

# The Burden of Drug Resistant Tuberculosis in a predominantly nomadic population in Uganda. A Mixed Methods Study

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## Research Article

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## Abstract

**Background:** Emergence of Drug Resistant Tuberculosis (DR-TB) has aggravated the Tuberculosis (TB) public health burden worldwide and especially in low income settings. We present findings from a predominantly nomadic population in Karamoja, Uganda with a high-TB burden (3,500 new cases annually) and sought to determine the prevalence, patterns, factors associated with DR-TB.

**Methods:** We used mixed methods of data collection. We enrolled 6890 participants who were treated for tuberculosis in a programmatic setting between January 2015 and April 2018. A cross sectional study and a matched case control study with conditional logistic regression and robust standard errors respectively were used to determine prevalence and factors associated with DR-TB. The qualitative methods included focus group discussions, in-depth interviews and key informant interviews.

**Results:** The overall prevalence of DR-TB was 41/6890 (0.6%) with 4/64197 (0.1%) among the new and 37/2693 (1.4%) among the previously treated TB patients respectively. The drug resistance patterns observed in the region were mainly rifampicin mono resistant (68.3%) and Multi Drug-Resistant Tuberculosis (31.7%). Factors independently associated with DR-TB were previous TB treatment, adjusted odds ratio (aOR) 13.070 (95%CI: 1.552 – 110.135) and drug stock-outs aOR 0.027 (95%CI: 0.002-0.364). The nomadic lifestyle, substance use, congested homesteads and poor health worker attitudes were a great challenge to effective treatment of TB.

**Conclusion:** Despite having the highest national TB incidence, Karamoja still has a low DR-TB prevalence. Previous TB treatment and drug stock outs were associated with DR-TB. Regular supply of anti TB medications and health education may help to stem the burden of TB disease in this nomadic population.

## Background

Worldwide Tuberculosis (TB) is one of the leading infectious diseases with the highest case fatality rate (1). In Sub Saharan Africa, drug resistance is becoming a great challenge in the fight against TB (2). Multidrug-resistant tuberculosis (MDR-TB) a global public health problem, is caused by TB bacteria that is resistant to at least isoniazid and rifampicin (3). DR-TB is transmitted through air from person to person but may sometimes develop when the bacteria becomes resistant to the drugs used to treat TB as a result of poor adherence to or wrong prescription of TB treatment (4). In many countries, treatment of MDR-TB is more than 7 times the treatment of susceptible TB and this may deter effectiveness of TB control programs (5, 6), this is because MDR-TB involves expensive second-line regimens given the prolonged treatment, but it poses serious financial challenges for families and health systems as a whole, especially in sub-Saharan Africa with economically constrained settings (7). The World Health Organization (WHO) anti-TB drug resistance surveillance data shows that there's an increasing number of new and previously treated TB cases in the world that have rifampicin or multidrug-resistant tuberculosis (8). The latest treatment outcome data shows over half of the MDR/RR-TB patients who start treatment are successful, mortality rate is at 18%, and those that fail on treatment are 8%. The treatment success in XDR-TB patients is a third. In 2016, WHO reported about 600,000 new cases of MDR/RR-TB and a Case fatality rate of 40% globally, 6.2% of these cases had extensively drug-resistant TB (XDR-TB). In the same period TB was responsible for 1.3 million HIV-negative and 374,000 HIV-positive deaths globally (9). This indicates TB is fatal and prevention efforts should be emphasized. Karamoja, in north-eastern Uganda, is considered by many a "hard to reach" sub-region(10). It is characterised by cattle rustling, insecurity from armed nomadic tribes, a semi-arid climate and a few economic activities (10) of which the local community has not been involved extensively. For years, infrastructure including roads, healthcare facilities and

adequate water had been specially lacking, making the sub-region the least socially and economically developed in Uganda(11). Karamoja is the region with the highest incidence of TB in Uganda(12) with 3,500 new cases identified and treated every year including increasing cases of MDR (13). Unfortunately, this is due to people who stop their treatment early. An estimated 40% of the TB patients fail to complete their course of treatment and abandon health care facilities (12, 13). The cost of treating a patient for drug-susceptible TB is estimated to be 258 US dollars in Uganda, however treating an MDR patient can cost more than 1,200 US dollars (14) which is beyond the reach of the average Ugandan(15). Some of the specific risk factors for TB in nomadic populations include poor living conditions (small and crowded Manyattas), Poor adherence due to the long distances travelled while raring cattle, TB knowledge gaps (16), higher perceived stigma (17), working conditions associated with high risk of TB transmission like working in the mines with crowded spaces and poor ventilation (18); and other factors such as diseases that damage immunity, malnutrition, smoking, and alcohol abuse (19) (13). Although a national survey on drug resistance prevalence, patterns and associated has been done(20), among nomadic populations in Uganda the patterns and associated factors of DR TB have not been documented. There still exist substantial knowledge gaps on anti-TB-drug resistance that ought to be addressed. It's therefore important that the burden and risk factors of DR-TB in nomadic populations are determined in order to inform policy makers of status of this community and the existing gaps in programming for their DR TB prevention needs. This study aimed to determine the prevalence, patterns and factors associated with and factors influencing DR-TB in a predominantly nomadic population in Uganda.

## **Materials and Methods**

We obtained ethical approval from the Research and Ethics Committees of Makerere University College of Health Sciences, Kampala. All patients who participated in the study gave written informed consent and a waiver of consent to access secondary data.

### **Study design**

We conducted a mixed methods study; a baseline cross sectional study was done using secondary data of 6890 TB patients reported in Karamoja region by the Uganda National Tuberculosis and Leprosy Control Programme from January 2015 to April 2018 to determine the prevalence and patterns of drug resistance. We then carried out a matched case control study and qualitative study concurrently to determine the factors associated with drug resistance among 41 DR-TB and 164 randomly selected susceptible TB patients. All sputum smear-positive patients who were registered for treatment during the enrolment period of all ages and consented to participate were enrolled.

### **Data Collection and management**

For each participant we collected the following information; social demographic characteristics, HIV status, nutrition status at diagnosis, history of TB treatment, disease classification and drug stock outs in facilities where patient was getting treatment using the health facility TB registers and anti TB drug stock cards used from January 2015 to April 2019. For the qualitative study we also obtained data about risk factors for anti-TB drug resistance including the number of people living and sleeping in a Manyatta, adherence to medication (measured by number of patients receiving proper DOT), health worker attitudes and substance use.

We defined a case as a TB patient with sputum culture positive for *Mycobacterium tuberculosis*, resistant to at least isoniazid and rifampicin and a control as a sputum smear-positive drug-susceptible TB patient.

We carried out 3 focus group discussions with the DR-TB patients and 2 focus group discussions with the health workers, 10 key informant interviews with TB district and facility health workers, structured interviews on 20 (10%) participants randomly selected from the enrolled patients within 4 weeks. Interviews were conducted by staffs that were independent of the clinic where data was collected and blinded to the group of participants.

### **Study variables**

#### **Dependent variable**

The Primary outcome in this study was Drug resistance to anti – TB drugs. It was measured as a categorical variable

#### **Independent variables**

**Patient Socio-demographic factors:** Age, Sex, marital status of the cases and control. These were measured as a categorical variables. Residence of the cases and controls; was measured as a continuous variable

**Clinical factors:** Type of patient, HIV status, Nutrition status, Disease classification of the subjects and these were measured as categorical variables.

**Drug related factors:** Drug stock out; this was measured as a categorical variable to determine whether a health facility had any TB drug stock outs in the period between Jan 2015 and January 2018

**Substance use:** Use of Alcohol, Herbal medicines, smoking status of the subjects were measured as categorical variables.

**Patient related factors:** Nutrition status of the subjects was measured as a categorical variable.

## **Data analysis**

For comparison of categorical variables, we used the  $X^2$  test or the 2-sided Fishers' exact test as appropriate. Univariate and multivariable analyses were done by conditional logistic regression. All significance testing was done at 5% confidence level. For qualitative data, we undertook thematic-content analysis for the qualitative data using Open code version 4.2.1 to generate themes from the interviews and followed by interpretation of the data generated.

## **Data Management**

Interviews were recorded, transcribed and analysed using open code. Quantitative data was double entered, cleaned, and edited in a statistical software EpiData version 3.1 and thereafter exported to STATA version 13.0. Adjustment was made for the effect of clustering in the data and all statistical analysis performed using STATA version 13.0. Discrepancies were checked against the raw data.

All methods were performed in accordance with the relevant guidelines and regulations under the declaration of Helsinki.

## Study participants flow chart

A total of 6890 people were reported to have received treatment for Tuberculosis in the period between January 2015 and April 2018. Of these 41 patients were found to have drug resistant tuberculosis. All the 41 patients and 164 controls were included in our study as showed in figure 1

The analysis was completed on 41 cases and 164 controls.

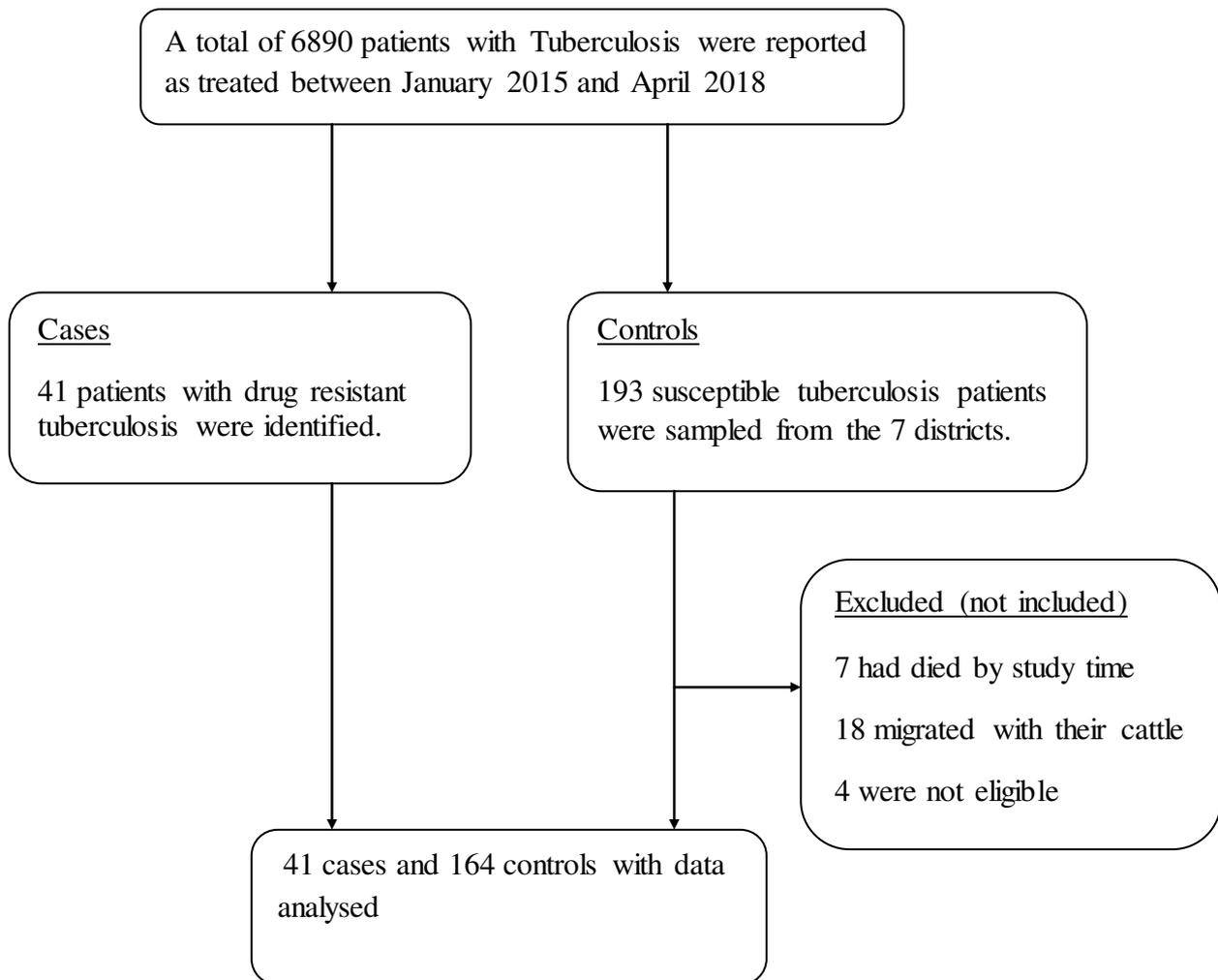


Figure1. Patient flow chart during the study in Karamoja region, 2018

## Results

The prevalence of DR-TB among patients with TB in Karamoja region in the period between January 2015 and April 2018 was 0.6%. Results of DR-TB are summarised in Table 1.

Table 1. Prevalence of Drug resistant tuberculosis among Patients with Tuberculosis in Karamoja region in the period between January 2015 and April 2018

Variable	Frequency(n)	Percentage (%)
<b>Overall</b>		
<b>n = 6890</b>	41	0.60
<b>According to Patient type</b>		
<b>New (n=4197)</b>	4	0.1
<b>Previous TB treatment (n=2693)</b>	37	1.4
<b>Age</b>		
<b>&lt;= 9 years (n = 756)</b>	1	0.1
<b>10 – 19 years (n = 1268 )</b>	5	0.4
<b>20 – 59 years (n = 4134)</b>	29	0.7
<b>&gt;= 60 years (732)</b>	6	0.8
<b>Sex</b>		
<b>Male (n = 4479)</b>	19	0.4
<b>Females (n = 2411)</b>	22	0.9
<b>District of Residence</b>		
<b>Abim (n = 584)</b>	2	0.03
<b>Amudat (n = 150)</b>	1	0.07
<b>Kaabong (n = 823)</b>	4	0.05

<b>Kotido (n = 721)</b>	6	0.08
<b>Moroto (n = 1523)</b>	2	0.01
<b>Nakapiripirit (n = 1161)</b>	16	0.14
<b>Napak (n = 1928)</b>	10	0.05

Among the TB patients with drug resistance in region, majority 28 (68.3%) had rifampicin mono-resistance while 13 (31.7%) had MDR-TB in Karamoja as summarised in Table 2.

**Table 2. Patterns of drug resistance among patients with Tuberculosis in Karamoja region between January 2015 and April 2018**

<b>Characteristics</b>	<b>RR n (%)</b>	<b>MDR n (%)</b>
<b>Overall</b>		
<b>Frequency (n)</b>	28 (68.3)	13 (31.7)
<b>Age</b>		
<b>&lt;= 19 years</b>	5 (17.9)	1(7.7)
<b>20 – 59 years</b>	21 (75.0)	8 (61.5)
<b>&gt;=60 years</b>	2 (7.1)	4 (0.3)
<b>Sex</b>		
<b>Males</b>	13 (46.4)	6 (46.2)
<b>Females</b>	15 (53.6)	7(53.8)
<b>Districts</b>		
<b>Abim</b>	0 (0.0)	2 (15.4)
<b>Amudat</b>	1 (3.6)	0 (0.0)
<b>Kaabong</b>	2 (7.1)	2 (15.4)
<b>Kotido</b>	4 (14.3)	2 (15.4)

<b>Moroto</b>	1 (3.6)	1 (7.7)
<b>Nakapiripirit</b>	13 (46.4)	3 (23.1)
<b>Napak</b>	7 (25)	3 (23.1)

The median age of participants was 37.5 years (interquartile range (IQR) 25 ranging from 6 to 80 years with more females (53.7%) having TB. The greatest proportion of TB patients (39%) was from Nakapiripirit district and was among married participants. A large percentage of the participants had a previous history of TB and was malnourished. Substance use was high among the participants and a small proportion (2.4%) had HIV. Most of the participants received services from a health centre that had at least one TB drug stock-out as shown in Table 3.

**Table 3. Characteristics of Demographic, Social Economic, and health services-related factors for 41 Cases and 164 Controls in Karamoja region between January 2015 and April 2018**

Characteristics	Frequency (n)	Percentage (%)	P-value
	Cases (N = 41)	Controls (N = 164)	
<b>Marital status</b>			
Married n (%)	26 (63.4)	126 (76.8)	0.034
Not married n (%)	15 (36.6)	38 (23.2)	
<b>Personal Health-related factors</b>			
<b>Category of patient</b>			
New n (%)	4 (9.8)	156 (95.1)	<0.001
Previous TB treatment n (%)	37 (90.2)	8 (4.9)	
<b>HIV status</b>			
Negative n (%)	39 (95.1)	156 (95.1)	1.000
Positive n (%)	2 (4.9)	8 (4.9)	
<b>Malnutrition</b>			
Yes n (%)	24 (58.5)	82 (50.0)	0.363
No n (%)	17 (41.5)	82 (50.0)	
<b>Disease classification</b>			
PTB n (%)	40 (97.6)	120 (73.2)	0.011
EPTB n (%)	1 (2.4)	44 (26.8)	
<b>Substance use</b>			

Yes n (%)	40 (97.6)	95 (57.9)	0.001
No n (%)	1 (2.4)	69(42.1)	
<b>Health services factors</b>			
Drug Stock out			
Yes n (%)	36 (87.8)	36 (22.0)	<0.001
No n (%)	5 (12.2)	128 (78.0)	

Marital Status (OR = 3.16), disease classification (OR = 17.09), category of TB patient (OR = 7.199) and substance use (OR = 1.798) and were found significantly associated with DR-TB. Among the health services factors, only drug stock out (OR = 0.023) was found significant as shown in table 4.

**Table 4. Bivariate analysis between independent factors and Drug resistant tuberculosis**

Variable	DR-TB		OR	95% CI	P
	Cases n (%)	Controls n (%)			
<b>Socio-demographic factors</b>					
<b>Marital status</b>					
Married	26 (63.4)	126 (76.8)	1		
Not married	15 (36.6)	38 (23.2)	3.16	1.09 – 9.14	<b>0.034</b>
<b>Clinical factors</b>					
<b>Category of patient</b>					
New	4 (9.8)	156 (95.1)	1		
Previous TB treatment	37(90.2)	8 (4.9)	7.20	3.47 – 14.91	<b>&lt;0.001</b>
<b>HIV status</b>					
Negative	39 (95.1)	156 (95.1)	1		
Positive	2 (4.9)	8 (4.9)	1	0.26 – 6.22	1
<b>Malnutrition</b>					
Yes	24 (58.5)	82 (50.0)	1		
No	17 (41.5)	82 (50.0)	1.44	0.66 – 3.16	0.363
<b>Substance use</b>					
No	1 (2.4)	31 (18.9)	1		
Yes	28 (68.3)	126 (76.8)	38.23	4.34 – 336.36	<b>0.001</b>
<b>Health services factors</b>					
<b>Drug Stock out</b>					

<b>No</b>	5(12.2)	128(78.0)	1		
<b>Yes</b>	36 (87.8)	36 (22.0)	43.97	10.43 – 185.37	<b>&lt;0.001</b>

In the CLR model, the aOR of two risk factors were found statistically significantly associated with DR-TB namely, category of patient and drug stock out. Among these patients, people with the risk was 70% lower among people who were getting treatment from facilities with no TB drug stock out compared to people who were getting treatment from facilities with TB drug stock outs. Substance use was found to confound drug stock out as shown in table 5.

**Table 5 . Multivariate analysis of independent factors and Drug resistant Tuberculosis in Karamoja**

<b>Variable</b>	<b>Cases n (%)</b>	<b>Controls n (%)</b>	<b>OR</b>	<b>95% CI</b>	<b>P</b>
<b>Predictors of DR-TB</b>					
<b>Category of patient</b>					
<b>New</b>	4(9.8)	156(95.1)	1		
<b>Previous TB treatment</b>	8(19.5)	4(2.4)	5.51	1.74 – 17.44	0.004
<b>Drug stock out</b>					
<b>No</b>	5(12.2)	128(78.0)	1		
<b>Yes</b>	36 (87.8)	36 (22.0)	20.1	3.62 – 112.57	0.001
<b>Confounders</b>					
<b>Substance use</b>					
<b>No</b>	1(2.4)	31(18.9)	1		
<b>Yes</b>	28 (68.3)	126 (76.8)	3.35	0.44 – 25.7	0.246

## **Qualitative findings**

### **The key themes that emerged from the qualitative analysis**

#### **Drug resistance is still a big problem.**

Drug resistance is a big issue among the nomadic in Karamoja and the numbers reported are much less than the actual numbers. This is because of the long distances travelled to access health services, poor retention, patients with TB who do not report to health facilities at all and their nomadic life style.

#### **Retention in care for susceptible TB patients is still poor.**

Retention in care for susceptible TB patients is very poor. There rate of lost to follow up and treatment failure is very high in the region.

#### **Too much Substance use**

Many of the adults take alcohol in their free time and community hours in the evenings while the pastoralists smoke a lot to keep warm. In addition many believe you have you use traditional herbs to get well.

#### **Poor adherence to TB medication**

There is very poor adherence especially when patients leave hospital to return home and when they go to the kraals. The community-based DOT is not yet functional.

#### **Lack of equipment and drug stock out**

Most of the health facilities have had more than one episode of drug stock out during the period under review and there are not enough equipment used for TB diagnosis like N95s and Gene Xpert.

## **Discussion**

The study found a low prevalence of DR-TB among new and previously treated TB patients respectively in Karamoja region. WHO classifies settings with a DR-TB prevalence of less

than 3% among new patients as having a low DR-TB burden (9). These findings were consistent with previous findings of an anti-TB drug resistance survey in Uganda (20). The low burden observed may be attributed to the low access to health care and movements in the region due to the nomadic life styles.

Nakapiripirit district had the highest number of DR-TB patients (0.14% of its TB patients reported in this period) followed by Napak and Kaabong districts.

These findings are however surprising because Karamoja is a region with the highest TB incidence in Uganda and only 40% of TB patients complete their treatment, majority abandon health care facilities due to their nomadic lifestyle (13). The region only has two rapid molecular diagnostic test centres and no centres that can perform mycobacteriology cultures this could be a reason for under detection of DR-TB cases. From our study over 90% of the DR-TB patients were previously treated susceptible TB (These include participants with Treatment relapse, Lost to follow up and Treatment failure) therefore prevalence of DR-TB maybe higher than observed.

31.7% DR-TB patients that were identified as MDR-TB and an additional 68.3% patients were found to have resistance to rifampicin placing these patients are just one step away from developing MDR-TB these results are in line with the Global TB report 2017 that showed that there are more RR patients than MDR-TB patients(9).

Previous history of TB treatment was significantly associated with developing DR-TB.

Patients who had previous history of treatment for TB had 5.51 times higher risk of developing MDR-TB than patients who did not have a history of previous treatment for TB this is also consistent with findings from studies in Ethiopia (21), (22) and (20).

Similar to previous studies, HIV status had no significant association with DR-TB (22) and (20). However this is contrary to the study in Ethiopia which found that patients who had HIV infection had three times higher risk than those who had no HIV infection to develop

DR-TB (21). They noted that this association had a marginal statistical significance showing that HIV infection is not a strong predictor of DR-TB infection in TB patients. Karamoja is one of the regions in the country with the lowest HIV prevalence of 3.4% (23).

In this study substance use was found to be significantly associated with DR-TB. Substance use increased the risk of developing DR-TB by 30%. However, majority of the DR-TB patients (70%, n = 29) were found to consume alcohol. Alcohol consumption is also one of the risk factors for the development of DR-TB. It might be associated with its substantial role in failure rate among new TB cases. Hence, it increases the rate of DR-TB cases. In other studies also alcohol consumption was frequently reported as one of the risk factors for DR-TB in Ethiopia (22).

The nutrition status of TB patients was not significantly associated with DR-TB this may result from the fact that most of the participants were malnourished by the time they were diagnosed. In addition Karamoja region is still battling with food security leaving most families with poor nutrition statuses. These resulted in no difference between the cases and controls.

### **Health services factors**

Having one or more TB Drug stock outs in health facilities treating susceptible TB was significantly associated with risk of developing DR-TB and this has been noted as one of the factors contributing to poor outcomes and risk for development of DR-TB especially in Health facilities in rural areas in Uganda (24, 25).

### **Socio – cultural factors**

Evidence from the qualitative method in this study showed that DR-TB is a stigmatized disease in Karamoja. However, the incidence is only increasing due poor adherence, poor living conditions where families live in poorly ventilated congested houses in a very close community (Manyattas) with very little economic activity, poor infrastructure, excessive

alcohol consumption, several drug stock outs in the health facilities and poor attitudes of health workers.

### **Limitations**

The study only characterized patients diagnosed through the National Tuberculosis and Leprosy Program supervised health facilities and does not account for drug resistance patterns among patients that did not have access to the health facilities. We do not have data about the size and characteristics of these patients.

The study used patients' self-reports on some variables like substance use which could have caused information bias towards the null.

There could also have been selection bias in this study, as those who had died and those that had migrated and could not be accessed were eliminated. It is possible that these are the patients who had developed Drug resistant TB. However, the impact of this may not have been big because other participants were identified and included in the study.

Health facilities with missing data on anti TB drug stock outs were left out of the study for objective two. It is possible that these facilities had more information on anti-TB drug stock outs that could significantly change our results.

### **Conclusion and Recommendations**

The national TB program should improve provision of TB drug supplies and expedite the process of decentralization of TB treatment initiation services to lower health facilities. The poor retention due to nomadic lifestyle is high and needs further investigation on when and where the pastoralists migrate to.

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## Declarations

## Availability of data and materials

All data generated or analysed during this study are included in this published article. The secondary data used in the study was accessed from the National TB registers in the facility, The anti TB drug stock cards in the Health facilities and from the District Health Information System 2 (DHIS2) with permission from Ministry of health. DHIS2 is a web-based information system used by all health facilities country wide as a health management information system (HMIS).

## Abbreviations

AIDS: Acquired Immune Deficiency Syndrome, CBTBC: Community-based tuberculosis (TB) Care; CEU: Clinical Epidemiology Unit; CI: Confidence Interval; DOT: Directly Observed Therapy; DR-TB: Drug Resistant Tuberculosis; DST: Drug susceptibility test; DTLS: District Tuberculosis and Leprosy Supervisor; FGD: Focus Group Discussion; HIV: Human Immuno-Deficiency Virus; IQR: Interquartile Range; MDRTB: Multidrug Resistant Tuberculosis; MOH: Ministry of Health; MSF: Medecins Sans Frontieres International; NTLP: National Tuberculosis and Leprosy Programme; SOMREC: School of Medicine

Research Ethics Committee; TB: Tuberculosis; UNCST: Uganda National Council of Science and Technology; WHO: World Health Organization

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## Contributions

BN conceived of the work, designed the work, acquired and drafted the work. EA.O. L, SN, ES, OD interpreted the data. WW and JI also interpreted the data and critical review of manuscript. JK, CK, AK and PL revised the manuscript critically for important intellectual content. All authors give final approval of the version to be published. All authors agree 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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## Ethics approval and consent to participate

Approval to carry out this research was sought from School of Medicine research and Ethics committee and UNCST. Permission to collect data was sought from Clinical Epidemiology Unit and each of the 7 district authorities in Karamoja. Signed informed consent and assent was sought from the study participants including Patients with TB, Health workers, District leaders in both the quantitative and qualitative components. A waiver to assess secondary was got from SOMREC. To ensure patient protection and confidentiality, any possible patient

identifiers were eliminated by use of serial numbers. A transport refund was given to all the participants in the qualitative study.

## Consent for publication

Not applicable

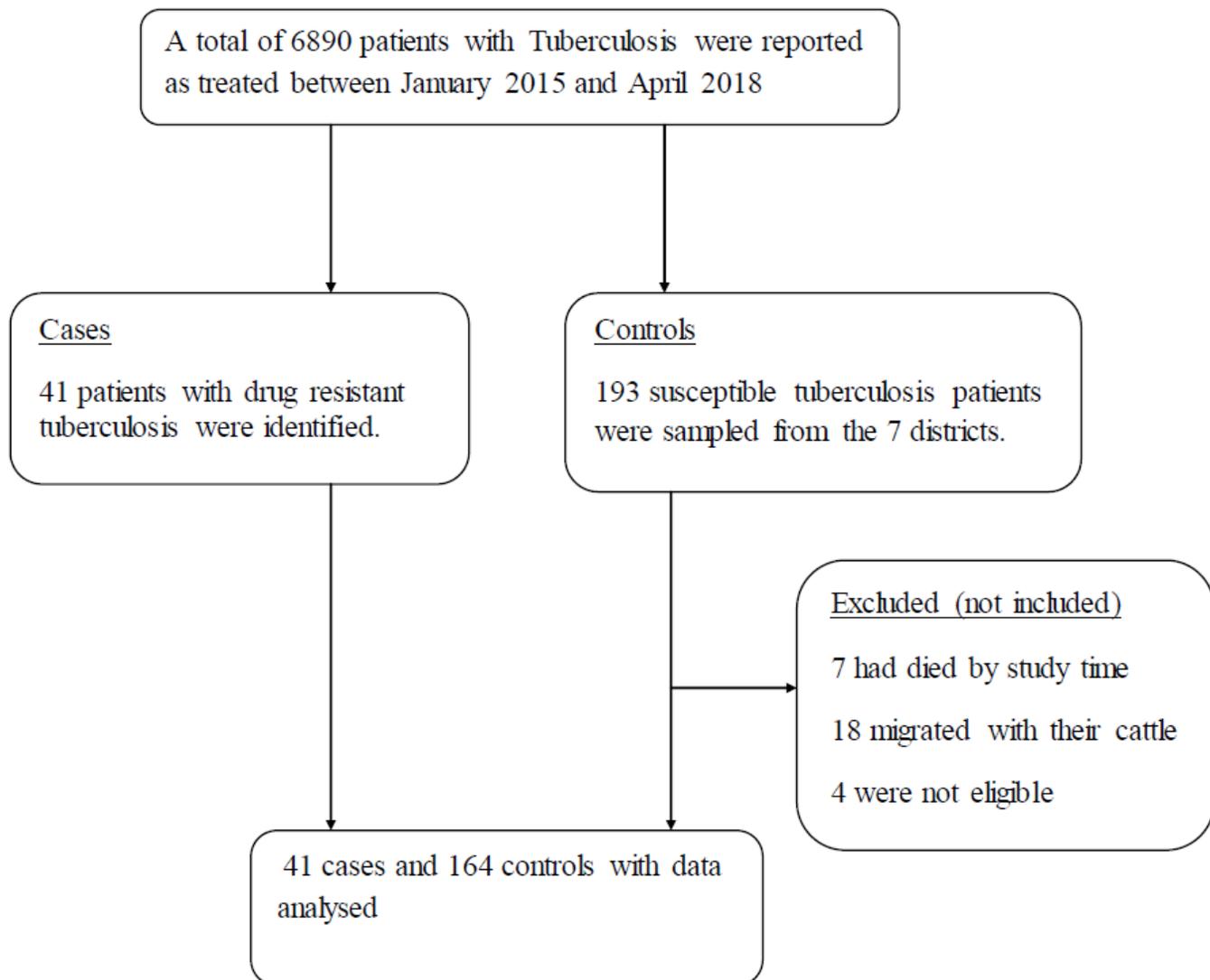
## Competing interests

The authors declare that they do not have any competing interest.

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# Figures



**Figure 1**

Patient flow chart during the study in Karamoja region, 2018