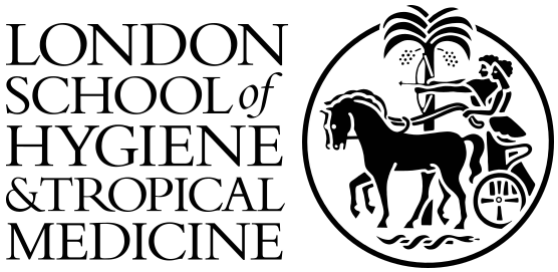

Title: A comparison of the yield and relative cost of four tuberculosis active case finding algorithms in Zimbabwe.

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ABSTRACT

Setting: 10 districts and 3 cities in Zimbabwe

Objective: To compare the yield and relative cost of identifying a case of tuberculosis (TB) using the three World Health Organization (WHO) recommended algorithms: WHO2b - symptom inquiry (SI) only; WHO2d - chest X-ray (CXR) after a positive SI; WHO3b - CXR only; and the Zimbabwe active case finding (ZimACF) algorithm – SI plus CXR to everyone.

Design: Cross-sectional study using data from the ZimACF project.

Results: 38,574 people were screened from April-December 2017 and 488(1.3%) were diagnosed with TB using the ZimACF algorithm. Using the WHO recommended algorithms, fewer TB cases would have been diagnosed. This ranged from 7% (34 cases) fewer with WHO3b, 18% (88 cases) with WHO2b, and 25% (122 cases) with WHO2d. Need for CXR ranged from 36%(WHO2d) to 100%(WHO3b). Need for bacteriological confirmation ranged from 7%(WHO2d) to 40%(ZimACF). The relative cost-per-case of TB diagnosed ranged from $180 with WHO3b to $565 for the ZimACF algorithm.

Conclusion: The ZimACF algorithm had the highest yield but at much greater cost-per-case than the WHO algorithms. The trade-off between cost and yield needs to be reviewed by the NTP and a decision to switch to algorithm WHO3b should be considered.

INTRODUCTION

Tuberculosis (TB) is the leading cause of deaths among infectious diseases globally. In 2017, nearly 1.2 million died and 10 million people were affected. [1, 2] Zimbabwe is among the 30 high-burden countries for TB.[3] Despite declining TB case notifications in the country, one-third of people with active disease remained undiagnosed in 2017. [1]

Active case finding (ACF) among high-risk groups (HRGs) is effective in identifying undiagnosed TB.[4-6] This leads to earlier initiation on treatment and thus reduce duration of being infectious and community transmission. [7] Modelling done in high-burden countries showed that implementing ACF over a 10 year period could reduce TB incidence and mortality by 27% and 44% respectively. [8] ACF is essential if global targets of the "End TB" Strategy are to be met. [8, 9]

Zimbabwe's National TB Programme (NTP) has been implementing ACF since 2017 and it is still ongoing. The aim is to identify people with undiagnosed TB cases in areas with estimated high proportions HRGs (see figure 1) and improve treatment coverage. World Health Organisation (WHO) is not clear on the most appropriate algorithm to use for ACF in resource-limited countries with high HIV and TB prevalence. [10] Countries are encouraged to select an algorithm that meets their primary objectives for ACF, consider their TB prevalence, HRGs being targeted, and the resources available.[4, 11, 12]

Around 10% of people diagnosed with active TB in some prevalence surveys are asymptomatic.[13-15] It is difficult to identify people with TB disease using symptoms alone in people living with HIV (PLHIV). It is often paucibacillary hence the need for clinical diagnosis.[16, 17] Zimbabwe which has a very high TB-HIV co-infection rate of 71%[1], so NTP designed an algorithm [18] which is appreciably different from those recommended by WHO [4] to address these concerns(table 1).

Literature that compares the yield and cost of WHO-recommended algorithms under programmatic condition is scarce. We only found one study from China that used data from elderly people from a TB prevalence survey.[19] However, the burden of both TB and HIV in their study population was much lower than that in Zimbabwe.

The ACF project in Zimbabwe is costly and consumes nearly 20% (over US$1.1 million dollars) of the total funding for TB in Zimbabwe annually and this was a concern for the NTP. They requested a review of the screening algorithm to determine if a comparable number of people with TB could be identified but at a reduced cost. The purpose of our study was to analyse the characteristics of the population screened in Zimbabwe and use the data to compare the yield and relative cost of identifying a case of TB if NTP had used one of the three WHO recommended algorithms.

METHODS

Study design

Cross-sectional study using data from the Zimbabwe ACF project.

Setting

General country profile

Zimbabwe is a developing country in Sub-Saharan African with a population of 17 million in 2017.[1] In the same year, 22.5% of the population lived in extreme poverty, defined as households whose per-capita consumption is less than 2100 calories.[20]

The public health system has four levels; central (tertiary), provincial, and district hospitals, and primary health centres. TB services are free in all public health facilities. Prior to implementation of ACF, diagnosis of TB was mostly based on passive case finding (PCF).

Study sites

We used all the available programme data from 10 districts (Beitbridge, Bubi, Chimanimani, Chiredzi, Masvingo, Matobo, Mutare, Nkayi, Sanyati, and Zvimba) and three city-areas (Harare, Chitungwiza and Kwekwe) that had been screened in 2017. These places were selected because they were estimated to have the highest prevalence of undiagnosed TB and targeted HRGs. Data from these places were also deemed suitable for our study.

Teams conducting screening used local knowledge to identify places that were most likely to have high numbers of undiagnosed TB cases in the district or city. Poor overcrowded communities; places near mines; popular business centres; and areas with limited access to health services were prioritised. People in these communities were sensitised and mobilised to come for free TB screening using social media, posters, meetings, print and electronic media. No incentives were given.

All people attending the outreach clinics were initially screened for TB symptoms by nurses. Everyone also had a digital CXR taken and this was interpreted by a doctor on site. Supervised spot sputum samples were collected from all presumptive TB cases and sent for bacteriological confirmation at the laboratory.

Diagnosis of active TB was through;

a) Bacteriological confirmation – sputum tests positive for TB on GeneXpert or;
b) Clinical diagnosis – the medical doctor makes a decision to diagnose TB based on the patient's history, symptoms, signs and CXR findings despite negative sputum results.

People were also screened for diabetes and HIV as important co-morbidities. Those diagnosed were initiated on treatment and linked with their nearest health facility. Tuberculosis preventive therapy (TPT) was not provided.

Study population

People screened for TB in Zimbabwe ACF project between April and December 2017.

Data source and variables

Data from the project stored in the central server was used. During screening, all data were entered electronically on a tablet. Anonymised data on age, sex, TB symptoms, chest X-ray (CXR) findings, bacteriological confirmation, HIV status, HRG, and TB diagnosis from the people screened were extracted. Information on operational costs for staff and the laboratory for the project was also collected.

Analysis and statistics

We used STATA version 13.0 *(StataCorp LP College Station, Texas, USA)* to analyse data. Encoding errors in seven records were identified using a logic check and excluded. We calculated the proportion diagnosed with active TB, number needed to be screened (NNS) and relative cost of identifying one case for individuals with different characteristics and HRGs.

The data were used to determine for each WHO algorithm, the number and percentage of people that would be screened for TB symptoms and undergo CXR. We also determined the number of presumptive TB cases that would have been identified after symptom screening alone, CXR alone or both sequentially. We then determined from these cases the number who had active TB diagnosed.

A McNemar's test was used to determine if the number of people diagnosed with TB by each of the three WHO algorithms was significantly different from the Zimbabwe algorithm at 5% significance level. The NNS was also calculated for each algorithm.

We estimated the cost-per-person for conducting symptom screening, having a CXR taken, and bacteriological confirmation (see table 2). We included only operational staff costs and laboratory consumables. Other costs related to procurement of capital equipment, depreciation, maintenance and insurance were assumed to remain constant for all the algorithms. Direct or indirect patient costs were also not included.

We calculated the relative cost-per-case diagnosed for each algorithm by dividing the total cost of the screening by the number of people diagnosed with TB. Sensitivity analysis was conducted to ascertain if our conclusions on relative cost-per-case for different algorithms remained the same if we altered the cost assumptions.

Ethics

Ethical clearance was sought and granted prior to the study by the Medical Research Council of Zimbabwe (MRCZ/E/198) and The International Union against Tuberculosis and Lung Disease Ethics Advisory Group (02/18).

RESULTS

A total of 38,574 people were screened for TB in Zimbabwe (Table 3). Almost two-thirds (61.6%) of them were females. The mean age (standard deviation) of the population was 48 (21) years. Active TB was diagnosed in 488(1.3%) persons, of whom 370(75.8%) were clinically diagnosed and 118(24.2%) were bacteriologically confirmed.

The HGRs were not mutually exclusive. Over half (54.9%) of the people screened belonged to more than one HRG while 41.0% of people screened did not belong to any of the targeted groups. In total, 1.8% of people with more than one HRG had TB and this was significantly higher *($p < 0.001$)* than the 0.6% among people who did not belong to any HRG.

The most common HRGs among the people screened were being a TB contact and being HIV positive. TB was more common among people previously treated for TB, those who were HIV positive, and miners.

In all the algorithms, symptom screening was the initial step for all people except for WHO3b where the CXR was used first (see Table 4). WHO2d algorithm at 13,710 (35.5%) would have had the lowest number of people needing to have a CXR done and interpreted by a medical doctor. With WHO2b algorithm, no CXR would be done.

The Zimbabwe algorithm had the highest number of presumptive TB cases that needed bacteriological confirmation, 39.6% (table 4). All the three WHO algorithms would have fewer numbers of presumptive TB cases identified compared to the Zimbabwe algorithm with WHO2d at 6.7% being the lowest.

Table 5 shows that, compared to the number of TB cases diagnosed by the Zimbabwean algorithm, all the three WHO-recommended screening algorithms would have had a statistically significant lower yield of TB cases identified *($p <0.001$)*. WHO3b, WHO2b and WHO2d had 7.0%, 18% and 25% fewer cases, respectively.

The lowest relative cost-per-case was with WHO3b algorithm ($180). It would have been over three times cheaper than the Zimbabwe algorithm ($565). Sensitivity analysis showed that despite varying the unit costs used in our model, WHO3b algorithm had a consistently lower cost-per-case of TB diagnosed compared to the Zimbabwe algorithm.

DISCUSSION

This is the first study to use data from an ACF program to compare the yield and relative cost of the WHO-recommended ACF screening algorithms in a high TB and HIV prevalence setting.

We found that the current Zimbabwe ACF algorithm gave the highest yield of TB cases diagnosed. The cost-per-case was triple that of TB diagnosed by the WHO3b algorithm. However, 7% of active TB cases would be missed by WHO3b algorithm. It is probable that cases missed would be diagnosed later by PCF in public health facilities. A median delay of about four weeks is expected with PCF compared to only one week when ACF is done. [21] ACF should complement rather than replace PCF in finding people with TB disease.[5, 11, 12, 22]

The number of people needing symptom screening, CXR and bacteriological confirmation was different for the algorithms and this impacts on the relative cost-per-case (table 4). Participants who did not belong to any HRG had a lower yield of TB and thus increased the cost per case diagnosed. If the NTP were to adopt the WHO3b algorithm plus improve the proportion of people with HRG who get screened, significant savings on staff and laboratory costs could be made.

The relative cost-per-case of TB diagnosed in this study are markedly different from a study carried out in China.[19] A similar method was used but data from only elderly people who participated in a TB prevalence survey were analysed. In contrast to our study, they reported that WHO3b algorithm had the best yield but was the most expensive. This is because direct smear microscopy was used for bacteriological confirmation which is markedly cheaper and less sensitive than GeneXpert. [23] Unlike in our study where operational staff costs were used to come up with the cost of a CXR, the China study used market costs which are more expensive. In addition, the NNS in the China study was more than double that from our study population reflecting a lower TB prevalence setting. Despite the expense, the Chinese study also recommended WHO3b algorithm to be used.

The strengths of our study were that it used all the available data from people screened in the Zimbabwean ACF project in normal programmatic conditions. Data was collected

electronically during screening. Each patient's file was verified by the team leader before the patient was discharged to minimise transcription errors. Our study also adhered to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[24]

Limitations of this study were that the costings model we used only generated indicative costs for the different algorithms. This means the costs cannot be used for international comparisons or designing a new program. Also, the results are from areas in Zimbabwe with the highest estimated prevalence of TB. Care therefore needs to be taken when generalising the results to areas with lower TB prevalence. Implementing ACF in such settings may not be cost-effective.[25] The study population was purposively sampled high-risk communities, and selection bias is also obvious in the male/female ratio.

The high number of females may reflect differences in health seeking behaviour between men and women. If more men had participated, a higher yield would have been expected and hence a lower the cost-per-case across all the algorithms we compared. There was no significant differences in the number of TB cases diagnosed by gender across all the algorithms.

A trade-off could be considered by the NTP when selecting the most appropriate ACF algorithm. Savings could be used to support other components of the program, particularly TPT which is recommended for PLHIV when active TB has been excluded.[18, 26] Unfortunately, TPT was not given and that was a missed opportunity. TPT among PLHIV has been shown to reduce the overall risk of developing TB by around 35%. [8, 27] By integrating TPT within the ACF program, Zimbabwe could get additional benefits of reducing TB incidence among PLHIV.

Conclusion

Our study demonstrated that the Zimbabwe ACF algorithm provides the highest yield of TB cases diagnosed. The WHO3b algorithm will miss seven percent of TB cases but is three times cheaper. The NTP should thus consider compromising between cost and yield and adopt the WHO3b algorithm.

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CONFLICT OF INTEREST

None declared.

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374 **TABLES AND FIGURES**

375

High-risk groups for TB in Zimbabwe:

- People living with HIV infection
- Contacts of TB patients
- Miners
- Healthcare workers (HCWs)
- People with diabetes mellitus
- Prisoners
- The elderly (≥65 years)

Figure 1: High risk groups for TB in

376 *Table 1: Comparison of the screening algorithm used in Zimbabwe in 2017 for tuberculosis*
377 *with three recommended by WHO,*

Algorithm	Step 1	Step 2	Step 3	Step 4
Zimbabwe	[a] **Symptom enquiry** *If negative or positive, go to step 2*	**CXR** *If **either one of steps 1 or 2** are positive, go to step 3*	[b] **Bacteriological confirmation** If positive = TB diagnosed *If negative go to step 4*	**Clinical review** Medical doctor reviews patient and can make a clinical diagnosis of TB
WHO 2b	[a] **Symptom enquiry** *If positive, go to step 2*	[b] **Bacteriological confirmation** If positive = TB diagnosed *If negative go to step 3*	**Clinical review** Medical doctor reviews patient and can make a clinical diagnosis of TB	
WHO 2d	[a] **Symptom enquiry** *If positive, go to step 2*	**CXR** *If positive, go to step 3*	[b] **Bacteriological confirmation** If positive = TB diagnosed *If negative go to step 4*	**Clinical review** Medical doctor reviews patient and can make a clinical diagnosis of TB
WHO 3b	**CXR** *If positive, go to step 2*	[b] **Bacteriological confirmation** If positive = TB diagnosed *If negative go to step 3*	**Clinical review** Medical doctor reviews patient and can make a clinical diagnosis of TB	

[a] Symptom enquiry was for cough of any duration, weight loss, fever, night sweats. The symptom enquiry in Zimbabwe did not include haemoptysis as recommended by WHO
[b] The GeneXpert was used as the diagnostic test of choice for bacteriological confirmation.
CXR – chest X-ray; TB – Tuberculosis; WHO – World Health Organisation

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Table 2: Indicative cost per patient screened in Zimbabwe, 2017*

Description	Indicative cost per patient screened (USD)
Symptom screening	$1.85
Chest X-ray	$0.93
Bacteriological confirmation [a]	$11.05

[*] *using only operational staff costs and laboratory consumables, not capital or maintenance costs*

[a] *GeneXpert was used for bacteriological confirmation*

383 *Table 3: Characteristics of the population screened and cases diagnosed with active*
384 *tuberculosis in Zimbabwe, 2017.*

Variable	Number screened for TB N (%)[a]		Number diagnosed with TB N (%)[b]		Number needed to screen N	Relative cost per case (USD)
All clients	**38,574**	**(100)**	**488**	**(1.3)**	**79**	**$565**
Gender						
Female	23,761	(61.6)	202	(0.9)	118	$820
Male	14,813	(38.4)	286	(2.0)	52	$385
Age group						
0 – 4 years	271	(0.7)	2	(0.7)	136	$1,045
5 – 14 years	1,471	(3.8)	12	(0.8)	123	$906
15 – 24 years	2,755	(7.1)	18	(0.7)	153	$973
25 – 34 years	6,109	(15.8)	50	(0.8)	122	$809
35 – 44 years	7,735	(20.1)	103	(1.4)	75	$524
45 – 54 years	6,510	(16.9)	99	(1.5)	66	$473
55 – 64 years	5,120	(13.3)	78	(1.5)	66	$482
≥ 65 years	8,603	(22.3)	126	(1.5)	68	$527
Number of HRGs						
People with no HRG	15,819	(41.0)	92	(0.6)	172	$1,108
People with only one HRG	1,597	(4.1)	7	(0.4)	228	$1,410
People with > 1 HRG	21,158	(54.9)	389	(1.8)	54	$422
Type of HRG						
Previously treated for TB	2,462	(6.4)	80	(3.3)	31	$276
HIV Status						
Positive [c]	6,562	(17.0)	174	(2.7)	38	$296
Negative	29,471	(76.4)	296	(1.0)	100	$700
Unknown	2,541	(6.6)	18	(0.7)	141	$952
Miner	3,439	(8.9)	69	(2.0)	50	$397
Prisoner	2,076	(5.4)	37	(1.8)	56	$451
TB contacts	7,250	(18.8)	129	(1.8)	56	$441
Health care workers	1,652	(4.3)	11	(0.7)	150	$925
Diabetic [d]	911	(2.4)	3	(0.3)	304	$2,151

[a] *Numbers in the brackets are column percentages;* [b] *Numbers in the brackets are row percentages*

[c] *HIV positive status was based on self-reported HIV positive status or confirmed status after testing*

[d] *Diabetics status was self-reported or a tested random blood glucose of more than 11.1mmol/L*

TB - tuberculosis, HIV - human immunodeficiency virus, HRG – High risk group, USD- United States dollars

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386 *Table 4: A comparison of the number of each test that would be required for the four*
387 *screening algorithms based on data from Zimbabwe ACF project, 2017.*

Algorithm	Total number screened	Number who had symptom screening N (%)[a]	Number of chest X-rays N (%)[a]	Number of GeneXpert tests N (%)[a]
Zimbabwe	38,574	38,574 (100.0)	38,574 (100.0)	15,260 (39.6)
WHO 2b	38,574	38,574 (100.0)	0 (0.0)	13,710 (35.5)
WHO 2d	38,574	38,574 (100.0)	13,710 (35.5)	2,595 (6.7)
WHO 3b	38,574	0 (0.0)	38,574 (100.0)	4,145 (10.8)

[a] *Numbers in brackets represent row percentages*

Zimbabwean – Zimbabwean algorithm: everyone is screened using both symptoms and chest X-ray and if either are positive, they go for bacteriological confirmation

WHO 2b – WHO algorithm: people are initially screened using symptoms and if positive they go for bacteriological confirmation

WHO 2d – WHO algorithm: people are initially screened for symptoms and if positive they go for a chest X-ray and if positive for bacteriological confirmation

WHO 3b – WHO algorithm: people are initially screened by chest X-ray and if positive go for bacteriological confirmation

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390 *Table 5: A comparison of the number of TB cases diagnosed, number needed to screen, and relative*

391 *cost per case diagnosed using four different screening algorithms based on data from Zimbabwe, 2017.*

Algorithm	Number screened N	Number diagnosed with active TB						Number needed to screen N	Relative cost per case (USD)
		All cases N (%)		Clinically diagnosed N (%)		Bacteriologically confirmed N (%)			
Zimbabwe	38,547	488	(1.3)	370	(75.8)	118	(24.2)	79	$565
WHO 2b	38,547	400[a]	(1.0)	294	(73.5)	106	(26.5)	96	$557
WHO 2d	38,547	366[a]	(0.9)	282	(77.0)	84	(23.0)	105	$308
WHO 3b	38,547	454[a]	(1.2)	358	(78.9)	96	(21.1)	85	$180

[a] *McNemar's test showed the number of active TB cases diagnosed was significantly different (p-value <0.001) compared to the Zimbabwean algorithm*

Zimbabwean – Zimbabwean algorithm: everyone is screened using both symptoms and chest X-ray and if ***either*** *are positive, they go for bacteriological confirmation*

WHO 2b – WHO algorithm: people are initially screened using symptoms and if positive they go for bacteriological confirmation

WHO 2d – WHO algorithm: people are initially screened for symptoms and if positive they go for a chest X-ray and if positive for bacteriological confirmation

WHO 3b – WHO algorithm: people are initially screened by chest X-ray and if positive go for bacteriological confirmation

USD – United States dollars

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