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HIV infection modifies the relationship between distance to a health facility and treatment success rate for tuberculosis in rural eastern Uganda

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ABSTRACT

Rationale: Distance from residence to a health facility especially in rural areas presents a physical barrier and may influence tuberculosis (TB) treatment outcomes.
Objectives: We examined the association between distance from residence to a health facility and TB treatment outcomes namely treatment success rate (TSR) and mortality, and whether HIV influences this relationship among people with TB in Kumi district in rural eastern Uganda.
Methods: In this cross-sectional design, we abstracted data from TB unit registers across four large health facilities. Travel of ≥5 km to a health facility was considered a long distance. The primary outcome was TSR and the secondary was mortality. We performed a generalized linear model with Poisson distribution with a log-link and robust standard errors to determine the association between distance and the study outcomes adjusting for potential confounders. We report the adjusted risk ratio (aRR) and 95% confidence interval (CI).
Measurement and results: Of 611 participants studied, 484 (79.2%) were successfully treated, 18 (2.9%) died, and 359 (58.7%) travelled a long distance to access TB treatment. Long-distance was significantly associated with lower TSR (aRR, 0.93; 95% CI, 0.89–0.96). Further analysis showed that longer distance was associated with lower TSR among HIV positive persons with TB (aRR, 0.83; 95% CI, 0.72–0.96), but not among HIV negative persons with TB (aRR, 0.94; 95% CI, 0.85–1.03). Although it was not significant, longer distance showed a tendency towards worse mortality among HIV positive people with TB (aRR, 2.78; 95% CI, 0.80–9.66), but not among HIV negative people with HIV (aRR, 0.21; 0.03–1.74).
Conclusions: A majority of people with TB travel long distances to access treatment. Long distances are associated with lower TSR and higher mortality and affect people with TB who are HIV positive but not HIV negative. Interventions should focus on improving access to treatment for people with TB who travel long distances.

1. Introduction

Tuberculosis (TB) continues to cause considerable morbidity and mortality globally despite being preventable and curable. TB is ranked among the top 10 infectious disease killers in the world, with deaths exceeding that caused by human immunodeficiency virus (HIV). At the end of 2019, about 7.1 million people fell sick with TB, and almost 1.4 million died [1]. Although successful treatment of TB is important in preventing transmission, reducing relapse, and preventing drug-resistant TB [2], most TB control programs particularly those in sub-Saharan Africa do not achieve the WHO desired treatment success rate (TSR) of at least 90%. A recent meta-analysis of sub-Saharan Africa showed only 76% of persons with bacteriologically confirmed pulmonary TB (BC-PTB) were successfully treated between 2008 and 2018 [3].

Although distance presents a physical barrier and may influence TB treatment success, only limited studies have been done to examine its influence. Several studies have examined other factors that influence TSR such as age, HIV status, and the category of persons with TB, residence, and sex [4–6]. A recent study in Uganda showed distance may negatively influence treatment success but the evidence did not reach statistical significance [7]. In Ethiopia, one study showed that TB case notification and treatment success rates were lower where there was a long-distance between a health facility and patients' residence [8]. The negative effect of travel distance on treatment outcomes might be more

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pronounced in rural areas as patients travel long distances. In Kumi district, rural eastern Uganda, almost three in 10 people travel ≥5 km (km) to access a health facility, public or private [9]. The majority of people with TB usually walk to receive TB services at these health facilities and face physical and economic barriers [10]. A patient is required to make a minimum of eight visits during the 6-month treatment period, with four visits in the first two months and a monthly visit in the last four months.

The multiple visits and the long travel distances have the potential to negatively impact TB treatment outcomes. However, limited studies have been done to examine the influence of the long travel distances on treatment outcomes among people with TB in this setting and whether this relationship is influenced by HIV infection.

Therefore, the main objective of this study was to determine the association between distance from the place of residence to a health facility with TSR and mortality among people with TB in Kumi district in rural eastern Uganda. We hypothesized that longer travel distances have negative effects on TSR and mortality among people with TB in this setting and that persons with HIV might be adversely affected by long distances. Understanding the influence of travel distances on TB treatment outcomes is important in generating evidence that might inform the district and the national TB control program in designing interventions for improved treatment outcomes among people with TB.

2. Methods and materials

2.1. Study setting

This study was conducted in Kumi district in eastern Uganda, a predominantly rural setting about 240 km from Kampala, the capital city. The district has about 239,268 people living according to the most recent census data, and 48.8% of the population is male [11]. We collected data at four health facilities that had high patient numbers, namely ≥100 persons with TB per year [12]. The study sites included the four largest health facilities in the district. These are Atutur and Kumi district hospitals and the two health centers (HC) of Kumi HC IV and Kanyum HC III. Kumi hospital is a private-not-for profit (PNFP) health facility while the rest are public or government-owned health facilities.

Each health facility has a district TB unit headed by a medical, clinical, or nursing officer. The district TB units provide TB diagnostic, treatment, and prevention services per the Uganda national TB control program guidelines.

2.2. Study design and measurements

We abstracted data from TB unit registers for the period 2015 to 2019. We used the data to conduct a cross-sectional study. We reported the findings of the study per the Standards for Reporting of Observational Studies in Epidemiology (STROBE) guidelines [13]. Our study population consisted of adult (≥15 years) persons with TB, whether new or previously treated in the period January 01, 2015, and March 30, 2019. Specifically, we considered persons with bacteriologically confirmed pulmonary TB (BC-PTB), clinically diagnosed pulmonary TB (CD-PTB), and extrapulmonary TB (EPTB). We excluded children and persons with drug-resistant TB because their treatment is highly specialized and they are treated at specialized treatment centers.

We abstracted demographic and clinical data like age in years and categorized them into various age bands of 15–24 years to reflect adolescent and young adults, 25–50 years for mid-age, and >50 years for older persons. The other demographic and clinical data included sex, type of persons with TB, TB/HIV comorbidity, year of treatment, the form of directly observed therapy (DOTs), and availability of treatment supporter. The treatment supporters' role includes providing reminders and encourage people with TB to bring sputa for follow-up testing, supporting treatment adherence and completion, providing emotional and physical support, and reminding people with TB about health facility visits and escorting them to health facilities [14].

The health facility-related data included the level of health facility, location of health facility, the distance between the participants' residence and health facility as <5 km versus ≥5 km, and type of health facility ownership. The treatment outcome data included cure, treatment completion, treatment failure, died, loss to follow-up, and treatment not evaluated, all defined per the WHO guideline (Supplementary material I).

Our primary outcome was TSR defined as persons with TB who have treatment outcomes of cure or treatment completed, and all the other treatment outcomes were regarded as unsuccessful treatment. The secondary outcome was all-cause mortality during TB treatment. The exposure was travel distance to a health facility classified as long-distance if patients travelled 5 km or more to a health facility to receive TB treatment. This cutoff of 5 km was based on the Uganda National Health Policy framework that aims to achieve universal access to basic health care package [15]. Accordingly, the population that lives within a 5 km radius to a health facility is considered to have accessible healthcare while that living 5 km and beyond are regarded to have difficult access to healthcare [16].

2.3. Statistical analysis

Data were entered in Epi-Data version 3.1 with quality control measures namely skip patterns, alerts, range, and legal values then exported to R statistical software version 4.0.2 for analysis using 5% as the level of statistical significance. We computed TSR as the percentage of persons with TB registered under DOTs in a particular year that completed treatment, whether with bacteriologic evidence of success (cured) or without (treatment completed). In the bivariate analysis, we cross-tabulated categorical variables by distance using either the Chi-square or Fisher's exact as statistical tests. For numerical variables, the *t*-test was used to assess mean differences.

We also performed a stratified analysis using the Mantel-Haenszel approach to establish whether the association between distance and the study outcomes was either modified or confounded by a third variable. In this analysis, we compared the stratum-specific measures of effect to detect effect modification and the unadjusted versus adjusted measures of effect to detect confounding. A test of homogeneity p-value <0.05 was considered suggestive of effect modification. In the absence of confounding, we reported the unadjusted measure of effect while for effect modification, we reported the separate stratum-specific measures of effect.

In the multivariate analyses, a generalized linear model (GLM) with Poisson distribution and log-link and robust standard errors was fitted to include the variables that showed statistical significance at the bivariate analysis. We report the results as adjusted risk ratio (aRR) with their 95% confidence interval (CI). We preferred the RR over the odds ratio (OR) because the outcome was large so the latter would overestimate the degree of association [17]. To prevent the violation of Poisson regression analysis assumptions [18], robust standard errors were used in the GLM analyses.

2.4. Ethical considerations

Our study received ethical review and approval from Clarke International University Research Ethics Committee (CIU-REC), with the approval number CIUREC/0164. Besides, we obtained administrative approval from the District Health Office. To ensure the anonymity of participant data, the research team had access only to the de-identified data.

3. Results

3.1. Characteristics of study participants

We studied 611 participants. The average age of the participants was 44.7 years, with a standard deviation of 16.9 years and 367 (60.1%) were females. We found 359 (58.7%) participants travel longer distances to access TB treatment, 484 (79.2%) achieved TSR, while 18 (2.9%) died. Table 1 summarizes the distribution of participant's characteristics stratified by distance to a health facility. Participants who travelled longer distances were on average older than those who travelled shorter distances: 46.1 ± 16.4 years versus 42.9 ± 16.9 years, $p = 0.018$.

A greater proportion of participants who travelled longer distances were aged 25–50 years (52.4%), males (57.9%), newly diagnosed with TB (85.5%), had CD-PTB (47.5%), and less likely to have HIV infection (69.6%). Our data show significant differences in TSR between participants who travelled longer distances (75.8%) compared to those who travelled shorter distances: 75.8% versus 84.1%, $p = 0.016$, respectively. Conversely, the proportion of mortality was similar between participants who travelled for longer distances compared to those who travelled for shorter distances: 12 (3.3%) versus 6 (2.4%), $p = 0.653$, respectively.

Table 1 further shows that participants who travelled longer distances were systematically different from those who travelled shorter distances concerning study site, and level and location of the health facility, and tuberculosis treatment outcomes. However, the participants were similar with regards to age categories, sex, types of persons with TB, the form of TB, TB/HIV status, types of DOTs, year of treatment, availability of a treatment supporter, and type of health facility ownership.

3.2. Association between distance and TSR among persons with TB

In the unadjusted analysis (Table 2), participants who travelled longer distances compared to those who travelled shorter distances were significantly less likely to achieve TSR (RR, 0.95; 95% CI, 0.92–0.99). However, those older than 50 years compared to 15–24 years (RR, 1.09; 95% CI, 1.02–1.16), and those who received TB treatment at a district hospital compared to HC III (RR, 1.09; 95% CI, 1.01–1.18) were significantly more likely to achieve TSR. TB/HIV comorbidity (RR, 0.99; 95% CI, 0.95–1.03), previous TB treatment (RR, 0.99; 95% CI, 0.0.94–1.05), having a TB treatment supporter (RR, 0.98; 95% CI, 0.94–1.05), and receipt of TB treatment at a peri-urban (RR, 1.02; 95% CI, 0.98–1.06) or PNFP health facility (RR, 1.03; 95% CI, 1.00–1.07) were not associated with TSR.

After adjusting for age categories and level of health facility, our data show that participants who travelled longer distances had 7% lower TSR compared to those who travelled shorter distances, with an adjusted risk ratio (aRR) of 0.93 (95% CI, 0.89–0.96). Participants older than 50 years compared to 15–24 years (aRR, 1.10; 95% CI, 1.03–1.17), and those who received TB treatment at a district hospital compared to HC III (aRR, 1.14; 95% CI, 1.05–1.23) were significantly more likely to achieve TSR.

3.3. Stratified analysis for the association between distance and mortality among persons with TB

In a stratified analysis, our data show that the association between distance and mortality was modified by HIV status (Homogeneity test, Chi-square value = 4.08, $p = 0.043$). The results for the stratified analysis are shown in Table 3. HIV modifies the relationship between distance and mortality. Among HIV-negative people with TB, long distances were associated with lower mortality but were associated with a higher risk for mortality among HIV-positive persons with TB. Age, level, and location of health facility did not demonstrate any significant effect modification.

Table 1
Table shows the general characteristics and treatment outcomes of study participants by distance to a health facility.

Characteristics	Level	All (n = 611)	Distance to a health facility		P value
			Shorter distances (n = 252)	Longer distances (n = 359)	
Age categories	15–24	76 (12.4)	39 (15.5)	37 (10.3)	0.151
	25–50	316 (51.7)	128 (50.8)	188 (52.4)	
	>50	219 (35.8)	85 (33.7)	134 (37.3)	
	mean (SD)	44.7 (16.7)	42.9 (16.9)	46.1 (16.4)	0.018
Sex	Male	367 (60.1)	159 (63.1)	208 (57.9)	0.231
	Female	244 (39.9)	93 (36.9)	151 (42.1)	
Type of persons with TB	New	529 (86.6)	221 (87.7)	308 (85.8)	0.576
	Previously treated	82 (13.4)	31 (12.3)	51 (14.2)	
Form of TB	BC-PTB	299 (48.9)	132 (52.4)	167 (46.5)	0.358
	CD-PTB	274 (44.8)	105 (41.7)	169 (47.1)	
	EPTB	38 (6.2)	15 (6.0)	23 (6.4)	
Person with TB/HIV	No	413 (67.6)	163 (64.7)	250 (69.6)	0.230
	Yes	198 (32.4)	89 (35.3)	109 (30.4)	
Year of treatment	2015	98 (16.0)	45 (17.9)	53 (14.8)	0.396
	2016	98 (16.0)	45 (17.9)	53 (14.8)	
	2017	164 (26.8)	67 (26.6)	97 (27.0)	
	2018	251 (41.1)	95 (37.7)	156 (43.5)	
Has treatment supporter	No	190 (31.1)	71 (28.2)	119 (33.1)	0.223
	Yes	421 (68.9)	181 (71.8)	240 (66.9)	
Type of DOTS	Community	605 (99.0)	247 (98.0)	358 (99.7)	0.091
	Facility	6 (1.0)	5 (2.0)	1 (0.3)	
Study site	A	275 (45.0)	67 (26.6)	208 (57.9)	<0.001
	B	46 (7.5)	32 (12.7)	14 (3.9)	
	C	119 (19.5)	91 (36.1)	28 (7.8)	
	D	171 (28.0)	62 (24.6)	109 (30.4)	
Level of health facility	HC III	48 (7.9)	34 (13.5)	14 (3.9)	<0.001
	HC IV	121 (19.8)	91 (36.1)	30 (8.4)	
	District Hospital	442 (72.3)	127 (50.4)	315 (87.7)	
Location of health facility	Rural	321 (52.5)	99 (39.3)	222 (61.8)	<0.001
	Peri-urban	290 (47.5)	153 (60.7)	137 (38.2)	
Type of health facility ownership	Public	440 (72.0)	190 (75.4)	250 (69.6)	0.142
	PNFP	171 (28.0)	62 (24.6)	109 (30.4)	
Treatment outcome	Cured	118 (19.3)	62 (24.6)	56 (15.6)	0.003
	Treatment completed	366 (59.9)	150 (59.5)	216 (60.2)	
	Died	18 (2.9)	6 (2.4)	12 (3.3)	

(continued on next page)

Table 1 (*continued*)

Characteristics	Level	All (n = 611)	Distance to a health facility		P value
			Shorter distances (n = 252)	Longer distances (n = 359)	
	Treatment failed	4 (0.7)	3 (1.2)	1 (0.3)	
	Lost to follow-up	30 (4.9)	13 (5.2)	17 (4.7)	
	Treatment not evaluated	75 (12.3)	18 (7.1)	57 (15.9)	
Treatment success	No	127 (20.8)	40 (15.9)	87 (24.2)	0.016
	Yes	484 (79.2)	212 (84.1)	272 (75.8)	

Table 2
Table showing the association between distance and TSR among persons with TB at unadjusted and adjusted analyses.

Characteristics	Level	Generalized linear model analyses			
		Unadjusted analysis		Adjusted analysis	
		RR	95% CI	aRR	95% CI
Distance to a health facility	< 5 km	1		1	
	≥ 5 km	0.95**	(0.92,0.99)	0.93***	(0.89,0.96)
Age categories	15–24	1		1	
	25–50	1.02	(0.95,1.08)	1.02	(0.96,1.09)
	>50	1.09**	(1.02,1.16)	1.10**	(1.03,1.17)
Person with TB/HIV	No	1			
	Yes	0.99	(0.95,1.03)		
Type of persons with TB	New	1			
	Previously treated	0.99	(0.94,1.05)		
Treatment supporter available	No	1			
	Yes	0.98	(0.94,1.02)		
Level of health facility	HC III	1		1	
	HC IV	1.06	(0.97,1.16)	1.08	(0.99,1.18)
	District Hospital	1.09*	(1.01,1.18)	1.14**	(1.05,1.23)
Location of health facility	Rural	1			
	Peri-urban	1.02	(0.98,1.06)		
Type of health facility ownership	Pubic	1			
	PNFP	1.03	(1.00,1.07)		
Study sites	A	1			
	B	0.93	(0.86,1.02)		
	C	0.99	(0.94,1.04)		
	D	1.02	(0.98,1.07)		

Note: 1) All the risk ratios are exponentiated coefficients with 95% confidence intervals in brackets; 2) * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ at 5% significance level; 3) RR: Crude risk ratio; 4) aRR: Adjusted risk ratio.

In the adjusted analysis, our data show that long-distance was associated with a tendency towards a lower risk of mortality among HIV negative persons with TB (aRR, 0.21; 0.03–1.74), but an almost three-fold higher risk of mortality among HIV positive persons with TB (aRR, 2.78; 95% CI, 0.80–9.66). Also, the longer distance was associated with the tendency to lower TSR among HIV negative persons with TB (aRR, 0.94; 95% CI, 0.85–1.03), but with 17% lower TSR among HIV positive persons with TB (aRR, 0.83; 95% CI, 0.72–0.96).

4. Discussion

Our study focused on determining whether travel distance from the place of residence to a health facility has an association with TSR and mortality among persons with TB in Kumi district in rural eastern Uganda. Our data show that the majority of people with TB travel longer

Table 3
Relationship between distance and study endpoints among people with TB with analysis stratified by HIV status.

Study endpoints	Subgroup	Crude RR (95% CI)	Adjusted RR (95% CI)$
Mortality	Among HIV negative persons (n = 413)	0.22 (0.02–2.08)	0.21 (0.03–1.74)
	Among HIV positive persons (n = 198)	2.99 (0.86–10.44)	2.78 (0.80–9.66)
TSR	Among HIV negative persons (n = 413)	0.94 (0.85–1.03)	0.94 (0.85–1.03)
	Among HIV positive persons (n = 198)	0.83** (0.72–0.96)	0.83* (0.72–0.96)

Note: 1) $: Adjusted for distance, age, and location of health facility; 2) All risk ratios are exponentiated coefficients with the 95% confidence intervals in brackets; 3) * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ at 5% significance level; 4) RR: Crude risk ratio; 5) aRR: Adjusted risk ratio.

distances to access treatment, and longer travel distance is associated with reduced TSR and a tendency towards increased mortality. The finding that people with TB who travel long distances to access treatment have decreased TSR is consistent with several studies [19–22]. Consistent with our findings, previous studies have reported that people with TB who reside in urban areas tend to have better TSR compared to those in rural areas [21,23–25].

In our study, the majority of those who travelled long distances are rural residents while those who travelled shorter distances are peri-urban residents. Our findings imply that longer travel distances tend to reduce access to and use of existing health services as well as continuity of care. It is therefore likely for people with TB who travel longer distances to frequently experience treatment interruptions that lead to compromised treatment adherence and ultimately low TSR. In agreement with these findings, a recent study in eastern Uganda reports that people with TB face physical and economic barriers that limit their access to and use of existing TB services [14]. Furthermore, our data show a tendency towards increased mortality among people with TB who travel long distances to receive treatment although the association did not reach statistical significance, however, the association did not reach statistical significance. This could be attributed to the relatively small sample size. We anticipate that with a larger sample size, this finding might be significant. This result is consistent with the findings of an earlier study in Kampala, Uganda that report a trend towards increased mortality among people with TB who travel ≥2 km to receive treatment compared to those who travel <2 km [7].

Longer travel distances might have caused discontinuity of TB care hence the trend towards increased mortality.

HIV modifies the effect of long-distance on mortality. Our data show that among HIV-negative people with TB, long distance was associated with a lower risk of mortality, but among those with TB/HIV, there seemed to be a higher risk for mortality for those traveling longer distances although the relationship did not reach statistical significance. The data suggest that longer distances affect people with TB/HIV more than those without HIV, probably due to complex interaction between HIV and TB, with each disease influencing the other's progression, severity, and response to treatment [26,27], notwithstanding travel distance. Besides, people with TB/HIV who have difficult access to health facilities do not comply with TB treatment [28] and this exacerbates their risk of mortality [29,30]. The risk of mortality further worsens with an increase in the number of barriers, namely physical and economic barriers [29]. Besides, the trend towards increased mortality in people with TB/HIV might have resulted from limited access to HIV care. Although efforts are in place to strengthen TB/HIV collaborative activities across most health facilities in Uganda, the majority of the TB units do not provide comprehensive HIV services to people with TB. Therefore, there is a possibility that a long distance from a place of residence to a TB treatment unit might also reflect a long distance to HIV

care. However, this data is not included in the current analysis and should be considered in prospective studies to strengthen the body of evidence.

Overall, our findings suggest the need to take deliberate measures in improving access to TB treatment thereby reducing the negative effects of longer travel distances on TSR and mortality among people with TB.

Notable interventions might include initiating mobile or decentralized TB clinics and targeted home-based TB care. In particular, a mobile pharmacy for TB treatment is a great possibility to address physical barriers. One study conducted in western Uganda demonstrated that a mobile anti-retroviral therapy (ART) pharmacy for people living with HIV remarkably improves ART adherence and viral load suppression [31]. This novel intervention should be replicated in settings with longer travel distances to improve access to TB treatment and ultimately increase TSR and reduce mortality. Consistent with a previous study [28], decentralizing TB diagnosis and treatment to lower-level health facilities is another option. Programmatically, the negative effects of longer travel distances on TSR and mortality should be a central concern for the district and national TB control programs since it undermines progress towards attaining the 2030 End TB Strategy goals of reducing TB incidence by 80%, mortality by 90%, and catastrophic expenses incurred by affected families to zero percent [1].

Our data show that a large majority of people with TB received treatment under the community-based DOTS (605 or 99.0%) compare to the facility-based DOTS (6 or 1.0%) which did not permit us to make a balanced comparison between the two approaches of DOTS. Although the community-based DOTS appears to be extensively implemented, distance remains a significant barrier to achieving TSR.

4.1. Study strengths and limitations

This study has some strengths. Our study is among the few to demonstrate the influence of travel distance on TSR and mortality among people with TB in resource-limited settings and to demonstrate the modifying effect of HIV. The data analysed covered 4 years and the study was sufficiently powered to demonstrate an association.

We applied the WHO standard definitions to define our outcomes thus reducing erroneous assignment of treatment outcomes to the study participants. However, there are limitations to consider. We analysed secondary data hence other potential confounders like baseline weight at TB treatment initiation and levels of adherence to TB treatment including several socioeconomic, cultural, and certain health systems factors that influence the study outcomes were not studied. The study was conducted in primarily a rural setting so the findings might not be generalizable to urban settings. Although data about sputum smear conversions were verified using the laboratory register to ascertain cure, we used routine data in the TB unit registers which may be prone to errors and missing values encountered in routine care settings in resource-limited settings. Poor outcomes from TB treatment may be secondary to limited access to HIV care, and this is not included in the analysis. We did not have access to standard measures of HIV disease progression, namely viral load, CD4 counts, access to ART, and hospitalization rates among others. This is a limitation in our analysis because these factors drive mortality among persons with TB. Our study also assumed that mortality resulted from TB or a related complication. However, the exact cause of death in this study is not known.

4.2. Conclusions and recommendations

Our study shows that a majority of people with TB travel long distances to access treatment in rural eastern Uganda, and longer travel distances are associated with lower TSR and higher mortality. HIV modifies the effect of long-distance on mortality. Interventions should thus focus on improving access to TB treatment among people with TB who travel long distances.

Ethics statement

Our study received ethical review and approval from Clarke International University Research Ethics Committee (CIU-REC), with the approval number CIUREC/0164. We obtained administrative approval from the District Health Office. To ensure the anonymity of participant data, the research team had access only to the de-identified data.

Declarations of interests

None.

Conflict of interest

None declared.

CRediT authorship contribution statement

Ben Olupot: Conceptualization, Data curation, Project administration. **Norbert Adrawa:** Validation, Writing - original draft. **Francis Bajunirwe:** Formal analysis, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Jonathan Izudi:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2021.100226.

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