A comparison of the yield and relative cost of active tuberculosis case-finding algorithms in Zimbabwe

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Setting: Ten districts and three cities in Zimbabwe.

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

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

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

Conclusion: The ZimACF algorithm had the highest case yield, but at a much higher cost per case than the WHO algorithms. It is possible to switch to algorithm WHO3b, but the trade-off between cost and yield needs to be reviewed by the Zimbabwean National TB Programme.

Tuberculosis (TB) is the leading cause of death from infectious diseases worldwide. In 2017, nearly 1.2 million died and 10 million people were affected.[1,2] Zimbabwe is among the world's 30 high TB burden countries.[3] Despite declining TB case notifications in the country, one third of people with the 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 of treatment and thus reduces the time the individual is infectious and the risk of community transmission.[7] Modelling done in high-burden countries has shown that implementing ACF over a 10-year period could reduce TB incidence and mortality by respectively 27% and 44%.[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 this is still ongoing. The aim is to identify people with undiagnosed TB cases in areas with estimated high proportions of HRGs (see Table 1) and improve treatment coverage. The 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, taking into account their TB prevalence, the HRGs being targeted and available resources.[4,11,12]

Around 10% of people diagnosed with active TB in some prevalence surveys are asymptomatic.[13–15] It is difficult to identify TB disease using symptoms alone in people living with HIV (PLHIV). PLHIV often have paucibacillary disease; clinical diagnosis is therefore necessary.[16,17] As Zimbabwe has a very high TB-HIV co-infection rate (71%),[1] the NTP designed an algorithm[18] appreciably different from those recommended by the WHO[4] to address these concerns (Table 2).

Literature comparing the yield and cost of WHO-recommended algorithms under programme conditions is scarce. We found only 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) of the total annual funding for TB in Zimbabwe. As this was a matter of concern, the NTP 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 the present 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

This was a cross-sectional study using data from the Zimbabwe ACF project.

Setting
General country profile

Zimbabwe is a developing country in sub-Saharan African (2017 population 17 million).[1] In 2017, 22.5% of the population lived in extreme poverty, defined as households whose per capita consumption is <2100 calories.[20]

TABLE 1 High-risk groups for TB in Zimbabwe

High-risk groups for TB in Zimbabwe:
- People living with HIV infection
- Contacts of TB patients
- Miners
- Healthcare workers
- People with diabetes mellitus
- Prisoners
- The elderly (≥65 years)

TB = tuberculosis; WHO = World Health Organization; HIV = human immunodeficiency virus.

The public health system comprises four levels—central (tertiary), provincial, and district hospitals and primary health centres. TB services are offered free of charge at all public health facilities. Before the implementation of ACF, diagnosis of TB was mostly based on passive case finding (PCF).

Study sites

We used all available programme data from 10 districts (Beitbridge, Bubi, Chimanimani, Chiredzi, Masvingo, Matobo, Mutare, Nkayi, Sanyati and Zvimba) and three cities (Harare, Chitungwiza and Kwekwe) that had been screened in 2017. These sites were selected as they were estimated to have the highest prevalence of undiagnosed TB and targeted HRGs. The data were also deemed reliable 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 offered.

All people attending the outreach clinics were initially screened for TB symptoms by nurses. All participants also underwent digital chest X-ray (CXR), which was interpreted by a physician on site. Supervised spot sputum samples were collected from all cases of presumptive TB and sent for bacteriological confirmation at the laboratory. Active TB was diagnosed 1) based on bacteriological confirmation, i.e., sputum tests positive for TB on Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA); or 2) by the physician based on the patient's history, symptoms, signs and CXR findings despite negative sputum results.

People were also screened for diabetes and human immunodeficiency virus (HIV) as important comorbidities. Those diagnosed with TB were registered and initiated on treatment onsite, and then referred to their nearest health facility for treatment follow-up. Those diagnosed with HIV or diabetes at the sites were also referred to the nearest health facility for treatment and follow-up. TB preventive therapy (TPT) was not provided.

Study population

The study population included individuals screened for TB by the Zimbabwe ACF Project between April and December 2017.

Data source and variables

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

Statistical analysis

We used STATA v13.0 (StataCorp LP, College Station, TX, 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 among individuals with different characteristics and HRGs.

The data were used to determine the number and proportion of people that would be screened for TB symptoms and undergo CXR according to each WHO algorithm. 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 been diagnosed with active TB.

A McNemar's test was used to determine whether 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 performing bacteriological testing to confirm diagnosis (Table 3). We included only operational costs of personnel and laboratory consumables. Other costs related to the procurement of capital equipment, depreciation, maintenance and insurance were assumed to remain constant for all the algorithms. Direct or indirect patient costs were also excluded.

We calculated the relative cost per case diagnosed according to 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 the various algorithms remained the same if cost assumptions were altered.

Ethics

Ethical clearance was sought and granted before the study by the Medical Research Council, Harare, Zimbabwe (MRCZ/E/198) and the International Union Against Tuberculosis and Lung Disease Ethics Advisory Group, Paris, France (02/18).

RESULTS

A total of 38 574 people were screened for TB in Zimbabwe (Table 4). Almost two thirds (61.6%) of these were female. The mean age of the population was 48 years (standard deviation 21). Active TB was diagnosed in 488 (1.3%) persons, 370 (75.8%) of whom were clinically diagnosed and 118 (24.2%) bacteriologically confirmed.

TABLE 2 Comparison of the screening algorithm used in Zimbabwe in 2017 for TB with three recommended by WHO

Algorithm	Step 1	Step 2	Step 3	Step 4
Zimbabwe	Symptom enquiry*: if negative or positive, go to Step 2	CXR: if either one of Steps 1 or 2 is positive, go to Step 3	Bacteriological confirmation†: if positive, TB diagnosed; if negative go to Step 4	Clinical review: physician can make a clinical diagnosis of TB after reviewing the case
WHO 2b	Symptom enquiry*: if positive, go to Step 2	Bacteriological confirmation†: if positive, TB diagnosed; if negative go to Step 3	Clinical review: physician can make a clinical diagnosis of TB after reviewing the case	
WHO 2d	Symptom enquiry*: if positive, go to Step 2	CXR: if positive, go to Step 3	Bacteriological confirmation†: if positive, TB diagnosed; if negative go to Step 4	Clinical review: physician can make a clinical diagnosis of TB after reviewing the case
WHO 3b	CXR: if positive, go to Step 2	Bacteriological confirmation†: if positive, TB diagnosed; if negative go to Step 3	Clinical review: physician can make a clinical diagnosis of TB after reviewing the case	

*Cough of any duration, weight loss, fever, night sweats. The symptom enquiry in Zimbabwe did not include haemoptysis as recommended by the WHO.
†Xpert was used as the diagnostic test of choice for bacteriological confirmation.
TB = tuberculosis; WHO = World Health Organisation; CXR = chest X-ray.

The HRGs 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, individuals with more than one high-risk factor were significantly more likely than those who did not belong to any HRG to have TB (1.8% vs. 0.6%; $P < 0.001$). 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 first step, except for WHO3b where CXR was used first (Table 5). As per the WHO2d algorithm, the lowest number of people would require CXR ($n = 13710$, 35.5%). With WHO2b algorithm, no CXR would be done.

The number of presumptive TB cases (39.6%) requiring bacteriological confirmation was highest with the Zimbabwean algorithm (Table 5). Fewer numbers of presumptive TB cases would have been identified with the Zimbabwe algorithm than all three WHO algorithms, with WHO2d having the lowest yield (6.7%). Table 6 shows that, compared to the number of TB cases diagnosed using the Zimbabwean algorithm, all of the three WHO-recommended screening algorithms would have identified statistically significantly fewer TB cases ($P < 0.001$). Respectively 7.0%, 18% and 25% fewer cases were identified using the WHO3b, WHO2b and WHO2d algorithms.

The WHO3b algorithm (US$180) had the lowest relative cost per case, which would have been more than three times cheaper than the Zimbabwean algorithm (US$565). Sensitivity analysis showed that despite varying the unit costs used in our model, the WHO3b algorithm had a consistently lower cost per case of TB diagnosed than the Zimbabwean algorithm.

DISCUSSION

This is the first study to use data from an ACF programme 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 three times that of TB diagnosed using the WHO3b algorithm; however, 7% of active TB cases would be missed if the WHO3b algorithm is used. It is probable that the cases missed would be diagnosed later using PCF in public health facilities. A median delay of about 4 weeks is expected with PCF compared to only 1 week

with ACF.[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 differed according to the algorithm used and this impacts the relative cost per case (Table 5). Participants who did not belong to any HRG had a lower yield of TB and thus increased the cost per case diagnosed. Our results in Table 4 indicate that compared to people with no high-risk factors, those with more than one had a higher yield of TB. Almost three times fewer people with more than one risk factor had to be screened to find a single case of TB. As this group of people has a higher yield and lower NNS, by adopting WHO 3b, which uses better targeting, the NTP can reduce staff workload and laboratory costs as fewer people would need screening. This would make the case-finding programme more cost-efficient.

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 in the Chinese study, but only data from elderly people who participated in a TB prevalence survey were analysed. In contrast to our study, this earlier study reported that the WHO3b algorithm had the best yield, but was also the most expensive. This is because direct smear microscopy was used for bacteriological confirmation, which is substantially cheaper and less sensitive than Xpert.[23] Unlike in our study, where operational staff costs were used to model 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 in our study population, reflecting a lower TB prevalence setting. Despite the expense, the Chinese study also recommended that the WHO3b algorithm be used.

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

TABLE 3 Indicative cost* per patient screened in Zimbabwe, 2017

Description	Indicative cost per patient screened $US
Symptom screening	1.85
Chest X-ray	0.93
Bacteriological confirmation†	11.05

*Only operational staff costs and laboratory consumables; capital and maintenance costs excluded.
†Xpert used for bacteriological confirmation.

TABLE 4　Characteristics of the population screened and cases diagnosed with active TB in Zimbabwe, 2017

Variable	Number screened for TB n (%)*	Number diagnosed with TB n (%)†	Number needed to screen n	Relative cost per case $US
All clients	38 574 (100)	488 (1.3)	79	565
Sex				
Female	23 761 (61.6)	202 (0.9)	118	820
Male	14 813 (38.4)	286 (2.0)	52	385
Age group, years				
0–4	271 (0.7)	2 (0.7)	136	1 045
5–14	1 471 (3.8)	12 (0.8)	123	906
15–24	2 755 (7.1)	18 (0.7)	153	973
25–34	6 109 (15.8)	50 (0.8)	122	809
35–44	7 735 (20.1)	103 (1.4)	75	524
45–54	6 510 (16.9)	99 (1.5)	66	473
55–64	5 120 (13.3)	78 (1.5)	66	482
≥65	8 603 (22.3)	126 (1.5)	68	527
Number of high-risk factors				
People with no high-risk factors	15 819 (41.0)	92 (0.6)	172	1 108
People with only one high-risk factors	1 597 (4.1)	7 (0.4)	228	1 410
People with >1 high-risk factors	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‡	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
Miners	3 439 (8.9)	69 (2.0)	50	397
Incarcerated	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
Patients with diabetes§	911 (2.4)	3 (0.3)	304	2 151

*Numbers in the brackets are column percentages.
†Numbers in the brackets are row percentages.
‡Self-reported or confirmed status after testing.
§Self-reported or tested (random blood glucose of >11.1 mmol/l).
TB = tuberculosis; $US = US dollar; HRG = high-risk group; HIV = human immunodeficiency virus.

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 STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines.[24]

Limitations of this study were that the costings model we used only generated indicative costs for the various algorithms. This means that the costs cannot be used for international comparisons or for designing a new programme. Furthermore, results are from areas in Zimbabwe with the highest estimated prevalence of TB. Care therefore needs to be taken when extrapolating from these results to areas with lower TB prevalence. Implementing ACF in such settings may not be cost-effective.[25] The study popu-

TABLE 5　A comparison of the number of each test that would be required for the four screening algorithms based on data from Zimbabwe ACF project, 2017

Algorithm*	Total screened n	Individuals who underwent symptom screening n (%)†	Individuals who underwent CXR n (%)†	Individuals who underwent Xpert testing n (%)†
Zimbabwean	38 574	38 574 (100)	38 574 (100)	15 260 (39.6)
WHO 2b	38 574	38 574 (100)	0	13 710 (35.5)
WHO 2d	38 574	38 574 (100)	13 710 (35.5)	2 595 (6.7)
WHO 3b	38 574	0	38 574 (100)	4 145 (10.8)

*Zimbabwean algorithm = everyone is screened using both symptoms and chest X-ray and if either are positive, undergo bacteriological confirmation; WHO 2b = people are initially screened using symptoms, and if positive, undergo bacteriological confirmation; WHO 2d = people are initially screened for symptoms; those who are symptom screen-positive undergo CXR; those with abnormal CXR undergo bacteriological confirmation; WHO 3b = people are initially screened using CXR, and if positive undergo bacteriological confirmation.
†Numbers in brackets represent row percentages.
CXR = chest X-ray; WHO = World Health Organization.

TABLE 6   A comparison of the number of TB cases diagnosed, number needed to screen, and relative cost/case diagnosed using four different screening algorithms, Zimbabwe, 2017

		Number diagnosed with active TB				
Algorithm*	Total screened n	All cases n (%)	Clinically diagnosed n (%)	Bacteriologically confirmed n (%)	Number needed to screen n	Relative cost/case $US
Zimbabwe	38547	488 (1.3)	370 (75.8)	118 (24.2)	79	565
WHO 2b	38547	400† (1.0)	294 (73.5)	106 (26.5)	96	557
WHO 2d	38547	366† (0.9)	282 (77.0)	84 (23.0)	105	308
WHO 3b	38547	454† (1.2)	358 (78.9)	96 (21.1)	85	180

* Zimbabwean algorithm = everyone is screened using both symptoms and chest X-ray and if either are positive, undergo bacteriological confirmation; WHO 2b = people are initially screened using symptoms, and if positive, undergo bacteriological confirmation; WHO 2d = people are initially screened for symptoms; those who are symptom screen-positive undergo CXR; those with abnormal CXR undergo bacteriological confirmation; WHO 3b = people are initially screened using CXR, and if positive undergo bacteriological confirmation.
† McNemar's test showed the number of active TB cases diagnosed was significantly different ($P < 0.001$) compared to the Zimbabwean algorithm.
TB = tuberculosis; $US = US dollars; WHO = World Health Organization.

lation was purposively sampled high-risk communities, and selection bias is also obvious in the male/female ratio.

The high number of females tested may reflect differences in health-seeking behaviour between men and women. Had more men participated, a higher yield would have been expected, and hence a lower cost per case across all the algorithms we compared. There was no significant difference in the number of TB cases diagnosed by sex 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 programme, particularly TPT which is recommended for PLHIV when active TB has been excluded.[18,26] Unfortunately, TPT was not offered and this 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 programme, Zimbabwe could have the additional benefit of reducing TB incidence among PLHIV.

CONCLUSION

Our study shows that the Zimbabwe ACF algorithm provides the highest yield of TB cases diagnosed. The WHO3b algorithm is less effective at identifying TB cases, but is three times cheaper. We therefore recommend that the Zimbabwean NTP adopt the WHO3b algorithm.

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Contexte : Dix districts et trois villes du Zimbabwe.

Objectif : Comparer le rendement et le coût relatif de l'identification d'un cas de tuberculose (TB) en utilisant les trois algorithmes recommandées par l'Organisation Mondiale de la Santé (OMS) : OMS2b, recherche des symptômes seulement; OMS2d, radiographie pulmonaire (CXR) après un résultat positif au test de dépistage de symptômes ; OMS3b, CXR seule ; et l'algorithme de recherche active des cas du Zimbabwe (ZimACF), test de dépistage de symptômes plus CXR à tous.

Schéma : Etude transversale basée sur les données du projet ZimACF.

Réultats : Des 38 574 personnes dépistées entre avril et décembre 2017, 488 (1,3%) ont eu un diagnostic de TB grâce à l'algorithme ZimACF. Avec les algorithmes recommandés par l'OMS, moins de cas de TB auraient été diagnostiqués. Ceci allait de 7% (34 cas) de moins avec OMS3b, 18% (88 cas) avec OMS2b et 25% (122 cas) avec OMS2d. Le besoin de CXR est allé de 36% (OMS2d) à 100% (OMS3b). Le besoin de confirmation bactériologique est allé de 7% (OMS2d) à 40% (ZimACF). Le coût relatif par cas de TB diagnostiqué est allé de 180 \$US avec OMS3b à 565 \$US pour l'algorithme ZimACF.

Conclusion : L'algorithme ZimACF a eu le rendement le plus élevé avec un coût par cas beaucoup plus élevé que les algorithmes OMS. Le compromis entre coût et rendement doit être revu par le Programme national de la lutte contre la Tuberculose qui doit envisager la décision de passer à l'algorithme OMS3b.

Marco de Referencia: Diez distritos y tres ciudades de Zimbabwe.

Objetivo: Comparar el rendimiento y el costo relativo de la detección de un caso de tuberculosis (TB) al utilizar los siguientes algoritmos recomendados por la Organización Mundial de la Salud (OMS): OMS2b, investigación de síntomas exclusiva; OMS2d, radiografía de tórax (CXR) tras una investigación de síntomas positiva; OMS3b, CXR exclusiva; y el algoritmo de búsqueda activa de casos de Zimbabwe (ZimACF), investigación de síntomas más CXR para todos.

Método: Fue este un estudio transversal a partir de los datos del proyecto ZimACF.

Resultados: Se examinaron 38 574 personas de abril a diciembre del 2017 y se diagnosticó tuberculosis en 488 de ellas (1,3%) mediante el algoritmo ZimACF. Si se hubiesen utilizado los algoritmos recomendados por la OMS se habrían diagnosticado menos casos de TB. Las diferencias oscilaron entre 7% casos menos (34 casos) con el OMS3b, 18% menos (88 casos) con el OMS2b y 25% menos (122 casos) con el OMS2d. La necesidad de una CXR varió entre 36% (OMS2d) y 100% (OMS3b). La necesidad de confirmación bacteriológica osciló entre 7% (OMS2d) y 40% (ZimACF). El costo relativo por caso de TB diagnosticado osciló entre 180 US\$ con el algoritmo OMS3b y 565 US\$ con el algoritmo ZimACF.

Conclusión: El algoritmo ZimACF ofreció el más alto rendimiento diagnóstico, pero con un costo por cada caso detectado mucho más alto que con los algoritmos de la OMS. Es importante que el Programa Nacional de Tuberculosis examine de nuevo la compensación recíproca entre el costo y el rendimiento y considere la decisión posible de adoptar el algoritmo OMS3b.