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***INFLUENCE OF HIV, SMOKING AND HYPERGLYCAEMIA  
ON THE REPORTING OF TB SYMPTOMS  
IN A TB PREVALENCE SURVEY***

by

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## Declaration page

I, Shahra Sattar, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature:

Signed by candidate

Date: 12 February 2013

## Dedication

*I would like to dedicate this work to the multitude of TB researchers, all over the world and throughout history, who have provided evidence for global strategies to prevent and treat the TB epidemic.*

*Their years of dedication and hard work have enabled us to alleviate the suffering of our patients and prevent the spread of disease in our community.*

*I would also like to dedicate this work to another great enabler, my husband, Razzaaq Mayman. His quiet, and steadfast support over the past two years has been the unseen force sustaining me through this degree.*

## Abstract

Tuberculosis (TB) is a global epidemic that has proved difficult to control due to the characteristics of the *Mycobacterium tuberculosis* bacillus. It is a slow-growing disease with a long delay between infection and the manifestation of symptoms, thus the infectious pool in the community is large, perpetuating transmission.

Furthermore, high-risk groups for developing active TB such as people living with the human immunodeficiency virus (HIV), those who have diabetes mellitus (DM) or those who smoke cigarettes have a much higher risk of contracting TB than the rest of the population and warrant intensified screening for TB.

In addition, TB cases with these additional influences may manifest their symptoms differently. Finding and treating cases in the community before they present to health facilities, a strategy known as active-case-finding, is gaining momentum as a way to decrease the infectious pool. This can be achieved through door to door community surveys using a TB symptom-screening questionnaire, and is an economical and practical tool to employ in poor, high burden areas. However, unlike for the high risk group of people infected with HIV, there is a lack of evidence supporting the adaptation of a symptom screening tool in other high risk groups.

In 2010, a TB prevalence survey was conducted in 24 high TB and HIV burden communities in Zambia and the Western Cape, South Africa. This prevalence survey served as the endpoint for the Zambia South Africa TB and AIDS Reduction study (ZAMSTAR).

This survey made use of a questionnaire that collected, among other information, data regarding individual TB symptom reporting, HIV status, diabetes mellitus status and cigarette smoking. Consenting participants were also encouraged to provide sputum samples for TB confirmation through 16s DNA sequencing, and blood samples for rapid HIV testing and glucose measurements. The data from this survey provided an opportunity to investigate the differences in symptom reporting between bacteriologically confirmed TB cases and TB cases with the additional influences of HIV, smokers, and those with hyperglycaemia.

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# PART A: PROPOSAL

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## TITLE:

### ***INFLUENCE OF HIV, SMOKING AND HYPERGLYCAEMIA ON THE REPORTING OF TB SYMPTOMS IN A TB PREVALENCE SURVEY***

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1. USAID
2. THE UNION
3. TREAT TB

**MENTORS:** David Coetzee, Nulda Beyers

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University of Cape Town

## PRINCIPAL INVESTIGATORS and CO-INVESTIGATORS

- Shahra Sattar – Principal Investigator. Develop study proposal, interpret results, write paper
- David Coetzee – Mentor, Supervisor
- Nulda Beyers – Mentor, co-investigator, co-supervisor on behalf of the ZAMSTAR team
- Helen Ayles – Co-investigator
- Peter Godfrey-Fausset – Co-investigator
- Cari van Schalkwyk – Statistician
- Sian Floyd – Statistician
- Donald Enarson – co-investigator

## INTRODUCTION

Symptom screening for tuberculosis (TB) is accepted as an effective tool to actively detect suspect TB cases who would benefit from confirmatory testing.(1,2) Recently, as part of the “3 I’s” initiative, TB case detection is moving from the established strategy of passive detection to active, or intensified, TB case-finding in people living with the human immunodeficiency virus (HIV). (3) While intensified case-finding has initially been promoted as an active case-finding strategy in HIV infected clients, there is a lack of knowledge directing symptom-screening strategies for active detection of TB cases with co-morbidities other than HIV.(4) The high prevalence of HIV, diabetes mellitus, and smoking in the general population, may impact on the classical presentations of TB and therefore on the effectiveness of a symptom screening tool to detect TB suspects. (4–6) This proposal aims to analyse data from a prevalence survey in 8 high burden TB communities in Cape Town, South Africa. The analysis aims to determine the prevalence of, and differences in, reported TB symptoms in respondents according to bacteriologically confirmed TB status, with or without the additional influences of HIV, smoking and hyperglycaemia.

## BACKGROUND

The World Health Organisation (WHO) reports 9.4 million incident and 14 million prevalent tuberculosis (TB) cases in 2009, and, that tuberculosis remains one of the leading causes of global mortality and morbidity.(7)

Global efforts to control TB have been based principally on case-finding and treatment as a means of decreasing transmission rates and incidence of disease. Case-finding can be passive or active. Passive case-finding is defined as detecting disease in patients who present to health facilities with symptoms suggestive of TB. Active, or intensified, case-finding is defined as actively seeking tuberculosis diagnosis in a target population – for example, a general outpatient clinic, specific patient populations at high risk for TB, or the general community. (4,8–10)

High risk groups for tuberculosis include people living with the human immunodeficiency virus (HIV), those with diabetes mellitus (DM) and smokers. These groups have a much higher risk of developing active TB compared to the general population without these additional influences. (11–15)

One of the strategies employed for active case-finding in populations is to use a symptom screening questionnaire as this has been shown to be an “efficient high yield strategy” in resource limited settings and is a widely accepted screening tool for tuberculosis. (8–10)

However, countries with high-TB burden are also the most resource limited and efforts in active case-finding are thus focused on the vulnerable groups at highest risk for developing active TB. (4,16)

There is a substantial amount of literature regarding diagnosis of symptomatic TB disease in high HIV prevalence populations, and a lack of literature on symptomatic TB screening in populations with other risk factors such as diabetes, and smoking. (4,17) Furthermore, there are currently only recommended evidence-based guidelines for symptom based algorithms for TB detection in the HIV positive population in order to reliably exclude TB, so that antiretrovirals (ARV) and isoniazid preventive therapy (IPT) against TB can be safely initiated.(4,18)

Symptom-based algorithms rely on the awareness or perception of TB symptom-complexes. However, additional influences of HIV, smoking or hyperglycaemia may impact on the reliability of self-reporting of symptoms. Thus the effectiveness of a symptom screening tool applied to any possible TB case in the community may be affected by additional risk factors that alter perceptions of the TB-symptom complex.(17,19–22)

In 2010, a large TB prevalence survey was conducted in 24 high TB and HIV burden communities in South Africa and Zambia, which served as the primary endpoint measurement for the three-year Zambia/South Africa TB and HIV Reduction study (ZAMSTAR). (23)

This prevalence survey provides a unique opportunity to analyse the differences between symptom-reporting in culture-confirmed TB cases diagnosed in the community with additional influences of HIV, smoking or diabetes mellitus, and cases that do not have these additional influences. By analysing this dataset, we hope to add to the evidence base of symptom reporting in high-risk groups for TB.

## 1. RESEARCH QUESTION

*Are TB cases with the additional influences of smoking, HIV or hyperglycaemia equally likely to report TB symptoms compared to TB cases without these influences?*

**2X2 table:**

		Reported Symptoms	
		Present	Absent
Co-morbidity	Present		
	Absent		

## **2. HYPOTHESIS**

**H0:** TB cases with co-morbidities are equally likely to report TB symptoms compared to TB cases without co-morbidities.

**Ha:** TB cases with co-morbidities are not equally likely to report TB symptoms compared to TB cases without co-morbidities.

## **3. OBJECTIVES**

### **Objectives**

(1) Determine the prevalence of hyperglycaemia, HIV and smoking amongst participants of the 2010 South African and Zambian TB prevalence survey of bacteriologically confirmed TB cases.

(2) Determine the prevalence of TB symptoms in bacteriologically confirmed TB cases, with or without co-morbid hyperglycaemia, HIV-infection, or concurrent smoking.

(3) Determine the differences in symptom reporting when screening for TB in high TB burden areas where a high proportion of cases also smoke or have additional influences of HIV infection and hyperglycaemia.

## **4. RESEARCH DESIGN AND METHODS**

### **Study design**

A cross-sectional study design will be employed for analysis. Data for the present will be drawn from a TB prevalence survey conducted during 2010 in purposively selected areas of

Zambia and South Africa, as part of the Zambia/South Africa TB and AIDS Reduction study (ZAMSTAR).

In 2010 the ZAMSTAR TB prevalence survey of about 100 000 participants was conducted as a joint collaboration between the Desmond Tutu TB Centre ( Stellenbosch University) in Cape Town South Africa, ZAMBART (University of Zambia, Zambia) and the London School of Hygiene and Tropical Medicine. This prevalence survey was conducted at the end of a three year TB and HIV intervention study conducted in the ZAMSTAR community sites throughout Zambia and South Africa.

The participants enrolled in the 2010 Prevalence survey gave written informed consent for questioning and sputum and blood testing. Consent forms were in English, and were translated into the most commonly spoken languages in the community. Participants read through the consent forms and were encouraged to ask questions regarding the study before signing. Those participants who could not read, had the consent forms read to them by study staff. Consented participants gave a sputum sample for culture and speciation of *Mycobacterium tuberculosis*, were encouraged to go for voluntary counselling and testing of HIV status (HCT), and by means of questionnaire were asked about their TB symptoms, smoking history, diabetic status and HIV status. Blood glucose measurements were obtained by means of finger-prick testing to determine the prevalence of hyperglycaemia. Written consent was also obtained for analysis of data collected.

### **Study Population and Sampling**

The study population comprises of South African and Zambian ZAMSTAR TB Prevalence survey respondents. This survey was conducted as a means of determining TB, HIV, diabetes and smoking prevalences in 8 communities in the Western Cape, South Africa and 16 in Zambia.

These ZAMSTAR communities had in the preceding three years been randomised to receive one of 4 possible community interventions in an attempt to decrease TB and HIV



prevalences in the community. Communities were defined as a population served by one primary health care diagnostic centre. Communities were then stratified into similar groups based on country and or urban population and then randomly allocated to one of the four intervention arms of the study.(10)

The ZAMSTAR prevalence survey occurred at the end of the intervention periods within each of the communities during 2010.

The prevalence survey was conducted in each of the communities in which the ZAMSTAR interventions occurred. These communities were subdivided into Standard Enumeration Areas (SEA) using national census maps and Google Earth. Each SEA within a sampling area of that community was given a sampling number and the order of selection determined by random number generation. Starting with the first randomly selected SEA all households within that SEA were visited and eligible adults were enumerated and interviewed with consent. In total 64 463 participants were enrolled across the 24 study sites in Western Cape, South Africa and in Zambia.

### **Sample Size**

The ZAMSTAR prevalence survey was not designed to answer our question. Thus the sample size is fixed and was the result of the ZAMSTAR protocol and study design. The ZAMSTAR prevalence survey assumed a TB prevalence in the control arm of 1%, and was powered to detect a 30% reduction in prevalence of tuberculosis from each intervention individually, and a further 30% reduction when both interventions were combined. (10)

### **Data Collection methods ZAMSTAR prevalence survey**

#### Questionnaire:

Trained research assistants recruited participants door-to-door in the community and administered a questionnaire. Questions were read to participants and recorded using handheld electronic devices which obtained information regarding demographics, TB status, reporting of TB symptoms, smoking history, diabetic status, and HIV status.

### Sputum:

The sputum samples were collected from these participants and were transported to the ZAMSTAR laboratories where they were inoculated for culture, subjected to TBcID and HAIN assays and then further speciated using 16s DNA sequencing for *Mycobacterium tuberculosis* complex. A positive 16s result for *Mycobacterium tuberculosis* complex was considered the definition of a positive TB case.

### HIV Blood samples:

Participants who consented to HCT had their HIV tests performed either in the house by trained study staff or were taken to a mobile testing tent in the community. Individuals who tested HIV-positive on Abbot Determine HIV 1/2 test had a confirmatory test using Unigold. If the 2 tests were discordant, a tie-breaker was done in the community health facility.

### Blood Glucose samples:

Participants' blood glucose measurements were recorded by means of finger-prick blood glucose testing performed in the homes or in mobile HCT tents using a glucometer. Those with a single random blood glucose level of more than 11.1mmol/L were referred to the local clinics for further diabetic work-up and management.

All data were entered using a Standard Query Language (SQL) database.

## **Extraction of Data for this study**

All enrolled ZAMSTAR prevalence survey participants will have their data analysed. The data sources will be extracted from a locked database from the ZAMSTAR survey and no names will be utilised.

The data sources include:

- The individual participant's responses to TB symptom and HIV, diabetes, and smoking questions asked using the ZAMSTAR prevalence survey questionnaire.
- The ZAMSTAR laboratory diagnosis of M.TB from sputum culture and speciation.
- The HCT and blood sugar results.

## 5. SPECIFIC VARIABLES AND DEFINITIONS

### Risk factors

**HIV status:** HIV positive participants were defined as those with a confirmed positive HIV rapid test result, supplemented by the self-reporting of HIV status for individuals who did not give a blood sample for HIV testing.

**Smoking:** "Current smokers" at the time of the survey were determined via questionnaire. Participants who answered "yes" to the question "have you ever smoked" and also answered that they had not stopped smoking were defined as current smokers.

**Hyperglycaemia:** Participants were defined as hyperglycaemic if a random capillary blood glucose was  $\geq 11.1$  mmol/L and/or if they self-reported that they were diabetic

### Symptom variables

These were obtained through answering yes/no questions regarding the experience of the following symptoms:

1. Cough
2. Chest pains
3. Fever
4. Night sweats
5. Unintentional loss of weight
6. Difficulty breathing

## **Data Analysis**

All ZAMSTAR TB prevalence survey respondents will be specifically categorised into those with or without co-morbidities, those with or without bacteriologically confirmed TB, and those who did or did not report TB symptoms. A univariate and multivariate statistical analysis will be undertaken using the statistical analysis programme STATA 12 for Windows (StataCorp LP, College Station, TX, USA). The measure of association used will be the odds ratio and corresponding 95% confidence interval. Odds ratios will be calculated overall for any co-morbidities by any symptoms reported, and for individual co-morbidities by individual symptom.

## **6. ETHICAL CONSIDERATIONS**

Ethics approval for the ZAMSTAR prevalence survey was obtained from the London School of Hygiene and Tropical Medicine Ethics committee, The University of Zambia Ethics Department and Stellenbosch University's Ethics Department. Ethics approval for this specific study has been approved by the International Union Against Tuberculosis and Lung Disease Ethics Advisory Group. The database is locked and unique barcode identifiers were used to ensure anonymity and protect participant information. No names will be revealed during the extraction of data for this study.

## **7. STRENGTHS AND LIMITATIONS**

### **Strengths**

The data required to answer the study question has been collected and cleaned, and is ready for analysis. The number of participants recruited was large, resulting in a wealth of individual data which adds to the power of the analysis. A major strength of the study is that it provides a large sample of TB cases confirmed through 16SDNA sequencing, detected in the community outside of the health system. Additionally, these cases have corresponding TB symptom, smoking, hyperglycaemia and HIV information acquired before diagnosis.

## Limitations

The ZAMSTAR prevalence survey was not specifically designed for this study question and the complexity of the study, along with the very large number of participants may result in missing data which could ultimately affect the power of the study. Furthermore, we are limited in the conclusion we can make regarding hyperglycaemia as the results are based on a single and random blood sugar reading.

## 8. IMPACT AND DISSEMINATION

These results would add to the knowledge of symptom-screening use for TB suspects in community surveys. The study has the potential to add insight into the reporting of symptoms among TB cases with co-morbidities and may inform symptom-based algorithms for *any* TB suspect cases during active case-finding in communities. We aim to disseminate any knowledge generated from this study through scientific manuscript publication.

## 9. PROJECT MANAGEMENT

Data has already been collected and analysis will occur once approval has been granted by the Human Research Ethics Committee of the Health Sciences Faculty at the University of Cape Town.

## 10. BUDGET

No budget is requested.

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## 12. APPENDICES

1. ZAMSTAR CONSENT FORM
2. ZAMSTAR TB PREVALENCE SURVEY QUESTIONNAIRE
3. ZAMSTAR SAMPLING FRAME

### Appendix 1: ZAMSTAR Consent Form



Barcode

#### **INFORMED CONSENT FORM FOR TB PREVALENCE SURVEY (PERSONS AGED 18 YEARS AND OLDER)**

##### **Declaration by participant**

I confirm that I have read the information sheet, and that the information and procedures involved in my taking part in this survey have been explained to me.

1. I confirm that I have had the opportunity to ask questions about the survey and that I am satisfied with the answers provided.
2. I have been given time and opportunity to read the information carefully, to discuss it with others and to decide whether or not to take part in this survey.
3. I understand that if I am diagnosed with TB, I will be informed and that I will be referred for treatment to my local TB clinic.
4. I understand that if the TB test is positive, the clinic will be informed. That the study team will look in the TB treatment register to see whether I have started and completed treatment.
5. I understand that if the TB test is positive, there will be further tests to determine whether the TB is sensitive to the normal treatment. If I have drug resistant TB, I understand that I will receive appropriate treatment.



6. I understand that the TB culture will be kept in a sample bank with only a bar code on (not my name) and that this sample can be used in future for further tests on the TB organisms
7. I understand that I may choose to get the result of my HIV test if I want the result
8. I understand that I will have pre-test and post-test counselling for HIV and that I will be referred to the clinic for care should the test be positive.
9. I understand that I may refuse the HIV test or that I may choose to have the test done, but not receive the results
10. I understand that the results of the blood sugar test will be given to me and that I will be referred to the clinic for appropriate care if my blood sugar is too high.
11. I understand that I will be given information about TB, HIV, diabetes, use of tobacco, and use of alcohol.
12. I understand that refusal to have HIV and Blood sugar tests done does not preclude me from participating in this study as long as I submit a respiratory sample for evaluation.
13. I understand that the research team can access my results from the VCT register if I previously tested at their outreach centre.
14. I understand that the researchers will keep all my personal information confidential.
15. I understand that I will not get any financial reward for taking part in this survey.
16. I understand that the results of this study will be published in scientific journals but that my name will never be used.
17. I understand that I may in future be requested to participate in follow-up studies but that I may decline at a later stage to take part in future studies.
18. I agree to take part in the survey.

By signing below, I (Please Print)

(First Name) \_\_\_\_\_ (Surname) \_\_\_\_\_

agree to take part in a research study entitled ZAMSTAR Prevalence Survey

Signed at (*place*) ..... on (*date (dd/mm/yyyy)*) \_\_\_\_\_

.....

Signature of participant

.....

Signature of witness if needed

**Declaration by Research Assistant**

I (First Name) \_\_\_\_\_ (Surname) \_\_\_\_\_

declare that:

- I explained the information in this document to .....
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use a interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*)

Signed at (*place*) ..... on (*date*) .....

.....

Signature of Research Assistant

.....

Signature of witness if needed

**Declaration by interpreter**

I (First Name) \_\_\_\_\_ (Surname) \_\_\_\_\_

declare that:

I assisted the investigator (*name*) ..... to explain the information in this document

to (*name of participant*) ..... using the language medium of Afrikaans/Xhosa.

- We encouraged him/her to ask questions and took adequate time to answer them.

- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) ..... on (*date*) .....

.....

Signature of interpreter ..... Signature of witness if needed

## Appendix 2: ZAMSTAR Prevalence Survey Questionnaire 2010

### SECTION 1

ALL QUESTIONS IN THIS SECTION MUST BE ANSWERED

#### HOUSEHOLD BARCODE

Q01\_INC Interviewer's code


Q02\_DAT Date today

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

Q03\_SEN Serial Number

--

Q04\_IND Individual Barcode

--

--

Q05\_HOH     **Are you the Head of Household?**     No    Yes

0	1
---	---

Q06\_SEX     **Sex**     M    F

1	2
---	---

Q07\_AGE     **Age**

--	--

Q08\_MAR     **Married to**

--	--

Q09\_DIS     **Disability?**

No Disability	1
Sight(blind/ severe visual impairment)	2
Hearing (deaf/ profoundly hard of hearing)	3
Communication(speech impairment)	4
Physical(needs wheelchair/ crutches)	5
Mental disability	6

Q10\_CON     **Consent**     No    Yes    Absent    Excluded

0	1	2	3
---	---	---	---

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**ONLY CONTINUE IF CONSENT IS GIVEN**

**SECTION 2 – FILL THIS SECTION AND SUBSEQUENT SECTIONS IN ONLY IF PERSON HAS GIVEN CONSENT**

Q11\_DOB **Date of Birth** (01/01/1800 if unknown)

**If not known, what was your age in**

Q11\_1\_DOB years at **your last birthday?**  
(999 if unknown)

D	D	M	M	Y	Y	Y	Y

Q12\_YLC How many years have you lived in this community?  
Write down actual number, zero if less than one year)

--

Q13\_RAC What is your race?  
Select only one option

Black	1
Coloured	2
Indian/Asian	3
White	4
Other	5

Q14\_COB What is your country of birth?  
(Drop down menu with SADC countries and few other Africa countries)


Q15\_HZS Before this survey, have you heard of or been involved with ZAMBART/ZAMSTAR (DTTC/ ZAMSTAR for SA)

No Yes

0	1
---	---

Q16\_CMS What is your current marital Status?

If married, Divorced or widowed, continue, If never married go to Q18

Never married	1
Currently married or living as married	2
Divorced or Separated	3
Widowed	4

Q17\_AFM Age at first marriage? (years)

Q18\_MOY What has been your main occupation during the past year?

Unemployed/working on own land	1
Occasional/seasonal employment	2
Employed (Formal employment or self-employed making money)	3
Unable to work	4
Student	5
Housewife/ home-maker	6

I would like to ask you about your current drinking and smoking habits

Q19\_CSH How would you classify your smoking habits?

Have never Smoked

1

Daily Smoker

2

Occasional smoker

3

Ex-Smoker

4

Q20\_CDH How would you classify your drinking habits?

Have never drunk

1

Daily drinker

2

Occasional drinker

3

Ex-drinker

4

Now I will ask questions about your education

Q21\_HEA What is the highest level of education you have attained?

No Formal Education

0

Grade 1-12(Indicate actual grade)Note Grade 8-12 is also Form 1 –form 5

College

20

University

30

If has attended school, continue, if No formal education go to Q23

Q22\_YES When was the last year you were in enrolled  
in School/College/University? Enter 9999 if year is not known

Y	Y	Y	Y
---	---	---	---

Q23\_OCC Please state main occupation at age 15 years?

Unemployed/ working on own land

1

Seasonal/Occasional employment

2

Employed (formal employment or self employed earning money)

3

Unable to work

4

Student

5

Housewife/home-maker

6

Can't remember

9

I would like to ask you about your health. (Current TB questions)

Q24\_CTB Are you currently on TB treatment? Probe and be sure only conventional treatment(on ATT)

No Yes

0	1
---	---

(If yes continue, If No goto Q35)

Q25\_FPS Where did you first present for your symptoms?

Government/Community clinic

1
---



Private Clinic/hospital	2
Government Provincial/District hospital	3
Pharmacy	4
Private Doctor	5
Traditional Healer	6
Sputum collection point	7

Q26\_TCA      Is TB treatment card available? (confirm by seeing the card)      No    Yes

**If yes continue, If No go to Q31**

0	1
---	---

Q27\_DTS      **Date treatment started**

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

Q28\_TTN      **TB treatment Number (from treatment card)**

--

Q29\_CAT      **Category of TB as recorded on card?**

Sputum smear Positive	1
Sputum smear Negative	2
Extrapulmonary	3
Unknown/not recorded	4

Q30\_TTC      **TB treatment Centre(as written on card)**

--

ASK QUESTION 31 TO 34 IF TB TREATMENT CARD NOT AVAILABLE

Q31\_MST Which month did you start treatment

January	1
February	2
March	3
April	4
May	5
June	6
July	7
August	8
September	9
October	10
November	11
December	12
Unknown	99

Q32\_SPT Was the sputum smear positive for TB?

No Yes Unk

0	1	9
---	---	---

Q33\_RTF Where are you receiving your TB treatment from?

Government/Community clinic

1

Private Clinic/hospital

2

Government Provincial/District hospital

3

Pharmacy

4

Private Doctor

5

Q34\_TTC TB treatment Centre

Questions about previous TB treatment

Previous TB treatment

Q35\_TTB Have you ever been on TB treatment before?

No Yes Unk

If yes continue, if no go to Q37

0	1	9
---	---	---

Q36\_HMT How many times?

Once

1

Twice

2

Three times

3

More than three times

4

Unknown

9

I would like to ask about your current state of health

Q37\_CHC Do you currently have a cough?

No Yes

If yes continue, if no go to Q41

0	1
---	---

Q38\_WBC How many weeks have you been coughing? Box write actual number of weeks

Q39\_CPS Do you currently produce sputum No Yes

0	1
---	---

Q40\_CCB Do you currently cough up blood? No Yes

0	1
---	---

Q41\_CAC Did you consult anybody for this cough? No Yes  
If yes continue, if no go Q47

0	1
---	---

Q42\_GHF Where did you go for help first?

Government /Community clinic	1
Private clinic/hospital	2
Government Provincial/ District hospital	3
Pharmacy	4
Private Doctor	5
Traditional healer	6
Sputum collection point (ZAMBART/ZAMSTAR/)	7

If 1, 2, 3 go to Q44 ...

Q43\_GCP If pharmacy/private/tradition healer, did you ever go to a government/community/sputum collection point No Yes

0	1
---	---

Q44\_ASS Did anyone ask for sputum samples? No Yes

If yes continue, if no go to Q 47

0	1
---	---

Q45\_DGS If yes, did you give sputum?

No Yes

If yes continue, if no go to Q47

0	1
---	---

Q46\_RES What was the result?

Negative for TB

0
---

Positive for TB

1
---

Unknown/can't remember

9
---

**Other symptoms**

Q47\_CCP Do you currently have chest pains?

No Yes

0	1
---	---

Q48\_CHF Do you currently have fever?

No Yes

0	1
---	---

Q49\_DNS Do you currently have drenching night sweats?

No Yes

0	1
---	---

Q50\_LWU In the last month have you lost weight unintentionally?

No Yes

0	1
---	---

Q51\_DBB Do you currently have difficulty breathing or shortness of breath?

No Yes

0	1
---	---

Now I will ask questions about Diabetes and HIV

Q52\_THD      Have you ever been told you have diabetes      No    Yes

**If Yes continue, if No go to Q55**

0	1
---	---

Q53\_CAT      If yes, are you currently on any treatment for diabetes?      No    Yes

**If yes continue If no go to Q55**

0	1
---	---

Q54\_TON      What treatment are you on?

Dietary only	1
Tablets	2
Insulin injections	3

Q55\_KHS      Do you know your HIV status?      No    Yes

0	1
---	---

Q56\_DHS      Are you willing to disclose your HIV status?      No    Yes

**If yes continue, if not willing to discuss go to Q60**

0	1
---	---

Q57\_HIV      What is your HIV status?

Negative	0
Positive	1

**If HIV status is Positive, continue, if no go to Q54**

Q58\_ART      Are you on Antiretroviral treatment( ART)      No    Yes

**If yes continue, if no go to Q54**

0	1
---	---

Q59\_LAR How long have you been on ART? Write down actual number of months

Q60\_CIR Are you circumcised?

No Yes unk

If yes continue, if no go to Q62

0	1	9
---	---	---

Q61\_WCI When were you circumcised?

Infant/Child	1
Adolescent	2
Adult	3
Unknown/Can't remember	9

Q62\_WEI Weight? Record weight in Kilograms

If not done, write 999.9

Q63\_HEI Height? Record height in centimeters

If not done, write 999.9

Q64\_ABC Abdominal Circumference? Record in centimeters

Write 999.9 if not done

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**SECTION 3**

**NOW RECORD BLOOD SUGAR AND HIV RESULTS HERE**

Q65\_BLG Blood Glucose.

Write actual Results below

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Q66\_HIV\_DET HIV Test result (Determine).

HIV result Negative	0
HIV result Positive	1
HIV test not done	9

Q67\_HIV\_UNI If positive, confirmatory HIV Test result (UniGold).

HIV result Negative	0
HIV result Positive	1
HIV test not done	9

Q68\_HSP HIV test results given to study participant?

No Yes

0	1
---	---

	Interview's	Date								Signature
		d	d	m	m	y	Y	y	y	



	code									
Interviewer										
Field manager										
1 <sup>st</sup> data entry										
2 <sup>nd</sup> data entry										

### Appendix 3: ZAMSTAR Sampling SOP



#### APPENDIX 3: Sampling and Enumeration SOP

**Aim:** To sample 5000 consenting adults who are representative of the community

The ZAMSTAR community is defined as a catchment area of one or more TB clinics with a minimum number of 25, 000 people in that area. The Intervention area is defined as the area within the ZAMSTAR community where interventions have been implemented. The sample area is defined as the whole intervention area or a part of the intervention area where it is expected that the interventions are most effective.

**Step 1:** National census maps of the ZAMSTAR community and Google earth will be used to generate electronic maps. Standard Enumeration Areas (SEAs) will be marked on these maps.

**Step 1a:** In consultation with the team leaders, the intervention area will be drawn onto electronic maps. The intervention area is the area where the interventions have actually been implemented and may differ (slightly) from the original planned area.

#### **Step 2: Sampling area rules and definition**

- Subdivide the SEAs within the intervention area into SEAs with <1000 people.
- Boundaries of selected SEA must be completely within the intervention area.
- Start circling clockwise around the clinic, select the enumeration areas and select the SEA's until;
  - The intervention area is included

OR

- 25,000 people are selected.
- If the community has 2 clinics, start circling around each clinic, select the enumeration areas and select the SEA until;
  - The whole intervention area is included

OR

- 12,500 people are selected.

**Step 3:** Each SEA within a sampling area will be given a sequential number and the order of selection will be determined by generating these numbers into a random order.

**Step 4:** Starting with the first randomly selected SEA- all households in the SEA will be visited and all adults who slept in the household in the last 24 hours will be enumerated and interviewed with consent.

**Step 5:** On completion of an entire SEA the next SEA will be visited and the same procedure completed. This will continue until a sample of 5000 adults have consented and been recruited. The SEA containing the 5000<sup>th</sup> adult must be completed.

**Step 6:** Where an adult is enumerated but not present at the time of the survey 2 further visits to the household will be made. These visits should be timed such that there is maximum chance of finding the absent adult and this timing will depend on the individual circumstances of the adult. These visits should be recorded in the diary of the research team.

**Step 7:** Where an adult cannot be found after 2 visits or in the case of non-consent by an adult the management form must be completed to indicate this.

**Step 8:** The first section of the questionnaire must be completed for every adult who is enumerated. In the case of the adult not being found or non-consent, only the first section of the questionnaire will be completed. The information given by the other household members regarding age and sex will be used, as this is the best data that is possible to collect

# Part B: Structured literature review

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## a) Objectives of Literature Review

- To introduce the global issues of tuberculosis (TB) detection in communities using symptoms screening.
- To examine the relationship of tuberculosis with the high risk groups of people living with the human immunodeficiency virus (HIV), those with diabetes mellitus (DM), and cigarette smokers.
- To discuss the benefits of using a symptom-screening tool in high risk groups to detect TB through active case-finding.
- To identify gaps in the literature.

## b) Literature search strategy

Internet search engine Google Scholar, the electronic database Pubmed, and the electronic databases of Stellenbosch University and the University of Cape Town were utilised.

Keywords inputted were: symptom screening; tuberculosis; active case-finding; TB screening in high risk groups; TB and non-communicable diseases; TB and smoking; TB and diabetes; TB and HIV; co-morbidity effects on TB symptom reporting; TB symptom reporting differences and influences.

## c) Quality and relevance criteria by which studies were included

Only scientific manuscripts published in peer-reviewed journals were included. All articles were published between 1998 and 2012. The reference lists of these articles were also reviewed for additional studies. TB experts were consulted to suggest appropriate articles and authoritative texts for consideration.

## d) Summary of literature

### Introduction

Current and previous strategies to control the global tuberculosis (TB) epidemic have had minimal success. Due to the characteristics of infection, the slow-growing nature of the bacillus and the long delay between infection and manifestation of TB symptoms, the infectious pool in the community is large. Passive case-finding at health facilities has been the mainstay of detection, but current strategies are moving towards active case-finding initiated by the provider in high burden areas and in high risk groups. TB symptom screening questionnaires are the most practical tool to utilise in poor high burden areas, but unlike for the high risk group of people living with HIV, there is a paucity of evidence surrounding adaptation of symptom screening tools in other high risk groups for TB such as those with diabetes mellitus or those who smoke cigarettes. This literature review aims to introduce the scope of the global TB problem, the interplay between TB and the high risk groups of HIV, those with diabetes mellitus and smoking, and how symptoms are manifested differently in these high risk groups.

### Disease overview

Tuberculosis (TB) is an infectious disease caused primarily by the bacillus *Mycobacterium tuberculosis*, but can also be caused by *Mycobacterium bovis* or *Mycobacterium Africanum*. The mycobacterium bacillus is propagated through air-borne spread and is inhaled by the host after coming into contact with an individual with active disease.(1) Thus the site of pathology is primarily the lungs, with respiratory disease characterised by pleural effusions, broncho-pneumonic processes, hilar lymphadenopathy and cavitation.(2) It can also be ingested through contaminated food sources, causing intestinal pathology. (1,3)Primary infection is asymptomatic in most individuals resulting in vague illness and latent TB. People

with latent TB have a 10% lifetime risk of developing active TB but high risk groups such as persons infected with the human immunodeficiency virus (HIV), those with diabetes mellitus, or those who smoke cigarettes are at much higher risk of developing active disease after infection. (4) Post-primary pulmonary tuberculosis symptoms manifest gradually, with the onset of symptoms taking many weeks hence a delay in the time between infection and manifestation of symptoms, and seeking help at health facilities.(5) The symptom complex most commonly complained of is a combination of a cough for longer than two weeks, haemoptysis, night sweats, fever, loss of weight, shortness of breath and pleuritic chest pain. (5) When TB causes disease in other organ systems, symptoms presented are appropriate to the system involved.(2) TB is treated with a combination of oral and injectable chemotherapeutic agents. Some mycobacteria are resistant to one or more of the first line chemotherapeutic regimens, and the patients will then be infected with what is known as multi-drug resistant TB (MDR-TB) or extremely drug-resistant TB (XDR-TB) and require specialised treatment regimens.(3) TB is curable, however up to 66% of individuals with TB will die without proper treatment. (4)

### **Global tuberculosis Epidemiology**

Although curable, TB remains a serious global threat to public health. (6) It is estimated that approximately one in every three people globally is infected with latent TB.(7) It is ranked as the second largest cause of death by infectious disease, HIV being the first. (8) In 2011, 8.7 million TB cases were reported world-wide, with 1.4 million deaths directly attributable to TB. It occurs in every country in the world, with the highest burden borne by developing countries in the regions of Asia and Africa. (9) This is intimately linked with levels of poverty. Overcrowding, poor living conditions, malnutrition and individual access to health facilities are considered major social causes of tuberculosis, and imperative to tackle in order to stop transmission.(10) According to the Global Tuberculosis Report 2012, South-East Asia and the Western pacific regions account for 60% of cases, with 24% of cases in the Africa region. The Africa region also has the highest death rates per capita from TB. (9) Global awareness of the scope of morbidity and mortality caused by TB resulted in The United Nations including the target of halting and reversing the global TB epidemic by 2015 in its Millenium Development Goals. (11) Since 2010, the global TB incidence rate has decreased by 2.2% and

since 1990 TB mortality has declined by 41%. But these overall achievements overshadow the slow progress made in the African Region, which is not on target to achieve the MDG for tuberculosis by 2015. Furthermore Africa hosts almost 80% of the global total of TB cases who also have HIV.(9)

### **Tuberculosis epidemiology in high risk groups of people infected with the human immunodeficiency virus, those with diabetes mellitus, and smokers**

The number one risk factor for developing TB in both those with latent and new TB infection is infection with HIV. TB is also the number one cause of death in persons with HIV, and approximately one in four AIDS-related deaths worldwide can be attributed to TB.(12) People living with HIV, have a far greater risk of developing active TB than those without HIV. The figures estimated by the World Health Organisation (WHO) show that people living with HIV are at 20 to 37 times greater risk of getting TB, and of dying of TB. (7,12) This is due to the fact that HIV hinders the body's cellular immune system, thus it both increases the chance of reactivating latent TB, and causes rapid progression of disease after infection or reinfection. (13)Furthermore, the African region had the greatest proportion globally of reported HIV-positive TB cases at 79%.(9)

Beside the additional threat of HIV, the increasing prevalence of non-communicable diseases, such as diabetes mellitus and smoking-related conditions, provides the next wave of high risk groups to target for TB control.(14). In places where HIV prevalence is low, non-communicable diseases such as and smoking, may contribute more to the development of active TB than HIV.(14)

Diabetes mellitus and the association with TB is a link that has been recognised since ancient times, and one that is backed up by strong scientific evidence. The rapid escalation of diabetes mellitus globally has been said to be as great a threat to global tuberculosis control in some areas as the rise of HIV. (15) The global prevalence of diabetes mellitus is expected to more than double by 2030 with 7 out of the 10 countries with expected highest diabetes mellitus prevalence also rated as high TB burdened countries. (14,16) People with diabetes mellitus are at much greater risk of developing active TB disease, in some cases

approximately 2-3 times greater risk, than those without diabetes mellitus. This is irrespective of geographical area or study design. (17) (18) The mechanisms by which tuberculosis infection risk is increased in people with diabetes mellitus are not specifically clear, but it is proposed that it hinders the functioning of immune system components (phagocytes, monocytes and lymphocytes) and thus retards the body's defence systems against TB. This is similar to the mechanisms induced by HIV and thus the clinical manifestations and presentations of TB in diabetes mellitus may be similar to those with HIV. (17)

The association between cigarette smoking and TB, regardless of the type of smoke exposure or TB outcomes, has been consistently demonstrated. Smokers, compared to those who do not smoke, have an increased risk of having a positive tuberculin skin test (TST), of having active TB and of dying of TB.(19) When considered in isolation, smoking is the top cause of preventable death worldwide, with most deaths occurring in low to middle income countries where TB prevalence is also high.(19) A mathematical modelling analysis undertaken in 2011 predicted that smoking would cause an excess of 18 million TB cases and 40 million TB deaths between 2010 and 2050 if the current smoking trend trajectory continued. The model also anticipates the effect of smoking would increase the TB cases by 7% and the deaths by 66% compared to models that did not account for smoking. (20)

These groups of people living with HIV, those with diabetes mellitus and those who smoke cigarettes are at higher risk of developing TB than those without these additional influences and thus warrant extra focusing of efforts in screening for and detecting TB.

### **Screening for TB**

The global control of TB is guided by three main strategies proposed by the World Health Organisation: finding and diagnosing cases and treating active disease, recognising latent infection and treatment of latent infection, and vaccination against TB using the BCG vaccine. However, treatment of latent infection is not practiced widely as standard procedure, and BCG vaccination coverage is limited as it is poorly effective in the prevention of adult cases. Thus the main focus of control is case-finding and active-disease treatment.(21)

Case-finding can be passive or active. Passive case-finding relies on patients presenting with symptoms of TB disease at health facilities where they are then screened, diagnosed and treated. Patients are essentially volunteering their symptoms to health care professionals. (21)

Passive case-finding, although currently the main mechanism for finding TB cases, is limited by the fact that:

- a large percentage of people who have bacteriologically confirmed TB do not experience symptoms for which they would consider seeking medical assistance and so are missed cases;
- those who do experience some symptoms do not necessarily fulfil the criteria required for further investigation and confirmation of TB (an estimated 50-60% of bacteriologically confirmed TB cases did not fulfil the TB symptom screening criteria of 2 to 3 weeks of cough);
- many persons with TB symptoms present at a late stage to health facilities and thus remain infectious in the community for long periods of time;
- and passive case-finding assumes that patients have good access to TB services which is often not the case in high burden areas.(22)

Active case-finding is proposed as a potential strategy for enhancing screening and detection in the general population and high risk groups.(22) This is also known as intensified case-finding or provider-initiated screening. It involves actively looking for tuberculosis by screening in communities, and in high risk groups to detect new cases of TB that would otherwise not be detected in the health facility and to detect cases earlier than they would normally present to the health facility. Earlier initiation of treatment will prevent the progression of disease and decrease the infectious period of an individual in the community. (22,23) Mathematical models using current WHO strategies, show that active case-finding would have substantial benefits in the fight against TB. For example, active case-finding using symptoms screening of the entire general community every seven years could detect up to 66% of smear-positive cases. This is based on the assumption that national TB control



programmes continue to expand, that there is capacity for further investigation in those reporting symptoms, and that at least 90% of those with active TB start treatment and attain cure.(23)

## Screening using symptoms

Symptom-screening is the primary tool in active-case-finding for tuberculosis and this has been shown to have a high-yield especially where resources are limited and TB burden is high.(21,24,25) Symptom screening implies that those who do not perceive that they have symptoms of TB, and those who may perceive they have symptoms but do not have easy access to TB services, are actively and systematically investigated depending on the rule of the screening tool.(22) The simplest and most cost-effective screening tool employed is a symptom questionnaire, asking primarily about duration of cough, ( more than two weeks), but also coughing up blood, loss of weight, night sweats, fever and malaise.(26,25) Other respiratory symptoms such as shortness of breath and chest pain may be considered.

Symptom screening is effective in detecting TB in primary health care settings. (27) However, symptom screening may not be as effective during active case-finding for TB. A community survey conducted in 2002 in South Africa compared the TB case yield using active versus passive case-finding, employing a symptoms questionnaire as the tool. They found that active case-finding (ACF) using a symptom screening tool detected TB cases, but that cases found in the community by active case-detection were less symptomatic than those presenting at the health facility in high burden areas. The figures presented showed that 41% (OR 3.72, 95%CI 1.47-9.34) of bacteriologically confirmed ACF cases did not cough, 85% (OR 3.20, 95%CI 1.03-9.93) of ACF cases did not have haemoptysis, 59% (OR 3.35, 95%CI 1.40 – 7.99) did not have night sweat, 89% (OR 4.28, 95%CI 1.21 -15.14) did not report fever and 56% (OR 11.14, 95% CI 4.17-29.74) did not report weight loss. (25) A similar study conducted in two Zambian communities showed that many participants in the community with bacteriologically confirmed TB did not meet the criteria for TB according to the screening algorithm using classical TB symptoms. Only 43% (N=79) met the criteria, with only 51% (N=79) of TB cases reporting any coughing.(28)

These and similar studies suggest that while symptom screening may not be sufficient to detect all cases of active TB, as those detected in the community may be less symptomatic, more sensitive screening tests may not be economically feasible or practical in poorly-resourced areas. (24,26,28,29)

### **Symptom screening in high risk groups**

The efficiency of using TB symptom screening as a means of detecting TB has been investigated in the high risk groups of people living with HIV but not those with diabetes mellitus and smokers. TB symptom presentation may be different for each of these high-risk groups thus the symptom-screening tool may need to be adapted for each these groups.

The WHO recommends collaborative TB/HIV activities such as “The Three I’s” (intensified case-finding, isoniazid preventive therapy and infection control) as part of the core TB and HIV prevention strategy.(12) Intensified case-finding involves actively screening for TB in HIV positive individuals. Recent guidelines for provider initiated TB screening have been developed following a large evidence base for TB symptom reporting in HIV positive individuals. Traditional symptom screening of a cough for more than three weeks has been shown to be insufficient for the detection of TB in people living with HIV, but may be useful in reliably excluding TB when no other screening tests are available. (24,30) These and other studies concluded that HIV-infected adults, who have any one of the symptoms of current cough, fever, loss of weight, or night sweats may have TB and should be investigated further. Furthermore, they showed that in the absence of these symptoms, one could reliably exclude TB in ART naive HIV-infected clients. (31)(32) The negative predictive value (NPV) of this screening rule was 97% ( 95% CI 97.4%-98.0%) and 90.0% ( 95%CI 88.6%-91.3%) at a TB prevalence of 5% and 20% respectively in HIV-positive people. (32) These results informed the current WHO algorithm for TB screening in HIV positive people in high HIV burden communities(33).

Intensifying case detection among patients with diabetes mellitus, and screening for TB in patients with diabetes mellitus on other indications besides symptoms is considered a high priority by the WHO and forms part of the research agenda in the fight against TB. (34)(35) The evidence base is not comprehensive enough for the development of a collaborative diabetes mellitus and TB framework such as that for HIV.(34) There are key research questions that remain unanswered, and that are necessary for the development of this framework, among them, how to screen for TB in patients with DM, and whether the clinical picture of TB is different in DM. (17, 36, 37)

The situation is similar with regards the effect of smoking on TB symptoms. (38)

### **e) Need for further research.**

There is a paucity of evidence to guide the adaptation of screening tools using symptoms in high risk groups for TB such as those with diabetes mellitus or those who smoke cigarettes. As has been explored in the literature review, active case-finding in the community using TB symptom screening is a necessary strategy for employment in the fight against TB. Thus, the literature review supports the need for the investigation of TB symptom manifestation in persons living with HIV, with diabetes mellitus and smokers, as they are high-risk groups for tuberculosis.

Data collected during a large TB prevalence survey conducted in 2010 in 24 communities across Zambia and the Western Cape South Africa, will be analysed to investigate the prevalence of self-reported symptoms of TB in cases with bacteriologically confirmed TB and controls without TB disease stratified by HIV, diabetes mellitus and smoker status

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# **PART C:** Journal ready manuscript

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**Journal formatted according to the guidelines required for the  
International Journal of Tuberculosis and Lung Disease**

*Variations on journal submission guidelines for thesis purposes:*

- *tables included in text as opposed to at the end of the manuscript*
- *Continuous line numbering omitted for ease of binding*

# Influence of human immunodeficiency virus, smoking and hyperglycaemia on tuberculosis symptoms in a tuberculosis prevalence survey

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## ABSTRACT

**Setting:** Tuberculosis prevalence survey conducted in 24 high tuberculosis and human immunodeficiency virus burden communities in Zambia and the Western Cape, South Africa.

**Objective:** To assess the effect of human immunodeficiency virus, hyperglycaemia, and smoking on self-reported tuberculosis symptoms.

**Design and methods:** Odds ratios and 95% confidence intervals were calculated for self-reported TB symptoms and smoking, human immunodeficiency virus (Abbot Determine HIV test), and/or hyperglycaemia (finger-prick glucose test) or self-reported diabetes mellitus categorised by TB status (confirmed through 16S DNA sequencing).

**Results:** Human immunodeficiency virus (OR 3.17 95%CI 2.66-3.87) and smoking (OR 1.27 95%CI 1.03-1.58) are risk factors for tuberculosis. Hyperglycaemia showed no association. Tuberculosis cases who smoke were less likely to report symptoms than non-smoking cases (OR 0.76 95%CI 0.54-1.07). Tuberculosis cases with human immunodeficiency virus were less likely to report any symptoms compared to participants in South Africa (OR 0.85 95%CI 0.64-1.14) without human immunodeficiency virus, but more likely in Zambia (OR 6.25 95%CI 3.26-11.97). Reporting 1 up to 3 symptoms of cough, fever, night sweats or loss of weight had NPVs of 60.3-92.5% in smokers without human immunodeficiency virus.

**Conclusions:** Smokers who do not report symptoms of cough, fever, night sweats or loss of weight can be excluded from further diagnostic testing.



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## INTRODUCTION

The prevalence of smoking, diabetes mellitus and human immunodeficiency virus (HIV) is increasing in the high tuberculosis-burdened areas of low to middle-income countries. These conditions are also risk factors for developing tuberculosis (TB). (1–5)

Tobacco smoking, the leading global cause of preventable death, has consistently been shown to be associated with an increased risk of TB infection, disease and mortality. (3,6,7) Recent modelling has suggested that should smoking trends continue along current trajectories, between 2010 and 2050 smoking would produce over 18 million TB cases and 40 million TB deaths (8).

TB is more common among diabetic patients.(9) It is estimated that among the countries with the highest TB burden, up to 12.5% of incident TB cases will be attributable to diabetes mellitus (DM) by 2013, raising the potential for TB and DM syndemics. (10,11)However, there is limited knowledge and experience on how to screen diabetic patients for TB in the most appropriate and cost-effective way. The convergence of the TB and diabetes mellitus epidemics motivates operations research on the yield of intensified case-finding among these patients. (10,12–15)

In people living with the human immunodeficiency virus (HIV), even in those on anti-retroviral therapy, TB is the leading cause of death: approximately 25% of all AIDS deaths globally are due to TB. Those living with HIV have between 20 and 37 times greater relative risk of TB than the rest of the population. (4,16,17) However, traditional symptom screening of a cough for more than three weeks has been shown to be insufficient for the detection of TB in those who are HIV-infected.(18)

Guidelines for active TB screening specifically among HIV-infected individuals have recently been developed by the World Health Organisation and are being implemented by national TB programmes. These guidelines recommend that adults and adolescents living with HIV who have any one of the symptoms of current cough, fever, loss of weight or night sweats may have active TB and should be evaluated for TB and other diseases. (19,20) No such evidence-based guidelines exist for clients with diabetes mellitus, and those who smoke. (11,13,21)

Passive TB case finding relies on patients volunteering symptom information, whereas active case-finding implies actively soliciting information and screening for tuberculosis. With the move towards active case finding (especially in areas with a high TB burden and high prevalence of HIV, diabetes mellitus, and smoking) it is important to determine whether self-reporting of TB

symptoms can be used as a screening tool for people who are HIV-infected, those who smoke or have diabetes mellitus.

Our study aims to investigate the prevalence of self-reported symptoms of TB in cases with bacteriologically confirmed TB and controls without TB disease, stratified by HIV, DM and smoker status, and identified during active case finding in a prevalence survey. We also aim to determine the predictive values, sensitivities and specificities of individual symptoms and groups of symptoms in determining TB in these risk groups.

## **METHODS**

### **Study setting and participants**

Data from a large household TB prevalence survey conducted in 8 communities in South Africa, and 16 in Zambia in 2010 were utilised for analysis. This survey in high TB and HIV burdened communities, identified the prevalence of culture-confirmed TB, the primary endpoint of the 3-year community randomised intervention trial called ZAMSTAR (The Zambia South Africa TB and AIDS Reduction study).<sup>(22)</sup> Geographical cluster sampling was used to randomly select census enumeration areas and people who slept in all the houses in the selected enumeration areas were eligible to participate in the prevalence survey. Adults (older than 18 years) were enrolled and gave written informed consent.

### **Data collection**

Trained research assistants recruited participants door-to-door in the community and administered a questionnaire which obtained information regarding demographics, reporting of TB symptoms, previous TB history, smoking history, diabetic status, HIV status regarding TB, and risk factors for TB. Questions were read to participants and recorded using handheld electronic devices.

All participants were also asked to provide sputum samples for TB culture. Samples were kept in a cool box and transported to the laboratory within 48 hours. Sputum smears were performed on all samples and each of the sputum samples were inoculated onto 2 MGIT tubes. Spoligo-typing was performed to check for laboratory cross-contamination on randomly selected positive samples handled on the same day. All positive cultures were further processed by doing a Ziehl-Neelson smear for acid fast bacilli and by performing MPB64 assays. Those samples that were positive on ZN and PMB64 were subjected to 16sRNA sequencing to confirm *Mycobacterium tuberculosis*. These confirmed cases were referred to their local clinics for further management.

Participants were encouraged by the research assistants to consent to HIV counselling and testing (HCT) and to have their glucose levels tested. HCT was performed either in the house or in a mobile HCT tent in the community, and managed according to in-country HCT guidelines. Individuals who tested HIV-positive on Abbot Determine HIV 1/2 test had a confirmatory test using Unigold. If the 2 tests were discordant, a tie-breaker was done in the health facility.

Rapid random blood glucose testing through the collection of a capillary blood sample was performed in the homes of participants or in the mobile HCT tents using a glucometer.

## Data variables and definitions

### Symptom Reporting

Participants were asked to provide yes/no responses to questions regarding their symptom experiences of current cough, chest pain, fever, night sweats, loss of weight and shortness of breath.

### Smoking

“Current smokers” at the time of the survey were determined via questionnaire. Participants who answered “yes” to the question “have you ever smoked” and also answered that they had not stopped smoking were defined as current smokers.

### HIV

HIV positive participants were defined as those with a confirmed positive HIV rapid test result, supplemented by the self-reporting of HIV status for individuals who did not give a blood sample for HIV testing.

### Hyperglycaemia

Participants were defined as hyperglycaemic if a random capillary blood glucose was  $\geq 11.1$ mmol/L and/or if they self-reported that they were diabetic.(23,24)

### TB case

Study participants whose sputum samples were positive for Mycobacterium tuberculosis on 16s RNA sequencing were considered TB cases.

## Data Analysis

Data were analysed using the statistical analysis programme STATA 12 for Windows (StataCorp LP, College Station, TX, USA). Odds ratios (OR) were calculated as a measure of association between reported symptoms and the influence of HIV, smoking, and hyperglycaemia for both confirmed TB cases and non-TB cases. Odds ratios and their 95% confidence intervals were calculated using a robust standard errors logistic regression model that adjusts for clustering at a community level. Interactions between TB and the influence of HIV, hyperglycaemia and smoking as well as differences between the two countries in self-reporting of symptoms were explored. Country of residence, age, sex, employment and education status were considered as possible confounders. The sensitivities, specificities and predictive values for TB in HIV positive, currently smoking and hyperglycaemic participants were calculated in lieu of the screening rule developed by Getahun et al. (19).

## Ethics

Ethics approval for the ZAMSTAR prevalence survey was obtained from the University of Zambia Research Ethics Committee and the London School of Hygiene and Tropical Medicine's Ethics Committee. Ethics approval for this study was obtained from The Human Research Ethics Committee of the University of Cape Town and from the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease as part of TREAT TB. No name identifiers were used during the collection of data during the ZAMSTAR TB Prevalence survey and participants were assigned unique bar code identifiers. No names were linked to results during data extraction from the locked ZAMSTAR database.

## RESULTS

A total of 123 790 participants were enumerated from all 24 sites and 90 601 (73.2%) consented. Of these 26 138 were excluded (missing, or contaminated specimens), leaving a total evaluable response of 64 463 participants. The response rate was thus 52.1%. 894 (1.4%) of the 64 463 were confirmed with TB, and 529 of these (59.2%) reported any TB symptoms. This is proportionally higher than the 21 792 (34.3%) non-TB cases reporting any symptoms.

**Table 1a: ZAMSTAR PREVALENCE SURVEY PARTICIPANT'S CHARACTERISTICS**

	Zambia(1)		South Africa (2)		Total	
participants	34446 (53.4%)		30017 (46.6%)		64463 (100.0%)	
	Non TB case n=34254 (99.4%)	TB case n=192 (0.6%)	Non TB case n=29315 (97.7%)	TB Case n=702 (2.3%)	Non TB case n=63569 (98.6%)	TB case n=894 (1.4%)
<b>Sex</b>						
<b>male (1)</b>	11546(33.7)	92(47.9)	10964(37.4)	333(47.4)	22510(35.4)	425 (47.5)
<b>female (2)</b>	22708(66.3)	100(52.1)	18351(62.6)	369(52.6)	41059(60.6)	469 (52.5)
<b>Age Categories (y)</b>						
<b>15-24</b>	12124(35.4)	45(23.4)	8650(29.5)	169(24.1)	20774(32.7)	214(23.9)
<b>25-34</b>	10047(29.3)	82(42.7)	8970(30.6)	197(28.1)	19017(29.9)	279(31.2)
<b>35-44</b>	5154(15.0)	42(21.9)	5436(18.5)	141(20.1)	10590(16.7)	183(20.5)
<b>45-54</b>	3142(9.2)	12(6.3)	373(1.3)	107(15.3)	6515(10.3)	119(13.3)
<b>55+</b>	3787(11.1)	11(5.7)	2886(9.9)	88(12.6)	6673(10.5)	99(11.1)
<b>Education</b>						
<b>none</b>	1959(5.7)	12(6.3)	1099(3.8)	40(5.70)	3058(4.8)	52(5.8)
<b>primary</b>	10979(32.1)	75(39.1)	5522(18.8)	189(26.9)	16501(26.0)	264(29.5)
<b>secondary</b>	18389(53.7)	98(51.0)	21429(73.1)	456(65.0)	39818(62.6)	554(62.0)
<b>tertiary</b>	2927(8.5)	7(3.7)	1265(4.3)	17(2.4)	4192(6.6)	24(2.7)
<b>Employed</b>						
<b>not employed</b>	21478(62.7)	114(59.4)	19709(67.2)	500(71.2)	41187(64.8)	614(68.6)
<b>employed</b>	12776(37.3)	78(40.6)	9606(32.8)	202(28.8)	22382(35.2)	280(31.3)
<b>Has symptoms</b>						
<b>no symptoms</b>	23878(69.7)	74(38.5)	17899(61.1)	291(41.5)	41777(65.7)	365(40.8)
<b>any symptoms</b>	10376(30.3)	118(61.5)	11416(38.9)	411(58.5)	21792(34.3)	529(59.2)
<b>Cough</b>						
<b>no</b>	30338(88.6)	106(55.2)	25683(87.6)	469(66.8)	56021(88.1)	575(64.3)
<b>yes</b>	3916 (11.4)	86(44.8)	3632(12.4)	233(33.2)	7548(11.9)	319 (35.7)
<b>Fever</b>						
<b>no</b>	32433(94.7)	145(75.5)	23929(81.6)	522(74.4)	56362(88.7)	667(74.6)
<b>yes</b>	1821(5.3)	47(24.5)	5386(18.4)	180(25.6)	7207(11.3)	227(25.4)
<b>shortness of breath</b>						
<b>no</b>	32224(9.4)	151(78.7)	26866(91.7)	578(82.3)	59090(93.0)	729(81.5)
<b>yes</b>	2030(5.9)	41(21.4)	2449(8.4)	124(17.7)	4479(7.1)	165(18.5)

	Zambia(1)		South Africa (2)		Total	
participants	34446 (53.4%)		30017 (46.6%)		64463 (100.0%)	
	Non TB case n=34254 (99.4%)	TB case n=192 (0.6%)	Non TB case n=29315 (97.7%)	TB Case n=702 (2.3%)	Non TB case n=63569 (98.6%)	TB case n=894 (1.4%)
<b>loss of weight</b>						
no	29850(87.1)	129(67.2)	25172(85.9)	486(69.2)	55022(86.5)	615(68.8)
yes	4404(12.9)	63(32.8)	4143(15.7)	216(30.8)	8547(13.5)	279(31.2)
<b>night sweats</b>						
no	32281(94.2)	150(78.1)	24675(84.2)	484(69.0)	56956(89.6)	634(70.9)
yes	1973(5.8)	42(21.88)	4640(15.8)	218(31.0)	6613(10.4)	260(29.1)
<b>chest pain</b>						
no	31428(91.8)	140(72.9)	26306(89.7)	559(79.6)	57734(90.8)	699(78.2)
yes	2826(8.3)	52(27.1)	3009(10.3)	143(20.4)	5835(9.2)	195(21.8)
<b>Number of Symptoms</b>						
no symptoms	23878(69.7)	74(38.5)	17899(61.1)	291(41.5)	41777(65.7)	365(40.8)
1 symptom	6412(18.7)	30(15.6)	5162(17.6)	125(17.8)	11574(18.2)	155(17.3)
2 symptoms	2332(6.8)	27(14.1)	3016(10.3)	81(11.5)	5348(8.4)	108(12.1)
3 symptoms	950(2.8)	30(15.6)	1696(5.8)	75(10.7)	2646(4.2)	105(11.7)
4 symptoms	424(1.2)	6(3.1)	916(3.1)	67(9.5)	1340(2.1)	73(8.2)
5 symptoms	200(0.6)	17(8.9)	443(1.5)	44(6.3)	643(1.0)	61(6.8)
6 symptoms	58(0.2)	8(4.2)	183(0.6)	19(2.7)	241(0.4)	27(3.0)
<b>Hyperglycaemia</b>						
no	26782(78.2)	139(72.4)	10035(34.2)	259(36.9)	36817(57.9)	398(44.5)
yes	936(2.7)	6(3.1)	2343(8.0)	52(7.4)	3279(5.2)	58(6.5)
missing	6536(19.1)	47(24.5)	16937(57.8)	391(55.7)	23473(36.9)	438(49.0)
<b>current smoker</b>						
no	31605(92.3)	162(84.4)	26545(90.5)	611(87.0)	58150(91.5)	773(86.5)
yes	2649(7.7)	30(15.6)	2770(9.5)	91(13.0)	5419(8.5)	121(13.5)
<b>HIV</b>						
negative	23930(69.9)	86(44.8)	15147(51.7)	302(43.0)	39077(61.5)	388(43.4)
positive	4894(14.3)	80(41.7)	2882(9.8)	143(20.4)	7716(12.1)	223(24.9)
missing	5430(15.9)	26(13.5)	11346(38.7)	257(36.6)	16776(26.4)	283(31.7)

Cough was the most commonly reported symptom among TB cases (35.7%), followed by loss of weight (31.2%) and night sweats (29.1%). 266 (29.8%) of TB cases reported 3 or more TB symptoms.

A total of 221 (24.9%) TB cases were HIV positive, 121 (13.5%) were current smokers, and 58 (6.5%) had hyperglycaemia. The proportions of HIV positive cases and smokers were lower in non-TB cases (12.1% and 8.5% respectively), and only marginally lower for hyperglycaemic non-TB cases (5.2%).

TB cases and non-TB cases comparisons were similar in both countries. There was a trend for less prevalence TB in the more educated participants. (**table 1a**).

Both HIV (OR 3.17 95% CI 2.66-3.87) and current smoking (OR 1.27 95% CI 1.03-1.58) were risk factors for TB when controlling for age, sex, community and education. However, hyperglycaemia was not a significant risk factor for TB (OR 0.94, 95% CI 0.7 – 1.27) (**Table 1b**). Hyperglycaemia was excluded from further analysis.

**Table 1b: Risk factor association with TB outcome**

	Univariate				Controlling for age, sex, education			
	OR	P-value	95% CI		OR	p-value	95% CI	
<b>HIV</b>								
<b>Zambia</b>	4.55	<0.001	3.35	6.18	4.18	<0.001	3.01	5.81
<b>South Africa</b>	2.54	<0.001	2.07	3.11	2.84	<0.001	2.30	3.52
<b>Both*</b>	2.91	<0.001	2.46	3.44	3.17	<0.001	2.66	3.78
<b>Current Smoker</b>								
<b>Zambia</b>	2.21	<0.001	1.49	3.27	1.27	0.287	0.82	1.98
<b>South Africa</b>	1.43	<0.001	1.14	1.79	1.24	0.085	0.97	1.59
<b>Both*</b>	1.68	<0.001	1.38	2.04	1.27	0.026	1.03	1.58
<b>Hyperglycaemia</b>								
<b>Zambia</b>	1.24	0.614	0.54	2.80	1.38	0.448	0.60	3.19
<b>South Africa</b>	0.86	0.326	0.64	1.16	0.84	0.292	0.61	1.16
<b>Both*</b>	1.64	0.001	1.24	2.16	0.94	0.707	0.70	1.27

\*also controlling for country

**Table 2a: Effect of smoking on symptom reporting by TB diagnosis (controlling for age, sex and country)**

	TB cases			Non TB cases		
	OR	95% CI		OR	95% CI	
<b>any symptom</b>	0.76	0.54	1.07	1.50	1.14	1.98
<b>two or more</b>	0.84	0.57	1.25	1.72	1.30	2.28
<b>three or more</b>	0.99	0.61	1.60	1.90	1.48	2.44
<b>four or more</b>	0.68	0.37	1.26	1.97	1.47	2.62
<b>cough</b>	1.06	0.73	1.54	1.62	1.29	2.03
<b>chest pain</b>	0.57	0.33	0.99	1.51	1.26	1.81
<b>fever</b>	1.07	0.62	1.84	1.26	0.90	1.77
<b>night sweats</b>	0.85	0.58	1.24	1.80	1.42	2.29
<b>loss of weight</b>	0.66	0.47	0.92	1.60	1.23	2.09
<b>shortness of breath</b>	0.58	0.26	1.28	1.50	1.28	1.77

TB cases were less likely to report any symptoms if they were current smokers (OR 0.76, 95% CI 0.54 – 1.07), compared to non-smokers (**Table 2a**). The effect of HIV on symptom presentation in TB cases varies markedly by country, with a bigger effect seen in Zambia. This was not the case with smoking. TB cases with HIV were less likely to report any TB symptoms in South Africa (OR 0.85, 95%CI 0.64 – 1.14), but significantly more likely to report their symptoms in Zambia (OR 6.25, 95% CI 3.26 – 11.97) (**Table 2b**).



The associations between risk factors and symptom presentation were different in non-TB cases. Participants were significantly more likely to report any TB symptoms if they were not a TB case but had either of the risk factors of HIV or smoking. The effect of HIV on symptom reporting in non-TB cases did not differ by country (**Tables 2a and 2b**).

Current cough was the most common symptom reported among all TB cases regardless of additional influences. The specific symptom reporting among smokers and HIV positive participants is variable. TB cases who smoke were less likely to report loss of weight than non-smoking TB cases, HIV positive cases were more likely to report chest pain, cough and loss of weight than HIV negative TB cases.

Both TB cases and non TB cases are more likely to report symptoms if HIV positive compared to HIV negative. Smokers who have TB are less likely to report symptoms than non-current smokers, whereas smokers who do not have TB are more likely to report symptoms than non-current smokers.

**Table 2b: Effect of risk factors on reporting of symptoms by TB diagnosis and country.(Controlling for age and sex)**

	SOUTH AFRICA						ZAMBIA						
	TB case			Non TB Case			TB case			Non TB Case			
HIV -infected	OR	95% CI		OR	95% CI		HIV -infected	OR	95% CI		OR	95% CI	
<b>any symptom</b>	0.85	0.64	1.14	1.39	1.30	1.49	<b>any symptom</b>	6.25	3.26	11.97	1.66	1.05	2.67
<b>two or more</b>	1.08	0.83	1.41	1.62	1.40	1.86	<b>two or more</b>	5.55	2.80	11.00	2.04	1.86	2.25
<b>three or more</b>	1.18	0.96	1.44	1.84	1.53	2.20	<b>three or more</b>	3.54	1.73	7.27	2.52	2.25	2.82
<b>four or more</b>	1.72	0.93	3.20	2.06	1.75	2.43	<b>four or more</b>	2.00	0.67	5.94	2.89	2.31	3.60
<b>cough</b>	1.14	0.78	1.67	1.56	1.46	1.67	<b>cough</b>	3.33	1.72	6.44	1.81	1.66	1.98
<b>chest pain</b>	1.48	1.00	2.18	1.61	1.48	1.76	<b>chest pain</b>	1.63	0.86	3.10	1.45	1.30	1.61
<b>fever</b>	0.88	0.60	1.29	1.25	1.09	1.43	<b>fever</b>	4.44	1.60	12.34	1.88	1.66	2.13
<b>night sweats</b>	1.10	0.77	1.58	1.52	1.30	1.78	<b>night sweats</b>	3.54	1.40	8.97	2.03	1.77	2.31
<b>loss of weight</b>	1.17	0.72	1.91	1.75	1.46	2.10	<b>loss of weight</b>	4.71	2.32	9.57	1.81	1.51	2.15
<b>shortness of breath</b>	1.32	0.77	2.24	1.42	1.26	1.60	<b>shortness of breath</b>	1.51	0.61	3.78	1.85	1.55	2.21

We applied the Getahun symptom screening rule to determine sensitivities, specificities and predictive values for TB in HIV positive, and currently smoking participants separately. (19)

**Table 3: Test characteristics of association of various symptoms with TB in groups identified by the ZAMSTAR prevalence survey**

	OR	NPV	PPV	Sens	Spec
<b>HIV negative 39465 (61.2%)</b>					
cough	4.14	99.3%	2.9%	34.8%	88.6%
fever	2.73	99.2%	2.3%	24.2%	89.5%
night sweats	4.11	99.2%	3.1%	29.6%	90.7%
weight loss	2.84	99.2%	2.2%	29.6%	87.1%
1 or more	3.17	99.4%	1.9%	57.2%	70.4%
2 or more	4.39	99.3%	3.1%	34.0%	89.5%
3 or more	7	99.2%	5.5%	19.1%	96.7%
<b>HIV positive 7939 (12.3%)</b>					
cough	3.7	98.1%	6.8%	44.4%	82.3%
fever	2.77	97.7%	6.0%	30.9%	86.1%
night sweats	2.9	97.8%	6.2%	31.8%	86.2%
weight loss	2.77	97.9%	5.5%	42.6%	78.9%
1 or more	3.1	98.5%	4.6%	67.3%	60.0%
2 or more	4.41	98.2%	7.4%	48.4%	82.4%
3 or more	4.74	97.8%	9.8%	26.5%	92.3%
<b>Non-smoker (HIV –ve) 36484 (56.6%)</b>					
cough	4.57	99.3%	3.0%	35.9%	89.1%
fever	2.96	99.2%	2.3%	25.4%	89.7%
night sweats	4.68	99.3%	3.3%	30.6%	91.4%
weight loss	3.32	99.3%	2.4%	32.1%	87.6%
1 or more	3.58	99.5%	1.9%	59.2%	71.2%
2 or more	5.06	99.3%	3.3%	35.9%	90.1%
3 or more	8.54	99.2%	6.2%	20.4%	97.1%
<b>Smoker (HIV –ve) 2981 (4.6%)</b>					
cough	1.7	98.70%	2.3%	26.7%	82.4%
fever	1.26	98.50%	1.8%	15.6%	87.3%
night sweats	1.34	98.60%	1.9%	22.2%	82.4%
loss of weight	0.54	99.10%	1.7%	88.9%	18.7%
1 or more	1.11	98.60%	1.6%	42.2%	60.3%
2 or more	1.18	98.50%	1.7%	20.0%	82.6%
3 or more	1.21	98.5%	1.8%	8.9%	92.5%

Irrespective of HIV or smoking status, the screening rule of 3 or more symptoms had high specificities and NPVs. Specificities for 3 or more symptoms ranged from 92.3% to 97.2%, and 97.8% to 99.4% for NPVs. There is almost no difference in NPVs and specificities between 1 or more symptoms, and 3 or more symptoms across risk factor status.

Sensitivities and PPVs were consistently low across risk factor status and number of symptoms reported except for current smokers who are HIV negative, where weight loss had a high sensitivity out of keeping with other individual symptoms at 88%. When examined by country, specificities, sensitivities, and predictive values were similar. However, the sensitivity of this screening rule was only considered high in Zambia, among HIV positive cases (81.3%). Specificities were low across all risk factors by country ranging from 50.7% to 66.7%.

## **DISCUSSION**

In table 1b we show that hyperglycaemia is not a risk factor associated with TB in this population, thus it was not considered for further analysis in ascertaining symptom-reporting likelihoods as there would be no added benefit in this population.

Furthermore, we were limited in that participants were only offered a single, random blood glucose test. This is not sufficient criteria to confirm a DM diagnosis, nor to make inferences regarding DM and TB symptoms during analysis. A recent study conducted in Tanzania, showed that TB cases with confirmed DM were less likely to report TB symptoms than TB cases without DM, but none of these were significant results.(25)

TB cases who smoke are generally less likely to report their TB symptoms than TB cases who do not smoke. However, screening for TB in people who smoke is still a valuable strategy as NPVs were high.

Thus utilising a screening rule similar to the one developed by the WHO for people living with HIV can reliably exclude smokers from requiring further diagnostic testing.

In conjunction with confirmed evidence, we found that HIV is a large risk factor for tuberculosis.

Interestingly we found that

HIV positive TB cases in Zambia are much more likely to report any symptoms compared to HIV negative TB cases, whereas they were less likely to report any symptoms in South Africa. This may be due to a difference in perception of symptoms between South African and Zambian participants. Or, it could be argued that the reason TB cases who are HIV positive are less likely to report their symptoms in South Africa is because of better TB/HIV integration services; thus TB cases are diagnosed earlier and have less time to develop and report their symptoms. However, the reporting of symptoms also depends on the stage of the disease in the individual and the risk of TB is more likely in persons with a lower CD-4 count which we have not taken into account in this study.(26)

### **Strengths and limitations**

The ZAMSTAR prevalence survey was not designed to answer our research question and the initial response rate was low. Furthermore the prevalence survey provided limited information on smoking, and we were unable to confirm a formal diagnosis of diabetes mellitus based on the single random blood glucose level. Thus, we were limited instead to perform the analysis with respect to hyperglycaemia with or without a stated diabetic status, as opposed to diabetes mellitus.

Almost half of the TB cases had missing data regarding hyperglycaemic status, with the largest proportions coming from South Africa. A similar picture is seen regarding HIV status as almost a third of the TB cases had missing HIV data, with three times the number of missing data coming from South Africa than Zambia.

Symptom outcomes recorded with HIV associated TB were very different between the two study countries, limiting the ability to make conclusions from analysis of a country-combined dataset.

Major strengths of the study are that these data provide a large sample of bacteriologically confirmed TB cases who were detected outside of the health care system, and who have corresponding TB symptom, smoking, hyperglycaemia and HIV information acquired before diagnosis.

## **CONCLUSION**

TB cases who smoke are generally less likely to report symptoms. Screening this high risk group is worthwhile as if they do not report the symptoms of cough, fever, night sweats or weight loss, can reliably be excluded from needing further diagnostic testing. Further investigation into the TB symptom reporting in diabetic patients is warranted.

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