7% of the total 267) reactive results. This means that in every 15 tests done, 1 result is a false negative.

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Conclusion Third generation RDTs were unable to detect a good number of acute positive cases and are therefore unreliable. There is therefore need for the use 4th generation Rapid test to capture the positive cases currently being missed out.

Keywords Sensitivity, Specificity, Accuracy, Positive predictive value, Negative predictive value

Introduction

According to WHO global HIV summary report, by the end of 2019 there was a total of 38 million people living with HIV, 2.5 million new infections and 1.7 million deaths each year, emphasizing that the global response would have to be sustained for at least several decades in order to curb the HIV epidemic [1]. Despite all the strategies put in place to help end the HIV/AIDS epidemic, there still remains a substantial number of people with HIV who are unaware of their infection and are still infecting others [2]. The only way to determine a person's HIV status is to have an HIV test. Globally about 20% of HIV infections are due to transmissions from recently infected individuals [3]. The World Health Organization recommends two sequential rapid diagnostic tests (RDTs) for HIV diagnosis, however third generation RDTs detect only HIV antibodies and may miss up to 75% of early HIV infections [4, 6–9].

Zambia has an adult HIV prevalence of 11.1% meaning failure to diagnose HIV in the weeks after an individual has acquired infection negatively impacts the epidemic control by increasing the likelihood of onward transmission [3]. The Zambia Public Health Service HIV testing algorithm has not changed substantially in the past decades, despite the introduction and wide use of new technology. It is very necessary to revise testing guidelines to more accurately reflect new technology and associated challenges [10]. The Zambian HIV test algorithm uses RDTs that only detect antibodies, which means that most acute infections are missed in the first line tests and may be falsely reported as negative. The national RDT algorithm in Zambia consists of a screening test (Determine® HIV 1/2) followed by confirmation of reactive specimens with a second rapid test (Uni-gold HIV 1/2). To test respondents via RDT, a blood sample is collected directly from a finger prick [11].

According to the CDC, guidelines for HIV testing continue to evolve with changes in testing technology and methods to reach persons who can benefit from these services. The ministry of health Zambia recommends the testing algorithm shown in Fig. 1 below,

Aim

The main aim of the study was to investigate the effectiveness of different HIV testing strategies used in Zambia. Early detection of HIV means early identification of people living with HIV, who are immediately linked to care and antiretroviral therapy. This decreases transmission of the virus, which reduces HIV new infection rates.

Methods

Study design and setting

The study used quantitative methods by comparing different variables of the five different HIV tests using statistical methods. The comparison between these diagnostic tests formed the foundation of this comparative evaluation of HIV testing techniques.

The study analyzed data collected during the STAR (Self testing Africa) study that took place between July 2016 and June 2017. The study data was collected from 2564 participants of M'tendere, Lusaka district and of Kanakantapa, Chongwe district of Zambia. 2574 participants took part in the study, among these 10 did not submit a sample for further analysis at the Lab and hence were excluded. The study population comprised of all individuals screened from the two different sites in Lusaka that had an HIV test on the 3 point of care tests and agreed to have 1 tube of blood sample collected and sent to the Laboratory for further tests. This population was selected because of the proximity to the research Laboratory and because it included both rural and urban population.

Samples were collected by trained personnel following participant informed consent and complete assessment. Samples analyzed included oral mucosa transudate using the OraQuick® HIV Self-Test (Oraquick), fingerprick blood was collected and tested on Alere Determine™ HIV1/2 (Determine), if positive on Determine it was then confirmed on Unigold™HIV1/2 (Unigold) test following the Zambian national testing algorithm. The results were provided to participants, and data stored in electronic devices, all participants with reactive test results were referred for HIV care and treatment at local health facility [12].

In addition to the three rapid tests performed at Point of Care, 10 mls whole blood was collected from each participant by trained personnel and sent to the Laboratory for further testing on fourth generation assays. At the Laboratory, the samples were double-span and plasma was separated and tested on the Abbot Architect HIV Ag/Ab Combo fourth generation instrument as the gold standard for the rapid tests. (12, 13–14) If result was reactive, it was then run on manual ELISA Genscreen™ ULTRA HIV Ag-Ab to confirm positivity.

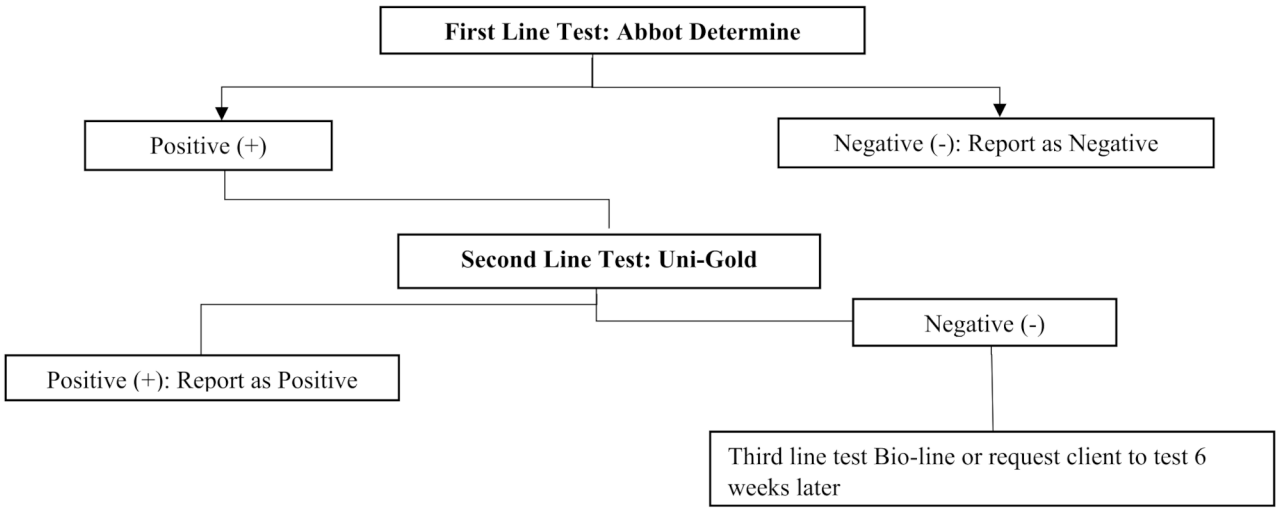

Fig. 1 Zambia national algorithm for HIV testing using rapid tests

Specificity and Sensitivity of the five different HIV testing strategies were measured by calculating the percentage of positive results yielded by these tests among all samples that tested positive for HIV based on detection of HIV positive results of the Abbot Architect test [15]. Rapid test positivity was calculated by comparing the characteristics of HIV-positive and HIV-negative results. The Results were reported in accordance with the Standards for Reporting of Diagnostic Accuracy: Sensitivity, specificity, positive and negative predictive values at 95% confidence intervals using SPSS version 25.0.

Inclusion and exclusion criteria

The study only included samples of participants who gave informed consent to participate in the STAR study [12] and who were tested on all 5 of the HIV test types being investigated. 2574 participants were screened but 10 did not give consent to giving a sample for laboratory testing. The 10 participants who did not give consent or did not give a third sample for Laboratory testing were excluded from the study.

Statistical analysis

Data was analyzed using Microsoft Excel spreadsheet for broader thematic analysis and SPSS version 25.0. Exact confidence intervals (CIs) were calculated according to the binomial distribution. Variables were summarized as frequencies and percentages with significant level at 0.05 (95%CI). Sensitivity, specificity, positive and negative predictive values were determined using cross-tables and standard formulas of the third generation HIV RDTs, the Abbot fourth generation immunoassay was used as the gold standard. Data from the STAR-Study were entered into a Microsoft excel sheet, checked for duplication and error and then subsequently exported to SPSS version 25 for analysis.

Study population

Of the total 2574 participants screened, 10 did not consent to further Laboratory testing, hence the total study population included 2564 males and females from Mtendere and Kanakantampa districts between the ages of 15 to 95 years.

Results

The study examined specimen of 2564 participants, which were tested on the 5 different HIV tests being investigated. The rapid diagnostic laboratory tests were evaluated based on a comparison test method. The investigation evaluated the test accuracy of five diagnostic assays for the identification of HIV based on sensitivity and specificity measures. Among the 2564 samples analyzed, 1043 (40.7%) were male and 1521 (59.3%) female. The 2564 samples were from participants of a wide range of ages from the age of 15 to as old as 95 years as show in Table 1. All participants below 18 years agreed to participate with guided parental consent.

The study included participants from two sites: Mtendere, representing the urban population and Kanakantampa the rural population. About 1955 (76.2%) participants were from Mtendere and 609 (23.8%) participants from Kanakantampa. There were more female (63.2%) than male (36.8%) participants in Mtenedere took part in the study, while in Kanakantampa more male (53.2%) participants took part in the study compared to females (46.8%). In both sites the highest participating ages range from 18 to 45 years of Age.

The table below compares gender and Age of participants to HIV test results of the Abbot, used as a

Table 1 Gender and age categories of participants compared to the gold standard HIV test results

Gender and Age of Participants compared to ABBOT Results						
	Abbot Architect Results (*N*)					
	Non-Reactive		**Reactive**		**Total**	
Gender of Participant	(*N*)	%	(*N*)	%	(*N*)	%
Male	960	37.4%	83	3.24%	1043	40.7%
Female	1337	52.1%	184	7.18%	1521	59.3%
Total	2297	89.6%	267	10.41%	2564	100.0%
Age Groups						
15–17	102	4.0%	6	0.23%	108	4.2%
18–25	1087	42.4%	64	2.50%	1151	44.9%
26–35	599	23.4%	104	4.06%	703	27.4%
36–45	275	10.7%	63	2.46%	338	13.2%
46–55	111	4.3%	22	0.86%	133	5.2%
56–65	71	2.8%	5	0.20%	76	3.0%
66–75	36	1.4%	2	0.08%	38	1.5%
76–85	12	0.5%	1	0.04%	13	0.5%
86–95	4	0.2%	0	0.00%	4	0.2%
Total	2297	89.6%	267	10.41%	2564	100.0%

The total mean age was 29.71 years (standard deviation 12.18). The mean age of the male participants was 30.89 (standard deviation 12.87) and 28.92 (standard deviation 11.63) for the females

Table 2 Comparison of the results of OraQuick, Determine and UniGold to the gold standard

Results of 3 Rapid Diagnostic tests compared to Abbot fourth generation test				
Rapid diagnostic test results		**Abbot Architect Results**		
		Non-Reactive	**Reactive**	**Total**
OraQuick Result	Non-Reactive	2297 (89.6%)	22(0.8%)	2319(90.4%)
	Reactive	0	245(9.6%)	245(9.6%)
	Total	2297(89.6%)	267(10.4%)	2564(100%)
Determine Result	Non-Reactive	2293(89.4%)	18(0.7%)	2311(90.1%)
	Reactive	4(0.2%)	249(9.7%)	253(9.9%)
	Total	2297(89.6%)	267(10.4%)	2564(100%)
Unigold Result	Non-Reactive	4(0.2%)	2(0.1%)	6 (0.3%)
	Reactive	0	247(9.6%)	247(9.6%)
	Not done	2293(89.4%)	18(0.7%)	2311(90.1%)
	Total	2297 (89.6%)	267(10.4%)	2564(100%)

reference. As expected, female participants (68.9%) had a higher positivity rate compared to male participants (31.1%). The age range with the highest positive results was 26 to 35 (38.9%) years.

The samples sent to the lab were processed and tested on the Abbot Architect and then all that were positive on Abbot Architect were confirmed using the Genscreen Biorad ELISA test. Table 2 shows a breakdown of how many tests from each Assay were reactive, non-reactive and not tested.

Of the 2564 samples tested on the Abbot Architect analyzer, 2297 (89.6%) were negative and 267 (10.4%) were positive as shown in the table. When compared to the gold standard test, OraQuick ADVANCE Rapid HIV-1/2 test detected 245(9.6%) reactive tests and 2319 (90.4%) non-reactive (22 reactive tests were missed), Abbot Determine™ HIV-1/2 test detected 249(9.7%) true reactive tests and 2315 (90.3%) non-reactive (it missed about 18 reactive tests). About 253 tests were reactive on both OraQuick and Determine, these reactive tests were confirmed on Uni-Gold™ Recombigen® HIV-1/2 rapid test which detected 247 (9.6%) reactive tests and 6 (0.3%) non-reactive, (compared to Abbot Architect, this test missed 20 reactive tests).

As shown in Table 2 above, the tests that were Non-Reactive on both OraQuick and ABBOT were 2297(89.6%), 245(9.6%) were Reactive on both tests. 22(0.8%) tests were Reactive on ABBOT and non-reactive on OraQuick, meaning that ABBOT picked up 22(0.8%) more positive tests that OraQuick tested as non-reactive. 4(0.2%) tests were Non-reactive on Oraquick but reactive on Determine and Unigold.

The confirmatory test for both OraQuick and Determine rapid tests, therefore only the tests reactive on Determine were tested on UniGold. Of the 253(9.9%)

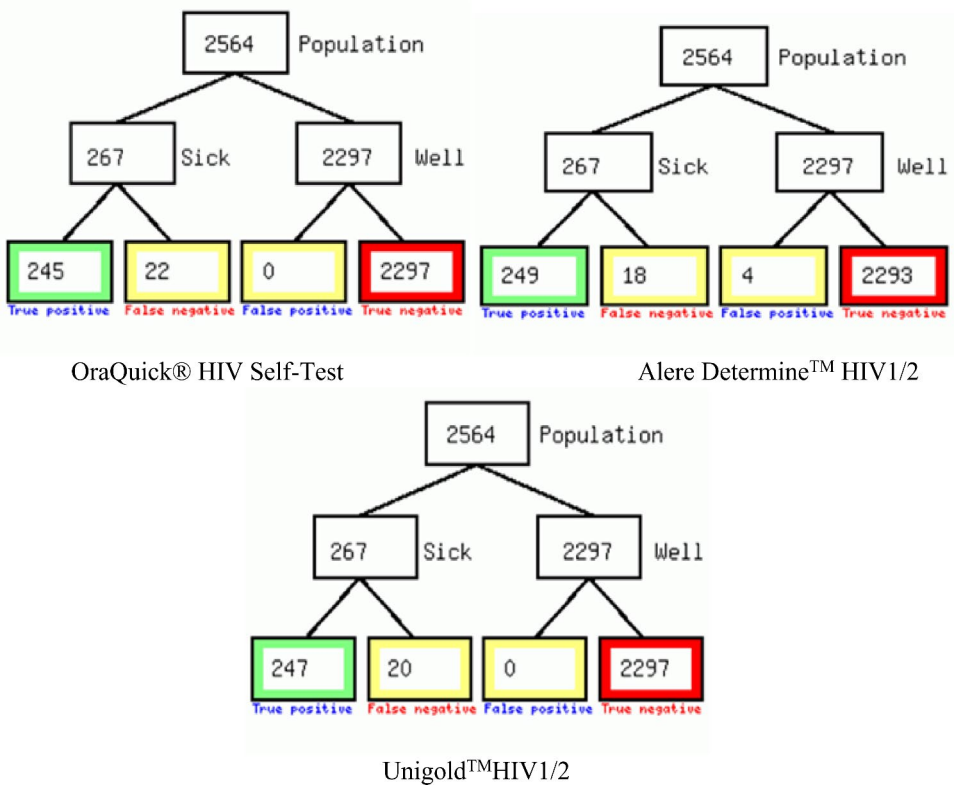

Fig. 2 summary of test results of the 3 RDTs

Table 3 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the 4 assays

Test (Assay)	OraQuick	UniGold	Determine	Abbot Architect
No of positive results(a)	245	247	249	267
No of Negative results(d)	2319	2313	2311	2297
False Negative results©	22	20	18	0
False Positive results(b)	0	0	4	0
Sensitivity (%)	91.8	92.5	93.3	100
Specificity (%)	100	100	99.8	100
PPV (%)	100	100	98.4	100
NPV (%)	99.1	99.1	99.2	100

tests tested on UniGold, 2(0.1%) were Non-Reactive on Unigold but reactive on Determine and Abbot Architect.

Referring to Fig. 2 above, 2293(89.4%) tests were non-reactive on both determine and Abbot Architect. 249 (9.7%) tests were reactive on both Abbot Architect and Determine. 18(0.7%) were Reactive on Abbot Architect and Non-reactive on Determine, showing that Abbot Architect has a higher sensitivity compared to Determine [16]. There were 4 tests that were reactive on Determine and non-reactive on Abbot Architect the reference test, showing a 0.2% low specificity rate of Determine.

The Abbot Architect as the reference standard, had 2297(89.6%) negative results and 267(10.4%) positive results, when compared to the other test results. When OraQuick results were compared to the gold standard, it was observed that of the 267 reactive results, OraQuick only detected 245 (91.8%) positive results and missed 22 (8.2%). When compared to Abbot Architect results, Determine 249 (93.3%) reactive and 18 tests negative on Determine but positive on ABBOT. The 249 Reactive results on Determine were confirmed on the UniGold test kit, of the 249 tested on UniGold, 247 were reactive and 2 gave false positive results. Compared to Abbot Architect results, UniGold was Reactive on 247 (92.5%) tests and gave 20 (7.5%) non-reactive results.

As shown in Table 3, OraQuick *ADVANCE*® Rapid HIV-1/2, Alere Determine HIV-1/2 and Uni-Gold Ultra HIV, at 95% CI had Sensitivities of: 91.8%, 93.3% and 92.5% respectively, of which when compared to the sensitivities reported by the manufacturers is quite low despite manufacturers reports of high sensitivity and specificity for these RDTs [17].

The specificities of OraQuick *ADVANCE*® Rapid HIV-1/2 and Uni-Gold HIV were the same (100.0%; 95% CI: 98.8–100.0) but slightly different from Alere Determine HIV-1/2 (99.8%). Negative predictive values (at 95% CIs) were 99.1, 99.2 and 99.1 for OraQuick *ADVANCE*® Rapid HIV-1/2, Alere Determine HIV-1/2, and Uni-Gold Ultra HIV respectively similar to Kashoshi study findings [16].

Discussion

The study established that the three-3rd generation HIV RDTs used at Point of Care for HIV testing though quite sensitive, still fail to detect a significant number of acute infections. About 1 in every 10 people tested using 3rd generation RDTs goes home with false negative results [18, 19]. In resource-limited or point-of-care settings, rapid diagnostic tests (RDTs), that aim to simultaneously detect HIV antibodies and p24 capsid (p24CA) antigen with high sensitivity, can pose important alternatives to screen for early infections [20, 21].

Given the brief window of acute HIV infection, the acute HIV prevalence in a population is very low at any given point in time, even among relatively high-risk groups. Consequently, a test must have exceptional performance characteristics to be useful, especially without additional confirmatory testing [19, 22]. The Determine®HIV-1/2 Ag/Ab Combo rapid test has been marketed as such a test, because it is relatively inexpensive and can be administered at the point of care [19, 23]. Although the performance characteristics of the Determine®HIV-1/2 Ag/Ab Combo rapid test were insufficient for use in clinical setting, field evaluation in other settings may be warranted to assess whether the test performs better. The Determine®HIV-1/2 Ag/Ab Combo rapid test has been previously evaluated with stored serum or plasma specimens [24, 25]. Despite this, HIV RDTs have some limitations since they cannot identify persons who are within the window period of an acute HIV infection because these individuals have not yet developed HIV-specific antibodies [26, 27]. Such individuals are highly infectious due to concurrent high plasma as well as vaginal and semen HIV-1 viral load [3, 28].

Conclusion

This study went out to establish the possibility of unacceptably low sensitivities of the RDTs Alere Determine HIV-1/2 and Uni-Gold HIV, using blood and, OraQuick ADVANCE® Rapid HIV-1/2 using mouth swabs in Zambia. This raises serious concerns about rapid test dependability and calls for stringent control measures as well as the need for 4th generation Ag-Ab RDTs and a cross-evaluation of all Rapid diagnostic tests results by a laboratory-based antigen testing, whenever feasible.

An alternative HIV testing algorithm, which includes a fourth-generation Determine® HIV-1/2 Ag/Ab Combo rapid test with a better sensitivity and specificity, is necessary [19, 25]. Developing and introducing a point-of-care test with adequate sensitivity and specificity for acute HIV detection is extremely challenging but very feasible. The Determine®HIV-1/2 Ag/Ab Combo rapid test was designed to provide a marginal reduction in the HIV window period by testing for both Antibodies and Antigens at point of care settings [13, 14, 19, 21, 24, 26–30].

Limitations

The data used in this study was secondary, and collected from another study, access to the data was not easy.

Abbreviations

Ab	Antibody
Ag	Antigen
AIDS	Acquired Immuno-Deficiency Syndrome
ART	Anti-Retroviral Therapy
CI	Confidence Interval
CDC	Centers for Disease Control and Prevention
EIA	Enzyme Immuno-Assay
ELISA	Enzyme Linked Immuno-Sorbent Assay
IgG	Immunoglobulin G
IgM	Immunoglobulin M
HIV	Human Immuno-deficiency Virus
HTC	HIV Testing and Counselling
MDG	Millennium Development Goal
MoH	Ministry of Health
NCHS	National Center for Health Statistics
NGO	Non-Governmental Organization
NPV	Negative Predictive Value
POC	Point of Care
PPV	Positive Predictive Value
RDT	Rapid Diagnostic Test
SD	Standard Deviation
SDG	Sustainable Developmental Goals
STAR	Self Testing Africa Study
UNAIDS	United Nations Program on HIV/AIDS
WHO	World Health Organization
ZDHS	Zambia Demographic and Health Survey

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Author contributions

LM and AT conceived the study. LM and AT conducted the data collection and drafting of Manuscript. LM, AT and MZ contributed to data analysis and led the writing of the manuscript. PS, MZ and PJC reviewed the manuscript. All authors read and approved the final manuscript.

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Not applicable.

Data availability
All data generated or analyzed during this study are included in this published Article supporting the article. For other data, these may be requested through the corresponding Author.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval and consent to participate
Ethical approval was granted by the University of Lusaka, medical Ethics Committee. All methods were carried out in accordance with relevant guidelines and regulations with relevant authorizations from Ministry of Health. Consent to participate was obtained. For participants with ages less than 18 years, informed consent was obtained from their parent(s)/guardian(s) as well. Informed consent was obtained from participants and management before the study.

Consent to publish
Not applicable.

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