Title:

Population impact of factors associated with prevalent pulmonary tuberculosis in Tanzania

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SUMMARY

SETTING: Tanzania, with an estimated tuberculosis (TB) prevalence of 295 per 100,000 adult population. Currently, there is no nationally representative information on factors associated with TB in Tanzania.

OBJECTIVE: To determine the demographic and clinical factors associated with bacteriologically-confirmed TB among adult general population of Tanzania.

DESIGN: A case-control study nested in a nationally representative TB prevalence survey: All patients with bacteriologically-confirmed pulmonary TB constituted 'cases' and a representative sample of people without bacteriologically-confirmed pulmonary TB constituted 'controls'. We calculated adjusted odds ratios (aORs) to identify factors associated with TB.

RESULTS: Age groups [25-34 years (aOR 3.7; 95%CI 1.5-8.8), 55-64 years (aOR 2.5, 95%CI 1.1-5.5)], male gender (aOR 1.6, 95%CI 1.1-2.3) and low body mass index (BMI) (aOR 1.7, 95%CI 1.1-2.8) were significantly associated with TB. Association with HIV and diabetes were not statistically significant. Population attributable fraction (PAF) was 2% (95%CI-2 to 5%) for diabetes and 3% (95%CI -2% to 8%) for HIV.

CONCLUSION: Being from older age groups, being male, and having low BMI were associated with bacteriologically-confirmed pulmonary TB. On a population level, classic risk factors for TB have no major effect on prevalent TB from which future transmission can derive.

Key words: Population-based, bacteriologically-confirmed TB, TB survey

INTRODUCTION

Tuberculosis (TB) is unequally distributed in the world, with the highest incidence rates found in developing countries. In 2012, World Health Organization (WHO) ranked the TB burden in Tanzania 16th in the world.[1]

A nationwide TB prevalence survey was conducted in 2011-2012 to establish a reliable estimate of the disease burden, as the WHO estimates were calculated using routine data with areas of uncertainty. The prevalence of bacteriologically confirmed pulmonary TB was 295/100,000 adult population. The survey estimated the case detection rate for smear-positive TB in 2012 to be between 42% and 54%.[2] This indicates that the National TB and Leprosy Programme (NTLP) misses a large proportion of TB cases in the community, a source of continued transmission of disease.

To cut the chain of transmission and end the tuberculosis epidemic, cases must be detected early.[1] In the 'End TB Strategy' WHO recommends early detection of tuberculosis by systematic screening in selected high-risk groups to reach missing cases.[3] Some examples of such high-risk groups include people who are in contact with TB cases, having previously been treated for TB, under-nourished, smokers, alcohol users, diabetes mellitus and HIV-infected patients.[4] WHO acknowledged that no global strategy can apply similarly to all settings across or within countries, and that a sound knowledge of country-specific disease epidemiology is essential, including mapping of factors associated with TB.[4]

To our knowledge, no national-level data on the factors associated with TB have been published from Tanzania. Some previous studies exist, but limited to district or regional level, small sample size, precluding nationally representative information.[5, 6] The national TB prevalence survey provided a unique opportunity to assess factors associated with TB at national level with cases and controls sampled from the general population. This information will be useful for the NTLP in Tanzania as they begin to adapt the global End TB strategy. Thus, in this study, we aimed to determine the demographic and clinical factors associated with TB among adult general population of Tanzania.

MATERIALS

Study design and population

This was a case-control study nested in a TB prevalence survey conducted among the adult population of Tanzania. The methodology of the prevalence survey has been described elsewhere.[2] The survey population included individuals aged 15 years and above who slept in the selected households for at least the two weeks preceding the day of survey.

- **Cases:** All bacteriologically confirmed pulmonary tuberculosis patients (any person with a positive sputum culture for *Mycobacterium tuberculosis,* OR at least two smear-positive for acid-fast bacilli, OR one smear-positive for acid-fast bacilli plus evidence of TB on diagnostic chest X-ray) identified in the prevalence survey.
- **Controls:** All study participants who were tested and found not to have bacteriologically confirmed pulmonary TB and not receiving TB treatment: i.e. all presumptive TB patients without TB and a random sample of individuals without presumptive TB.

Data collection

Consenting participants were screened for TB by a symptom-questionnaire and a chest X-ray (CXR). Individuals with symptoms or CXR findings suggestive of TB were identified as 'presumptive TB' and were requested to submit three sputum specimens and interviewed using a structured questionnaire for information regarding demographics and factors associated with TB. Two specimens were assessed by microscopy in a field laboratory; the third was transported to the Central Tuberculosis Reference Laboratory (CTRL) for culture in Lowenstein Jensen medium.

Of the participants without presumptive TB, we randomly selected ten per cluster to serve as additional controls (additional to all those with presumptive TB but without bacteriologically confirmed TB). This ensured a study population in which controls were derived from the general population that consist of participants with or without presumptive TB. Every tenth survey participant who was not identified as having presumptive TB was requested to participate. If one refused, we requested the next eligible person and continued until we enrolled at least ten individuals in each cluster. The reason to include ten controls is rather pragmatic. First, this number would be logistically feasible for the study teams. Second, with this number we could

simply spread the controls over the total number of days that participants could be enrolled in the study. To avoid clustering, individuals were enrolled on three days (four people on day one and two, and two people on day three). These individuals also underwent all the procedures offered to those with presumptive TB as outlined above. As a result of this sampling strategy, we have taken a sample of the survey participants to be given a clinical work-up, and from this sample we have taken all cases and all non-cases. Doing so does not introduce bias leading to spurious associations in the study sample that are not present in the general population because this selection of participants for a clinical work-up was independent of exposure variables and the outcome. Using appropriate survey weights makes the results of the analysis representative for the general population.

Our prevalence survey aiming at a relative precision of 25% was powered on a point prevalence of smear-positive TB in the general population of 145/100000, which translates into a point prevalence of 260/100000 in the adult population. With a sample size of around 50000, we expected a number of smear-positive TB cases of 130.

The exploratory variables included age, sex, height, weight, socio-economic position, marital status, education, smoking (never/ever), alcohol use (never/ever), previous history of TB, diabetes mellitus (self-reported), HIV status. Information on the socio-economic position of the participants was collected through an assets-score at the household level. We used a principal component analysis to compute an asset score for each individual and grouped all the study participants into three categories – low, medium and high socio-economic position – using cutoffs based on tertiles.[7] HIV testing was done following national guidelines. In the initial clusters the sequence of rapid tests was *SD Bioline*, followed by *Determine*. The diagnosis was made if both tests were positive; if still indeterminate, the final diagnosis was made by *Unigold*. During the survey, the national guideline changed. Accordingly, the diagnosis of HIV in the survey was made by the successive use of *Determine* and *Unigold*. Again, HIV was diagnosed when both rapid test were positive.

Statistical analysis

Data were double entered and validated using EpiData version 3.1 (The EpiData Association, Odense Denmark). Data were analyzed using STATA 13.1 (StataCorp, College Station, TX, USA) with a complex survey design approach in which all observations were weighted for sampling strategy, non-response, and availability of interview data and sputum results. Survey weights were re-scaled to the initial enrolled population. The details of weighting are described in the Box**.**

We compared demographic and clinical characteristics of cases and controls in an univariable analysis. We conducted multivariable logistic regression analysis to assess the independent effects of each factor associated with TB after adjusting for potential confounding effects of other variables. The multivariable regression model included variables with a *P*-value < 0.2 in univariable analysis. The population attributable fraction (PAF) of diabetes and HIV as a-priori identified 'modifiable' factors associated with TB was estimated using the "punaf" command. This method computes the ratio of the log of two scenario means for the outcome of interest, being the data as is, and data in which an exploratory variable of interest is set for all to be absent. This estimate is the population unattributable fraction, from which PAF is calculated. The methodology is able to handle multivariable models and data obtained from a complex survey design.[8] The level of significance was set at $P \leq 0.05$.

Ethics

The National Medical Research Coordinating Committee, Zanzibar Medical Research and Ethics Committee, and the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France approved the study. All the participants provided written informed consent to participate in the study.

RESULTS

In the prevalence survey, 50447 individuals aged ≥15 years were screened for TB. Of these, 7163 participants (6302 presumptive TB patients and 861 non-presumptive TB) were requested to provide sputum specimens and be interviewed. Information on sputum results and factors associated with TB was present for 6073(85%) participants. Of these, 159 individuals were bacteriologically confirmed to have pulmonary TB (cases). Of the 159 bacteriologically confirmed cases, 22 were culture positive smear positive, 69 were culture positive smear negative, and 68 were culture negative smear positive. Furthermore, 66 cases were asymptomatic. Of the 5914 participants without study-defined bacteriologically confirmed TB, 71 were either on TB treatment, or information regarding their current TB treatment status was missing, and the remaining 5843 individuals were considered 'controls' (Figure 1). After applying survey weights, we had 152 cases and 5850 controls for analysis.

Participants' socio-demographic characteristics are shown in table 1. In univariable analysis, the chance of bacteriologically confirmed TB was higher among persons aged 25-34 years and 55-64 years compared to those aged 15-24 years, and among men compared to women. Residents of Zanzibar were less likely to have TB compared to mainland semi-urban residents.

Table 2 shows clinical characteristics of participants. On univariable analysis, those with previous TB were more likely to have TB compared to those who had no previous history, as were those with low BMI compared to those with normal BMI.

Multivariable analysis of selected factors associated with TB is shown in table 3. The results remained similar to the univariable analysis. Place of residence was omitted from the multivariable analysis given no cases in the Zanzibar stratum.

Population attributable fraction was calculated for diabetes and HIV. For diabetes it was found to be 2% and for HIV it was 3% (Figure 2). Due to lack of association, we did not assess PAF for alcohol use and smoking.

DISCUSSION

This is the first study examining factors associated with prevalent TB on a national scale in Tanzania. We found more bacteriologically confirmed TB among persons of older age, among men, and among persons with low BMI. Surprisingly, we did not find statistically significant association with education, socio-economic position, history of previous TB, smoking, alcohol drinking, diabetes mellitus or HIV. The population impact of HIV and diabetes on prevalent TB was rather small. With prevalent TB being the pool of future transmission, these findings should result in a re-assessment of NTLP priority activities.

Age was observed to be associated with TB disease, as demonstrated in other studies,[9-11] with a high likelihood of having TB disease observed amongst older individuals (55 to 64 years). This correlates with the results of the prevalence survey which showed bacteriologically confirmed TB prevalence per 100,000 adult population in the respective age groups was 42, 303, 323, 260, 673, 709.[2] This is in contrast to the TB programme notification data where the notification rates among elderly people are less as compared to younger age groups,[12, 13] thus indicating that older age groups are under-diagnosed in the programme. Data from another sub-study done on the same survey have shown that there was no difference in care seeking behavior between the older and the younger individuals with tuberculosis-associated symptoms.[14] Therefore the low number of notified cases in the older age group is likely a consequence of low level of suspicion by health staff when dealing with elderly people. NTLP should train the health care workers to have a higher index of suspicion when screening elderly patients when they visit health care facilities. Moreover, NTLP should set up a screening programme for elderly people as a strategy to improve case finding. NTLP could train community health workers to screen elderly people in the community for TB symptoms (e.g., cough of >2 weeks' duration), and to refer those who will be found to have symptoms to a nearby health facility for TB testing and further management. However, it remains to be seen what an appropriate screening algorithm is in the elderly population.

The increased risk of TB in men is well known and has been attributed to multiple factors. Some have suggested biological factors[15] while others attribute to social behaviors of men which

increases their chance of exposure to TB.[15, 16] The higher risk among men is reflected in the TB notification in Tanzania where 65% of reported cases in 2012 were men.[12]

A person who had TB in the past (treated or not) has a higher risk of TB than a person who never had TB.[17] In our study we see a point estimate indicating an association of TB with a past history of TB, but only statistically significant in the univariable analysis and not in multivariable analysis, probably due to few numbers of events. This group could be targeted for increased case detection. One possible approach could be to follow-up the successfully treated TB patients for a period of two years after treatment, to detect recurrent tuberculosis at the earliest and start appropriate treatment. It is suggested that the risk of recurrence in two years is about 4% and that about 90% of the relapses occur within two years of treatment completion.[17]

Malnutrition causes impairment of immune response.[18] Several studies have shown low BMI to be associated with TB.[19,20] In our study those with low BMI were 70% more likely to have TB compared to those with normal BMI. But these results should be interpreted with care as low BMI is also fairly consistently a result of TB, and our findings would then be the result of reverse causality.[20]

Diabetes is known to adversely affect body immunity by impairing the innate and adaptive immune responses, thereby accelerating the proliferation of TB.[18] Several studies have shown diabetes to be associated with TB,[18, 21] but the association was not statistically significant in this study. Since the ascertainment of diabetes in our study was done by self-reporting, it is possible that people with undetected diabetes were misclassified[22, 23] with consequent underestimation of the association.[23] However, given the evidence from other studies and the increasing burden of diabetes in Tanzania,[24] this is an important target group for TB screening.[25] WHO and The Union have developed a collaborative framework for care and control of tuberculosis and diabetes. One of the recommendations in the framework is to screen all diabetes patients for TB.[25] In Tanzania, diabetes clinics have been set-up as separated units within the health system.[26, 27] These diabetes clinics provide a platform in which NTLP can use as entry points for active TB case finding. A study which was done in Mwanza, Tanzania, revealed that screening

of TB at diabetes clinics is possible and the point prevalence of tuberculosis among adults with diabetes was 7-fold higher than that reported in the general population.[28]

While several studies have shown HIV as an independent risk factor for TB, we did not find a statistically significant association in our study.[10, 18, 29] This may be due to several factors. First, we had small number of cases and hence underpowered to detect an association. Second, we used prevalent TB cases (which are by definition survivors), so it is possible that some of the HIV cases with TB might have died and are not included in the study. Third, declining HIV burden and increasing coverage of anti-retroviral therapy (ART) in Tanzania might be influencing this analysis. A factor strongly associated with an outcome on an individual level (like HIV and TB) does not have to have much population impact, if the exposure (e.g. HIV) is not common in the population at large. Declining HIV prevalence in the general population makes population impact low even though HIV is strongly associated with TB. Availability of ART, especially for those who start the treatment early, prevents HIV patients to develop opportunistic infections such as TB. [30-33] Studies in 1990s showed that about 30% of incident tuberculosis cases were attributable to HIV.[5, 34] In our study PAF of prevalent tuberculosis for HIV was 3%.

A strength of this study was that it was part of a large nationally representative, community-based survey with strong internal and external monitoring of field activities. Also, the effect of non-response and missing data were mitigated by detailed weighting of these events in the analysis and the use of appropriate survey techniques for estimation. Having a sample of controls chosen from the general population, rather than just from the patients with presumptive TB during screening, is a novel approach and gave the opportunity to assess effects on population level. The careful selection of controls resulted in an unbiased study population representative for the general population.

The study had several limitations. As described before, we were underpowered to detect many associations, given the low number of TB cases detected in the survey. Since we used prevalent cases found with both exposure and outcome measurement done at the same point, it is impossible to establish temporality of association. Also, a prevalence study surveys only survivors and associations found in the study are a function of both risk of and survival after the

event. Another limitation relates to self-reported nature of alcohol drinking and smoking data. The data collectors were part of NTLP, known to disapprove alcohol drinking and smoking, and might therefore have caused the respondents to provide socially desirable responses. We think this might have led to under-reporting of the prevalence of smoking and drinking, and an underestimate of the effect of these two factors on TB. Furthermore, data collected concerning smoking and alcohol use could not be broken down in levels of smoking and alcohol use and this might have also affected our analysis. We lacked information on factors associated with TB and smear results for 15% of participants, who might be different from those whom we had their information, and this could have affected our estimates. We could not include prisons, refugee camps, mines, and other institutionalised populations in the study, who are known to have higher risk of having TB compared to the general population.[35, 36] Also children under the age of 15 years were not included in the prevalence survey and this might have influenced our results since factors associated with TB in children might be different from those for TB in adult.

CONCLUSION

In conclusion, being from older age group (55 to 64 years), being male, and having low BMI were associated with bacteriologically confirmed TB. The associations with HIV and diabetes were not statistically significant. NTLP should consider targeted screening activities in these groups who are more likely to have TB to reach 'missed' cases and eliminate TB. On a population level, classic risk factors for TB have no major effect on prevalent TB from which future transmission can derive.

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Contributors

MS, AMVK, PC, SGM, SE, VD, FvL, and SGH participated in the design, planning, and data collection of the study. MS and FvL managed and cleaned the data. MS, PC, AMVK, SGH and FvL analysed the data. MS, AMVK, PC, SGH, and FvL interpreted the results and wrote the manuscript. All authors contributed to the writing of the manuscript, read, and approved the final version.

Declaration of interests

None declared.

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Table 1. Socio-demographic characteristics of tuberculosis (TB) cases and controls in a national tuberculosis prevalence survey in Tanzania, 2012

Characteristic		Cases N (%)	Controls N (%)	Crude OR (95% CI)	*P* value
Total		152 (100)	5850 (100)		
Mean age in years (SD)		39 (17)	38 (18)		
Age in years					
	15-24	24 (16)	1788 (31)	1	
	25-34	54 (36)	1228 (21)	3.3 (1.4-7.6)	0.006
	35-44	30 (20)	1030 (18)	2.2 (1.0-4.8)	0.051
	45-54	12 (8)	643 (11)	1.5 (0.6-3.6)	0.409
	55-64	18 (12)	612 (11)	2.2 (1.0-4.7)	0.040
	65 and older	13 (9)	548 (9)	1.8 (0.8-4.3)	0.167
	Not recorded	0 (0)	1 (0)		
Sex					
	Female	66 (43)	3308 (57)	1	
	Male	86 (57)	2542 (44)	1.7 (1.2-2.5)	0.008
Place of residence (strata)					
	Semi-urban	33 (21)	1352 (23)	1	
	Zanzibar	0 (0)	165 (3)	0.1 (0.0-0.6)	0.014
	Urban	25 (17)	843 (14)	1.2 (0.6-2.6)	0.557
	Rural	94 (62)	3490 (60)	1.1 (0.6-2.0)	0.691
Education					
	Higher education	2 (1)	62 (1)	1	
	Secondary	17 (11)	860 (15)	0.8 (0.1-6.2)	0.826
	Primary	85 (56)	3402 (58)	1.0 (0.1-8.7)	0.989
	None	48 (32)	1518 (26)	1.3 (0.2-10.9)	0.808
	Not recorded	0 (0)	8 (0)		
Marital status					
	Never married	44 (29)	1502 (26)	1	
	Married/cohabiting	82 (54)	3415 (58)	0.8 (0.5-1.5)	0.487
	Separated/widowed	25 (17)	921 (16)	0.9 (0.5-1.7)	0.813
	Not recorded	0 (0.0)	12 (0)		
Socio-economic position					
	High	38 (25)	1742 (30)	1	
	Medium	53 (35)	2014 (34)	1.2 (0.6-2.3)	0.563
	Low	61 (40)	2094 (36)	1.3 (0.8-2.4)	0.320

OR = Odds Ratio, CI = Confidence Interval, TB = tuberculosis, SD = Standard Deviation
Percentages have been rounded off to zero decimals and Odds ratios have been rounded off to one decimal point
Information on the socio-economic position of the participants was collected through an assets-score

Table 2. Behavioural and clinical characteristics of tuberculosis (TB) cases and controls in a national tuberculosis prevalence survey in Tanzania, 2012

Characteristic		Cases N (%)	Controls N (%)	Crude OR (95% CI)	*P* value
Total		149 (100)	5924 (100)		
History of previous TB					
	No	128 (84)	5414 (93)	1	
	Yes	24 (16)	417 (7)	2.4 (1.2-4.7)	0.012
	Not recorded	0	19 (0)		
Body Mass Index (kg/m2)					
	<18.5	47 (31)	1177 (20)	1.7 (1.1-2.8)	0.030
	18.5-24.9	84 (55)	3590 (61)	1	
	25-29.9	15 (10)	765 (13)	0.9 (0.3-2.1)	0.719
	≥30	4 (2)	269 (5)	0.6 (0.2-1.5)	0.254
	Not recorded	3 (2)	49 (1)		
Smoking					
	Never smoker	125 (82)	4814 (82)	1	
	Ever smoker	27 (18)	1026 (18)	1.0 (0.6-1.7)	0.946
	Not recorded	0	11 (0)		
Alcohol use					
	Never used	103 (68)	3989 (68)	1	
	Ever used	49 (32)	1852 (32)	1.0 (0.7-1.5)	0.894
	Not recorded	0	10 (0)		
Diabetes					
	No	146 (96)	5794 (99)	1	
	Yes	4 (2)	45 (1)	3.1 (0.6-16.4)	0.186
	Not recorded	3 (2)	12 (0)		
HIV Status					
	Negative	139 (92)	5549 (95)	1	
	Positive	12 (8)	301 (5)	1.6 (0.9-3.1)	0.128

OR = Odds Ratio, CI = Confidence Interval, TB = tuberculosis

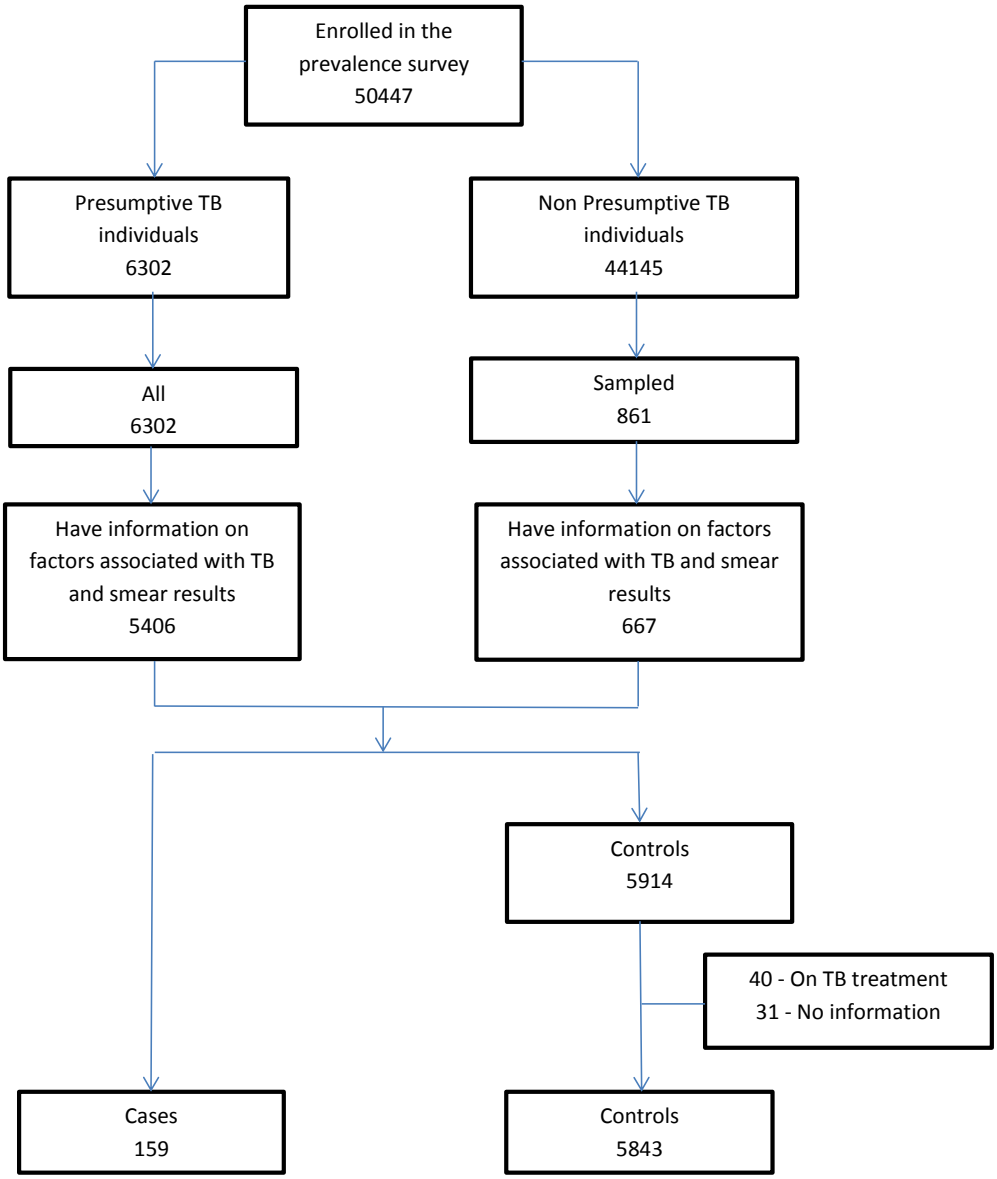
Percentages have been rounded off to zero decimals and Odds ratios have been rounded off to one decimal point

Information on the socio-economic position of the participants was collected through an assets-score

Table 3. Adjusted Odds ratios of factors associated with tuberculosis in a national tuberculosis prevalence survey in Tanzania, 2012

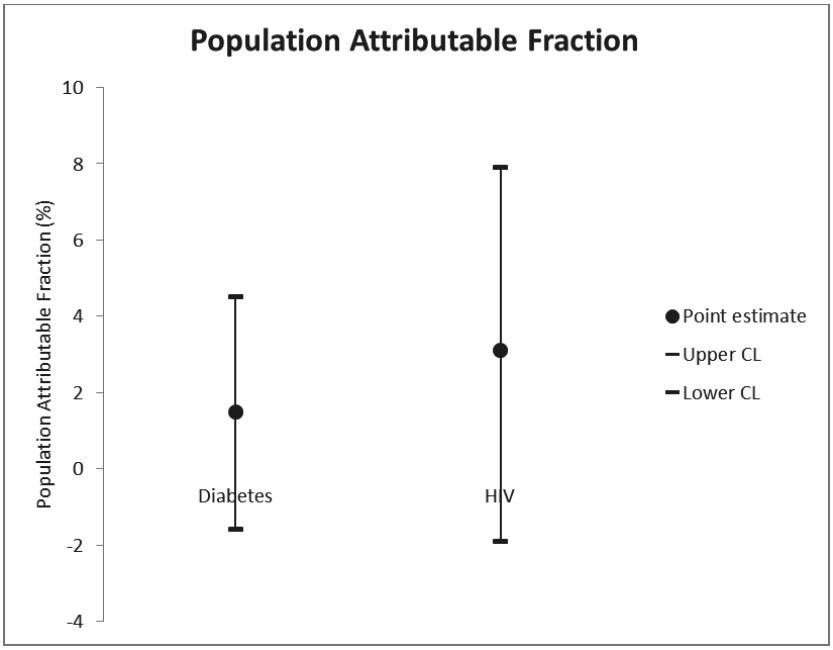
Characteristic		Adjusted OR*	*P* value
Age (years)			
	15-24	1	
	25-34	3.7 (1.5-8.8)	0.004
	35-44	2.3 (1.0-5.4)	0.053
	45-54	1.6 (0.6-4.2)	0.380
	55-64	2.5 (1.1-5.5)	0.028
	65 and older	1.9 (0.8-4.6)	0.167
Sex			
	Female	1	
	Male	1.6 (1.1-2.3)	0.024
History of previous TB			
	No	1	
	Yes	1.9 (0.9-3.9)	0.087
Body Mass Index (kg/m2)			
	<18.5	1.7 (1.1-2.8)	0.028
	18.5-24.9	1	
	25-29.9	0.9 (0.3-2.2)	0.725
	≥30	0.6 (0.2-1.7)	0.307
Diabetes			
	No	1	
	Yes	3.4 (0.8-14.2)	0.097
HIV Status			
	Negative	1	
	Positive	1.5 (0.7-2.9)	0.281

OR = Odds Ratio, CI = Confidence Interval, TB = tuberculosis
Odds ratios have been rounded off to one decimal point
*Adjusted for age, sex, history of previous TB, Body Mass Index, diabetes, and HIV



TB = Tuberculosis

Figure: Flowchart of study participants of a case control study nested in national prevalence TB survey, Tanzania, 2011-12



CL = confidence level

Figure 2. Population Attributable Fraction for diabetes and HIV