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Knowledge, attitude and practice of healthcare workers on isoniazid preventive treatment in Tanzania; a health facility-based cross-sectional study

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Abstract

Background Tuberculosis (TB) remains a significant public health concern globally, particularly in regions with a high prevalence of HIV/AIDS. In Tanzania, the co-occurrence of TB and HIV poses a substantial challenge to healthcare systems. Isoniazid Preventive Therapy (IPT) has become an important intervention to mitigate the risk of TB infection among individuals living with HIV. Despite its proven efficacy, the extent of knowledge, attitude, and practice of healthcare workers (HCWs) in Tanzania is not well-documented. This study aimed to evaluate the levels of knowledge, attitude, and practice regarding IPT among healthcare workers.

Methods A cross-sectional study was carried out among healthcare workers working at TB/HIV clinics in 12 regions of Tanzania mainland. A semi-structured questionnaire was administered to the respondents consisting of social demographic characteristics, knowledge, attitude, and practice questions. Data were analyzed using Stata version 14.0.

Results A total of 464 respondents were interviewed, with 282 (60.8%) being female. The mean age was 36.4 years (SD = 11.0). Among the interviewed, 255 (55.0%) were nurses. Regarding knowledge, attitude, and practice on IPT, 217 (46.8%), 220 (47.0%), and 422 (90.9%) respondents respectively demonstrated adequacy in these domains. Factors such as gender, university education, professional role in healthcare practice, cumulative work experience of one year or more, tenure at a TB/HIV clinic of one year or longer, and attendance at IPT-related training emerged as significant determinants. These factors influence respondents' knowledge, attitude, and practice towards IPT.

Conclusion The findings underscored a notable knowledge gap and a less favourable attitude towards IPT among HCWs, despite commendable practices. Addressing this disparity through targeted training interventions for healthcare workers holds promise for enhancing their understanding and attitude toward IPT, thereby fostering increased acceptance and utilization of this preventive therapy.

Keywords IPT · TB/HIV · HCWs · Tanzania

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Abbreviations

IPT	Isoniazid preventive treatment
HCW	Healthcare workers
AOR	Adjusted odds ratio
CTC	Care and treatment centers
PLHIV	People living with HIV
SSA	Sub-saharan africa

1 Background

Tuberculosis (TB) is one of the top global public health burdens of the twenty-first century. In 2022, an estimated 10.6 million people fell ill with TB worldwide [1]. While TB is reported as the leading killer among People Living with HIV, it affects people of all populations [1]. People living with HIV are 16 times more likely to fall ill with TB than people without HIV [2–4]. Globally, about 167,000 people were reported to die of HIV-associated TB in 2022 [1]. In 2021, the Asia and African regions contributed to nearly 45% of global TB cases [1]. In the past decade, the WHO and National TB Programs (NTP) have intensified efforts in TB prevention using both long and short-term TB Preventive Treatment (TPT) plans[5] to mitigate the progression from latent TB infection to clinically active form of TB disease. Half of the 30 highly TB-burdened countries worldwide are found in the Sub-Saharan Africa (SSA) region [5, 6]. The use of isoniazid in PLHIV with latent tuberculosis (LTB) infection to stop the onset of active TB disease has been reported to be reliably effective in many studies [7, 8].

Tanzania is among the 15 SSA countries with the highest TB and TB/HIV coinfection burden [9, 10]. According to the National Tuberculosis and Leprosy Program (NTLP), the TB incidence rate in 2021 was estimated to be 208/100,000 population. To mitigate the increasing risk of TB infection in the country, the NTLP rolled out Isoniazid Preventive Treatment (IPT) among PLHIV and < 5 household contacts of bacteriologically confirmed TB patients since 2011 [11].

Despite HCWs being among the central players in TB prevention programs, particularly TPT services, information about their level of Knowledge, Attitude, and Practices (KAP) on TPT is rare in SSA countries. However, evidence from elsewhere indicates that the knowledge gap among HCWs is among the barriers to IPT uptake. A study in Nigeria for example documented that, there is slightly over half of the HCWs had adequate knowledge of the IPT guidelines, and the majority self-reported that they practised them [12]. In South Africa, a study reported a 44% level of knowledge of IPT among HCWs [13].

In Tanzania, KAP on IPT among HCWs is yet to be documented which makes this study the first of its kind. Assessing KAP towards IPT among the health workforce gives room to identify the knowledge gaps, on misconceptions, and performance-related challenges that directly impact the quality of care, particularly in IPT service delivery. We conducted this study to evaluate the level of knowledge, attitude, and practice among HCWs to shed light on the existing gaps and pave the way for informed interventions that strengthen healthcare systems, improve patient outcomes, and contribute to the global efforts to combat the dual burden of TB and HIV.

2 Methods

2.1 Study design

A health facility-based cross-sectional study was conducted to assess healthcare workers' knowledge, attitude, and practice towards IPT in selected health facilities in Tanzania.

2.2 Study area

The study was conducted in 100 health facilities from 12 regions of mainland Tanzania. The regions included; Dar es Salaam, Mara, Dodoma, Ruvuma, Tanga, Simiyu, Mbeya, Kagera, Mwanza, Shinyanga, Pwani, and Geita. The regions selected were those under the support of the Global Fund in the TB preventive program for PLHIV.

2.3 Study population

The study included healthcare workers working in both TB clinics and at the Care and Treatment Centers (CTC) in selected regions of mainland Tanzania.

2.4 Sample size and sampling procedure

The sample size was estimated using a single proportion formula with the assumption that 50% of healthcare workers had adequate knowledge of IPT, an intra-class coefficient (ICC) of 0.05, a cluster size of five, and an expected response rate of 95%, the study required a sample size of 486 healthcare workers for estimating the expected proportion with 5% absolute precision and 95% confidence. A list of all health facilities offering TB/HIV care and treatment in each study region was obtained. Following that a total of eight health facilities offering TB/HIV services were selected at random from each study region making a total of 96 health facilities in 12 regions. In all selected health facilities interviews were made with five randomly selected healthcare workers from TB/HIV clinics.

2.5 Data collection

Data was collected through face-to-face interviews using a semi-structured questionnaire adapted and modified from previous studies [12, 13]. The questions were modified to reflect the country-specific context. The questionnaire was uploaded to a server located at the National Institute for Medical Research (NIMR), Muhimbili Medical Research Centre. Later questionnaire was downloaded onto Android mobile devices using the Open Data Kit (ODK) application for data collection.

2.6 Study variables and measurement

2.6.1 Independent variable

Included respondents' social demographic characteristics.

2.6.2 Dependent variable

Knowledge knowledge was obtained using nine questions including; whether IPT reduces the risk of TB infection in HIV-positive patients, eligibility to receive IPT, criteria for screening eligible PLHIV for IPT, IPT dose used for TB prevention in adults living with HIV, the interval should IPT be replenished/re-filled for PLHIV and ways to assess whether patient adheres to IPT. The minimum score was 0 and the maximum was 9. Those who scored 0–4 were classified as having poor knowledge and 5–9 were classified as having adequate knowledge of IPT. This classification has been used in previous studies [12, 13].

Attitude Eight Likert scale questions with five options ranging from 'strongly disagree', 'disagree', 'neutral', 'agree', and 'strongly agree' were used to measure attitude. The maximum score was 32 indicating a positive attitude and the minimum was 0 indicating a negative attitude. A Bloom's cut-off system for categorizing attitude scores was adopted [14–16]. A cut-off of ≥ 80% was classified as a positive attitude toward IPT.

Practice Five questions were used to measure the practice of healthcare workers in the implementation of IPT services to PLHIV and under five contacts of TB index cases. The questions had three options 'Yes always', 'Sometimes', and 'No'. The maximum score was 10 indicating good practice and the minimum score was 0 indicating poor practice. Based on Bloom's cut-off a healthcare provider who scored ≥ 90% of the correct practice questions (9 points out of 10) was classified as good practice [16]. The reason for using a 90% cut-off point is the mandatory requirement of healthcare workers to follow guidelines and practice on IPT [11, 17].

2.7 Statistical data management and analysis

Collected data were transferred to Stata, a statistical software for data analysis (Stata Corp, Texas-USA, version 14.0) for cross-checking, data cleaning, and analysis. Descriptive statistics were generated to obtain mean and standard deviation, frequency, and percentages. Bloom's cut-off point was used to determine adequate knowledge (≥ 50%) positive

attitude ≥ 80% and good practice ≥ 90%. A bivariate analysis was done using chi-square to test for association between knowledge and social demographic characteristics of the respondents. A generalized linear mixed model was used to fit the outcome variable against the predictors. Any variable whose univariable test had a p-value < 0.25 along with all variables of known to be importance to the study were included into multivariable analysis [18]. Knowledge, attitude, and practice were used as dependent variables while participant social demographic characteristics were taken as predictors. Odds Ratios were calculated at a 95% confidence interval with data regarded as statistically significant only if $p < 0.05$.

3 Results

3.1 Social demographic characteristics of the study participants

A total of 464 healthcare workers were interviewed, 282 (60.8%) with an average age of 36.4 years (SD = 11 years), and over half of them (54 0.1%) were working in the rural setting. The majority of respondents 347 (74.8%) fell within the age range of 18 to 45 years, while only 9 (1.9%) were aged 60 years or older. Regarding marital status, 243 (52.4%) respondents were married. Of the total respondents, 255 (55.0%) were nurses, 145 (31.2%) were clinicians, and 28 (6.0%) were pharmacists. Education-wise, diploma holders constituted the largest group 241 (51.9%), followed by certificate holders 96 (20.7%), with only 54 (11.6%) having attained university degrees (Table 1).

Table 1 Social demographic characteristics of the healthcare workers ($n = 464$)

Variable	Frequency	Percent
Sex		
Male	182	39.2
Female	282	60.8
Age group (years)		
18–31	221	47.6
32–45	126	27.2
Above 45	117	25.2
Mean (SD)	36.4	11.0
Marital status		
Married	243	52.4
Single	202	43.5
Divorced/widowed/separated	19	4.1
Level of education		
Secondary education	73	15.7
Certificate	96	20.7
Diploma	241	51.9
University education	54	11.6
Profession		
Nurse	283	61.0
Clinician	153	33.0
Pharmacist	28	6.0
Facility level		
Hospital	143	30.8
Health Centre	192	41.4
Dispensary	129	27.8
Facility ownership		
Public	370	79.7
Private	94	20.3
Location		
Urban	213	45.9
Rural	251	54.1

3.2 Healthcare workers' knowledge, attitude, and practice of isoniazid preventive treatment

Out of 464 interviewed healthcare workers, 217 (46.8%), 220 (47.4%), and 422 (90.9%) had adequate knowledge, positive attitude, and good practice toward IPT respectively. The level of education exhibited a statistically significant association with a level of knowledge ($p = 0.009$). Those with university education demonstrated higher levels of good knowledge 35 (64.8%) compared to those with secondary education 27 (37.0%). Additionally, the level of health facility was significantly associated with the level of knowledge ($p = 0.004$). Those working in hospitals demonstrated a higher level of good knowledge 80 (55.9%) compared to dispensaries 64 (49.6%) and health centres 73 (38.0%). Healthcare workers' attitude was significantly associated with working experience ($p = 0.019$). Those with less than one year of experience had a lower prevalence of positive attitude 8 (26.7%) compared to those with one year or more 212 (48.8%). The level of education was found to be statistically associated with good practice on IPT ($p = 0.026$). Other demographic and professional characteristics such as sex, age group, marital status, profession, facility ownership, and location did not exhibit statistically significant associations with knowledge, attitude, and practice ($p > 0.05$) (Table 2).

3.3 Determinants of adequate knowledge, positive attitude, and better practices on IPT among healthcare workers

A multivariable logistic regression was fitted between the participant's sociodemographic characteristics and the knowledge, attitude, and practice of IPT. Females were 1.32 times more likely to have positive attitudes ($p = < 0.001$) than their male counterparts, while individuals aged 40 years and above exhibited adequate knowledge (AOR = 1.76; 95% CI 1.68–1.85, $p = < 0.001$). Married participants were having lower odds of positive attitudes (AOR = 0.79, 95% CI 0.41–1.53, $p = 0.487$) and divorced/widowed/separated individuals showing reduced odds of good practices (AOR = 0.27; 95% CI 0.13–0.56, $p = 0.001$). Higher education levels were associated with adequate knowledge, positive attitudes, and better practices. Nurses were more likely to have adequate knowledge (AOR = 1.43; 95% CI 1.39–1.48, $p < 0.001$), while pharmacists exhibited lower odds of good practices (AOR = 0.26, 95% CI 0.10–0.65, $p = 0.004$). Healthcare workers with more than one year of working experience and those who attended IPT training had higher odds of adequate knowledge, positive attitudes, and better practices (Table 3).

4 Discussion

A thorough perusal of the literature shows that this is the first study to assess knowledge, attitude, and practice (KAP) on IPT and the associated factors among healthcare workers in Tanzania. The findings suggest a complex coherence of knowledge, attitude, and practice parameters. The low level of adequate knowledge and positive attitude among healthcare workers implies a potential gap in their understanding of IPT, which could impact the effectiveness of preventive measures to be implemented. It may further indicate a lack of enthusiasm or reluctance among health workers, which could affect their engagement in IPT services. However, the observed good practice suggests that despite the challenges in knowledge and attitude, the majority of healthcare workers were effectively implementing IPT.

In the current study, less than half of the healthcare workers had adequate knowledge of IPT. Our findings are similar to the studies done in Indonesia, and South Africa which found that 30.6% and 43.1% had adequate knowledge of IPT, respectively [13, 19–21]. However, studies conducted in Nigeria and Ethiopia found a higher level of adequate knowledge of IPT among healthcare workers above 50% [12, 22, 23]. Having less than half of healthcare workers with adequate knowledge of IPT may lead to suboptimal implementation, compromised patient care, and an increased risk of preventable health issues in the community. Healthcare workers must undergo retraining to guarantee that they are all well-versed in IPT. The program implementers might also need to come up with better strategies for delivering training including conducting a pre-assessment of training needs and identifying areas in which HCWs require additional knowledge.

Our study revealed that 47.0% of the healthcare workers had a positive attitude towards IPT. These results are different from the study conducted in Indonesia, South Africa, India, and Australia which found a positive attitude of above 50% [13, 19, 23–25]. The presence of fewer healthcare workers with positive attitudes may be attributed to limited awareness and education about IPT and challenges in healthcare infrastructure. In the current study, a noteworthy percentage of healthcare workers (90.9%) demonstrated good practices in IPT services. This might have been influenced by the presence

Table 2 Relationship between knowledge, attitude, and practice on IPT and social demographic characteristics of respondents ($n=464$)

Variable	Knowledge		*p*-value	Attitude		*p*-value	Practice		*p*-value
	Inadequate n(%)	Adequate n(%)		Negative attitude n(%)	Positive attitude n(%)		Poor n(%)	Good n(%)	
Total	247(53.2)	217(46.8)		244(52.6)	220(47.4)		42(9.1)	422(90.9)	
Sex									
Male	101(55.5)	81(44.5)	0.433	96(52.7)	86(47.2)	0.955	14(7.7)	168(92.3)	0.412
Female	146(51.8)	136(48.2)		148(52.5)	134(47.5)		28(9.9)	254(90.1)	
Age group (years)									
18–31	123(55.7)	98(44.3)	0.598	118(53.4)	103(52.4)	0.370	14(6.3)	207(93.7)	0.120
32–45	65(51.6)	61(48.4)		60(47.6)	66(52.4)		13(10.3)	113(89.7)	
Above 45	59(50.4)	58(49.6)		66(56.4)	51(43.6)		15(12.8)	102(87.2)	
Marital status									
Single	114(56.4)	88(43.6)	0.243	105(52.0)	97(48.0)	0.910	13(6.4)	189(93.6)	0.168
Married	132(51.0)	127(49.0)		136(52.5)	123(47.5)		26(10.0)	233(90.0)	
Level of education									
Secondary education	46(63.0)	27(37.0)	0.009	45(61.6)	28(38.4)	0.158	9(12.3)	64(87.7)	0.026
Certificate	57(39.4)	39(40.6)		44(45.8)	52(54.2)		15(15.6)	81(84.4)	
Diploma	125(51.9)	116(48.1)		130(53.9)	111(46.1)		14(5.8)	227(94.2)	
University education	19(35.2)	35(64.8)		25(46.3)	29(53.7)		4(7.4)	50(92.6)	
Profession									
Nurse	149(52.6)	134(47.4)	0.950	157(55.5)	126(44.5)	0.291	30(10.6)	253(89.4)	0.107
Clinician	83(54.3)	70(45.7)		74(48.4)	79(51.6)		8(5.2)	145(94.8)	
Pharmacist	15(53.6)	13(46.4)		13(46.4)	15(53.6)		4(14.3)	24(85.7)	
Facility level									
Dispensary	65(50.4)	64(49.6)	0.004	66(51.2)	63(48.8)	0.930	13(10.1)	116(89.9)	0.734
Health centre	119(62.0)	73(38.0)		102(53.1)	90(46.9)		15(7.8)	177(92.2)	
Hospital	63(44.1)	80(55.9)		76(53.2)	67(46.8)		14(9.8)	129(90.2)	
Facility ownership									
Public	198(53.5)	172(46.5)	0.810	192(51.9	178(48.1)	0.552	32(8.6)	338(91.4)	0.548
Private	49(52.1)	45(47.9)		52(55.3)	42(44.7)		10(10.6)	84(89.4)	
Location									
Urban	106(49.8)	107(50.2)	0.168	119(55.9)	94(44.1)	0.192	22(10.3)	191(89.7)	0.377
Rural	141(56.2)	110(43.8)		125(49.8)	126(50.2)		20(8.0)	231(92.0)	
Working experience									
Less than one year	20(66.7)	10(33.3)	0.127	22(73.3)	8(26.7)	0.019	1(3.3)	29(96.7)	0.259
One year & above	227(52.3)	207(47.7)		222(51.2)	212(48.8)		41(9.4)	393(90.6)	
Working experience at TB/HIV clinic									
Less than 1 year	46(60.5)	30(39.5)	0.163	45(59.2)	31(40.8)	0.206	9(11.8)	67(88.2)	0.354
One year and above	201(51.8)	187(48.2)		199(51.3)	189(48.7)		33(8.5)	355(91.5)	

of clear guidelines and IPT circulars focused on increasing IPT service uptake. This finding implies overwhelming efforts to improve IPT coverage forgetting the core aspects of training to incentivise HCW towards well-informed and technical decision-making in IPT service delivery.

Healthcare workers who were aged 40 years and above were 76% more likely to have adequate knowledge of IPT compared to those aged below 40 years indicating a potential correlation between age and knowledge. This suggests the need for targeted educational efforts among younger healthcare professionals to improve their knowledge of IPT. However, the current results are different from those observed in an earlier study done in Ebonyi State, Nigeria which they found that ages 35 years and below were more likely to have adequate knowledge of IPT [12]. The difference can be attributed to the fact that the earlier study was done in one state and had a sample size of 85 healthcare workers, unlike the current study.

Table 3 Logistic regression for the determinants of knowledge, attitude, and practice on IPT

Variable	Knowledge		Attitude		Practice	
	AOR(95%CI)	*p*-value	AOR(95% CI)	*p*-value	AOR(95% CI)	*p*-value
Sex						
Male	1		1		1	
Female	1.49(0.63–3.52)	0.367	1.32(1.20–1.45)	< 0.001	1.45(0.23–9.20)	0.693
Age group (years)						
Below 40 years	1		1		1	
40 years and above	1.76(1.68–1.85)	< 0.001	1.14(0.73–1.77)	0.573	0.60(0.17–2.18)	0.440
Marital status						
Married	1.40(0.94–2.09)	0.100	0.79(0.41–1.53)	0.487	0.49(0.34–0.71)	0.000
Single	1		1		1	
Divorced/widowed/separated	0.86(0.20–3.66)	0.841	0.70(0.09–5.45)	0.733	0.27(0.13–0.56)	0.001
Level of education						
Secondary education	1		1		1	
Certificate	1.15(0.18–7.29)	0.883	1.72(1.04–2.82)	0.033	0.71(0.43–1.17)	0.180
Diploma	2.08(0.73–5.99)	0.173	1.31(0.99–1.72)	0.059	1.90(1.37–2.64)	0.000
University education	4.48(1.78–25.79)	0.023	2.00(1.20–3.35)	0.008	1.89(0.26–13.55)	0.528
Profession						
Nurse	1.43(1.39–1.48)	0.000	0.75(0.50–1.11)	0.145	0.62(0.32–1.19)	0.151
Clinician	1		1		1	
Pharmacist	1.28(0.85–1.94)	0.237	1.66(1.27–2.15)	0.000	0.26(0.10–0.65)	0.004
Others	0.72(0.64–0.81)	0.000	0.60(0.05–7.05)	0.683	0.58(0.23–1.59)	0.964
Facility level						
Hospital	1		1		1	
Health centre	0.53(0.35–0.80)	0.002	1.13(0.68–1.86)	0.639	0.79(0.24–2.60)	0.144
Dispensary	0.95(0.39–2.30)	0.910	1.02(0.61–1.69)	0.945	0.56(0.26–1.22)	0.694
Facility ownership						
Public	1		1		1	
Private	0.98(0.53–1.83)	0.960	1.01(0.71–1.42)	0.976	0.75(0.10–5.79)	0.780
Location						
Urban	1		1		1	
Rural	0.92(0.85–0.99)	0.048	1.50(0.86–2.65)	0.157	1.68(1.38–2.04)	0.000
Working experience						
Less than one year	1		1		1	
One year & above	1.42(1.05–1.92)	0.023	2.93(1.99–4.30)	0.000	0.11(0.04–1.90)	0.863
Working experience at TB/HIV clinic						
Less than 1 year	1		1		1	
One year and above	1.13(0.59–2.16)	0.713	0.97(0.69–1.35)	0.835	5.20(3.23–8.38)	0.000
Ever attended IPT training						
No	1		1		1	
Yes	1.98(1.63–2.40)	0.000	1.89(1.54–2.31)	0.000	2.15(1.81–2.56)	0.000

University education was found to be a significant factor in adequate knowledge of IPT among healthcare workers. Healthcare workers with a University education were 4.48 times more likely to have adequate knowledge of IPT compared to those with secondary education. The finding was supported by a study conducted in Pune, India [26]. This suggests that healthcare workers with a university education have a more in-depth and specialized curriculum at the university level, exposure to advanced training, and a higher likelihood of engaging in continuous professional development [27]. A mentorship program should be emphasized to improve IPT knowledge among healthcare workers who do not have a university education. Those who ever attended IPT training were 98% more likely to have adequate knowledge of IPT. These results are similar to the study conducted in South Africa and Brazil

[13, 28]. Suggesting that continuous training should be offered to healthcare workers regularly to improve their knowledge of IPT.

The likelihood of female HCWs' positive attitude toward IPT compared to their male counterparts suggests a need to emphasize targeted interventions and awareness campaigns to address gender disparities among HCWs which may influence their attitude towards preventive therapies. Those who had a working experience of more than one year at TB/HIV clinics were 5.20 times more likely to have good practices on IPT. These results are similar to the study conducted in Indonesia [19]. This might have been influenced by the availability of circulars at hand in health facilities.

5 Limitations

The inability of some healthcare workers to participate due to their busy hospital schedules resulted in a reduction of the sample size from 486 to 464 participants. Additionally, the study's scope was confined to healthcare facilities in 12 regions supported by global funds, representing various levels of healthcare facilities. Therefore, caution should be exercised when generalizing the findings to the entire country, as the study may have not fully captured the diversity of healthcare settings and practices across Tanzania.

6 Conclusion

The modest level of knowledge and attitude towards IPT among healthcare workers is an issue of concern, particularly given its crucial role in preventive therapy for TB. Despite this knowledge and attitude gap, there appears to be a positive direction in the application of good practices related to IPT within the healthcare setting. This situation highlights the need for targeted educational interventions to enhance healthcare workers' attitudes and understanding of Isoniazid and its use in TB prevention.

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Author contributions JJM contributed to study design, sample size estimation, data collection, data management, analysis and interpretation, drafting of the article, performing critical revisions of the article, and facilitating final approval of the version to be published.

FCA, AMR, VAN, MLM, WMM, AAR, BJN, VEW,OAK, EJM, CEM and NSR contributed to the initial design of the study including data collection tools and an overall review of the manuscript.

AMK overall supervisor.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate The ethical clearance was obtained from the National Health Research Ethics Committee (NatHREC) of the Tanzanian National Institute for Medical Research (NIMR) with a certificate No. NIMR/HQ/R.8a/Vol.IX/4256. All participants were asked to provide written informed consent for their participation. Permission to conduct the study was sought from respective authorities in the selected regions, districts, and health facilities. Confidentiality of participant information was maintained during the data collection and analysis process. All experiments were performed in accordance with relevant guidelines and regulations.

Consent for publication Not applicable.

Competing interests All authors declare no competing interests.

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