Investigating the potential impact and suitability of tuberculosis active case-finding approaches in the rapidly changing environment of urban Blantyre, Malawi

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Declaration of Authorship

I, Helena Rosemary Anne Feasey, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Millions of cases of Tuberculosis (TB) go undiagnosed each year. Several approaches are recommended to fill this gap, including community-based active case-finding (ACF). This PhD investigates undiagnosed TB in communities and primary care health clinics in Blantyre, Malawi, and the potential direct and indirect (health promotion) impact of community-based ACF in identifying people with undiagnosed TB. It includes:

- A prospective cohort analysis of outpatients at a primary health-care clinic using linked entry and exit interviews. Patients were lost at every stage of the TB diagnosis cascade, with same-day sputum submission only achieved in 4.7% of those clinically indicated to test for TB.
- A tuberculosis prevalence survey in Blantyre. A prevalence of 150-189 per 100,000 adult residents was identified, consistent with a several-fold reduction from levels identified in a 2013-14 National TB Programme prevalence survey. Some groups, notably men, remain disproportionately affected.
- A systematic review of the impact of ACF beyond directly diagnosed patients for TB, using routine case-notification rate (CNR) ratios as a measure of indirect effect. Twelve studies were identified, with two linked qualitative studies, but these provided insufficient evidence to reach firm conclusions, mainly due to study design issues.
- A cluster-randomised trial of door-to-door ACF in Blantyre to assess both direct and indirect impact of ACF on TB case-notifications. No detectable impact was found, with adjusted 91-day CNR ratios 1.12 (95% CI: 0.61-2.07) for bacteriologically-confirmed TB and 0.86 (95%CI: 0.63-1.16) for non-ACF (routinely) diagnosed TB patients. Lack of impact was likely due to several previous years of TB ACF screening activity and rapid declines in TB burden.

These results highlight the need for resources to be targeted most effectively to reach those with undiagnosed TB in an environment with rapidly changing TB epidemiology. In Blantyre, approaches likely to bring the highest yield are optimised facility-based screening and ACF targeted to high-risk groups, such as men, or geographic hotspots.

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Note to the reader

Internal hyperlinks have been used throughout this thesis. When reading the thesis on a computer, the reader may click on a hyperlink to refer back to a relevant section. Once finished, the reader can click Alt and $\leftarrow$ (at the same time) to return to the original location.

Abbreviations and acronyms

AIDS	Acquired Immunodeficiency syndrome
ACF	Active case-finding
ART	Anti-retroviral therapy
BCG	Bacille Calmette-Guerin (vaccine)
CAD	Computer-assisted detection
CHAM	Christian Health Association of Malawi
COM-B	Capability, Opportunity, Motivation – Behaviour model
CNR	Case notification rate
CRP	C-reactive protein
DHO	District Health Office
DXCR	Digital chest x-ray
ECF	Enhanced case-finding
ePAL	Electronic patient locator
EPTB	Extra pulmonary Tuberculosis
FIND	Foundation for Innovative New Diagnostics
GFC	Global focus country
HBM	Health Belief Model
HIV	Human immunodeficiency virus
ICF	Intensified case-finding
IGRA	Interferon gamma release assay
IPT	Isoniazid preventive therapy
KAP	Knowledge, attitudes and perceptions
LAM	Lipoarabinomannan
LAMP	Loop-mediated isothermal amplification
LMICs	Low and middle income countries
LJ	Löwenstein–Jensen
LPA	Line-probe assay
MDR/RR TB	Multi-drug resistant / Rifampicin resistant Tuberculosis
MDRTB	Multi-drug resistant tuberculosis
MGIT	Mycobacterium Growth Indicator Tube
MoH	Ministry of Health
mWRDs	Molecular WHO recommended rapid diagnostic tests
NAAT	Nucleic acid amplification tests

NNS	Number needed to screen
NTP	National TB Programme
OPD	Outpatient department
PCF	Passive case-finding
PLHIV	People living with HIV
SDG	Sustainable development goal
TB	Tuberculosis
TPT	Tuberculosis preventive treatment
TST	Tuberculin skin test
UNAIDS	Joint United Nations Programme on HIV/AIDS
The Union	International Union Against Tuberculosis and Lung Disease
VR	Vital registration
WHO	World Health Organization

Chapter 1

Introduction

1.1 TB burden and epidemiology

1.1.1 Global TB burden

Tuberculosis (TB) was responsible for an estimated 1.6 million deaths in 2021 [1], second only to COVID-19 as the leading cause of adult mortality from a single infectious agent globally. There were also an estimated 10.6 million new people with TB worldwide in 2021, with a substantial gap between incident and, diagnosed and notified cases of TB of 4.1 million cases [1]. To reach these 'missing millions' the World Health Organization (WHO) created the target of 40 million people newly diagnosed and notified with TB 2018-2022. Progress has been made, but as of 2021 we have only reached 66% of this target (26.3 million). In addition, the overall net reduction in TB incidence between 2015 and 2021 was only 10% - just halfway to the first 2015-2020 milestone of the End TB strategy.

Deaths and TB incidence rates fell between 2005 and 2019, but global estimates for 2020-21 show a reversal of this trend, with TB incidence rate increasing by 3.6% 2020 to 2021 [1]. This reflects the large fall in the number of people diagnosed and reported with TB caused by disruption to routine health services during the COVID-19 pandemic. This overall pattern also occured in all WHO regions, except for Europe where the decline in overall case notifications continued, and Africa which recovered from a small reduction in 2020 to levels above 2019 in 2021. Malawi followed the pattern of the African region [2]. Variation in trends between regions and countries are likely due to differences in severity of impact of COVID-19, extent of restrictions and resilience of health systems.

The highest burden of TB is in adult men, who accounted for 57% of all TB cases in 2021, with 32% in adult women and 11% in children [1]. Men are also more than twice as likely to have bacteriologically-confirmed TB in prevalence surveys than women with an overall sex ratio of 2.21 (95% CI 1.92-2.54) in an analysis of 56 surveys [3].

1.1.2 TB burden in Africa

The WHO Africa region accounts for a substantial proportion of the global TB burden with 32% of TB-related deaths and 23% of global TB incidence (the second highest incidence globally with 212 per 100,000 population) [1, 4]. Africa was an exception with regards to COVID-19 impact on TB disease – the region showed a continued decline in deaths in 2020 and 2021 and incidence also decreased during 2020-21, reflecting a relatively limited regional impact of the COVID-19 pandemic on TB case notifications [1, 3]. The WHO Africa region also just passed the first End TB strategy milestone with a reduction in incidence of 22% since 2015.

Despite these successes in reducing TB burden in Africa, millions of people with TB still go undiagnosed each year with only 60% of new cases diagnosed and notified in 2021, the same proportion as worldwide [4]. HIV-positive TB incidence (42 per 100,000 population) and mortality (12 per 100,000 population) are also highest in the WHO Africa region reflecting the co-epidemic of TB with HIV in many African countries.

1.1.3 The HIV co-epidemic in Africa

People with HIV are up to 26 times more likely to develop active TB disease in their lifetime [5, 6] and the proportion of people with a new episode of TB who are also living with HIV is highest in countries in the African Region, exceeding 50% in parts of southern Africa [1]. This reflects the global burden of HIV, with the Africa region much more severely affected [7, 8] than other regions. There were 25.6 million people living with HIV in Africa in 2021, more than two-thirds of people living with HIV worldwide.

The global mortality and burden from HIV/AIDS increased steadily from the 1990s to a peak in 2004 [7] and has since been declining – claiming 68% fewer lives in 2021 than in 2004 [8]. There was a steep decline in HIV deaths in eastern and southern Africa with 42% fewer deaths in 2016 compared to 2010, largely due to successful anti-retroviral therapy (ART) scale-up [9] and improvements in prevention of mother to child transmission [10]. ART coverage increased from 23% in 2010 to 60% in 2016 [9], and now in 2021 78% of all PLHIV are on treatment in the African region [8]. Between 2010 and 2019 the rate of HIV transmission from mother to

child reduced from 27 to 17% in sub-Saharan Africa [11].

ART reduces both TB incidence and TB case-fatality rates for PLHIV [12] and as such, the improved management of the HIV co-epidemic is reflected in the steady decline in proportion of all incident cases of TB among PLHIV to 6.7% globally in 2021 [1] and 19.8% in the African region [4].

1.1.4 TB risk factors

Susceptibility to TB is influenced directly by a number of common proximate risk factors, notably HIV, undernourishment, smoking, diabetes, alcohol use disorders, indoor air pollution and poor living/working conditions. These are in turn related to socioeconomic status [13].

TB risk factors can increase the risk of progression from infection to disease (such as HIV, undernourishment, smoking, diabetes, alcohol use disorders and indoor air-pollution) or increase the risk of TB transmission (poor living or working conditions such as overcrowding) [14]. HIV has the highest relative risk for TB of more than 20 (although reduced by two-thirds by ART [15]) , whilst undernourishment, diabetes, alcohol use disorders and indoor pollution increase the risk of developing active TB between 1.5 (indoor pollution) and 4 times (malnutrition) [13, 16].

The relative prevalence and thus importance of these risk factors differs by regions and countries. In modelled estimates, HIV (594,000 [468,000 – 736,000]) and undernourishment (630,000 [547,000 – 720,000]) are the risk factors with the highest population attributable fraction in the WHO Africa region, with the additional risk factors of alcohol use disorders (171,000 [113,000 – 240,000]), smoking (92,000 [56,000-137,000]) and diabetes (72,000 [47,000-102,000]) contributing far fewer cases [4].

These risk factors are linked to socioeconomic status of individuals and countries, with TB prevalence following a strong socio-economic gradient and the poorest having the highest risk. TB incidence tends to be higher in settings that favour transmission and/or late diagnosis: developing urban areas with overcrowding and poor living and working conditions, including air pollution [14]. Living in an informal urban settlement is a recognised risk factor for TB and is monitored as part of the TB sustainable development goal (SDG) monitoring framework to track progress on the proportion of urban population living in informal settlements or slums [1].

1.2 Natural history of tuberculosis disease

Tuberculosis is a spectrum of disease states caused by *Mycobacterium tuberculosis* with a small percentage due to *Mycobacterium bovis* [6]. *M. tuberculosis* is a slow growing bacterium which has two distinct phases - actively growing and a persistent slow growing or non-growing state [17]. This means *M. tuberculosis* can persist in a host for decades.

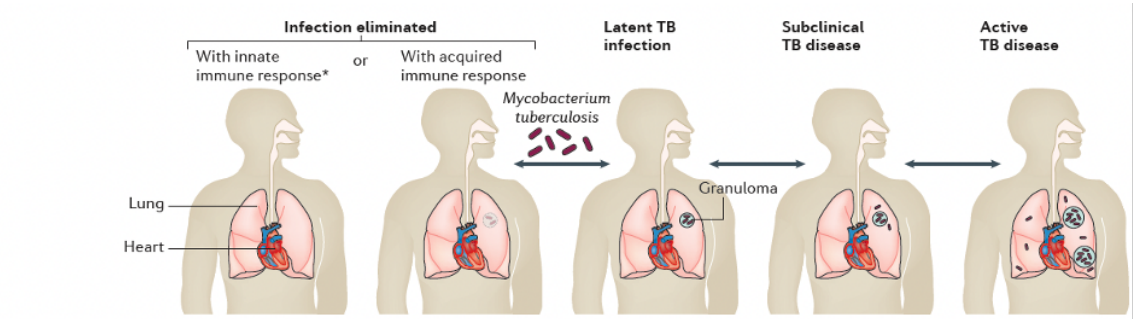
TB is an obligate pathogen that typically affects the lung, leading to pulmonary TB, but can also affect other sites (extrapulmonary TB or EPTB) [1]. Pulmonary TB accounts for the majority of cases and is the main transmissible form of disease. Prevention of EPTB also focuses on preventing transmission from pulmonary TB cases [18] since for *M. tuberculosis* transmission bacilli must be breathed out and inhaled by another person.

Once inhaled, *M. tuberculosis* is breathed into the lungs. If the bacterium breaches the body's first line of defence it infects the lung parenchyma [6]. Infection can be eliminated at this stage either through innate or acquired T cell immune response (Figure 1.1). If the infection persists the body's defences create a granuloma to contain it, within which mycobacteria continue to replicate [6]. People with infection contained in this state have either latent TB (not expected to progress to disease in near future) or incipient TB (likely to progress but doesn't cause detectable abnormalities) [19, 20]. In simple terms, if the granuloma is overloaded with bacilli it will fail to contain the infection leading to subclinical or active disease and bacilli may travel around the body leading to disseminated or extrapulmonary TB. People who are immunocompromised, including those with HIV, have a higher risk of progression from infection to active disease [6].

Typical symptoms of active TB disease are fever, weight loss, night sweats, fatigue and lack of appetite and those with pulmonary TB patients can also have chronic cough and haemoptysis (coughing up blood) [6].

TB is transmitted by the airborne route when breathed out by someone with pulmonary TB. The most infectious patients are those with high bacillary load, often with smear-positive active disease and usually with cough [6]. However, cough is not required for transmission [21], with transmission also seen through singing, speaking and tidal (or restful) breathing [20]. Asymptomatic patients, who test positive for bacteriological TB disease, can also transmit the disease. These patients are often described as subclinical [20, 22, 23]: an estimated 68% of global transmission may be from those with subclinical disease [24].

Figure 1.1: The spectrum of TB — from *Mycobacterium tuberculosis* infection to active (pulmonary) TB disease. [6]



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

From recent analysis of prevalence survey results approximately half of all patients with undiagnosed prevalent TB may be subclinical [25], although this may overestimate subclinical disease as it relies on the symptom screen used in the survey (e.g. cough of $\geq$ 2 weeks). Some participants identified as asymptomatic in prevalence surveys will have other tuberculosis-suggestive symptoms such as chest pain or weight loss [26], and some patients may also have intermittent symptoms, including cough, that is then mistakenly attributed to other conditions [27]. Subclinical TB includes both patients with no symptoms and those in whom symptoms are not recognised [20].

Only some people infected with *M. tuberculosis* progress to active TB disease during the course of their lifetime - for an estimated 5-15% this will take between a few months to a few years, with the remainder having a persistent risk of disease [6]. Recent modelling suggests 93% of progression to minimal disease (pathological damage but not infectious) occurs within two years of infection, but that only 63% and 38% of subclinical and clinical disease respectively occurred within this period [28], suggesting progression to active disease often occurs over a longer period of time.

Overall then, tuberculosis occupies a spectrum from infection through to active disease but improvement and resolution are also possible at each stage - with or without treatment [6]. Screening and diagnostic tests are used to help identify which state people are in and can be combined in different algorithms but even the 'gold standard' of culture can miss cases [29, 30] – especially in those with subclinical disease.

1.3 TB diagnostic pathways

1.3.1 Detecting (latent) TB infection

There are two types of tests for *M. Tuberculosis* infection or latent tuberculosis infection (LTBI): skin tests, with the tuberculin skin test (TST) the most widely used, and interferon gamma release assays (IGRAs) for blood [31]. Both types are indirect tests that detect an acquired cellular immune response and not presence of the bacteria itself [32]. WHO has also recently approved additional IGRAs [33, 34] and newer skin tests using *M. tuberculosis* specific antigens (Cy-TB, formally known as C-TB), Diaskintest and C-TST) [34]. Skin tests and IGRAs can detect if someone has been infected with *M. Tuberculosis* but neither have high predictive probability for short term progression to TB disease [31] [32], with only 2-4% progressing to active TB disease within six years in cohort studies based in high income settings [35]. However, this is still a substantially higher risk than the risk of TB disease in those testing negative for TB infection [34]. Of note, due to the difficulty in maintaining supplies and the limited prognostic value, testing for TB infection is not required to start high-risk groups (such as PLHIV unlikely to have active TB disease) on TB preventive treatment (TPT) [34].

1.3.2 Screening for TB disease

Diagnosis of TB disease commonly has two steps – firstly screening or triaging to identify those with high likelihood of having TB disease, followed by diagnostic tests. Triaging is the process of providing expedited diagnosis for someone who has presented to a health facility [36] whereas screening is performed in a population who may not see themselves as unwell and wouldn't necessarily seek care. Although very similar procedures are used in both the distinction is important since TB prevalence is typically much higher in triage populations and as screening populations are not demonstrably unwell, and so tend to have a higher proportion of early-stage disease, screening tests (such as chest X-ray) may have different predictive values [36].

The most commonly used WHO recommended methods for TB screening and triage are symptom screens and chest X-ray. Different symptom screens are recommended in different situations but the ones included in the WHO guidelines are prolonged cough (2 weeks or more), cough of any duration, any TB symptom (cough, haemoptysis, fever, night sweats and weight loss) and the WHO-recommended four symptom screen (current cough, fever, weight loss or night sweats) for adults and adolescents living with HIV [36]. The different symptom screens have varying levels of sensitivity and specificity (e.g. prolonged cough sensitivity 25-

50% and specificity 92-95%; any TB symptom sensitivity 77-84% and specificity 67-74% [37, 38]) with the “any TB symptom” screen preferred by the WHO in general population screening due to higher sensitivity [36].

Chest X-ray is considered the most accurate screening tool for the general population and high-risk groups though, with chest X-ray, positive for any abnormality, the only screening tool to meet the WHO target product profile of >90% sensitivity and >70% specificity [36]. Chest X-ray can reveal lung abnormalities which may be caused by TB disease before symptoms develop. Screening can be based on some specific abnormalities considered suggestive of TB disease but screening based on any abnormality is more sensitive. Since chest X-ray identifies abnormalities associated with pathological changes, and not symptoms, it can identify people with non-symptomatic clinical TB disease, who would not be identified by a symptom screen. Chest X-rays may also reveal other pulmonary diseases, which is of particular benefit in aiding more general diagnosis in a triage setting [38].

Chest X-ray previously had limited utility in resource-limited settings due to a lack of both equipment for high quality digital imaging and highly trained human readers [39]. However, more accessible, portable and affordable equipment is now available and several computer-assisted detection (CAD) software packages have been reviewed and recommended by the Foundation for Innovative New Diagnostics (FIND) [40] and WHO [36]. In 2021 WHO recommended CAD may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease. Sensitivity of CAD varies between populations and contexts though with lower sensitivity in older adults and those with past TB disease [41].

Molecular WHO recommended rapid diagnostic tests (mWRDs) (i.e. GeneXpert and Truenat) have also been approved by the WHO for screening among high-risk groups after a review of five studies [36] and were used successfully in a cluster-randomised trial in Vietnam [42]. In the WHO review mWRDs had sensitivity of 69% and specificity of 99% when used as a screening tool [36]. Using an mWRD as a screening tool requires significant resources, however, including substantial investment to increase capacity of diagnostic networks. Current recommendations are that scale-up of mWRDs for diagnostic testing should be prioritised over use in screening in most settings. Additionally, in 2021 conditional WHO recommendations included use of the inflammation marker C-reactive protein (CRP) as a screening test amongst PLHIV [36]. The TB screening tools included in the Who guidelines can be used alone or in various combinations, with different tools recommended for different high-risk groups.

1.3.3 TB diagnostic tests

Following a positive screening or triage test, confirmatory bacteriological tests (smear microscopy, molecular tests and culture) are normally required, although in some situations, particularly when a sample for confirmation is difficult to acquire or the patient is critically ill, clinical diagnosis alone is sufficient to start TB treatment.

Smear microscopy, where technicians look for the mycobacteria through a microscope, is widely used for TB diagnosis in LMICs [43, 44]. It is a relatively fast and inexpensive method for TB diagnosis but is highly operator dependent, resulting in significant differences in accuracy with sensitivity ranging from 25–82% [44] and has low sensitivity in high-risk groups such as PLHIV and children. This lack of sensitivity means mWRDs are now the preferred first line test for TB diagnosis [45].

The most widely used mWRDs are the Xpert (MTB/RIF and MTB/RIF Ultra) assays. These amplify mycobacterial DNA in order to detect *M. tuberculosis* DNA [43]. Since these assays detect DNA they can also detect mutations leading to drug resistance and so are particularly recommended in areas of high multi-drug resistant TB (MDRTB) prevalence [45]. Although more sensitive than smear microscopy, Xpert is expensive and requires continuous access to power [44]. Truenat is another molecular test recommended by the WHO, with similar sensitivity to Xpert. Truenat tests are battery powered and initially designed to only run one test at a time so Xpert is still in wider use [46].

Other molecular tests recommended by WHO in certain situations, but not currently widely used, include line-probe assays (LPA), Loop-mediated isothermal amplification (TB LAMP) and some medium-complexity automated nucleic acid amplification tests (NAAT) [45]. In addition, the lateral flow lipoarabinomannan (LAM) assay detects the lipoarabinomannan antigen in urine, and is recommended for all people living with HIV (PLHIV) with advanced HIV disease or severe illness requiring admission. Since LAM uses a urine sample it is of particular benefit for those unable to provide a sputum sample and in diagnosing extrapulmonary TB [47]. In HIV-positive adults, irrespective of TB symptoms, AlereLAM has a 62% sensitivity in inpatient settings and 31% sensitivity in outpatient settings [45]. More sensitive LAM tests are currently in development.

Culture – where the mycobacteria is grown on media – remains the gold standard diagnostic test for TB [44]. The specimen can be cultured in either solid (e.g. Löwenstein–Jensen or LJ) or liquid (e.g. BACTEC Mycobacterium Growth Indicator Tube (MGIT) 960 system) media with WHO advocating for dual use of these systems where practical. Culture can also identify drug

susceptibility [45]. However, even though liquid culture returns results faster than solid culture, it still has a mean time to detection of 12.8 days [44] and requires substantial laboratory facilities and expertise. Culture is therefore not recommended as a first line diagnostic test in resource-poor settings [45].

Sputum is the most common sample for these TB diagnostic tests, however it can be difficult to acquire sputum samples from some presumptive TB patients, particularly in those without a cough, children and in those who are very sick. Urine samples can be used to test for TB with LAM and also in Xpert assays, and stool is now also recommended by WHO as a sample for Xpert in children [34]. Developing methods to use alternative samples to sputum will address major access barriers to TB diagnosis with work ongoing on mouth swabs [48, 49], face mask sampling for bioaerosols [50, 51] and blood tests [52]. Of these mouth or tongue swabs currently look to be the most promising with FIND's Director of TB, Morten Ruhwald, predicting 2023 to be the 'year of the swab' [53].

1.3.4 TB diagnosis algorithms

The available screening and diagnostic tools can be combined in different ways to create algorithms most appropriate for the local setting. The ideal screening strategy should use the most sensitive and specific screening algorithm with a high total yield, few false positives, low numbers needed to screen (NNS), low cost and high client acceptability [36]. Generally, an algorithm of chest X-ray screening followed by confirmatory Xpert testing will achieve the lowest NNS and highest case detection (87%), but resource requirements for these tools are prohibitive in some settings meaning symptom screening and smear microscopy may be used instead [37].

1.4 TB treatment and prevention

Once diagnosed with TB disease, current standard treatment is a six-month regimen of four first-line anti-microbials: isoniazid, rifampicin, pyrazinamide and ethambutol [6] with some four-month regimens now also recommended in certain situations [1], and a new 8-week bedaquiline–linezolid regimen recently shown to be non-inferior [54]. With currently-recommended treatments about 85% of people can be cured [1].

TB mycobacteria can be resistant to any of the recommended drugs and both RR rifampicin resistant (RR) and multi-drug resistant (MDR – defined as resistant to at least isoniazid and rifampicin) TB are widely recognised and reported [6]. In 2021 it was estimated 3.6% of people

with a first episode of TB disease had MDR/RR-TB and 18% of those previously treated [1]. These proportions have been similar since 2015. The highest proportions (>50% of previously treated cases with MDR/RR -TB) are found in the Russian Federation and in several countries in Eastern Europe and Central Asia. In Malawi, an estimated 2.3% of new cases had MDR/RR-TB in 2021 and 6.3% of previously-treated cases – just 93 people – were diagnosed with drug resistant TB [4]. Treatment for those with drug resistant TB is more difficult and requires regimens with substantially more side effects, even with the new bedaquiline-based regimens [1].

TB prevention interventions are aimed at interruption of transmission. These include providing early diagnosis and effective treatment for people with TB disease, vaccination (although the current vaccine - Bacille Calmette-Guerin or BCG - is more effective at protecting children from severe forms of TB than in preventing smear-positive TB disease in adults) [1], and TB preventive treatment. Preventive treatment is aimed at reducing the risk of progression from TB infection to TB disease in patients with evidence of TB infection and an epidemiological and/or immunological risk factor for progression to TB disease. TB preventive treatment (TPT) for drug-susceptible TB consists of either isoniazid for at least 6 months (isoniazid preventive therapy - IPT) or regimens containing a rifamycin for shorter durations, with the shortest effective regimen currently being one month [55]. The efficacy of these TPT treatments ranges from 60%-90% [55]. Because of the low predictive value of tests for TB infection discussed above, and potential toxicity (including potential fatal adverse drug reactions), indications for TB preventive treatment are limited to people living with HIV, household contacts of bacteriologically-confirmed pulmonary TB cases and clinical risk groups (e.g. those receiving dialysis) [1]. However, primary prevention of TB can only be achieved through tackling the risk factors and social determinants of TB by working collaboratively with those working towards poverty reduction at both a national and international level [13].

1.5 Measuring TB burden

Accurately quantifying disease burden is difficult, so WHO estimates the global TB burden through recorded deaths and estimated incidence, primarily based on TB case-notification data[1]. Mortality estimates are most reliable in countries with a well-functioning vital registration (VR) system, but most countries in Africa lack a high-quality VR system meaning mortality is estimated from TB incidence and the case fatality rate [56]. TB incidence cannot be measured directly at national level though, since this would require large-scale, expensive,

extremely large cohort studies. Therefore, TB incidence is also estimated by the WHO based on prevalence surveys (where available) and case-notification systems, together with expert opinion and modelling [56].

1.5.1 Prevalence surveys

TB prevalence surveys are cross-sectional population-based surveys of a random sample of the population in which the number of people with bacteriologically-confirmed TB is measured They give a direct measurement of the absolute burden of disease caused by TB with a recommended relative precision of 20 – 25%. [57] and use a clustered sampling strategy to make it feasible to reach the required sample size. However, surveys generally exclude those aged under 15 and extra-pulmonary TB (EPTB) due to difficulties with field-based diagnosis in these groups with currently available tools. Clinically diagnosed cases (those not confirmed by bacteriological tests) are also not included [57] although these represent an increasing proportion of notified TB cases [1, 3].

Repeated prevalence surveys allow assessment of trends of prevalence and whether targets for reductions in TB prevalence have been met [57], although these have only been conducted in a few countries [58]. Prevalence surveys can also identify reasons for local under-diagnosis of TB, revealed through comparison of the prevalence with case-notification rates.

In prevalence surveys participants are screened through both interview (symptom screening) and chest X-ray, with those identified with presumptive TB asked to provide two sputum samples for the bacteriological diagnostic TB tests of smear microscopy, molecular tests (typically Xpert) and culture [57].

Following the setting of the 2015 End TB Strategy targets in 2006, the WHO established the Global Task Force on TB Impact Measurement to enable assessment of whether the targets were met [58]. This taskforce identified 22 global focus countries (GFC) for prevalence surveys with high TB prevalence and a need for improved burden measurement, including 13 in the African region. From 2007 – 2016 twelve prevalence surveys were completed in Africa: nine of the 13 African GFCs [58] and three further countries (Gambia, Sudan and Zimbabwe) [59]. The prevalence of bacteriologically-confirmed TB in those $\geq$15 years ranged from 119 per 100,000 population in Rwanda to 638 per 100,000 population in Zambia with an overall male:female ratio of 2.0 [59].

The 2013-14 Malawi National Tuberculosis Prevalence Survey found a national prevalence of bacteriologically-confirmed TB in those $\geq$15 years of 452 per 100,000 population and a

male:female ratio of 1.5 [58, 60]. Prevalence was much higher in urban areas (1,014 (95% CI 486-1542) per 100,000) than in rural and semi-urban areas (373 (95% CI 239-506) and 393 (95% CI 0-910) per 100,000 respectively). There were 31,579 participants (81% of the eligible population) across 74 clusters, four of which were in Blantyre, with sensitive screening criteria of any lung abnormality on chest X-ray, or any of a broad range of TB symptoms (including cough, chest pain, weight loss, night sweats, fatigue, fever and shortness of breath) for $\geq$1 week.

1.5.2 Case-notifications

TB case-notifications are the number of cases of TB detected within a given year – those diagnosed and reported through routine national surveillance systems to the WHO [61]. TB notification is usually mandatory, with national agencies, such as NTPs responsible for enforcement [62]. Case definitions and key measurements are set by the WHO with template reporting forms and logs which can be customized according to local need [63]. Cases are notified at the district level within countries, collated nationally and then reported to WHO. Cases are classified as bacteriologically-confirmed (one from whom a biological specimen is positive by smear microscopy, culture or WRD - such as Xpert MTB/RIF [63]) or clinically diagnosed, and are further classified by anatomical site of the disease, history of previous treatment, drug resistance and HIV status. Standard WHO definitions enable combination of data and effective comparison across countries and regions. In many countries, WHO estimates of TB burden, and subsequent trend analysis, rely on these case-notification data, underpinned by additional sporadic population level surveys for undiagnosed TB disease or TB infection.

Extensive data is often collated on those who are diagnosed and start TB treatment (including treatment outcomes) but little data is collected on those who test for TB (people with presumptive TB), although this varies substantially by country and region.

1.6 TB diagnosis gap

Identifying the prevalence to case-notification ratio through comparing data from prevalence surveys and local case-notification data reveals widespread global underdiagnosis of TB disease. In the 24 countries where prevalence surveys were conducted 2007-2016 best estimates of TB prevalence, based on survey results, were higher than pre-survey estimates in 15 countries (including Malawi) [57]. Quantification of this gap between TB incidence (estimated based on prevalence) and those notified, using prevalence-to-notification ratios, led to

an increased focus on early case detection through both facility-based and community-wide case finding [64].

In 2021, of the estimated 9.9 million new cases of TB only 5.8 million (59%) were officially notified to national authorities and reported to WHO [1]. This gap is due to a mixture of underreporting of detected cases, particularly where private healthcare is involved, and underdiagnosis (either due to people not accessing health care or because they are not diagnosed when they do)[65]. Men account for more of the diagnosis gap than women with a median prevalence-to-notification ratio of 2.6 compared to 1.6 for women in a meta-analysis of prevalence surveys and case-notification data [2].

These people who go undiagnosed have been termed the 'missing millions'. To find these and reduce the diagnosis gap the WHO End TB strategy includes the target that 90% of people who develop TB should be notified and treated by 2025 [66]. And in 2018 the 'Find. Treat. All. Initiative' was launched by the WHO in collaboration with the Stop TB Partnership and Global Fund to Fight AIDS, Tuberculosis and Malaria with a target of detecting and treating 40 million additional people with TB by 2022 [65, 67] but by 2021 only 26.3 million (66% of the target) people had been treated [1]. These are challenging targets since the natural history of tuberculosis makes it difficult to diagnose and the current diagnostic tools are inadequate.

1.7 Definitions and rationale of TB case-finding strategies

To fill the diagnosis gap, WHO guidelines outline two pathways to TB case detection: the patient-initiated pathway and the screening pathway [68]; and three approaches to TB case finding: passive case-finding, active case-finding and enhanced case-finding [69]. In both passive and enhanced case-finding the TB test is patient-initiated, and screening can either be implemented in the community through active case-finding (ACF) or at facilities using symptom screening (see Table 1.1).

In 2011 WHO suggested the term 'patient-initiated pathway' should be used instead of 'passive case-finding' as the term 'passive' is "misleading since the approach requires both active health-seeking and responsive health systems" [68]. However, the terms passive, active and enhanced case-finding were subsequently used in the 2013 WHO TB screening guidelines [69] and are still widely used in TB prevention including the Malawi National Tuberculosis Programme (NTP) [70].

Table 1.1: Definitions of approaches to TB case detection

Term	Definition[68]	Term	Definition[69]	Community action?	Test location
Patient-initiated pathway	This pathway includes the following steps: (1) recognizing symptoms by the sick individual or caretaker; (2) accessing an appropriate health-care provider; (3) identifying patients with suspected TB by health-care workers; (4) successfully applying all required steps in an appropriate diagnostic algorithm, using quality-assured diagnostic tools; (5) referring to the appropriate place of treatment and/or notification	**Passive case-finding**	A patient-initiated pathway to TB diagnosis involving: (1) a person with active TB experiencing symptoms that he or she recognizes as serious; (2) the person having access to and seeking care, and presenting spontaneously at an appropriate health facility; (3) a health worker correctly assessing whether the person fulfils the criteria for suspected TB; and (4) the successful use of a diagnostic algorithm with sufficient sensitivity and specificity	No	Facility
		Enhanced case-finding	Enhanced case-finding uses health information or education to provide information about what type of health-seeking behaviour is appropriate when people experience symptoms of TB; this type of case-finding may be combined with improving access to diagnostic services	Yes	Facility
Screening pathway	The identification of presumptive TB disease among people who do not actively seek and receive care for symptoms or signs compatible with TB	**Facility-based** **symptom screening / Intensified case finding**	. . . the systematic identification of people with suspected active TB, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly	No	Facility
		Active case-finding	Active case-finding is a systematic approach to screening for active TB. . . that is normally implemented outside of health facilities	Yes	Community

In 1974 WHO advised against 'indiscriminate' mass (active) case-finding [71] and patient-initiated pathways became the main approach used by NTPs in countries with high TB burdens [68]. WHO did continue to recommend active screening for selected risk groups (such as close contacts of people with TB and immigrants from areas with a high prevalence of the disease)[71]. The 2013 screening principles gave additional conditional recommendations for systematic screening for active TB including, geographically defined subpopulations with extremely high levels of undetected TB and populations who have very poor access to health care, such as people living in urban slums [69]. These guidelines were further reviewed in 2021 with systematic screening for TB disease recommended among the general population in areas with an estimated TB prevalence of 0.5% or higher (reduced from 1% or higher in 2013) [36].

1.7.1 Patient-initiated pathway: passive and enhanced case-finding

The patient-initiated pathway to diagnosis relies on people having symptoms and then presenting to health facilities for care. This pathway would therefore miss those people with subclinical TB disease (those who would screen negative on a TB symptom screen or who may experience symptoms (for example cough) which are not recognised as requiring medical attention [72]). This could be up to half of prevalent TB cases [25].

In passive and enhanced case-finding (ECF), recognition of their own symptoms makes people aware of the need to access health facilities for investigations and diagnosis. Recent modelling estimates the typical duration of asymptomatic bacteriologically-confirmed TB to be around 6 months, although it is much shorter for PLHIV, and also varies by gender and setting [73]. Once symptomatic, there is also delay in care seeking (previously referred to as "patient delay") particularly in LMICs, with 42% of pulmonary tuberculosis patients delaying care seeking by a month or more [74] and a mean delay of 81 days from onset of symptoms [75]. Patients with lower levels of education and those who have sought initial care from informal providers are more likely to delay contact with formal health providers [74].

Delayed care seeking could be partly due to financial insecurities due to a combination of required time away from work to attend health facilities, cost of healthcare in some settings and potential catastrophic costs of a TB diagnosis [1, 76], with lower personal income associated with increased diagnostic delay [77]. A lack of faith in the primary health care system arising from poor communication and equipment and drugs shortage, and experience of rudeness or lack of confidentiality from health workers are also key barriers to TB testing in facilities [78]. In addition, in some African countries (including Malawi), men have been found to delay

care-seeking for tuberculosis symptoms due to an expectation to provide for their families and a fear of not having control over their health, or of being 'looked at as less than men' [79]. Although in patriarchal settings in South America, where women's health is considered to be of lower priority than that of men [80], women are more likely to have delayed TB diagnosis [81]. Enhanced case-finding could help shorten care seeking delays by increasing knowledge of TB symptoms but these access barriers would still remain.

1.7.2 Screening pathway: facility-based screening and active case-finding

TB screening can be conducted both within health facilities and in the community.

1.7.2.1 Facility-based screening

Provider initiated screening in facilities is often referred to as "intensified case finding" or ICF, particularly by HIV programmes implementing ICF for PLHIV attending HIV care services, [82]. In this approach, a target group, with high risk of undiagnosed TB, is identified for systematic screening when attending the health facility, with the strongest recommendation being for PLHIV to be screened each time they attend a facility [36]. Other groups and venues for targeted facility-based screening include pregnant women, people with diabetes, prison clinics, occupational health clinics for some industries such as mining, and general outpatient departments [82, 83]. The prevalence of undiagnosed TB in clinics is often higher than in the community [84, 85] and facility-based interventions have high potential screening yields [82] with a lower number NNS than at other screening locations [86].

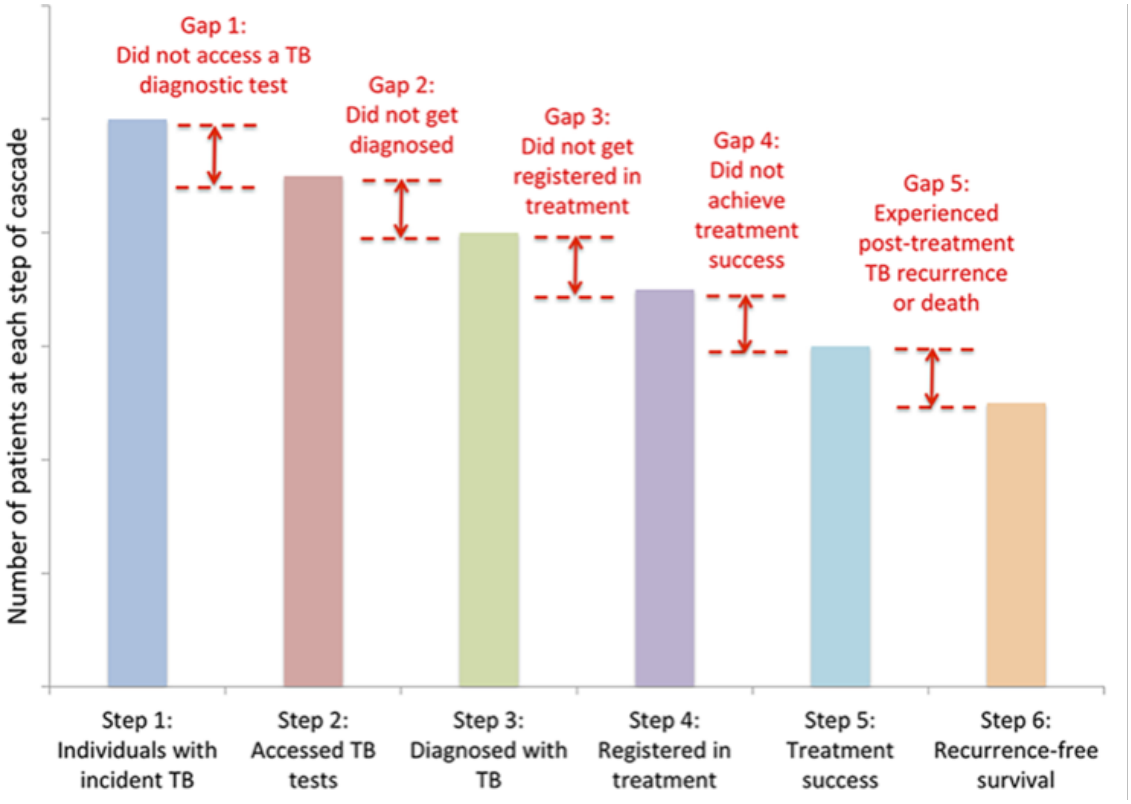
Passive case-finding and facility-based screening are not mutually exclusive. Passive case-finding can be complemented by screening – for example, if all people seeking care are systematically asked about TB symptoms [69]. Systematic screening is usually recommended by NTP guidelines [70, 87, 88] but is often not fully implemented in practice due to high patient load, shortage of trained personnel and frequent interruption of laboratory supplies [89]. Screening guidelines adherence and quality of care can be examined through standardised patients [90] and care cascades.

1.7.2.1.1 TB care cascades and pathway analysis

A TB care cascade is a model for evaluating patient retention across sequential stages of care required to achieve a successful treatment outcome [91], which quantifies gaps in care delivery and adherence to guidelines. Care cascades have been extensively used to evaluate HIV care delivery (e.g. the UNAIDS 90:90:90 global strategy for HIV)[92], but have only recently

been used to evaluate TB care [91]. Although patient pathway analysis [93] and quantifying health system delays have previously been used by TB programmes to understand loss to follow-up [94]. Figure 1.2 shows the generic model for a care cascade for active TB recently developed by Subbaraman et al [91].

Figure 1.2: A generic model for a care cascade for active TB [91]



In an analysis of TB care cascades across countries, which used just four steps (incidence, diagnosed, treatment started and treatment completed) it was estimated the largest gap was between incidence and diagnosed rate [95] in high burden countries. And in the TB care cascade constructed for patients with any form of TB in India in 2013 the largest gap was for those who did not access a TB test (between Step 1: the individuals with incident TB and Step 2: Accessed TB tests)[96]. Therefore, examining the accessing TB and diagnosis steps in more detail is likely to lead to the greatest potential improvement.

Adherence to guidelines in this diagnosis step has been shown to be as low as only 9% ordering a chest X-ray and 4% a sputum test in India (for a classic TB case presenting with cough for 2-3 weeks and fever)[90]. Future care cascades for TB are likely to have further steps tracking treatment of and recovery from increasingly recognised and widespread post-TB lung disease [97].

1.7.2.2 Active case-finding

ACF is a systematic proactive, provider-initiated approach to the identification of those with active TB within the community, often using door-to-door interactions. For example DETECTB in Zimbabwe compared two techniques: mobile van and door-to-door visits [98]. In contrast, ECF encourages people with TB symptoms to attend community testing facilities through the use of advocacy, communication and social motivation (for example providing written materials and information for sharing with household members [99]). The key difference between the two is the individual interaction between a participant and healthcare worker (where the participant submits sputum for TB testing) for diagnosis that occurs in ACF but not in ECF [83]. In ACF there is normally direct testing in the community but in ECF the testing effect is an indirect one in health facilities.

ACF for TB disease can be conducted in the entire population, generally in defined areas of high TB prevalence [36] – such as high-density, low-income urban neighbourhoods or slums, and remote rural populations who have little access to healthcare [100]. Alternatively ACF can be targeted at selected subpopulations who may be at higher risk of being exposed to or developing TB disease [36] including PLHIV, indigenous populations, miners and people experiencing homelessness. ACF is also conducted in congregate settings including prisons, nursing homes and migrant camps which can have high TB transmission and prevalence [83, 101].

There are several different approaches to ACF, with mass radiography the approach used successfully in Europe and the United States prior to the 1960s [83]. Mass radiography was successful in detecting a large pool of prevalent cases and likely contributed to a significant reduction in TB burden but was too expensive and logistically complicated to be implemented at a population level in low and middle-income countries [102]. Subsequently the focus changed to using symptom screening as a first step in community settings.

The ACF approaches mostly employed in the last 40 years and included in a recent systematic review are door-to-door screening, sputum collection by community health workers or volunteers and mobile camps or clinics [100]. The ACF intervention is also often accompanied by other co-interventions to further increase rates of TB diagnosis such as facility-based screening, laboratory upgrading and household contact investigation [100].

ACF interventions can employ different screening algorithms with the most appropriate screening and detection tools chosen for the local situation [83]. The screening needs to be sensitive enough to identify most people with a high likelihood of TB, and the diagnostic confirmation

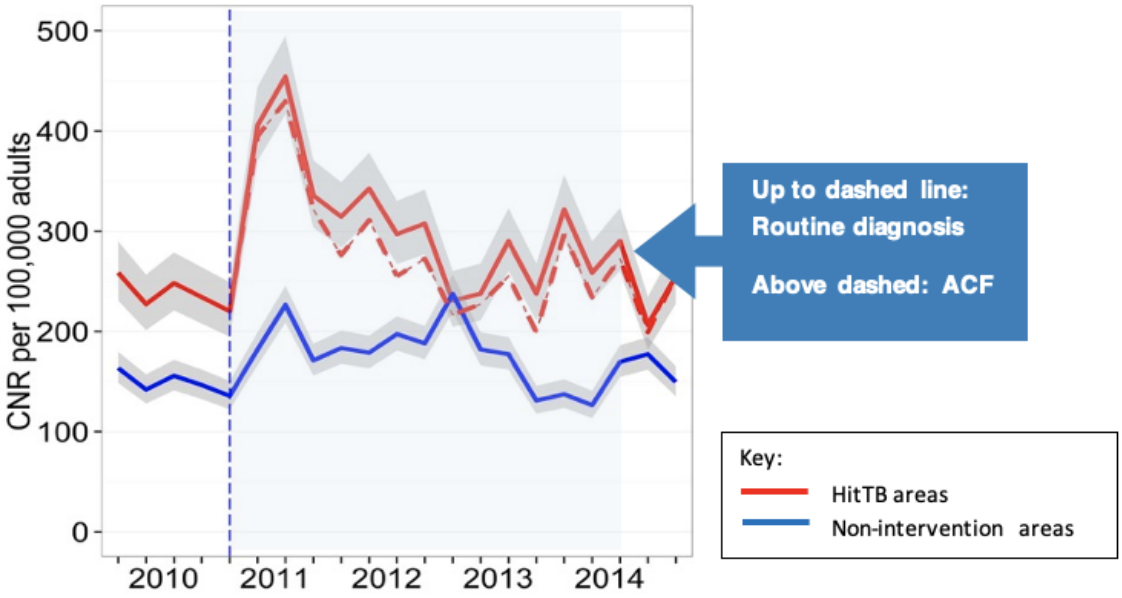
should be highly specific [36]. In recent years most ACF has used a TB symptom screen as the first step, but chest X-ray is also used, and in some instances a TB infection test (such as tuberculin skin test) [100]. The successful ACT3 study in Vietnam also used mWRDs as screening tool with all participants asked to provide sputum for Xpert tests, regardless of symptoms [42].

The aim of screening or ACF for TB is to ensure that TB is detected early and treatment is initiated promptly in those who have asymptomatic or symptomatic tuberculosis disease and who have not sought care, or been already identified through existing diagnostic services [83, 100, 103]. TB patients identified through ACF are more likely to be at an earlier stage of disease [81], for instance less likely to be smear-positive, or have severe chest X-ray changes such as cavitation [103]. Identifying patients earlier has two ultimate goals – firstly to improve individual outcomes and secondly reducing TB transmission by shortening of the duration of infectiousness and subsequently reducing the incidence of TB [69].

A recent systematic review found that ACF can positively affect the community epidemiology of tuberculosis when implemented with sufficient coverage and intensity in high-prevalence settings [100]. The intensity of interventions depends on how many people in the target population are reached, how often people are reached and what diagnostic algorithm is used (e.g. who is eligible for sputum-based tests). Most of the studies identified assessed the impact of ACF on TB case notification rates but three cluster-randomised trials assessed ACF effect on TB epidemiology.

The ACT3 trial in Vietnam using the intensive door-to-door strategy of Xpert for all, regardless of symptoms, reported a 45% reduction in bacteriologically-confirmed tuberculosis [42]. In comparison, no effect was found by the less intensive ZAMSTAR study in Zambia and South Africa, which used community mobilisation with sputum drop-off and a symptom-based and smear microscopy screening algorithm [104]. In addition, the DETECTB study in Zimbabwe [105], which was characterised as medium intensity (with mobile vans and door-to-door symptom-based and smear-based screening) [100], showed a reduction in culture-confirmed tuberculosis of 41%. Context specific factors, such as TB prevalence, access to health care and social norms, will also have affected the relative success of these different ACF approaches [100]. Finally, the 'medium intensity', door-to-door, symptom-based and smear or Xpert screening (diagnostic test depended on HIV status) intervention in the recently reported TREATS study in Zambia and South Africa, showed no impact on incidence of TB infection or the prevalence of active TB at population level [106].

Figure 1.3: Adult smr+ve case notification rates (CNR) during the HitTB study in Blantyre [107]



Overall though the review found mixed evidence and we are therefore still unsure of the most effective ACF approaches [100]. Impact evaluation of TB case-finding interventions is technically difficult and expensive and therefore has often not been included in programmatic or research studies [103] but there is a need for more robust evaluation in future.

1.7.2.2.1 Potential indirect impact of ACF

ACF could have potential indirect as well as direct impact on TB case-notifications. For example, ACF was previously conducted in Blantyre, Malawi through the research-led HitTB study in 2010-2014. This study saw a large increase in TB case-notifications but the majority of this increase came from routine diagnosis in health centres, with the ACF itself (i.e. sputum submitted to the ACF team) contributing only a small proportion of the increase (Figure 1.3)[107].

ACF in the HitTB study was not specifically designed to increase testing in health facilities but still had a substantial indirect impact on facility testing. Paradoxically, ECF Interventions which are designed to have this effect are often not successful (for example the ZAMSTAR study which used social mobilisation with additional sputum collection showed no significant effect on undiagnosed TB, and did not increase case-notification rates)[104].

Indirect effects of ACF have been reported in the DETECTB study in Zimbabwe [98] and a Vietnam study [108]. However, some other ACF studies have led to a reduction in facility testing or TB notifications [109, 110], or no significant difference in facility notification rates

[111], and in other studies underlying facility notification rates are not reported, so this cannot be assessed [98]. It is therefore not known how widespread the potential indirect effect of ACF on facility-based testing is.

ACF could have possible behavioural impacts leading to participants being more likely to attend a facility for a test or be more likely to accept a test if offered, or staff being more likely to offer tests, potentially leading to increased facility-based case-notifications.

1.7.2.2.1.1 Does ACF influence behaviour-change in facility-based TB testing?

The TB case-notification rate increase at health facilities during HitTB suggests the ACF led to behaviour change around facility-based TB testing, potentially due to its door-to-door / street-level nature, a major difference to ECF. This enables a direct person-to-person interaction, whereas in ECF the 'messenger' (person who conveys the message) is more removed from the community (e.g. on the radio).

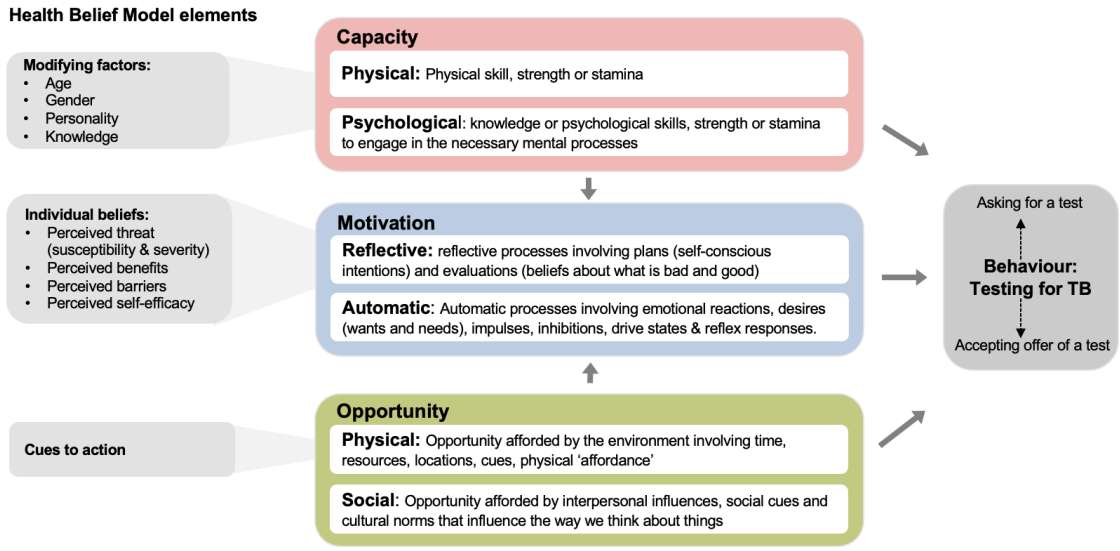
Some evidence suggests increased knowledge of TB generated by ACF is not the determining factor that leads to action in the form of health-seeking and increased rates of individual testing [112]. The level of awareness of TB messages (e.g. get tested if cough for more than two weeks) was shown to be high (90.6%) two years after a previous ACF intervention in Blantyre in both the ACF and non-intervention areas [112]. 'Brand recognition' of the ACF Trial (TBithe) was also high in both groups, probably due to a 'spillover' effect and social diffusion of ideas. Therefore, it seems likely that the higher rates of case-notifications through health centres seen within ACF areas are due to another effect such as a prompt or cue to action, reinforcing social norms or priming people to the idea of providing sputum for TB testing in cases of prolonged cough. However, this was a small study (118 community participants) with an under-representation of men (86.4% female), and as identified by the WHO further research is needed on the indirect effects of screening, given the importance of health-seeking behaviour in TB diagnosis and the potential of ACF to impact this [36].

1.7.2.2.1.2 Behaviour change theories

The potential behavioural drivers of TB testing can be explored through the COM-B (Capability, Opportunity, Motivation – Behaviour) model or framework of behaviour change[113], together with elements of the Health Belief Model[114] (as shown in Figure 1.4).

The Health Belief Model was developed in the 1950s specifically for TB diagnosis [114] so has a particular relevance and it is useful to refer back to it to ensure all the elements are considered. However, this model was developed when behaviour change science was in its

Figure 1.4: Health Belief Model mapped to COM-B model



infancy and it has an over-reliance on conscious reflective thought processes and volitional control [115], with external social and environmental influences only included as the add-ons 'cues to action' or 'modifying factors'.

The COM-B model was developed in 2011 and has the advantages of including a range of thought processes and external influences while still remaining relatively simple. The processes leading to behaviours are complex and often models that try to incorporate all the elements (for example Triandis' Theory of Interpersonal Behaviour [116]) become too unwieldy to be practically applied.

In addition, COM-B was developed as part of the Behaviour Change Wheel (a framework to help develop interventions), so findings using this model can subsequently be more easily translated into behaviour change techniques, interventions and policies for implementation.

1.8 Aim and Objectives

As presented above, there are multiple different options for TB case-finding or screening but we are still unsure of the most effective strategies. Since TB case-finding approaches also need to be context specific, we first need to fully understand the local context before assessing the impact of different approaches.

This thesis aims to enhance the evidence base on effective TB case-finding strategies in order to improve access to TB diagnosis in high burden settings.

Objectives

Current TB diagnosis context in Blantyre:

1. Using facility surveillance data from Blantyre, to construct a TB diagnosis cascade for facility-based TB diagnosis, identify the gaps at which patients are lost from the pathway and examine patient-level factors associated with request for sputum for TB testing by facility-based clinicians in Blantyre
2. Through analysis of cross-sectional community survey data, including a chest X-ray and symptom screening algorithm, estimate the community prevalence of TB disease in high to middle density residential areas of urban Blantyre.

Direct and indirect impact of active case-finding in Blantyre:

3. Through systematic review, to determine whether TB active case-finding in addition to standard case detection—and compared to standard case detection alone—has indirect as well as direct impact, assessed through proxy behavioural outcomes and effects on routine facility-based TB case-notifications.
4. Through analysis of SCALE cluster randomised trial geo-location data, to examine the direct and indirect population-level impact of community-based ACF on overall and routine facility-based TB case-notifications.

The first two thesis objectives focus on understanding the current TB diagnosis context in Blantyre – both in facilities and the community. TB case-finding research has previously been conducted in urban communities in Blantyre, with little known about facility-based testing. The Malawi NTP recommends screening of specific groups within facilities [70], but the extent to which this was followed in practice was unknown. In addition, the most recent TB prevalence estimates for Blantyre came from the national TB survey in 2013-14 which found an urban

prevalence of bacteriologically-confirmed TB of 1,014 per 100,000 adults (15+ years) [58, 60]. However, this was for all urban areas across Malawi (with only a limited number of people from Blantyre City included).

The second two thesis objectives then examine both the direct and indirect impact of active case-finding in Blantyre. The potential indirect impact of ACF was identified as a research gap by WHO in 2021 [36], and the most recent systematic review of ACF demonstrated the extent to which we are still unsure of the best approaches with mixed evidence even for direct ACF impact [100].

1.9 Thesis outline

The outline of the rest of the thesis is as follows:

- Chapter 2 – study setting and data sources
- Chapter 3 – Published analysis of a prospective cohort attending primary care in Blantyre to construct a TB diagnosis cascade and assess completion of recommended TB screening steps
- Chapter 4 – Submitted for publication TB prevalence survey data for urban Blantyre
- Chapter 5 – Published systematic review of the indirect impacts of community-based active case-finding interventions on wider TB detection and determinants of subsequent TB testing behaviour
- Chapter 6 – Submitted for publication analysis of a cluster-randomised trial of door-to-door ACF to investigate both direct and indirect impact on TB case notifications.
- Chapter 7 – Discussion of findings and implications

1.10 References

1. World Health Organization. Global Tuberculosis Report 2022
2. Horton KC, MacPherson P, Houben RM, White RG, Corbett EL. Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. PLoS Med. 2016;13(9):e1002119.
3. Soko RN, Burke RM, Feasey HRA, Sibande W, Nliwasa M, Henrion MYR, et al. Effects of Coronavirus Disease Pandemic on Tuberculosis Notifications, Malawi. Emerg Infect Dis. 2021;27(7):1831-9.
4. Data reported by countries to WHO and estimates of tuberculosis burden generated by WHO for the Global Tuberculosis Report [Internet]. 2022 [cited 14/12/2022]. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.
5. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G. Tuberculosis and HIV co-infection. PLoS Pathog. 2012;8(2):e1002464.
6. Pai M, Behr MA, Dowdy D, Dheda K, Divangahi M, Boehme CC, et al. Tuberculosis. Nature Reviews Disease Primers. 2016;2(1):16076.
7. Ortblad KF, Lozano R, Murray CJL. The burden of HIV: insights from the Global Burden of Disease Study 2010. AIDS. 2013;27(13):2003-17.
8. World Health Organization. Key facts HIV. 2022.
9. Joint United Nations Programme on HIV/AIDS (UNAIDS). Ending AIDS, Progress towards the 90-90-90 targets; Global AIDS update 2017. 2017.
10. Vrazo AC, Sullivan D, Ryan Phelps B. Eliminating Mother-to-Child Transmission of HIV by 2030: 5 Strategies to Ensure Continued Progress. Global Health: Science and Practice. 2018;6(2):249-56.
11. Astawesegn FH, Stulz V, Conroy E, Mannan H. Trends and effects of antiretroviral therapy coverage during pregnancy on mother-to-child transmission of HIV in Sub-Saharan Africa. Evidence from panel data analysis. BMC Infectious Diseases. 2022;22(1):134.
12. Dodd PJ, Shaweno D, Ku C-C, Glaziou P, Pretorius C, Hayes RJ, et al. Transmission modeling to infer tuberculosis incidence, prevalence, and mortality in settings with generalized HIV epidemics. medRxiv. 2022:2022.10.07.22280817.

13. World Health Organization EbEBaASK. Equity, social determinants and public health programmes. 2010.

14. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: The role of risk factors and social determinants. Social Science Medicine. 2009;68(12):2240-6.

15. Lawn SD, Harries AD, Williams BG, Chaisson RE, Losina E, De Cock KM, et al. Antiretroviral therapy and the control of HIV-associated tuberculosis. Will ART do it? Int J Tuberc Lung Dis. 2011;15(5):571-81.

16. Lönnroth K, Castro KG, Chakaya JM, Chauhan LS, Floyd K, Glaziou P, et al. Tuberculosis control and elimination 2010–50: cure, care, and social development. The Lancet. 2010;375(9728):1814-29.

17. Beste DJ, Espasa M, Bonde B, Kierzek AM, Stewart GR, McFadden J. The genetic requirements for fast and slow growth in mycobacteria. PLoS One. 2009;4(4):e5349.

18. Ayed HB KM, Marrakchi C, Rekik K, Hammami F, et al. Extrapulmonary Tuberculosis: Update on the Epidemiology, Risk Factors and Prevention Strategies. Int J Trop Dis. 2018;1:006.

19. Drain PK, Bajema KL, Dowdy D, Dheda K, Naidoo K, Schumacher SG, et al. Incipient and Subclinical Tuberculosis: a Clinical Review of Early Stages and Progression of Infection. Clin Microbiol Rev. 2018;31(4).

20. Kendall EA, Shrestha S, Dowdy DW. The Epidemiological Importance of Subclinical Tuberculosis. A Critical Reappraisal. Am J Respir Crit Care Med. 2021;203(2):168-74.

21. Patterson B, Wood R. Is cough really necessary for TB transmission? Tuberculosis (Edinb). 2019;117:31-5.

22. Barry CE, 3rd, Boshoff HI, Dartois V, Dick T, Ehrt S, Flynn J, et al. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat Rev Microbiol. 2009;7(12):845-55.

23. Esmail H, Barry CE, 3rd, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis. Philos Trans R Soc Lond B Biol Sci. 2014;369(1645):20130437.

24. Emery JC, Dodd PJ, Banu S, Frascella B, Garden FL, Horton KC, et al. Estimating the contribution of subclinical tuberculosis disease to transmission – an individual patient data analysis from prevalence surveys. medRxiv. 2022:2022.06.09.22276188.

25. Frascella B, Richards AS, Sossen B, Emery JC, Odone A, Law I, et al. Subclinical Tuberculosis Disease—A Review and Analysis of Prevalence Surveys to Inform Definitions, Burden, Associations, and Screening Methodology. Clinical Infectious Diseases. 2021;73(3):e830-e41.

26. Stuck L, van Haaster AC, Kapata-Chanda P, Klinkenberg E, Kapata N, Cobelens F. How "Subclinical" is Subclinical Tuberculosis? An Analysis of National Prevalence Survey Data from Zambia Clinical Infectious Diseases. 2022;75(5):842-8.

27. Esmail H, Dodd PJ, Houben R. Tuberculosis transmission during the subclinical period: could unrelated cough play a part? Lancet Respir Med. 2018;6(4):244-6.

28. Horton KC, Richards AS, Emery JC, Esmail H, Houben RMGJ. Re-evaluating progression and pathways following Mycobacteria tuberculosis infection within the spectrum of tuberculosis disease. medRxiv. 2022:2022.12.14.22283422.

29. Shi J, Dong W, Ma Y, Liang Q, Shang Y, Wang F, et al. GeneXpert MTB/RIF Outperforms Mycobacterial Culture in Detecting Mycobacterium tuberculosis from Salivary Sputum. BioMed Research International. 2018;2018:1514381.

30. Nguyen HV, de Haas P, Nguyen HB, Nguyen NV, Cobelens FGJ, Mirtskhulava V, et al. Discordant results of Xpert MTB/Rif assay and BACTEC MGIT 960 liquid culture to detect Mycobacterium tuberculosis in community screening in Vietnam. BMC Infectious Diseases. 2022;22(1):506.

31. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. 2018.

32. Zellweger JP, Sotgiu G, Corradi M, Durando P. The diagnosis of latent tuberculosis infection (LTBI): currently available tests, future developments, and perspectives to eliminate tuberculosis (TB). Med Lav. 2020;111(3):170-83.

33. World Health Organization. Use of alternative interferon-gamma release assays for the diagnosis of TB infection: WHO policy statement. 2022.

34. World Health Organization. WHO operational handbook on tuberculosis: module 3: diagnosis: tests for tuberculosis infection. 2022.

35. Abubakar I, Drobniewski F, Southern J, Sitch AJ, Jackson C, Lipman M, et al. Prognostic value of interferon- release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB): a prospective cohort study. Lancet Infect Dis.

2018;18(10):1077-87.

36. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease. 2021.

37. Van't Hoog AH, Onozaki I, Lonnroth K. Choosing algorithms for TB screening: a modelling study to compare yield, predictive value and diagnostic burden. BMC Infect Dis. 2014;14:532.

38. Nathavitharana RR, Yoon C, Macpherson P, Dowdy DW, Cattamanchi A, Somoskovi A, et al. Guidance for Studies Evaluating the Accuracy of Tuberculosis Triage Tests. The Journal of Infectious Diseases. 2019;220(Supplement 3):S116-S25.

39. Stop TB Partnership. Screening and Triage for TB using Computer-Aided Detection (CAD) Technology and Ultra-portable X-Ray Systems: A Practical Guide. 2021.

40. Foundation for Innovative New Diagnostics (FIND). Digital Chest Radiography and Computer-Aided Detection (CAD) Solutions for Tuberculosis Diagnostics, Technology Landscape Analysis. 2021.

41. Nel M, Franckling-Smith Z, Pillay T, Andronikou S, Zar HJ. Chest Imaging for Pulmonary TB-An Update. Pathogens. 2022;11(2).

42. Marks GB, Nguyen NV, Nguyen PTB, Nguyen TA, Nguyen HB, Tran KH, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. N Engl J Med. 2019;381(14):1347-57.

43. Treatment Action Group. An Activist's Guide to Tuberculosis Diagnostic Tools. 2017.

44. Gill CM, Dolan L, Piggott LM, McLaughlin AM. New developments in tuberculosis diagnosis and treatment. Breathe. 2022;18(1):210149.

45. World Health Organization. WHO consoliated guidelines on tuberculosis. Module 3: Diagnosis. Rapid diagnostics for tuberculosis infection. 2021 update. 2021.

46. Annabel Kanabus. Truenat TB Test on Tbfacts.org 2023 [Available from: https://tbfacts.org/truenat/].

47. Ricks S, Denkinger CM, Schumacher SG, Hallett TB, Arinaminpathy N. The potential impact of urine-LAM diagnostics on tuberculosis incidence and mortality: A modelling analysis. PLOS Medicine. 2020;17(12):e1003466.

48. Wood RC, Andama A, Hermansky G, Burkot S, Asege L, Job M, et al. Characterization

of oral swab samples for diagnosis of pulmonary tuberculosis. PLoS One. 2021;16(5):e0251422.

49. Luabeya AK, Wood RC, Shenje J, Filander E, Ontong C, Mabwe S, et al. Noninvasive Detection of Tuberculosis by Oral Swab Analysis. J Clin Microbiol. 2019;57(3).

50. Williams CM, Abdulwhhab M, Birring SS, De Kock E, Garton NJ, Townsend E, et al. Exhaled Mycobacterium tuberculosis output and detection of subclinical disease by face-mask sampling: prospective observational studies. Lancet Infect Dis. 2020;20(5):607-17.

51. Williams CM, Muhammad AK, Sambou B, Bojang A, Jobe A, Daffeh GK, et al. Exhaled Mycobacterium tuberculosis Predicts Incident Infection in Household Contacts. Clinical Infectious Diseases. 2022.

52. Sutherland JS, van der Spuy G, Gindeh A, Thuong NTT, Namuganga A, Owolabi O, et al. Diagnostic Accuracy of the Cepheid 3-gene Host Response Fingerstick Blood Test in a Prospective, Multi-site Study: Interim Results. Clin Infect Dis. 2022;74(12):2136-41.

53. Morten Ruhwald, editor The TB diagnostics pipeline. SS-05 TB diganostic tools: leveraging COVID-19 innovations. Union World Conference on Lung Health; 2022; Online.

54. Paton NI, Cousins C, Suresh C, Burhan E, Chew KL, Dalay VB, et al. Treatment Strategy for Rifampin-Susceptible Tuberculosis. New England Journal of Medicine. 2023.

55. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment. 2020.

56. Philippe G CS, Carel P, Katherine F.,. Methods used by WHO to estimate the Global burden of TB disease. 2016.

57. World Health Organization. Tuberculosis Prevalence Surveys: a handbook. 2011.

58. World Health Organization. National Tuberculosis Prevalence Surveys 2007-2016. 2021.

59. Law I, Floyd K. National tuberculosis prevalence surveys in Africa, 2008-2016: an overview of results and lessons learned. Trop Med Int Health. 2020;25(11):1308-27.

60. Ministry of Health National TB Control Programme. Technical report: Malawi tuberculosis prevalence survey (2013–2014). 2016.

61. World Health Organization. The Global Health Observatory / Indicator Metadata Registry List / Notified cases of tuberculosis [Available from: https://www.who.int/data/gho/

indicator-metadata-registry/imr-details/333.

62. Uplekar M, Atre S, Wells WA, Weil D, Lopez R, Migliori GB, et al. Mandatory tuberculosis case notification in high tuberculosis-incidence countries: policy and practice. Eur Respir J. 2016;48(6):1571-81.

63. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014 and January 2020). 2013.

64. Team UIA. Independent Assessment of National TB Prevalence Surveys Conducted Between 2009-2015. 2016.

65. World Health Organisation. Global Tuberculosis Report 2018. World Health Organisation; 2018.

66. World Health Organisation. The End TB Strategy. 2015.

67. World Health Organisation. Joint Initiative "FIND. TREAT. ALL. ENDTB" 2018 [Available from: http://www.who.int/tb/joint-initiative/en/.

68. World Health Organisation. Early detection of Tuberculosis. An overview of approaches, guidelines and tools. 2011.

69. World Health Organization. Systematic screening for active tuberculosis. Principles and recommendations. 2013.

70. Republic of Malawi Ministry of Health. National Tuberculosis Control Programme - Programme Manual, Eighth Edition. Malawi: Malawi Ministry of Health, Unit CHS; 2018.

71. WHO Expert Committee on Tuberculosis. WHO Expert Committee on Tuberculosis Ninth Report. World Health Organisation (WHO); 1974.

72. Dowdy DW, Basu S, Andrews JR. Is passive diagnosis enough? The impact of subclinical disease on diagnostic strategies for tuberculosis. Am J Respir Crit Care Med. 2013;187(5):543-51.

73. Ku C-C, MacPherson P, Khundi M, Nzawa Soko RH, Feasey HRA, Nliwasa M, et al. Durations of asymptomatic, symptomatic, and care-seeking phases of tuberculosis disease with a Bayesian analysis of prevalence survey and notification data. BMC Medicine. 2021;19(1):298.

74. Getnet F, Demissie M, Assefa N, Mengistie B, Worku A. Delay in diagnosis of pulmonary tuberculosis in low-and middle-income settings: systematic review and meta-analysis.

BMC Pulmonary Medicine. 2017;17(1):202.

75. Bello S, Afolabi RF, Ajayi DT, Sharma T, Owoeye DO, Oduyoye O, et al. Empirical evidence of delays in diagnosis and treatment of pulmonary tuberculosis: systematic review and meta-regression analysis. BMC Public Health. 2019;19(1):820.

76. Teo AKJ, Singh SR, Prem K, Hsu LY, Yi S. Duration and determinants of delayed tuberculosis diagnosis and treatment in high-burden countries: a mixed-methods systematic review and meta-analysis. Respir Res. 2021;22(1):251.

77. Bonadonna LV, Saunders MJ, Guio H, Zegarra R, Evans CA. Socioeconomic and Behavioral Factors Associated with Tuberculosis Diagnostic Delay in Lima, Peru. The American Journal of Tropical Medicine and Hygiene. 2018;98(6):1614-23.

78. Kumwenda M, Desmond N, Hart G, Choko A, Chipungu GA, Nyirenda D, et al. Treatment-Seeking for Tuberculosis-Suggestive Symptoms: A Reflection on the Role of Human Agency in the Context of Universal Health Coverage in Malawi. PLoS One. 2016;11(4):e0154103.

79. Chikovore J, Hart G, Kumwenda M, Chipungu GA, Desmond N, Corbett L. Control, struggle, and emergent masculinities: a qualitative study of men's care-seeking determinants for chronic cough and tuberculosis symptoms in Blantyre, Malawi. BMC Public Health. 2014;14:1053.

80. Onifade DA, Bayer AM, Montoya R, Haro M, Alva J, Franco J, et al. Gender-related factors influencing tuberculosis control in shantytowns: a qualitative study. BMC Public Health. 2010;10:381.

81. Saunders MJ, Tovar MA, Collier D, Baldwin MR, Montoya R, Valencia TR, et al. Active and passive case-finding in tuberculosis-affected households in Peru: a 10-year prospective cohort study. Lancet Infect Dis. 2019;19(5):519-28.

82. Stop TB Partnership. StopTB Field guide 4: Intensified TB Case Finding at Facility Level. 2018.

83. Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. Int J Tuberc Lung Dis. 2005;9(11):1183-203.

84. Aggarwal AN. Tuberculosis transmission at healthcare facilities in India. Lung India. 2009;26(2):33-4.

85. Mohammed H, Oljira L, Roba KT, Ngadaya E, Manyazewal T, Ajeme T, et al. Tuberculosis Prevalence and Predictors Among Health Care-Seeking People Screened for Cough of Any Duration in Ethiopia: A Multicenter Cross-Sectional Study. Front Public Health. 2021;9:805726.

86. Garg T, Chaisson LH, Naufal F, Shapiro AE, Golub JE. A systematic review and meta-analysis of active case finding for tuberculosis in India. The Lancet Regional Health - Southeast Asia. 2022;7.

87. Ministry of Health - Republic of Kenya. Integrated guideline for Tuberculosis, Leprosy and Lung Disease. 2021.

88. National Tuberculosis Program DoH, Republic of the Phlippines,. Manual of Procedures 6th edition. 2020.

89. Mnyambwa NP, Philbert D, Kimaro G, Wandiga S, Kirenga B, Mmbaga BT, et al. Gaps related to screening and diagnosis of tuberculosis in care cascade in selected health facilities in East Africa countries: A retrospective study. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2021;25:100278.

90. Das J, Kwan A, Daniels B, Satyanarayana S, Subbaraman R, Bergkvist S, et al. Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study. Lancet Infect Dis. 2015;15(11):1305-13.

91. Subbaraman R, Nathavitharana RR, Mayer KH, Satyanarayana S, Chadha VK, Arinaminpathy N, et al. Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. PLoS Med. 2019;16(2):e1002754.

92. Bain LE, Nkoke C, Noubiap JJN. UNAIDS 90-90-90 targets to end the AIDS epidemic by 2020 are not realistic: comment on "Can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades". BMJ global health. 2017;2(2):e000227-e.

93. Hanson CL, Osberg M, Brown J, Durham G, Chin DP. Conducting Patient-Pathway Analysis to Inform Programming of Tuberculosis Services: Methods. J Infect Dis. 2017;216(suppl 7):S679-s85.

94. Claassens MM, du Toit E, Dunbar R, Lombard C, Enarson DA, Beyers N, et al. Tuberculosis patients in primary care do not start treatment. What role do health system delays play? Int J Tuberc Lung Dis. 2013;17(5):603-7.

95. Kim J, Keshavjee S, Atun R. Health systems performance in managing tuberculosis: analysis of tuberculosis care cascades among high-burden and non-high-burden countries. J Glob Health. 2019;9(1):010423.

96. Subbaraman R, Nathavitharana RR, Satyanarayana S, Pai M, Thomas BE, Chadha VK, et al. The Tuberculosis Cascade of Care in India's Public Sector: A Systematic Review and Meta-analysis. PLoS Med. 2016;13(10):e1002149.

97. Allwood BW, Byrne A, Meghji J, Rachow A, van der Zalm MM, Schoch OD. Post-Tuberculosis Lung Disease: Clinical Review of an Under-Recognised Global Challenge. Respiration. 2021;100(8):751-63.

98. Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. Lancet. 2010;376(9748):1244-53.

99. Aluoch JA, Oyoo D, Swai OB, Kwamanga D, Agwanda R, Edwards EA, et al. A study of the use of maternity and child welfare clinics in case-finding for pulmonary tuberculosis in Kenya. Tubercle. 1987;68(2):93-103.

100. Burke RM, Nliwasa M, Feasey HRA, Chaisson LH, Golub JE, Naufal F, et al. Community-based active case-finding interventions for tuberculosis: a systematic review. Lancet Public Health. 2021.

101. World Health Organization. Optimizing active case-finding for tuberculosis: Implementation lessons from South-East Asia. 2021.

102. Miller C, Lonnroth K, Sotgiu G, Migliori GB. The long and winding road of chest radiography for tuberculosis detection. European Respiratory Journal. 2017;49(5):1700364.

103. Kranzer K, Afnan-Holmes H, Tomlin K, Golub JE, Shapiro AE, Schaap A, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. Int J Tuberc Lung Dis. 2013;17(4):432-46.

104. Ayles H, Muyoyeta M, Du Toit E, Schaap A, Floyd S, Simwinga M, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. Lancet. 2013;382(9899):1183-94.

105. Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ, et al. Comparison of two active case-finding strategies for community-based diagnosis of symp-

tomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): A cluster-randomised trial. The Lancet. 2010;376(9748):1244-53.

106. L. Telisinghe SF, M. Litunga, B. Kangololo, O. Shibwela, T. Gachie, A. Schaap, E. Sakala, K. Shanaube, S. Fidler, R. Hayes, H. Ayles„ editor The effect of community-wide TB screening and HIV testing with linkage-to-care on TB case notification rates: results from the Zambian HPTN 071 trial sites. The Union World Conference on Lung Health; 2022 09/11/2022.

107. MacPherson PW, E.; Choko, A.; Nliwasa, M.; Mdolo, A.; Chiume, L.; Corbett, E. Pre and post-intervention prevalence surveys will be conducted to establish whether the ACF leads to a reduction in TB prevalence World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union); Cape Town. South Africa2015.

108. Marks GBP, N. T. B.; Thu Anh, N.; Hoa, N. B.; Khanh, L. B.; Ho, J.; Fox, G. J.; Nhung, N.V. . Effect of population-wide screening on the prevalence of TB: a cluster randomised controlled trial in Viet Nam. World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union); 26 October 2018; The Hague, The Netherlands2018.

109. Parija D, Patra TK, Kumar AM, Swain BK, Satyanarayana S, Sreenivas A, et al. Impact of awareness drives and community-based active tuberculosis case finding in Odisha, India. Int J Tuberc Lung Dis. 2014;18(9):1105-7.

110. Joshi B, Chinnakali P, Shrestha A, Das M, Kumar AM, Pant R, et al. Impact of intensified case-finding strategies on childhood TB case registration in Nepal. Public Health Action. 2015;5(2):93-8.

111. Yassin MA, Datiko DG, Tulloch O, Markos P, Aschalew M, Shargie EB, et al. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. PLoS One. 2013;8(5):e63174.

112. Monk EJM, Kumwenda M, Nliwasa M, Mpunga J, Corbett EL. Factors affecting tuberculosis health message recall 2 years after active case finding in Blantyre, Malawi. Int J Tuberc Lung Dis. 2018;22(9):1007-15.

113. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6:42.

114. Rosenstock IM. Historical Origins of the Health Belief Model. Health Education Monographs. 1974;2(4):328-35.

115. Taylor RB, M.; Campling, N.; Carter, S.; Garfied, S.; Newbould, J.; Rennie, T. A Review of the use of the Health Belief Model (HBM), the Theory of Reasoned Action (TRA), the Theory of Planned Behaviour (TPB) and the Trans-Theoretical Model (TTM) to study and predict health related behaviour change. National Institute for Health and Care Excellence, UK; 2007.

116. Triandis HC. Values, attitudes, and interpersonal behavior. Nebr Symp Motiv. 1980;27:195-259.

Chapter 2

Methods

The data collection and analysis for this thesis was conducted in Blantyre city in Malawi and some elements were based on previously existing research platforms, including: enhanced surveillance of TB treatment registrations; and the PROSPECT randomised trial.

2.1 Study site

2.1.1 Malawi

Malawi is a landlocked country located in south-eastern Africa (see Figure 2.1), bordered by Zambia, Tanzania, and Mozambique. Malawi's estimated population of 19.65 million in 2021 is expected to double by 2038 [1]; this follows a growth rate of 2.9% per annum between 2008 and 2018 [2]. Malawi has a young population with a median age of 17 years and just 4% aged 65 years or older [2]. Life expectancy at birth was 65.6 years in 2019, substantially increased from 44.7 years in 2020 [3]. However, the under-five mortality rate remains high at 41.9 per 1,000 live births [4].

An estimated 16% of Malawi's population lived in urban areas (mostly the four major cities of Lilongwe, Blantyre, Mzuzu and Zomba) in 2018, and 84% lived in rural areas [2]. In contrast to many other countries in southern and eastern Africa that have experienced rapid urbanisation, the proportion living in urban areas has increased slowly from 14.4% in 1998 to 15.3% in 2008 [2]. Malawi's economy is heavily dependent on agriculture, which employs over 80% of the population [1] but it is a very low return activity [5], contributing to Malawi being designated one of the 46 least developed countries in the world by the United Nations [6].

In Malawi 73% of people live on less than $1.90 a day [5] and 50.7% lived in poverty (defined as those whose total expenditure is below the estimated cost-of-basic-needs) in 2019/20, only a 0.8% reduction from 2015/16 [7]. This varied considerably by place of residence, with 56.6% of people from rural areas living in poverty compared to 19.2% in urban areas in 2019/2020 [7].

Figure 2.1: Maps showing location of Blantyre, Malawi in sub-Saharan Africa
Adapted from https://commons.wikimedia.org/wiki/File:Malawi_location_map.svg

2.1.2 Blantyre

The city of Blantyre, located in the southern region of Malawi (Figure 2.1), is the second largest city and commercial centre of Malawi. In 2018 the southern region contributed 44.1% of the population with 800,264 people or 4.6% of the national population living in Blantyre city itself [8]. The city had a growth rate of 1.9% per annum in 2018 [8] and so an estimated population of approximately 831,000 in 2020. 89.7% of the city population were literate [8].

Overall the population density for Blantyre City was 3,334 persons per square kilometre in 2018 [8], but density is much higher in the informal settlements where over 65% of the city's population lives in about 23% of the land [9]. Cholera and other disease outbreaks are common in these informal settlements due to poor sanitation [9].

2.1.3 TB and HIV burden

Malawi is classed as an area of high burden for TB/HIV by the WHO [10]. In 2014 the national TB prevalence of pulmonary TB among adults aged 15 years or older was 452 per 100,000 population (0.45%), whilst that for urban areas was 1,014 per 100,000 (around 1%) [11]. An estimated 55% of new TB cases were detected and notified in 2021, and of those TB patients with known HIV status 45% were HIV-positive [12]. The National HIV prevalence was 8.9% in 2020 [13] and amongst all adults living with HIV in the country viral load suppression was 87.9% - a substantial increase on 68.3% in 2016 [14]. HIV prevalence is higher in Blantyre (at 14.2%) than nationally, and viral load suppression lower at 81.0% [13].

2.1.4 Health service provision in Blantyre

Healthcare services in Blantyre are provided by the Malawi Ministry of Health (MoH), local government District Health Office (DHO), and the private sector [15]. The private sector is split into both non-profit and for-profit with non-profit services provided by Christian Health Association of Malawi (CHAM) and other non-governmental organisations. The MoH and CHAM have a mutually beneficial relationship whereby the government contracts out to CHAM to provide many free-at-point-of care services such as maternal and child health.

There are three levels to the health system with primary care clinics, a secondary level of private, CHAM and district (on the outskirts of the city and more rural areas) hospitals, and the main tertiary referral hospital for Blantyre and the southern region: Queen Elizabeth Central Hospital (QECH). Since primary health facilities often lack staff and necessary resources many patients go directly to district hospitals and QECH [15]. To address this and provide some gatekeeping a primary care clinic (called Gateway) was established right next to QECH. Overall there is a severe shortage of healthcare staff, equipment and medical supplies in the health system, with a vacancy rate for clinical staff of 33% and 20-25% of medical equipment out of service in 2016, as well as regular shortages of essential medical supplies [16].

2.1.5 TB programme in Blantyre

In line with MoH guidelines [17] TB screening should be conducted in all 13 government health clinics in Blantyre, as well as at QECH. Private health clinics should also screen patients for TB, but in practice this rarely happens beyond the four non-government facilities which also offer publicly funded TB treatment (Blantyre Adventist hospital, Mwaiwathu hospital, Chitawira Clinic and the CHAM run Mlambe hospital).

TB screening is mostly conducted through TB symptom screen (with enquiry for any of the four WHO TB symptoms), but x-ray is also used where available (e.g. at hospitals, and some mobile screening units now deployed in the city) [17]. The NTP uses both smear microscopy and Xpert diagnostic tests, with Xpert increasingly becoming the default. In 2015 smear microscopy was still the mainstay of diagnosis [17], but by 2018 60% of TB diagnostic tests in Blantyre were Xpert, increasing to approximately 85% in 2021 [18]. However only 68% of TB cases in Malawi were bacteriologically-confirmed in 2021 [12], reflecting the increasing proportion of clinically-diagnosed cases.

The Malawi NTP screening approach [17] was based on the 2013 WHO guidelines [19] and is in the process of being updated to reflect WHO 2021 recommendations [20] (Table 2.1).

Facility-based testing, either through symptom screening or patient-initiated passive case finding, is the standard in Malawi. Although the NTP also now advocates active community-based case finding in targeted settings [17]. The national guidelines state that all HIV-positive patients who have one of the WHO recognised TB symptoms and all HIV-negative people presenting to the outpatient department (OPD) with a cough of longer than two weeks should be considered a 'presumptive TB case' and be tested for TB [17], however in practice this often does not happen. The only MoH data systematically collected on TB testing describes the number of people tested and how many are positive for each clinic. The clinics record other information on paper 'presumptive TB registers' but these are not collated.

In government clinics, presumptive TB patients are offered HIV testing and counselling [17], with HIV status included in the TB treatment register. There is high uptake of this HIV testing with WHO reporting that 99% of TB patients had known HIV status in Malawi in 2021 [12]. QECH and eight of the 13 government clinics in urban Blantyre have Xpert machines for conducting TB diagnostic tests and one clinic has smear microscopy facilities. In the other four smaller clinics without diagnostic facilities, sputum samples from presumptive TB patients are sent to the larger clinics with Xpert machines for testing.

15 health facilities in Blantyre offer WHO-recommended directly observed TB treatment (DOTS) as part of the Malawi Essential Health Package [17]. These are QECH, 10 government clinics, one CHAM facility (Mlambe) and three private facilities (Blantyre Adventist hospital, Mwaiwathu hospital and Chitawira clinic), with the treatment publicly funded and free at point-of-care irrelevant of provider status. If patients are diagnosed with TB at other facilities, they are referred to one of these 15 for treatment. Some patients resident within urban Blantyre also receive free DOTS at Chiradzulu hospital, which is administered by the neighbouring

Table 2.1: WHO and Malawi Guidelines for systematic TB screening

WHO screening guidelines	**Malawi NTP Tuberculosis Guideline**	
	Included?	**Description**
Strong recommendations		
Household contacts and other close contacts	Yes	Contact investigation
People living with HIV (PLHIV) at each health facility visit	Yes	Symptom screening for PLHIV
Current and former workers with silica exposure	Yes	Mining communities
In prisons and other penitentiary institutions	Yes	Prisoners
Conditional recommendations		
People with untreated fibrotic chest X-ray lesion	Yes	Included in screening algorithm where X-rays are available
Where prevalence is $\geq$ 100 per 100,000, those with a risk factor for TB who are seeking care or who are already in care (in 2013 generally among those seeking health care)	Yes	Symptom screening of all people presenting to OPD, maternal and child health and HIV clinics
General population in areas with est. prevalence 0.5% or higher	Yes	Active case finding in: • urban intervention clusters • rural hotspots
Sub populations with structural risk factors for TB inc people in urban slums, homeless people and those living in remote areas	Yes	

district health office. TB Officers, employed by the District Health Office, register patients for TB treatment and oversee their treatment in each of these facilities.

2.1.6 Malawi-Liverpool-Wellcome Research Programme (MLW)

The Malawi-Liverpool-Wellcome Research Programme (MLW) is one of the Wellcome Trust's major overseas programmes and is situated on the site of the main Blantyre tertiary referral hospital (QECH). It is a partnership between Kamuzu University of Health Sciences (KUHeS) in Malawi, Liverpool School of Tropical Medicine, and the University of Liverpool, but hosts researchers from many different institutes. MLW has a strong programme developing local researchers and research themes include vaccines, infection biology and population health with a major focus on infectious diseases such as TB, HIV and malaria. MLW hosts several now ISO-accredited laboratories including a TB research laboratory, sited at the nearby KUHeS

campus which was established by my primary supervisor. I was based at MLW throughout my work for this thesis.

2.2 Data sources

The four manuscripts in this thesis use several different data sources:

Table 2.2: Overview of data sources used in this thesis

Objective	Chapter	Title	Data source
1	3	Tuberculosis diagnosis cascade in Blantyre, Malawi: a prospective cohort study	Entry and exit interviews with outpatient department attendees in pilot of PROSPECT study
2	4	Prevalence of Bacteriologically-Confirmed Tuberculosis in Urban Blantyre, Malawi 2019-20: Substantial Decline Compared to 2013-14 National Survey	Cross-sectional prevalence survey conducted amongst adults 18 years or older in middle-to-high density urban Blantyre
3	5	Do community-based active case-finding interventions have indirect impacts on wider TB case detection and determinants of subsequent TB testing behaviour? A systematic review	Literature search of of PubMed, EMBASE, Scopus and the Cochrane Library for papers published between 1 Nov 2010 and 13 April 2020
4	6	Impact of active case-finding for tuberculosis on case-notifications in Blantyre, Malawi: a community-based cluster-randomised trial (SCALE)	Enhanced surveillance of TB treatment registration (case notifications) in Blantyre, including geolocation

The literature search in the Chapter 5 systematic review and the prevalence survey in Chapter 4 are described in detail in the manuscripts and were conducted specifically for these research questions. However, the pilot data used for the Chapter 3 diagnosis cascade and the enhanced surveillance system used to assess outcomes for the Chapter 6 ACF trial had multiple applications so the wider context is discussed below.

2.2.1 PROSPECT trial pilot

The 'Pragmatic Randomised study to Optimise Screening, Prevention and Care for Tuberculosis and HIV' (PROSPECT) trial was conducted in Blantyre 2018-2019 [21]. The study aimed to investigate the effectiveness and cost-effectiveness of optimised HIV and TB diagnosis and linkage to care interventions in reducing time to TB diagnosis and prevalence of undiagnosed TB and HIV in primary care [22]. It was conducted with adult (18 years and above) patients attending the outpatient department at the Bangwe health centre [22]. A pilot phase of entry and

exit interviews for all patients attending the OPD from May to September 2018 was conducted to estimate the number of eligible participants per day [22] and assess the feasibility of different aspects of the study. The data for the first thesis objective, presented in Chapter 3, came from this pilot phase of the PROSPECT study. The overall PROSPECT trial found that digital computer-aided chest X-ray (DCXR-CAD) with universal HIV screening significantly increased the timeliness and completeness of HIV and TB diagnosis [21].

2.2.2 Enhanced surveillance of TB registration in Blantyre

Enhanced surveillance of all patients registering for TB treatment in Blantyre has been in place since 2011, through a collaboration between MLW, the District Health Office (DHO) and the NTP [23]. Details on all patients started on TB treatment are entered into paper registers at the facilities where they receive treatment, by DHO-employed TB officers. In the enhanced surveillance this data, and further clinical and demographic information, is additionally captured electronically by the TB officers, who also obtain a confirmatory sputum sample which is tested by microscopy and culture at the KUHeS TB laboratory.

Since 2015, the TB officers further record the geolocation of the patient's household through a previously evaluated [23, 24] satellite map application or electronic patient locator (ePAL). In ePAL high-resolution maps are labelled with locally important points of reference, which TB patients can search for, and once the map is centred on the nearest point of interest to their household they can scroll and zoom the map to identify the building. A long press on the map screen then records a set of GPS co-ordinates for the selected household.

The electronic records are reconciled with the NTP treatment registers every quarter and each month, a randomly selected 5% sample of people with GPS co-ordinates recorded undergoes home tracing for data validation purposes [25].

The enhanced surveillance system thus includes clinical and demographic information for all TB patients registering for treatment in Blantyre since 2011, and since 2015 the GPS co-ordinates of their household as well. This system was used to provide data for the TB case notification outcomes for the 'Sustainable Active Case-finding for Lung hEalth' (SCALE) trial presented in Chapter 6.

2.3 References

1. World Bank. The World Bank in Malawi, Overview 2022 [Available from: https://www.worldbank.org/en/country/malawi/overview].
2. National Statistical Office (NSO). 2018 Malawi Population and Housing Census Main Report.
3. World Health Organisation. data.who.int, Malawi [Country overview] 2023 [
4. UNICEF. UNICEF Data: Malawi country profile. 2023 [Available from: https://data.unicef.org/country/mwi/].
5. Caruso GDCS, Lina Marcela for The World Bank, . Malawi Poverty Assessment : Poverty Persistence in Malawi - Climate Shocks, Low Agricultural Productivity, and Slow Structural Transformation (English). 2022.
6. Development UNCoTa. UN list of least developed countries 2022 [Available from: https://unctad.org/topic/least-developed-countries/list].
7. National Statistical Office (NSO) GoM. 2020 Malawi Poverty Report. 2021.
8. National Statistical Office (NSO). 2018 Malawi Population and Housing Census. Blantyre City Report. 2021.
9. United Nations Human Settlements Programme (UN-HABITAT). Malawi: Blantyre Urban Profile. 2011.
10. World Health Organization. Global Tuberculosis Report 2022. 2022.
11. World Health Organization. National Tuberculosis Prevalence Surveys 2007-2016. 2021.
12. Data reported by countries to WHO and estimates of tuberculosis burden generated by WHO for the Global Tuberculosis Report [Internet]. 2022 [cited 14/12/2022]. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.
13. PHIA Project. Malawi Population-based HIV Impact Assessment (MPHIA) Summary Sheet 2020-2021. 2022.
14. PHIA Project. Malawi Population-based HIV Impact Assessment 2015-2016. 2018. Columbia University; 2016.
15. Moumié Maoulidi for Millennium Cities Initiative (MCI). Health Needs Assessment for Blantyre, Malawi. Working Paper Series No. 29/2013 2013.

16. Government of the Republic of Malawi. Health Sector Strategic Plan II 2017–2022, Towards universal Health coverage In: Ministry of Health Malawi Government. 2017.

17. Republic of Malawi Ministry of Health. National Tuberculosis Control Programme - Programme Manual, Eighth Edition. Malawi: Malawi Ministry of Health, Unit CHS; 2018.

18. Belaineh Girma MNTP. TB testing data set for Blantyre. Recieved 21/12/212021.

19. World Health Organization. Systematic screening for active tuberculosis. Principles and recommendations. 2013.

20. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease. 2021.

21. MacPherson P, Webb EL, Kamchedzera W, Joekes E, Mjoli G, Lalloo DG, et al. Computer-aided X-ray screening for tuberculosis and HIV testing among adults with cough in Malawi (the PROSPECT study): A randomised trial and cost-effectiveness analysis. PLOS Medicine. 2021;18(9):e1003752.

22. MacPherson P, Webb EL, Lalloo DG, Nliwasa M, Maheswaran H, Joekes E, et al. Design and protocol for a pragmatic randomised study to optimise screening, prevention and care for tuberculosis and HIV in Malawi (PROSPECT Study). Wellcome Open Res. 2018;3:61.

23. MacPherson P, Choko AT, Webb EL, Thindwa D, Squire SB, Sambakunsi R, et al. Development and validation of a global positioning system-based "map book" system for categorizing cluster residency status of community members living in high-density urban slums in Blantyre, Malawi. Am J Epidemiol. 2013;177(10):1143-7.

24. MacPherson P, Khundi M, Nliwasa M, Choko AT, Phiri VK, Webb EL, et al. Disparities in access to diagnosis and care in Blantyre, Malawi, identified through enhanced tuberculosis surveillance and spatial analysis. BMC Medicine. 2019;17(1):21.

25. Soko RN, Burke RM, Feasey HRA, Sibande W, Nliwasa M, Henrion MYR, et al. Effects of Coronavirus Disease Pandemic on Tuberculosis Notifications, Malawi. Emerg Infect Dis. 2021;27(7):1831-9.

Chapter 3

Tuberculosis diagnosis cascade in Blantyre, Malawi: a prospective cohort study

To understand the facility-based TB diagnosis context in Blantyre I analysed prospective cohort data from entry and exit outpatient interviews to construct a TB diagnosis cascade. The cascade model assesses patient progression and retention through sequential stages of care required to achieve a successful outcome, in order to quantify gaps in care delivery and adherence to guidelines. I found patients were lost at every stage of the TB care cascade: asked about cough, asked for sputum, gave sputum and received same-day results. Numbers requiring sputum tests were almost double diagnostic capacity. Overall same day sputum submission following all steps of the diagnosis cascade was achieved in only 4.7% if clinically indicated. Quality of care and diagnostic capacity needs to be improved, with infection control strategies implemented, and reporting on early steps of the TB care cascade formalised.

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Surname/Family Name	Feasey		
Thesis Title	Investigating the potential impact and suitability of tuberculosis active case-finding approaches in the rapidly changing environment of urban Blantyre, Malawi		
Primary Supervisor	Prof Liz Corbett		

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Date	13 March 2023

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Date	13 March 2023

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RESEARCH ARTICLE Open Access

Tuberculosis diagnosis cascade in Blantyre, Malawi: a prospective cohort study

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Abstract

Background: Tuberculosis (TB) control relies on early diagnosis and treatment. International guidelines recommend systematic TB screening at health facilities, but implementation is challenging. We investigated completion of recommended TB screening steps in Blantyre, Malawi.

Methods: A prospective cohort recruited adult outpatients attending Bangwe primary clinic. Entry interviews were linked to exit interviews. The proportion of participants progressing through each step of the diagnostic pathway were estimated. Factors associated with request for sputum were investigated using multivariable logistic regression.

Results: Of 5442 clinic attendances 2397 (44%) had exit interviews. In clinically indicated participants ($n = 445$) 256 (57.5%) were asked about cough, 36 (8.1%) were asked for sputum, 21 (4.7%) gave sputum and 1 (0.2%) received same-day results. Significant associations with request for sputum were: any TB symptom (aOR:3.20, 95%CI:2.02–5.06), increasing age (aOR:1.02, 95%CI:1.01–1.04 per year) and for HIV-negative participants only, a history of previous TB (aOR:3.37, 95%CI:1.45–7.81). Numbers requiring sputum tests (26/day) outnumbered diagnostic capacity (8–12/day).

Conclusions: Patients were lost at every stage of the TB care cascade, with same day sputum submission following all steps of the diagnosis cascade achieved in only 4.7% if clinically indicated. Infection control strategies should be implemented, with reporting on early steps of the TB care cascade formalised. High-throughput screening interventions, such as digital CXR, that can achieve same-day TB diagnosis are urgently needed to meet WHO End TB goals.

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Background

Tuberculosis (TB) is the leading infectious cause of death worldwide and an estimated 10 million people developed TB disease in 2019 [1, 2]. TB control relies on early diagnosis and treatment, as reflected in the World Health Organization (WHO) End TB 2025 target of ≥90% of people who develop TB being notified and treated [3]. To achieve this the WHO recommends systematic TB screening for priority risk groups in order to reduce poor disease outcomes and TB transmission [4]. These recommendations are reflected in many National TB Programme (NTP) guidelines [5–8].

The TB care cascade model assesses patient progression and retention through sequential stages of care required to achieve a successful treatment outcome [9], in order to quantify gaps in care delivery and adherence to guidelines. Care cascades have been extensively used to evaluate HIV care delivery [10], but have only recently been applied by TB programmes [9] to expand analysis beyond standardised treatment outcome reporting [11] and ad hoc diagnostic pathway analysis [12].

In Subbaraman et al's generic model for a care cascade for active TB the first gap is identified as not accessing a TB diagnostic test [9]. This first gap is repeatedly the largest in many settings [13, 14], in keeping with the numerous issues relating to sputum-based tests [15].

Recent studies have emphasised variability in TB diagnosis cascades in high burden countries. In India, only 12–17% of standardised patients were correctly asked to test for TB [16], whereas in Nairobi, Kenya [17] this was 50% and a systematic review found a range for all patients from 4% in Thailand to 84% in South Africa [18]. However, most high-burden TB countries, do not routinely collect data to estimate adherence to systematic TB screening guidelines in health facilities.

WHO recommends people living with HIV are systematically screened for TB each time they visit a health facility and that in high-burden TB settings systematic screening for TB in other selected high risk groups may also be appropriate [4]. These risk groups include older people and those previously treated for TB. However, an estimated 29% of new TB cases are still not identified or officially notified, partly due to failure to diagnose active TB in people accessing healthcare [1, 19]. Examining TB test access for these risk groups and subsequent steps in the TB diagnosis cascade will be critical for efficient TB programme design.

The aims of this study were to: construct a TB diagnosis care cascade; describe the proportion of "clinically-indicated" patients (defined by the Malawi National guidelines [5]) who progressed through each step of the diagnosis cascade in a primary care clinic; and investigate factors associated with being offered a TB test.

Methods

Study design

A prospective cohort of adults aged 18 years and older was recruited from May to September 2018. The study formed part of the pilot phase of a randomised trial at Bangwe health clinic in Blantyre, Malawi [20].

Study site and population

Patients self-presenting to free-of-charge acute-care services in Bangwe Health Centre – a government primary care clinic – were recruited prospectively. There are no physicians at the clinic; care is provided by nurses and clinical officers, who conduct consultations, including TB symptom screening, with the patients. There is a GeneXpert machine for TB sputum diagnosis and TB treatment is available on site. TB prevalence in Blantyre was 1% in 2013 [21] and 113 new registrations for TB treatment were recorded at Bangwe health centre during 2018 (unpublished data).

Malawi National TB Programme guidelines state that all adults with HIV presenting to healthcare facilities with any TB symptom (any of cough, night sweats, fever or weight loss) should receive a sputum test for TB [5]. For HIV-negative adults sputum tests are recommended for all those with weight loss or other TB symptoms of two weeks or more. For the purposes of this study 'clinically indicated to submit sputum' was defined as adults with HIV with any TB symptom and HIV-negative adults with weight loss or a chronic cough (two weeks or more), since duration data was not collected for night sweats or fever. A sensitivity analysis was conducted with an alternative definition including any symptom of any duration for people without HIV infection.

Data collection

Research assistants stationed at the registration desk in the acute-care clinic asked all patients for verbal consent to participate. A fingerprint scan with demographic details was recorded electronically at entry interview. Additional research assistants positioned by the two clinic exits asked all adults leaving the clinic to participate in exit interviews. Participants provided written or witnessed fingerprint (if illiterate) consent for exit interviews.

Entry and exit interviews were linked through digital fingerprint bio-identification. Entry interviews recorded age, sex and WHO recommended TB symptom screening [4, 22]. Exit interviews asked about care received at the clinic and included self-reported HIV status and previous TB diagnosis; whether a health worker had enquired about cough; if they had been asked to submit sputum; if they submitted sputum; and if sputum results had been received. For simplicity, the exit interview enquiry about symptom screening referred only to cough,

as this is the most commonly recognised TB symptom in Malawi [23]. Questionnaires were kept brief to minimise inconvenience and maximise the completeness of capture (see Suppl Table 2 for full questionnaires).

Statistical methods

Summary statistics compared characteristics (collected at clinic entry) of participants who had exit interviews with those who had not (χ^2 and Kruskal-Wallis tests). Participant characteristics were also compared by HIV status (HIV-positive, HIV-negative, status unknown/never tested). "Chronic cough" was defined as cough ≥2 weeks. "Any TB symptom" included any reported cough, fever, weight loss or night sweats [24].

Diagnosis care cascades were constructed based on all participants, and separately for clinically-indicated groups: HIV-negative participants with weight loss or chronic cough and people living with HIV (PLHIV) with any TB symptom. Generic care cascade Step 2 'Accessed TB tests' [9] was expanded to explore symptom enquiry (cough); request to submit sputum; and sputum submission.

Univariable and multivariable logistic regression were used to investigate associations of clinical and demographic characteristics with request for sputum submission. Separate models were fit for 'any TB symptom' and specific individual TB symptoms. Sex, age and symptom variables included in the Malawi Tuberculosis Guideline [5] were included a priori in the multivariable models.

Those who reported a cough and being on TB treatment or isoniazid preventive therapy (IPT) at clinic entry were removed from the cascade and multivariable analysis.

Ethical considerations

Approval was received from the research ethics committees of the College of Medicine, Malawi and Liverpool School of Tropical Medicine. All participants provided written informed consent (or witnessed, thumb-print consent if illiterate).

Data and reproducibility

Data and code to reproduce this analysis is available from *https://github.com/petermacp/tbcascade*.

Results

Clinic attendee characteristics

Of 5442 clinic attendances 2397 (44%) had matched exit interviews, mainly reflecting limited study capacity to interview everyone leaving the clinic (Fig. 1). Five individuals declined to participate in entry interviews and were not included in the study. None refused to participate in exit interviews.

Participants with matched exit interviews had similar characteristics to those with just an entry interview, with some differences: men were more likely to complete an exit interview (37.5% vs 34.2%, $p = 0.012$) as were those with any TB symptom (57.2% vs 54.4%, $p = 0.044$). This was consistent for cough, fever and night sweats. Those completing exit interviews were older than those who did not (median age 28 vs 27 years) (Suppl Table 1).

Exit interviewee characteristics

Of the 2397 with matched exit interviews 900 (37.5%) were male. Median age was 28 years (range 18–89). A total of 849 (35.4%) had a cough, with 221 (9.2%) having chronic cough, and 1370 (57.2%) having any TB symptom. Previous TB treatment was reported by 141 (5.9%). Among HIV positive participants (292, 12.2%) almost all were taking antiretroviral therapy (ART) (276, 94.5%). Of those completing exit interviews 1485 (62.0%) self-reported good health.

HIV positive participants were more likely than HIV-negative or status-unknown participants to be female (72.9% vs 62.7 and 50.7%, $p < 0.001$) and older (median age 36 years vs 27 years and 27.5 years for HIV-positive, HIV-negative and HIV-unknown respectively, $p < 0.001$) (Table 1). PLHIV were also more likely to be taking TB treatment (14.9% vs 3.2 and 1.8%), on IPT (21.5% vs 1.1 and 1.8%) and to report previous TB (22.6% vs 3.6 and 3.0% for HIV-positive, HIV-negative and HIV-unknown respectively) (all $p < 0.001$). A higher proportion of PLHIV had chronic cough (15.1%) compared to HIV-negative (8.2%) or unknown-status participants (9.5%, $p = 0.001$).

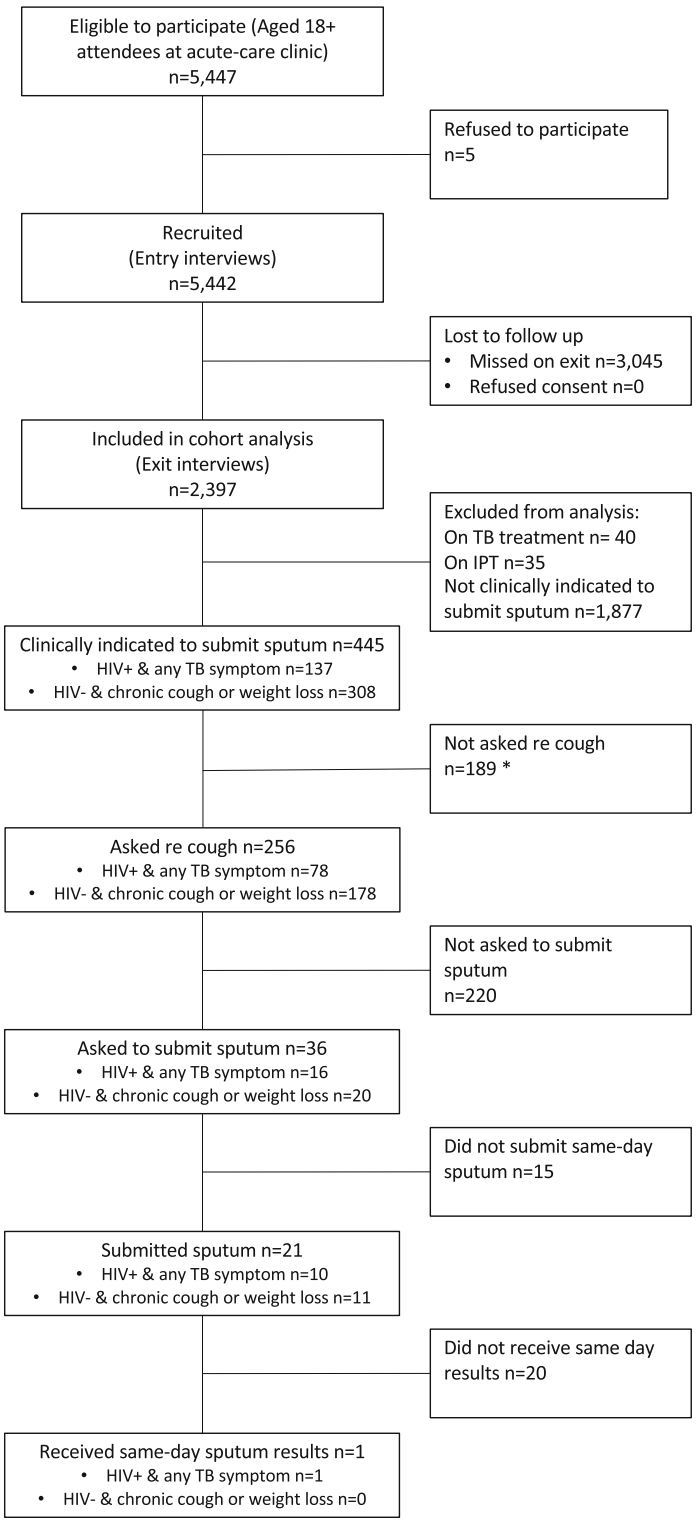
75 participants who reported being on TB treatment (40 people) or isoniazid preventive therapy (IPT) (35 people) were not included in the cascade or multivariable analysis.

TB diagnosis cascades

Of all 2322 exit interview participants analysed 1322 (56.9%) were asked by health workers about cough, 118 (5.1%) were asked to submit sputum, 46 (2.0%) gave same-day sputum and 3 (0.1%) received same-day results.

445 participants were clinically-indicated to submit sputum (HIV-negative participants with weight loss or chronic cough, and PLHIV with any TB symptom). 256 (57.5%) of these reported having been directly asked about coughing, with 36 of those (36/445, 8.1% of total) asked to submit a sputum sample; 21/445 (4.7%) provided same-day sputum and 1/445 (0.2%) received same-day sputum results (Fig. 1).

Diagnosis care cascades were constructed separately for each clinically-indicated group: HIV-negative participants with weight loss or chronic cough and PLHIV with



* Includes 4 clinically-indicated participants who were asked to submit sputum but were not asked about cough. 3 of these submitted sputum and 1 did not.

Fig. 1 Consort diagram of cohort participants and progress through steps of the TB diagnosis cascade

Table 1 Baseline characteristics of exit interview participants by HIV status

	HIV+ (*N* = 292)	HIV- (*N* = 1809)	Don't know/never tested (*N* = 296)	*P* value
Sex (Female)	213 (72.9%)	1134 (62.7%)	150 (50.7%)	< 0.001
Age Median (Range)	36 (18–70)	27 (18–87)	27 (18–89)	< 0.001
Age 18–29	89 (30.5%)	1031 (57.0%)	159 (53.7%)	< 0.001
30–39	98 (33.6%)	391 (21.6%)	46 (15.5%)	
40–49	68 (23.3%)	190 (10.5%)	25 (8.4%)	
50–59	22 (7.5%)	95 (5.3%)	27 (9.1%)	
60–89	15 (5.1%)	102 (5.6%)	39 (13.2%)	
Cough	121 (41.4%)	618 (34.2%)	110 (37.2%)	0.044
Cough days (if cough) Median (Range)	7 (1–3650)	4 (1–2190)	4 (2–1095)	0.001
Chronic cough¶	44 (15.1%)	149 (8.2%)	28 (9.5%)	0.001
Weight loss	65 (22.3%)	223 (12.3%)	28 (9.5%)	< 0.001
Fever	92 (31.5%)	550 (30.4%)	92 (31.1%)	0.915
Night sweats	56 (19.2%)	342 (18.9%)	63 (21.3%)	0.629
Any symptoms†	181 (62.0%)	1007 (55.7%)	182 (61.5%)	0.035
Previous TB	66 (22.6%)	66 (3.6%)	9 (3.0%)	< 0.001
On TB treatment*	18 (14.9%)	20 (3.2%)	2 (1.8%)	< 0.001
TB treatment last 6 months*	2 (1.7%)	7 (1.1%)	0 (0.0%)	0.446
On IPT*	26 (21.5%)	7 (1.1%)	2 (1.8%)	< 0.001
ART	276 (94.5%)	0 (0%)	0 (0%)	< 0.001
Self-reported general health				
Very Good	5 (1.7%)	58 (3.2%)	13 (4.4%)	0.062
Good	159 (54.5%)	1091 (60.3%)	159 (53.7%)	
Fair	122 (41.8%)	622 (34.4%)	119 (40.2%)	
Poor/Very poor	6 (2.1%)	38 (2.1%)	5 (1.7%)	

† Any TB symptom: cough, or weight loss, or fever, or weight loss
¶ Cough of 14 days or longer
* Only recorded if patient had cough

any TB symptom (Fig. 2). In the 308 HIV-negative participants with chronic cough, 57.8% were asked about cough, 6.5% were also asked for sputum, 3.6% gave sputum and none received same-day results. Among the 137 PLHIV with any TB symptom 56.9% were asked about cough, 11.7% were also asked for sputum, 7.3% gave sputum and 0.7% received same-day results. Overall sputum submission for TB testing was achieved in 5.4% (24/445) of clinically-indicated participants with 4.7% (21/445) successfully progressing through all steps of the diagnosis cascade to this point (four clinically indicated participants were requested to give sputum but had not been asked about cough).

Of the 118 requested to submit sputum 78 (66.1%) were not classed as clinically indicated. Of these 10/78 (12.8%) had unknown HIV status and TB symptoms, 27/78 (34.6%) were HIV-negative with no chronic cough or weight loss but had night sweats or fever of unknown duration and 17/78 (21.8%) were HIV-negative with cough of < 2 weeks as their only TB symptom. 24/78 (30.8%) participants (of whom 2 were HIV-positive) reported being asked to submit sputum but did not report any TB symptoms.

Using a more sensitive definition for clinically indicated participants (HIV-positive with any TB symptom and HIV-negative with chronic cough or weight loss, night sweats or fever of any duration) reduced the proportion of clinically indicated participants asked to submit sputum to 5.7% (8.1% in original definition) and those who submitted sputum to 2.4% (4.7% originally).

For all clinically-indicated groups, the biggest gap in the diagnosis cascade was between symptom enquiry and requesting sputum with 49.4% (220 of 445 who were clinically indicated for sputum testing) lost at this stage compared to 42.5% (189/445) not asked about cough and 3.4% (15/445) not giving sputum despite health worker request. For HIV-negative participants with weight loss or chronic cough, clinicians requested sputum for 11.2% (20/178) of those they had asked about cough and in PLHIV with any TB symptom this was 20.5% (16/78).

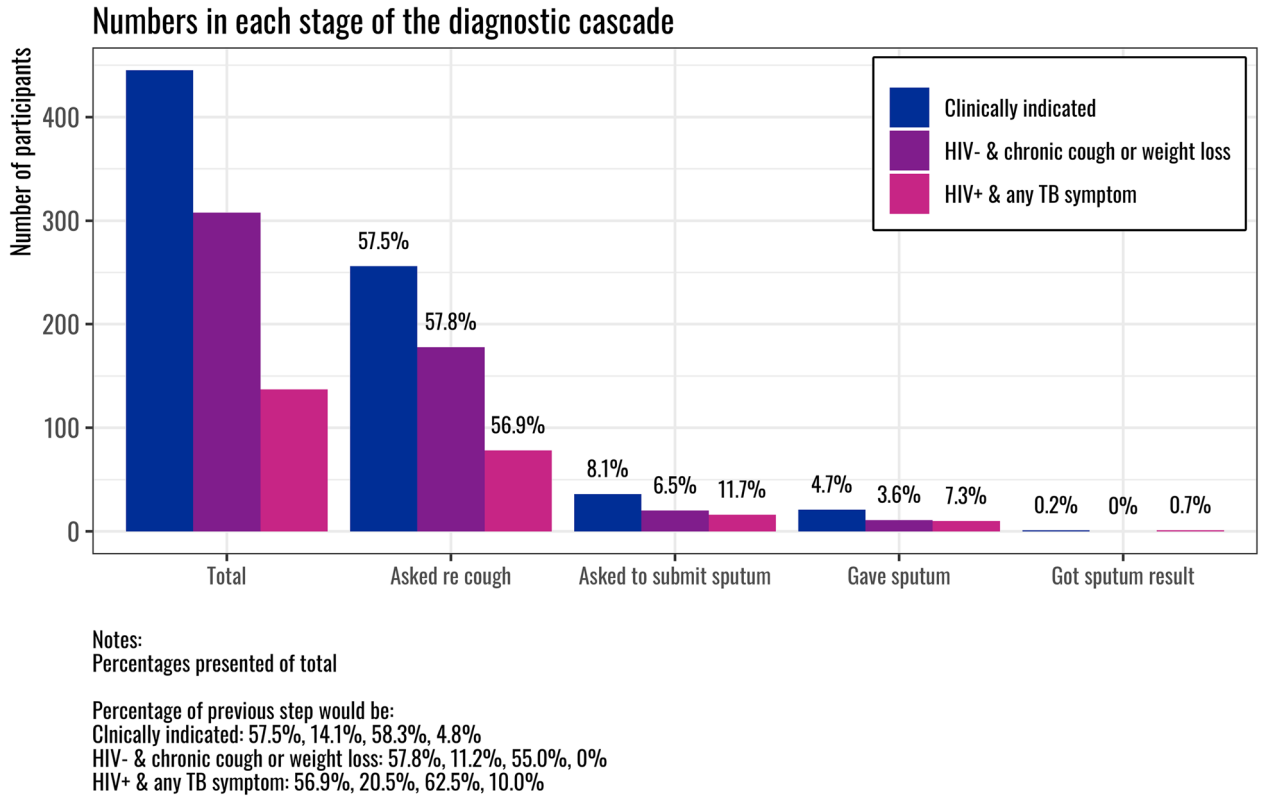


Fig. 2 Diagnosis care cascades for groups clinically indicated for TB sputum tests

Factors associated with being asked to submit sputum

On univariable analysis for all participants (Table 2), factors significantly associated with being asked to submit sputum included: older age (OR: 1.02, 95%CI: 1.01–1.03 per year increase in age), previous TB treatment (OR: 2.13, 95%CI: 1.08–4.20); being HIV-positive (OR: 1.69, 95%CI: 1.02–2.80); and presence of any TB symptoms (cough< 2 weeks OR: 2.48 (95%CI: 1.70–3.61), chronic cough OR: 3.32 (95%CI:2.07–5.33), weight loss OR: 2.52 (95% CI: 1.63–3.89), fever OR 2.10 (95% CI: 1.44–3.06) and night sweats OR 1.86 (95%CI: 1.23–2.80)).

Table 2 Univariable and multivariable associations with being asked to submit sputum: all participants. *n* = 2322

Variable	Unadjusted OR		Adjusted OR Any TB symptom		Adjusted OR Individual symptoms	
	OR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Sex	1.02 (0.69–1.49)	0.936	1.01 (0.68–1.49)	0.975	1.08 (0.73–1.62)	0.695
Age	1.02 (1.01–1.03)	< 0.001	1.02 (1.01–1.04)	< 0.001	1.02 (1.01–1.03)	0.002
Previous TB	2.13 (1.08–4.20)	0.026	1.64 (0.79–3.37)	0.183	1.59 (0.75–3.37)	0.224
HIV + *	1.69 (1.02–2.80)	0.040	1.42 (0.84–2.42)	0.191	1.45 (0.85–2.49)	0.174
Any TB symptom†	3.27 (2.07–5.18)	< 0.001	3.20 (2.02–5.06)	< 0.001	–	–
Cough < 2 weeks	2.48 (1.70–3.61)	< 0.001	–	–	3.43 (2.23–5.28)	< 0.001
Chronic cough	3.32 (2.07–5.33)	< 0.001	–	–	3.71 (2.10–6.56)	< 0.001
Weight loss	2.52 (1.63–3.89)	< 0.001	–	–	1.54 (0.96–2.47)	0.076
Fever	2.10 (1.44–3.06)	< 0.001	–	–	1.43 (0.94–2.18)	0.096
Night sweats	1.86 (1.23–2.80)	0.003	–	–	1.05 (0.66–1.68)	0.827

* Reference group: HIV-negative. Status unknown not presented
† Any TB symptom: cough, or weight loss, or fever, or weight loss
¶ Cough of 14 days or longer

On multivariable analysis increasing age (adjusted OR: 1.02, 95%CI: 1.01–1.04 per year) and any TB symptom (adjusted OR: 3.20, 95%CI: 2.02–5.06) remained significantly associated with being asked to submit sputum for all participants. In the individual symptoms multivariable model presence of cough (both under and over 2 weeks duration) was the only symptom still significantly associated with request for sputum (cough< 2 weeks adjusted OR 3.43, 95%CI: 2.23–5.28, chronic (≥2 weeks) cough adjusted OR: 3.71, 95%CI: 2.10–6.56) (Table 2).

On stratification by HIV status all these factors remained significantly associated for HIV-negative participants, but only the presence of any TB symptom (OR: 8.24, 95%CI: 1.08–37.68, adjusted OR: 8.18, 95%CI: 1.85–36.21) and chronic cough (OR: 10.84, 95%CI: 3.66–32.09, adjusted OR: 13.06, 95%CI: 3.69–46.28) were significantly associated with request for sputum amongst PLHIV (Table 3).

Sputum test throughput and capacity

If all patients clinically indicated for a TB test did submit sputum (445/44% [percentage completing exit interview] = 1011 over the 78 working days of the study) that would result in ~ 26 sputum samples on each working day (13 patients a day, each with two samples). The clinic laboratory has one GeneXpert machine to process TB samples, with a maximum throughput of 8–12 samples a day (4 samples per cartridge with 2 h run time plus preparation).

Discussion

This study found that same day sputum submission for TB testing following all steps of the diagnosis cascade was achieved for only 4.7% of participants among whom sputum testing was indicated according to Malawi national guidelines, with patients lost at every stage of the TB diagnosis care cascade. Failure to request sputum by clinicians despite elicited symptoms led to the biggest single gap in the diagnosis care cascade, followed by not asking about symptoms. This suggests that: interventions focusing on health worker behaviour may have the greatest potential for retaining presumptive TB patients within the diagnosis cascade; there appears to be inconsistent application of guidelines and infection control practices; and that we must formalise and strengthen reporting on the early steps in the TB care cascade. Additional important epidemiological groups such as men [1] should be given equal priority to PLHIV within national TB guidelines. However, if guideline adherence is improved, novel high-throughput triage testing approaches will also be needed to reach the required capacity.

Adherence to sputum-request guidelines in 4.7% (21/445) of patients sits at the bottom of the range (4–84%) identified in a recent systematic review [18]. When taken together with a TB treatment initiation rate of 85–94% [25] and TB treatment success rate of 82% in Malawi [19], our data suggests that the overall TB cascade in Malawi is more similar to that for India than that for South Africa. In India gap 1 (did not access a TB diagnostic test) accounted for 50% of all patient losses, whereas in South Africa, low treatment success led to the largest gap in the cascade [9, 13, 16].

To reduce these substantial gaps in accessing TB tests a multi-faceted approach is required to identify logistical barriers and change health worker behaviours. Facility-based screening relies on health worker behaviour (asking about symptoms and requesting sputum) which leads to the biggest gaps and therefore offers the greatest potential for improvement. Suspicion of malaria or bacterial investigations may contribute to not requesting sputum [26] but further investigation is needed to confirm what structural factors drive health worker behaviour.

This study demonstrates a low level of adherence to National TB Programme guidelines. This is the case

Table 3 Univariable and multivariable associations with being asked to submit sputum by HIV status

	HIV-positive *n* = 248				HIV-negative *n* = 1782			
	Univariable		Multivariable		Univariable		Multivariable	
	OR (95% CI)	P value	aOR (95% CI)	P value	OR (95% CI)	P value	aOR (95% CI)	P value
Sex	1.15 (0.40–3.29)	0.801	1.08 (0.35–3.32)	0.891	1.04 (0.67–1.62)	0.867	1.18 (0.74–1.87)	0.485
Age	1.02 (0.98–1.06)	0.394	1.02 (0.98–1.06)	0.383	1.02 (1.01–1.04)	0.001	1.02 (1.01–1.04)	0.008
Previous TB	0.51 (0.11–2.28)	0.367	0.52 (0.11–2.48)	0.413	3.66 (1.67–8.06)	0.001	3.37 (1.45–7.81)	0.005
Any TB symptom†	8.24 (1.80–37.68)	0.001	8.18 (1.85–36.21)	0.006	2.56 (1.56–4.20)	< 0.001	-*	-*
Cough < 2 weeks	1.28 (0.44–3.72)	0.645	-*	-*	2.59 (1.68–4.01)	< 0.001	3.16 (1.94–5.13)	< 0.001
Chronic cough¶	10.84 (3.66–32.09)	< 0.001	-*	-*	2.37 (1.30–4.33)	0.004	2.56 (1.25–5.25)	0.010

† Any TB symptom: cough, or weight loss, or fever, or weight loss
¶ Cough of 14 days or longer
* Multivariable analysis for HIV+ presented for Any TB symptom model, for HIV- presented model includes individual symptoms. Other symptoms (weight loss, fever and night sweats included in model but not presented: no significant relationship on multivariate analysis)

even with groups identified as high risk within both the Malawi and WHO guidelines, such as those who have previously had TB and PLHIV. Health workers operate in challenging conditions with average patient consultation times < 3 min [27], a high turnover of staff and regular supply stock outs [28]. As such, measures undertaken to improve adherence to guidelines and increase the proportion of clinically-indicated patients who access TB tests need to be pragmatic. Strategies such as FAST - Finding TB cases Actively, Separating safely and Treating effectively – [29] are effective in increasing testing and infection control not only for TB but also other respiratory infections. In Malawi, some elements of FAST, such as cough monitors, have been inconsistently implemented, due to limited availability of resources. However, our analysis shows the large gap in cough and symptom enquiry that could be met by universal cough monitors. Implementing strategies such as FAST consistently is critical for all low and middle income countries (LMICs), especially in the midst of the COVID-19 pandemic.

In addition, enhanced monitoring and central collation of data are essential to tracking individual clinic performance. Malawi, as is typical for LMICs, collects and reports comprehensive data on TB case notification and treatment success at clinic level, but only reports the number of TB tests per facility per quarter, without further diagnostic steps. A WHO recommendation to report numbers of screened presumptive TB cases, disaggregated by age, gender and HIV-status globally, would allow greater focus on the earlier steps of the TB care cascade.

Despite TB prevalence in men being over twice as high as among women in LMICs [30] and in Malawi a ratio of male to female cases of 1.5 [1, 19], in our study sex was not associated with being requested to submit sputum. In Malawi, the ratio of prevalent-to-notified cases of TB – an indication of how long patients take to be diagnosed - is 1.5 times higher among men than women [30]. Men should, therefore, be considered as much of a priority group within TB guidelines as PLHIV in countries with a high male-to-female case ratio. Notably, men are less likely than women to seek health care early on in their illness [31], making it critical to manage them efficiently when they do present to a facility.

Finally, if all patients attending the outpatient clinic were screened for TB as per the guidelines, the current Xpert facilities would only be able to process up to a half of the required samples. It is unknown to what extent this lack of diagnostic capacity may influence test decisions among the health workers. If guideline adherence and increased identification of presumptive TB patients is subsequently improved a novel high-throughput approach to triage testing using new diagnostics (e.g. computer aided diagnostics for X-rays) will also be required for LMICs to increase capacity [32, 33].

Study limitations include the single site nature of this study, limiting generalisability, although the study site is typical of urban primary care clinics in Malawi so likely representative of primary care in the areas with highest TB burden in the country [21]. Due to limited research staff capacity we interviewed only 44% of clinic attendees with men and those with TB symptoms more likely to complete an exit interview (Suppl Table 1), potentially resulting in selection bias and overestimation of the proportion who are clinically-indicated. However, this is mitigated by high participation in those approached. Symptoms, HIV status and testing practices were self-reported, potentially resulting in social desirability bias in measurement of these variables, with HIV-positive status under-reported by up to 40% in Malawi [34] and extensive dual HIV and TB stigma [35]. Although healthcare workers would be dependent on the same self-report of TB symptoms to assess eligibility for sputum testing and the proportions progressing through each step of the diagnosis cascade were similar for all HIV status groups. In addition, 69.5% of patients asked to submit sputum were not clinically-indicated to do so as per our definition and 30.8% of those had no reported TB symptoms at all – it is unknown why sputum was requested from these patients.

Conclusion

Same-day sputum submission for TB testing following all steps of the diagnosis cascade was achieved in only 4.7% of those clinically indicated. Requesting sputum after eliciting symptoms is the key point of the cascade to intervene. Interventions are needed to optimise TB screening guidelines, formalise reporting, increase guideline adherence and improve diagnostic capacity, in order to reduce the most significant gaps early in the TB care cascade and to reach the required testing capacity to meet the WHO End TB goals.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-021-05860-y.

Additional file 1 Table S1. Characteristics of adult acute clinic attendances by exit interview participation.

Additional file 2.

Abbreviations

TB: Tuberculosis; WHO: World Health Organisation; NTP: National TB Programme; PLHIV: People living with HIV; IPT: Isoniazid preventive therapy; CI: Confidence Interval; OR: Odds Ratio; aOR: Adjusted Odds Ratio; FAST: Finding TB cases Actively, Separating safely and Treating effectively; LMICs: Low and middle income countries

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Authors' contributions
Designed the study: PM, HF, ELW, MN, SBS, ELC, HM. Formal analysis: HF, PM, LM, Funding acquisition: PM. Writing - first draft: HF, PM, ELC. Writing - reviewing and editing: HF, PM, ELC, HEDB, ELW, MN, LM, HM, TD, WK, MK, SBS. The author(s) read and approved the final manuscript.

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Availability of data and materials
The dataset supporting the conclusions of this article is available in the Github repository, *https://github.com/petermacp/tbcascade*.

Ethics approval and consent to participate
Approval was received from the research ethics committees of the College of Medicine, Malawi and Liverpool School of Tropical Medicine. All participants provided written informed consent (or witnessed, thumb-print consent if illiterate).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. World Health Organisation. Global Tuberculosis Report. 2020, 2020.
2. World Health Organisation. Global Tuberculosis Report. 2019, 2019.
3. World Health Organisation. The End TB Strategy. 2015.
4. World Health Organisation. Systematic screening for active tuberculosis. In: Principles and recommendations; 2013.
5. Republic of Malawi Ministry of Health. National Tuberculosis Control Programme - Programme Manual. 8th ed. Malawi: Malawi Ministry of Health, Unit CHS; 2018.
6. National Tuberculosis LLDP. Guideline for integrated Tuberculosis, leprosy and lung disease in Kenya. 2017.
7. Uganda National Tuberculosis and Leprosy Control Programme MoH, Republic of Uganda. Manual for Management and Control of Tuberculosi and Leprosy. 2017.
8. Directorate General of Health Services MoHaFW, Dhaka, Bangladesh. National Guidelines on TB/HIV Management Program Collaboration & Implementation ManualNational Guidelines on TB/HIV Management and Program Collaboration and Implementation Manual. 2016.
9. Subbaraman R, Nathavitharana RR, Mayer KH, Satyanarayana S, Chadha VK, Arinaminpathy N, et al. Constructing care cascades for active tuberculosis: a strategy for program monitoring and identifying gaps in quality of care. PLoS Med. 2019;16(2):e1002754.
10. Bain LE, Nkoke C, Noubiap JJN. UNAIDS 90–90-90 targets to end the AIDS epidemic by 2020 are not realistic: comment on "Can the UNAIDS 90–90-90 target be achieved? A systematic analysis of national HIV treatment cascades". BMJ global health. 2017;2(2):e000227-e.
11. Claassens MM, du Toit E, Dunbar R, Lombard C, Enarson DA, Beyers N, et al. Tuberculosis patients in primary care do not start treatment. What role do health system delays play? Int J Tuberc Lung Dis. 2013;17(5):603–7.
12. Hanson CL, Osberg M, Brown J, Durham G, Chin DP. Conducting Patient-Pathway Analysis to Inform Programming of Tuberculosis Services: Methods. J Infect Dis. 2017;216(suppl_7):S679-s85.
13. Subbaraman R, Nathavitharana RR, Satyanarayana S, Pai M, Thomas BE, Chadha VK, et al. The tuberculosis Cascade of Care in India's public sector: a systematic review and meta-analysis. PLoS Med. 2016;13(10):e1002149.
14. Kim J, Keshavjee S, Atun R. Health systems performance in managing tuberculosis: analysis of tuberculosis care cascades among high-burden and non-high-burden countries. J Glob Health. 2019;9(1):010423.
15. World Health Organisation. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. 2014.
16. Das J, Kwan A, Daniels B, Satyanarayana S, Subbaraman R, Bergkvist S, et al. Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study. Lancet Infect Dis. 2015;15(11):1305–13.
17. Daniels B, Dolinger A, Bedoya G, Rogo K, Goicoechea A, Coarasa J, et al. Use of standardised patients to assess quality of healthcare in Nairobi, Kenya: a pilot, cross-sectional study with international comparisons. BMJ Glob Health. 2017;2(2):e000333.
18. Divala THL, J.E., Bulterys, M., Lutje, V., Corbett, E. L., Schumacher, S., Macpherson, P. Missed opportunities for diagnosis and treatment in patients with tuberculosis symptoms: a systematic review. PREPRINT (Version 1) available at Research Square [+https://doiorg/1021203/rs222742/v1+]. 2020.
19. World Health Organisation Global Tuberculosis Report 2018. World Health Organisation; 2018.
20. MacPherson P, Webb EL, Lalloo DG, Nliwasa M, Maheswaran H, Joekes E, et al. Design and protocol for a pragmatic randomised study to optimise screening, prevention and care for tuberculosis and HIV in Malawi (PROSPECT study). Wellcome Open Res. 2018;3:61.
21. Law I, Floyd K. National tuberculosis prevalence surveys in Africa, 2008-2016: an overview of results and lessons learned. Tropical Med Int Health. 2020;25(11):1308–27.
22. Getahun H, Kittikraisak W, Heilig CM, Corbett EL, Ayles H, Cain KP, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. PLoS Med. 2011;8(1):e1000391.
23. Monk EJM, Kumwenda M, Nliwasa M, Mpunga J, Corbett EL. Factors affecting tuberculosis health message recall 2 years after active case finding in Blantyre, Malawi. Int J Tuberc Lung Dis. 2018;22(9):1007–15.
24. World Health Organisation. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource constrained settings. 2011.
25. MacPherson P, Houben RM, Glynn JR, Corbett EL, Kranzer K. Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. Bull World Health Organ. 2014;92(2):126–38.
26. Roy M, Muyindike W, Vijayan T, Kanyesigye M, Bwana M, Wenger M, et al. Implementation and operational research: use of symptom screening and sputum microscopy testing for active tuberculosis case detection among HIV-infected patients in real-world clinical practice in Uganda. J Acquir Immune Defic Syndr. 2016;72(5):e86–91.
27. Sosola A. An assessment of prescribing and dispensing practices in public health facilities of southern Malawi: University of Malawi; 2007.
28. Shieshia M, Noel M, Andersson S, Felling B, Alva S, Agarwal S, et al. Strengthening community health supply chain performance through an integrated approach: using mHealth technology and multilevel teams in Malawi. J Glob Health. 2014;4(2):020406.
29. Barrera E, Livchits V, Nardell E. F-A-S-T: a refocused, intensified, administrative tuberculosis transmission control strategy. Int J Tuberc Lung Dis. 2015;19(4):381–4.
30. Horton KC, MacPherson P, Houben RM, White RG, Corbett EL. Sex differences in tuberculosis burden and notifications in low- and middle-income countries: a systematic review and meta-analysis. PLoS Med. 2016;13(9):e1002119.
31. Chikovore J, Hart G, Kumwenda M, Chipungu GA, Desmond N, Corbett L. Control, struggle, and emergent masculinities: a qualitative study of men's care-seeking determinants for chronic cough and tuberculosis symptoms in Blantyre, Malawi. BMC Public Health. 2014;14:1053.

32. Nathavitharana RR, Yoon C, Macpherson P, Dowdy DW, Cattamanchi A, Somoskovi A, et al. Guidance for Studies Evaluating the Accuracy of Tuberculosis Triage Tests. J Infect Dis. 2019;220(Supplement_3):S116-s25.
33. Yoon C, Dowdy DW, Esmail H, MacPherson P, Schumacher SG. Screening for tuberculosis: time to move beyond symptoms. Lancet Respir Med. 2019;7(3): 202–4.
34. Fishel JD, Bernard Barrère, Sunita Kishor. Validity of data on self-reported HIV status in Malawi and Uganda and implications for measurement of ARV coverage. DHS Methodological Reports.No. 10. . Rockville, Maryland, USA: ICF International; 2014.
35. Chikovore J, Hart G, Kumwenda M, Chipungu G, Desmond N, Corbett EL. TB and HIV stigma compounded by threatened masculinity: implications for TB health-care seeking in Malawi. Int J Tuberc Lung Dis. 2017;21(11):26–33.

Publisher's Note

Supplemental Table 1: Characteristics of adult acute clinic attendances by exit interview participation

	Exit Interviewed (N=2397)	Not exit interviewed (N=3025)	Total (N=5422)	P value
Sex				0.012
Female	1497 (62.5%)	1989 (65.8%)	3486 (64.3%)	
Male	900 (37.5%)	1036 (34.2%)	1936 (35.7%)	
Age				
Median (Range)	28 (18, 89)	27 (18, 89)	28 (18, 89)	0.001
Cough				
No	1548 (64.6%)	2053 (67.9%)	3601 (66.4%)	0.011
Yes	849 (35.4%)	972 (32.1%)	1821 (33.6%)	
Weight loss				
No	2081 (86.8%)	2629 (86.9%)	4710 (86.9%)	0.920
Yes	316 (13.2%)	396 (13.1%)	712 (13.1%)	
Fever				
No	1663 (69.4%)	2178 (72.0%)	3841 (70.8%)	0.035
Yes	734 (30.6%)	847 (28.0%)	1581 (29.2%)	
Night sweats				
No	1936 (80.8%)	2502 (82.7%)	4438 (81.9%)	0.065
Yes	461 (19.2%)	523 (17.3%)	984 (18.1%)	
Any symptoms†				
No	1027 (42.8%)	1379 (45.6%)	2406 (44.4%)	0.044
Yes	1370 (57.2%)	1646 (54.4%)	3016 (55.6%)	
Chronic cough¶				
No	2176 (90.8%)	2724 (90.1%)	4900 (90.4%)	0.365
Yes	221 (9.2%)	301 (9.9%)	522 (9.6%)	

† Any TB symptom: cough, or weight loss, or fever, or weight loss.
¶ Cough of 14 days or longer

Chapter 4

Prevalence of Bacteriologically-Confirmed Tuberculosis in Urban Blantyre, Malawi 2019-20: Substantial Decline Compared to 2013-14 National Survey

To estimate community TB burden and provide local estimates to guide targeted interventions, I led a TB cross-sectional survey to estimate the community prevalence of TB disease in high to middle density residential areas of urban Blantyre. The screening algorithm was cough of any duration and/or abnormal X-ray, followed by microscopy, Xpert MTB/Rif and mycobacterial culture on two sputum samples with adults (18+) from randomly selected households in 72 clusters. 85% of eligible adults participated with an estimated TB prevalence of 150-189 per 100,000 adult population. Men had a substantially higher burden than women (complete case adjusted odds ratio 2.70 [95%CI: 1.26-5.78]), and other significant risk factors for prevalent TB were working age (25-49 years) and previous TB treatment, but not HIV status. This estimated TB prevalence for Blantyre was considerably lower than the 1,014 per 100,000 estimated for urban Malawi from the 2013-14 national survey, but some groups, notably men, remain disproportionately affected.

This paper was submitted to PLoS Global Health in April 2023 and is under review.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1806428	**Title**	Mrs
First Name(s)	Helena Rosemary Anne		
Surname/Family Name	Feasey		
Thesis Title	Investigating the potential impact and suitability of tuberculosis active case-finding approaches in the rapidly changing environment of urban Blantyre, Malawi		
Primary Supervisor	Prof Liz Corbett		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

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	Mpunga, Peter MacPherson, Elizabeth L Corbett
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the protocol, led the implementation including all CRFs and SOPs, I led data collection and analysis, and I led writing of the manuscript as first author.

SECTION E

Student Signature	Helena Feasey
Date	17 April 2023

Supervisor Signature	Elizabeth Corbett
Date	17 April 2023

Prevalence of Bacteriologically-Confirmed Tuberculosis in Urban Blantyre, Malawi 2019-20: Substantial Decline Compared to 2013-14 National Survey

Short title: Reduced Tuberculosis Prevalence in Blantyre, Malawi

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Abstract (299 words)

Recent evidence shows rapidly changing tuberculosis (TB) epidemiology in Southern and Eastern Africa, with need for subdistrict prevalence estimates to guide targeted interventions. We conducted a TB prevalence survey to estimate current TB burden in Blantyre city, Malawi. From May 2019 to March 2020, 215 households in middle/high-density residential Blantyre, were randomly-selected from each of 72 clusters. Consenting eligible participants (household residents ≥ 18 years) were interviewed, including for cough (any duration), and offered HIV testing and chest X-ray; participants with cough and/or abnormal X-ray provided two sputum samples for microscopy, Xpert MTB/Rif and mycobacterial culture. TB disease prevalence and risk factors for prevalent TB were calculated using complete case analysis, multiple imputation, and inverse probability weighting. Of 20,899 eligible adults, 15,897 (76%) were interviewed, 13,490/15,897 (85%) had X-ray, and 1,120/1,395 (80%) sputum-eligible participants produced at least one specimen, giving 15,318 complete cases (5,895, 38% men). 29/15,318 had bacteriologically-confirmed TB (189 per 100,000 complete case (cc) / 150 per 100,000 with inverse weighting (iw)). Men had higher burden (cc: 305 [95% CI:144-645] per 100,000) than women (cc: 117 [95% CI:65-211] per 100,000): cc adjusted odds ratio (aOR) 2.70 (1.26-5.78). Other significant risk factors for prevalent TB on complete case analysis were working age (25-49 years) and previous TB treatment, but not HIV status. Multivariable analysis of imputed data was limited by small numbers, but previous TB and age group 25-49 years remained significantly associated with higher TB prevalence.

TB prevalence for Blantyre was considerably lower than the 1,014 per 100,000 for urban Malawi in the 2013-14 national survey, at 150-189 per 100,000 adults, but some groups, notably men, remain disproportionately affected. TB case-finding is still needed for TB elimination in Blantyre, and similar urban centres, but should focus on reaching the highest risk groups, such as older men.

Introduction

The high tuberculosis (TB) incidence in Southern and Eastern African countries has been driven by generalised HIV epidemics [1], together with poverty and urbanisation. In the WHO African Region, TB incidence declined by 22% between 2015 and 2021 [2], concurrent with continuing decreases in HIV incidence and HIV-related deaths [3, 4]. In Malawi, estimated TB incidence has declined from 338 per 100,000 in 2010 to 132 per 100,000 in 2021 [2]. The most recent national TB prevalence survey conducted in 2013-14 estimated an urban prevalence of bacteriologically-confirmed pulmonary TB of 1,014 per 100,000 adults (15+ years) [5, 6] (including Blantyre, the second largest city in Malawi), prompting government and donor investment in TB case-finding activities focused on urban areas. In this time of rapidly declining estimated TB incidence, understanding true TB burden can support more effective National TB Programme (NTP) interventions as countries work towards TB elimination goals TB [7]. As epidemics decline, TB is likely to become more concentrated in marginalised and harder-to-reach groups, requiring increasingly targeted case-finding strategies [8, 9].

TB case-notification rates (CNRs) have been declining in Blantyre [10], likely reflecting the combined effects of increasing coverage with antiretroviral therapy (ART) [11, 12] and use of TB preventive therapy for people living with HIV (PLHIV), as well as TB case-finding and prevention activities. HIV testing and treatment services have been successfully scaled-up to reach UNAIDS 90-90-90 targets for 2020 in Malawi [12, 13]. However, case-notifications are an imperfect guide to TB burden in a population, since they do not include people with TB who remain undiagnosed or may not reach care [2]. As such, low TB CNRs can reflect either under-notification or low incidence of TB.

While TB prevalence surveys are laborious and expensive they likely provide the least biased approach to estimating disease burden [14].

The Sustainable Community-based Active case-finding for Lung hEalth (SCALE) trial was designed to investigate the impact of door-to-door active case-finding (ACF) on TB case-notification rates and, if sufficiently powered, the prevalence of undiagnosed TB [15] in Blantyre. In 2019-2020, a TB prevalence survey was, therefore, conducted in all SCALE clusters before the ACF intervention to determine the baseline prevalence of undiagnosed TB and re-evaluate power for intended trial outcomes. The aim was to estimate the burden of TB amongst adults 18 years or older in middle-to-high density urban Blantyre, Malawi.

Methods

We undertook a cluster-based, cross-sectional TB prevalence survey in middle- to high-density residential areas of Blantyre, Malawi between May 2019 and March 2020. Blantyre City is located in the Southern Region of Malawi, and has a population of approximately 800,250 [16] mostly living in several informal urban settlements built on underserviced land [17]. Although health care is free at the point of care, poorly developed road networks limit access to health and other municipal services. These informal settlements were the focus of this study, which excluded the smaller, central, and more affluent residential and industrial areas. Informal residential areas were demarcated into 72 clusters of approximately 4,400 adult residents each using Community Health Worker catchment area boundaries and population estimates from a city-wide enumeration census conducted with Blantyre District Health Office (DHO) in 2015. The study covered approximately 75% of the geographical area of Blantyre City.

In each cluster, 115 households were randomly selected from a sampling frame of all household GPS co-ordinates obtained from Google Earth, aiming to recruit 215 adults (aged 18 and above) per cluster. Each household was visited at least three times to maximise recruitment of all adult household members, with an initial visit to sensitise household members and book survey appointments. Survey teams covered two clusters per week, with initial activities taking four to five days per cluster, followed by repeat visits to include previously unavailable residents in March 2020.

Household residents were defined as those who usually ate and slept in the same residence. All adult (18 years and over) household residents were eligible for participation if willing and able to provide written or witnessed informed consent. A household questionnaire was conducted with one consenting adult household member (the household head if present) to capture household-level variables including socioeconomic indicators and the age and sex of all household residents. Individual questionnaires were then conducted with all consenting household members, including socio-demographics, a symptom screen for cough of any duration, and brief details of previous HIV and TB testing and care. Participants reporting cough were given two sputum pots, with one collected immediately for microscopy and culture, if possible, and the second collected for Xpert MTB/Rif after an hour or more. All participants were asked to attend a temporary tented digital chest X-ray and HIV testing camp located within each cluster during recruitment days.

Chest X-ray used Min X-ray Commander CMDR-2S-T, with films classed as normal or having any abnormality by a trained radiographer, with reference to results of Qure.ai (version 2) computer-aided detection software. All participants with abnormal X-rays were requested to provide two spot sputum samples. The first sample was taken immediately and the second an hour later. HIV testing used OraQuick (OraSure) and Determine (Alere) finger-prick tests in parallel, with confirmation by Uni-Gold (Trinity Biotech) for positive results, was offered to all participants not on ART. Participants on ART were offered Uni-Gold (Trinity Biotech) confirmatory testing only.

All participants with abnormal X-rays (any abnormality) were referred to an X-ray clinic for review by clinician in a tented community clinic the following week. Those identified as HIV positive and not on ART through the onsite HIV testing were given onsite counselling and referred to the local government HIV clinic for ART initiation.

Laboratory methods

Sputum samples were processed in the Malawi-Liverpool-Wellcome (MLW)/Kamuzu University of Health Sciences (KUHeS) TB Laboratory, with the first specimen used for fluorescent microscopy (auramine) and liquid culture (Bactec MGIT 960, Becton Dickinson, Franklin Lakes, NJ, USA) and the second specimen used for microscopy and Xpert MTB/Rif (Cepheid, Sunnyvale, CA, USA). Mycobacterial Growth Indicator Tube (MGIT) positive samples were confirmed by Ziehl-Neelsen microscopy (morphology/cording) and MPT64 (SD Bioline, Yongin, Republic of Korea) antigen testing to identify *Mycobacterium tuberculosis (*MTB). Those negative on MPT64 were further incubated at different temperatures on Löwenstein-Jensen (LJ) slopes and classified as non-tuberculous mycobacteria or MTB based on subsequent morphology and growth characteristics.

Participants with positive microscopy, Xpert or MTB culture results were classified as having bacteriologically-confirmed TB. For this survey, an Xpert MTB/Rif G4 trace result was considered positive for MTB. Smear-positive TB participants were defined as those with a direct smear indicating acid fast bacilli. Confirmed TB participants were actively traced for assisted registration for TB treatment at local government clinics.

Statistical methods

The calculated sample size of 14,511 participants was based on the ability to estimate an overall TB prevalence of 900 per 100,000 with absolute precision of +/- 250,000 per 100,000 (relative precision 27.8%) and a design effect to account for clustering of 2.25. Based on previous work by NTP and our research group in Blantyre, a relatively high non-participation rate of 25% was also assumed. This final sample was rounded up to 15,500 adults (215 per cluster).

Data was summarised by frequencies, percentages, and medians as appropriate, with chi-squared tests to examine differences between groups, such as participation rate by sex.

Following WHO-recommended best-practice analytical methods [18, 19], we estimated TB prevalence using logistic regression models with robust standard errors (calculated from observed between-cluster variability) to account for clustering using three approaches to missing data: 1) complete case analysis (excluding participants eligible for sputum submission but for whom smear, Xpert MTB/Rif and/or culture data were missing); 2) multiple imputation of missing values for sex, age, HIV status, symptom status, X-ray status, sputum results, previous TB, TB contact, crowding and wealth variables, and 3) imputation of missing data for those eligible for sputum submission (cough or abnormal X-ray) with inverse probability weighting to represent all eligible individuals. For multiple imputation of missing values, the predictive mean matching imputation model included all the variables investigated as predictors of bacteriologically-confirmed and smear-positive TB in the multivariable regression

model, twenty-five imputed datasets were created, and estimates were combined using Rubin's rules [20]. Sensitivity analysis was also conducted for an alternate definition of a complete case, restricted to participants with available sputum result data and those who completed both screens.

All analyses were done with R version 4.2.1, using packages including mice [21], lmtest [22] and sandwich [23]. This prevalence survey was part of the SCALE trial with registration number ISRCTN11400592.

Data and reproducibility

Data and code to reproduce this analysis is available from *https://osf.io/eu2xf/.*

Ethics

The survey protocol was approved by the ethics committee of the London School of Hygiene and Tropical Medicine and Kamuzu University of Health Sciences in Malawi. Written (or witnessed thumbprint if illiterate) informed consent was obtained from all participants.

Results

Between May 2019 and March 2020, 20,899 eligible adults were enumerated in 7,175 randomly selected and visited households, although many were not physically present during the household visit. 76% (15,897) participated in the survey and underwent symptom screen; 13,490 (85%) had chest X-ray. 1,394/15,897 (9%) participants were eligible to submit sputum through reporting a cough of any duration and/or abnormal X-ray. Of these, 1,140 (82%) submitted at least one sputum sample and 900 submitted two sputum samples (Figure 1).

Participation rates varied substantially by sex and age group. Participation was higher in women (9,766 of 11,283 [86.6]) than men (6,131 of 9,616 [63.8%], χ^2 p<0.001). The participation rate was highest in people aged 18-24 years (5997 of 7149 [83.9%]) and lower in those aged 25-49 years (8,006 of 10,881 [73.6%]) and 50+ years (1,885 of 2,476 [76.1%], χ^2 p<0.0001). The difference in age participation was driven by men, with the lowest participation rates in working-age men (2,738/4,854 [56.4%] men aged 25-49).

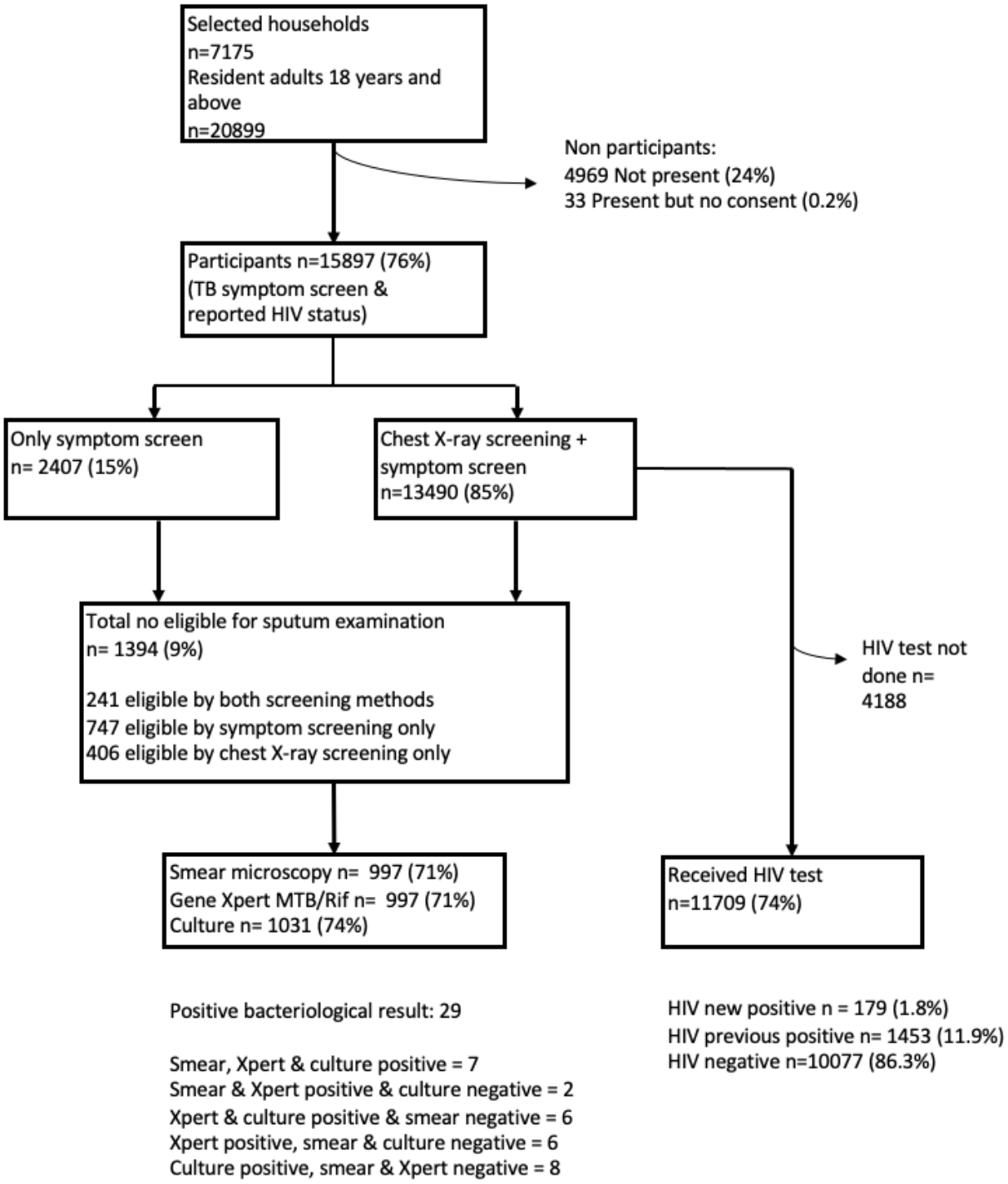
HIV results were available for 11,709 participants of whom 179 (1.8%) were newly identified as HIV-positive, whilst 1,453 (11.9%) were confirmed as previously-known HIV-positive. Overall, 1,971/15,897 (12.4%) participants were identified as HIV-positive, of whom 1,741/1,971 (88.3%) were taking ART.

199 Previous TB was reported by 456 of 15,897 (2.9%) participants, with 24 (24/15897

200 [0.2%]) currently on TB treatment; 721 (4.5%) reported knowing someone who had

201 received TB treatment in the last 12-months.

202 **Figure 1: Schematic diagram of number of participants screened for TB & HIV**



203

Of the 1,395 participants eligible to submit sputum 1,120 had valid smear results, 1,075 valid culture results, and 900 valid Xpert MTB/Rif results. 579 sputum-eligible participants were missing valid results from at least one sputum tests giving 15,318 complete cases (Table 1). 29 participants were identified with bacteriologically-confirmed TB (one of whom was already on TB treatment). Of those 29, nine were smear-positive (all confirmed by Xpert MTB/Rif or culture) and the others Xpert/culture positive and smear negative (Figure 1 & Supplementary Table 1).

Table 1: Prevalence of TB disease per 100,000 adults, with robust standard errors used to calculate 95% confidence intervals

	Total (n)	TB (n)	Prevalence (95% CI)		
			Complete case	Fully imputed	Inverse weighting
All participants	15318	29	189 (132-272)	139 (71-272)	150 (76-297)
Sex					
Female	9423	11	117 (65-211)	97 (54-176)	100 (55-183)
Male	5895	18	305 (144-645)	198 (94-415)	225 (105-479)
Age					
18-24	5811	5	86 (36-207)	82 (37-183)	65 (27-158)
25-49	4356	19	246 (92-657)	189 (77-468)	197 (73-531)
50+	582	5	281 (81-966)	277 (93-821)	283 (85-938)
HIV status					
HIV negative	15318	23	171 (114-257)	126 (84-189)	148 (97-228)
HIV positive	5895	6	320 (130-783)	270 (116-628)	292 (122-693)
Previous diagnosis					
No previous TB	14895	25	168 (113-248)	128 (87-189)	143 (96-214)
Previous TB	423	4	946 (329-2687)	613 (214-1742)	794 (270-2308)

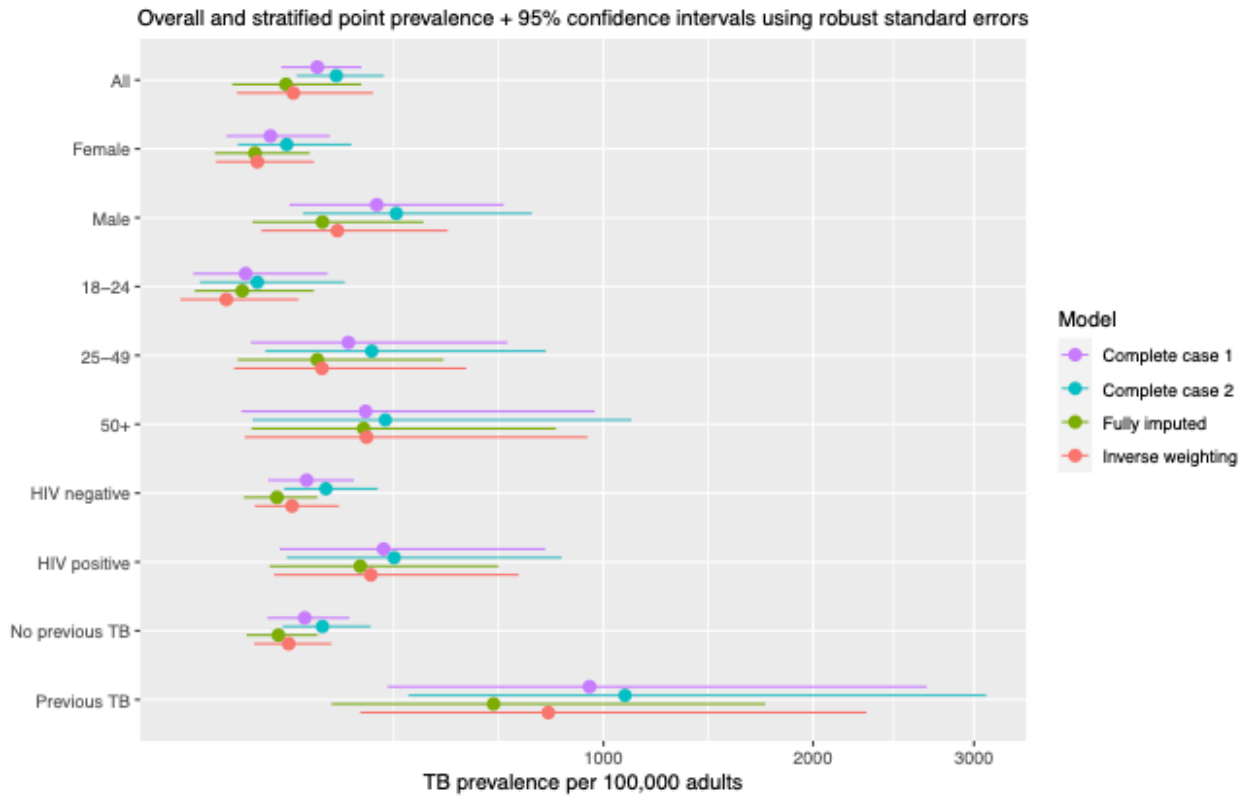
Notes:
HIV status as identified through testing in prevalence survey, or if no test as reported in individual survey
5 of complete cases no age recorded (3 HIV negative, 1 HIV positive & 1 HIV unknown)
626 participants with HIV unknown status but no TB cases amongst them
Previous TB includes one currently on TB treatment

Of the 29 participants identified with bacteriologically-confirmed TB, 18 (62%) were male and the highest number were in the 25-49 age group (19 [66%]) (Table 1). In total 6/29 (21%) with bacteriologically-confirmed TB were living with HIV, of whom five

were taking ART and one was newly diagnosed. In addition, four (14%) of the 29 identified with prevalent TB reported a previous TB diagnosis (one currently on treatment) and two (7%) reported knowing someone who had started TB treatment in the last 12 months. Fourteen had a cough, of whom nine also had an abnormal chest X-ray. Twelve (41%, 95% CI: 24-61%) had an abnormal chest X-ray but no cough, and for three participants their cough result was missing (two had normal X-ray and one X-ray result was also missing). Overall, of the 29 participants with prevalent bacteriologically-confirmed TB, ten (34%, 95% CI: 18-54%) reported no TB symptoms at household survey (cough, fever, night-sweats or weight-loss) (Supplementary Tables 1 & 2).

The overall prevalence of bacteriologically-confirmed TB was: 189 per 100,000 adults (95% CI 132-272) for the complete case model; 139 per 100,000 adults (95% CI: 71-272) for the multiple imputation model; and 150 per 100,000 adults (95% CI: 76-297) for the inverse probability weighted model (Figure 2). Sensitivity analysis with the alternate complete case definition gave a TB prevalence of 223 per 100,000 adults (95% CI: 155-320).

Figure 2: Estimated tuberculosis prevalence by different analytical models



TB prevalence varied considerably by sex, age, and HIV status. The inverse probability weighting model is considered to give the single best estimate of TB prevalence [19] and in our study we considered it most likely to be closest to the true prevalence since it adjusted for the low participation rates amongst working age men (i.e. those aged 25-49 years). In this model male TB prevalence was more than twice as high as female prevalence (225 per 100,000 [95% CI: 105-479] for males vs. 100 per 100,000 [95% 55-183] for females). TB prevalence was highest in the age group 50 years and over (283 per 100,000 [95% CI: 85-938). TB prevalence was also higher in people living with HIV (PLHIV) at 292 per 100,000 (95% CI: 122-693) compared to HIV-negative people (148 per 100,000 [95%CI: 97-228]).

The inverse probability weighting model gave a smear-positive TB prevalence of 37 per 100,000 adults (95% CI: 9-169) (Supplementary Table 3). Smear-positive prevalence was higher for males (84 per 100,000 [95% CI: 18-400]) than females (18 per 100,000 [95%CI: 4-71]), higher amongst PLHIV (132 per 100,000 [95% CI: 33-520]) than those who are HIV negative (42 per 100,000 [95% CI: 20-88]), and highest in the age group 50 years and over (141 per 100,000 [95% CI: 23-852]). The overall highest smear-positive TB prevalence was amongst those who had previously been treated for TB at 349 per 100,000 (95% CI: 74-1640) compared to 42 per 100,000 (95% CI: 21-86) for those with no previous treatment.

On univariable analysis, male sex (OR 2.62, 95% CI: 1.17-6.14, compared to female), being aged 25-49 years (OR 2.86, 95% CI: 1.07-7.68 compared to 18-24 years) and previous TB (OR 5.68, 95% CI: 1.96-16.42, compared to no previous TB treatment were associated with increased odds of prevalent TB (Table 2). On multivariable analysis using the recommended inverse-weighting approach, only previous TB treatment (aOR 3.96, 95% CI: 1.16-13.49) and the age group 25-49 years (aOR 2.69, 95% CI: 1.00-7.26) remained significant predictors of prevalent TB (Table 2). Contact with someone with TB in the last 12 months, male sex, HIV status, crowding and wealth were not significantly associated with prevalent TB in the fully adjusted model. However, this multivariable analysis was limited by the small numbers of participants diagnosed with TB in each category. Due to the small numbers we present age and HIV variables with only three and two categories respectively but analysis with full WHO recommended age and HIV categories is presented in Supplementary Tables 4 and 5.

Table 2: Risk factors for prevalent bacteriologically-confirmed TB, with robust standard errors used to calculate 95% confidence intervals

		Multivariate analysis		
Variable	Univariate OR	Complete case OR (95% CI)	Fully imputed OR (95% CI)	Inverse weighting OR (95% CI)
Sex				
Female	1	1	1	1
Male	2.62 (1.24-5.55)	2.70 (1.26-5.78)	2.03 (0.95-4.34)	2.04 (0.98-4.27)
Age, years				
18-24	1	1	1	1
25-49	2.86 (1.07-7.68)	2.97 (1.10-8.04)	2.33 (0.85-6.39)	2.69 (1.00-7.26)
50+	3.27 (0.95-11.32)	2.78 (0.78-9.87)	2.73 (0.87-8.59)	3.09 (0.92-10.42)
HIV/ART status				
HIV-	1	1	1	1
HIV+	1.87 (0.76-4.60)	1.28 (0.38-4.29)	1.70 (0.66-4.39)	1.42 (0.55-3.64)
Previous TB	5.68 (1.96-16.42)	3.95 (0.87-17.81)	3.29 (1.00-10.87)	3.96 (1.16-13.49)
TB contact (within 12 months)	1.59 (0.38-6.71)	1.38 (0.31-6.09)	1.31 (0.29-5.86)	1.29 (0.28-6.05)
Crowding, persons per room				
<1	1	1	1	1
1-2	1.50 (0.70-3.24)	1.67 (0.73-3.81)	1.69 (0.84-3.42)	1.96 (0.96-4.00)
>2	2.00 (0.44-9.04)	2.50 (0.45-13.86)	2.64 (0.50-13.82)	1.91 (0.37-9.73)
*Wealth quartile**				
1	1	1	1	1
2	0.66 (0.21-2.08)	0.65 (0.20-2.11)	0.59 (0.18-1.97)	0.63 (0.17-2.31)
3	1.24 (0.47-3.26)	1.13 (0.40-3.19)	1.05 (0.37-2.96)	1.01 (0.36-2.86)
4 (top)	0.81 (0.28-2.32)	0.68 (0.20-2.28)	0.64 (0.20-2.08)	0.70 (0.22-2.21)

* Probability of being below the poverty line from 1 (most likely) to 4 (least likely)

Significant predictors of prevalent smear-positive TB were male sex (OR 5.35 [95% CI: 1.02-52.74]) and reported previous TB (OR 9.86, 95% CI: 1.00-52.01) on univariable analysis, but no predictors were significant on multivariable analysis, likely due to the small numbers involved (only nine smear-positive TB cases identified).

Discussion

The main finding from this survey is that the estimated adult prevalence of bacteriologically-confirmed pulmonary TB in Blantyre from this survey – 150 per 100,000 in the inverse probability weighted model – was more than 80% lower than the previous estimates for urban areas in the 2013-14 Malawi National TB Prevalence Survey (1,014 per 100,000 adults aged 15+) [5, 6]. This large decrease in TB prevalence over six years is likely due to both extensive local case-finding efforts and the concurrent rapid scale-up and high coverage of ART for treatment of HIV [12], and potentially TB preventive therapy for PLHIV. As expected [24], TB prevalence was higher amongst men, PLHIV, and those reporting previous TB, as well as among people aged 50 years and over. More than half of survey participants (52%) identified with TB through the survey did not self-report cough, and so would not have been identified through the symptom screen alone, highlighting the benefit of including X-ray or other screening strategies able to identify subclinical TB [25]. As TB epidemics decline in Southern and Eastern Africa, TB disease is likely to become increasingly concentrated in marginalised and hard-to-reach groups requiring adaptive targeted strategies informed by evidence such as local prevalence surveys.

Between the 2013-2014 NTP prevalence survey and this 2019-2020 survey, annual TB case notification rates, including bacteriologically confirmed TB, had been declining in Blantyre [10] with concurrent steep reductions in the percentage of primary care clinic attendees with bacteriologically-confirmed TB following self-presentation for investigation of TB symptoms. [26, 27]. As such, the pronounced decline in the prevalence of undiagnosed TB that we infer from comparing our results to the 2013-14

national survey is almost certainly correct, although our survey still demonstrates under-diagnosis of TB in Blantyre with a prevalence to case-notification ratio of 4.49 (95% CI: 0.98–11.91) as reported elsewhere [10]. Undiagnosed infectious TB remains well above TB elimination targets, underscoring the need to continue appropriately targeted case-finding activities in Blantyre.

Our survey was intended to inform endpoints for a TB case-finding intervention trial, and so used random household sampling in purposively selected study-clusters, and 18+, not 15+, age to define adults as in the 2013-14 National survey. If anything, however, this is likely to over-estimate the municipal burden of undiagnosed TB in Blantyre City compared to National 2013-14 estimates. Our survey area covered most of urban Blantyre, from both geographic and population perspectives. Nationally, Blantyre City has the highest TB case-notifications, reflecting the more densely populated higher HIV-prevalence southern region of Malawi, making our finding even more striking as the 2013-14 urban estimates included cities with lower case-notifications [28, 29].

As expected from the literature [24] and recent national TB prevalence surveys [5, 6], TB prevalence was considerably higher amongst men than women, with the sex ratio increased from 1.33 (95% CI 0.94-1.87) in 2014 to 2.04 (95% CI 0.98-4.27) in this survey, highlighting the need for future case-finding efforts targeted at men. We had limited power to address HIV as a risk factor for undiagnosed TB, with only 6 of 29 (21%) people with prevalent TB being HIV positive, but this does suggest a decrease compared with an estimated 45% of patients diagnosed with TB being HIV-positive in

the 2013-14 national TB prevalence survey [30]. This decrease is consistent with more complete diagnosis of HIV, better TB prevention (ART, isoniazid) and better implementation of sensitive (Xpert-based) screening guidelines for patients attending ART clinics in Malawi [7, 31]. It also reflects the estimated 20% decline in HIV prevalence in Blantyre from 17.7% in 2015-16 to 14.2% in 2020-21 [32], and the concurrent improved management of HIV through ART, as evidenced by viral load suppression increasing from 59.5% in 2015-16 [3] to 81.0% in 2021 [32]. Although PLHIV have much higher incidence of TB disease, driving higher case-notifications at facilities, HIV has less impact on undiagnosed prevalent TB due to more rapid progression [33, 34]. In this survey in Blantyre, as in prevalence surveys across much of Africa [35, 36] most patients with undiagnosed infectious TB in the community were HIV-negative (23 out of 29 patients) As TB and HIV prevalence continues to fall, future community case-finding activities will need to be targeted at those at highest risk; for example in this prevalence survey, working age and older men who accounted for over half of all infectious TB patients, and tend to report suboptimal health-seeking [37] placing them at risk of remaining undiagnosed for prolonged periods without detection.

Previous TB treatment and older age groups were associated with higher undiagnosed TB prevalence, but other measured potential risk factors [38] (such as crowding and wealth) were not strongly associated with undiagnosed TB in this study. In part this may reflect our small number of cases. Nevertheless, the proportions of participants with infectious TB who had been previously treated (10% versus 14%) or were currently on TB treatment (3% vs 3%) were strikingly similar in 2019-20 and the 2013-

14 National survey, and are consistent with a well-functioning routine treatment programme in Malawi. The age-group at greatest risk of TB (older adults) is also consistent with the 2013-14 National Survey findings, aligns with the known natural history of TB in endemic settings, and may also indicate the “aging” HIV epidemic in this global region [3, 32].

Half (15/29, 52%) of participants identified with TB in our Blantyre survey did not have a cough and would have been missed if only a cough symptom screen was used, and a third (10/29) had none of the WHO four TB symptoms. This aligns with other TB prevalence surveys [25] where typically half of those identified with TB were asymptomatic on the symptom screen. Again this has implications for future case-finding approaches, which should consider intensified screening with highly sensitive tools, such as digital chest X-ray, to identify people with subclinical TB in communities and clinics [39]. However, this may be less applicable in areas with higher TB prevalence since the pronounced declines in undiagnosed TB reported above were achieved in Blantyre with minimal systematic screening for sub-clinical TB.

This study has some limitations, including low precision from the small number of cases in our survey, due to lower than anticipated prevalence, and low rates of participation, particularly amongst working age men. Lower male participation has been seen in nearly all TB prevalence surveys [35], and future surveys should explore methods to increase participation such as further community engagement and study sites/times that are accessible to everyone, including working men, to reduce potential bias from under-participation and/or missing data. However, estimates from the use

of different analytical models and imputation methods did not vary considerably suggesting bias due to missing data was limited. Two TB patients were diagnosed with TB but with records showing no cough and a normal X-ray, suggesting inaccurate data. Strengths of the survey include offering HIV testing, high rates of sputum submission from those eligible (82% overall and 60% amongst those with no cough but abnormal chest X-ray) [40], linkage to care for those diagnosed with TB and the use of all three sputum tests (smear microscopy, Xpert MTB/Rif and MGIT culture) to ensure high-sensitivity once sputum was submitted.

Our study demonstrates a substantial decrease in TB prevalence in urban Malawi over the eight years before the COVID-19 pandemic. To build on this and reverse any increase due to COVID-19 [41], future case-finding in Blantyre and similar urban centres in sub-Saharan Africa, should target the highest risk groups such as working-age and older men.

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References

1. Surie D, Borgdorff MW, Cain KP, Click ES, DeCock KM, Yuen CM. Assessing the impact of antiretroviral therapy on tuberculosis notification rates among people with HIV: a descriptive analysis of 23 countries in sub-Saharan Africa, 2010-2015. BMC Infect Dis. 2018;18(1):481.
2. World Health Organization. Global Tuberculosis Report 2022. 2022.
3. PHIA Project. Malawi Population-based HIV Impact Assessment 2015-2016. 2018. Columbia University; 2016.
4. Joshi K, Lessler J, Olawore O, Loevinsohn G, Bushey S, Tobian AAR, et al. Declining HIV incidence in sub-Saharan Africa: a systematic review and meta-analysis of empiric data. J Int AIDS Soc. 2021;24(10):e25818.
5. Ministry of Health National TB Control Programme. Technical report: Malawi tuberculosis prevalence survey (2013–2014). 2016.
6. World Health Organization. National Tuberculosis Prevalence Surveys 2007-2016. 2021.
7. Republic of Malawi Ministry of Health. National Tuberculosis Control Programme - Programme Manual, Eighth Edition. Malawi: Malawi Ministry of Health, Unit CHS; 2018.
8. European Centre for Disease Prevention and Control. Guidance on tuberculosis control in vulnerable and hard-to-reach populations. 2016.
9. Trauer JM, Dodd PJ, Gomes MGM, Gomez GB, Houben R, McBryde ES, et al. The Importance of Heterogeneity to the Epidemiology of Tuberculosis. Clin Infect Dis. 2019;69(1):159-66.
10. Khundi M, Carpenter JR, Corbett EL, Feasey HRA, Soko RN, Nliwasa M, et al. Neighbourhood prevalence-to-notification ratios for adult bacteriologically-confirmed tuberculosis reveals hotspots of underdiagnosis in Blantyre, Malawi. PLoS One. 2022;17(5):e0268749.
11. Burke RM, Henrion MYR, Mallewa J, Masamba L, Kalua T, Khundi M, et al. Incidence of HIV-positive admission and inpatient mortality in Malawi (2012-2019). Aids. 2021;35(13):2191-9.
12. Kanyerere H, Girma B, Mpunga J, Tayler-Smith K, Harries AD, Jahn A, et al. Scale-up of ART in Malawi has reduced case notification rates in HIV-positive and HIV-negative tuberculosis. Public Health Action. 2016;6(4):247-51.
13. Chirwa Z, Kayambo F, Oseni L, Plotkin M, Hiner C, Chitsulo C, et al. Extending beyond Policy: Reaching UNAIDS' Three "90"s in Malawi. Front Public Health. 2018;6:69.
14. Borgdorff MW. New measurable indicator for tuberculosis case detection. Emerg Infect Dis. 2004;10(9):1523-8.
15. Feasey HRAK, M.; Nzawa Soko, R.; Bottomley, C.; Chiume, L.; Nliwasa, M.; Twabi, H.; Mpunga, J.A.; Fielding, K.; MacPherson, P.; Corbett, E.L. . OA17-324-09 Impact of active TB case-finding on case notifications in Blantyre, Malawi: a community-based cluster-randomised trial (SCALE). The Union World Conference on Lung Health; Virtual2022.
16. National Statistical Office (NSO). 2018 Malawi Population and Housing Census. Blantyre City Report. 2021.

17. United Nations Human Settlements Programme (UN-HABITAT). Malawi: Blantyre Urban Profile. 2011.
18. World Health Organization. Tuberculosis Prevalence Surveys: a handbook. 2011.
19. Floyd S, Sismanidis C, Yamada N, Daniel R, Lagahid J, Mecatti F, et al. Analysis of tuberculosis prevalence surveys: new guidance on best-practice methods. Emerg Themes Epidemiol. 2013;10(1):10.
20. Rubin DB. Multiple Imputation after 18+ Years. Journal of the American Statistical Association. 1996;91(434):473-89.
21. van Buuren S. G-OK, Vink G. et al,. mice: Multivariate Imputation by Chained Equations R package 2022 [Available from: https://cran.r-project.org/web/packages/mice/index.html.
22. Hothorn T. ZA, Farebrother R.W. et al,. lmtest: Testing Linear Regression Models R Package 2022 [Available from: https://cran.r-project.org/web/packages/lmtest/index.html.
23. Zeileis A. LT, Graham N., Koell S. . sandwich: Robust Covariance Matrix Estimators R Package 2022 [Available from: https://cran.r-project.org/web/packages/sandwich/index.html.
24. Horton KC, MacPherson P, Houben RMGJ, White RG, Corbett EL. Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. PLoS Medicine. 2016;13(9).
25. Frascella B, Richards AS, Sossen B, Emery JC, Odone A, Law I, et al. Subclinical Tuberculosis Disease—A Review and Analysis of Prevalence Surveys to Inform Definitions, Burden, Associations, and Screening Methodology. Clinical Infectious Diseases. 2021;73(3):e830-e41.
26. MacPherson P, Webb EL, Kamchedzera W, Joekes E, Mjoli G, Lalloo DG, et al. Computer-aided X-ray screening for tuberculosis and HIV testing among adults with cough in Malawi (the PROSPECT study): A randomised trial and cost-effectiveness analysis. PLoS Med. 2021;18(9):e1003752.
27. Divala TH, Fielding KL, Kandulu C, Nliwasa M, Sloan DJ, Gupta-Wright A, et al. Utility of broad-spectrum antibiotics for diagnosing pulmonary tuberculosis in adults: a systematic review and meta-analysis. Lancet Infect Dis. 2020;20(9):1089-98.
28. Nyirenda T. Epidemiology of Tuberculosis in Malawi. Malawi Med J. 2006;18(3):147-59.
29. The World Bank. Policy Brief: Optimizing Investments in the Tuberculosis Response in Blantyre, Lilongwe, and Mzimba Districts, Malawi: Results of a TB Allocative Efficiency Study. . 2020.
30. Data reported by countries to WHO and estimates of tuberculosis burden generated by WHO for the Global Tuberculosis Report [Internet]. 2022 [cited 14/12/2022]. Available from: https://www.who.int/teams/global-tuberculosis-programme/data.
31. World Health Organisation. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. 2011.
32. PHIA Project. Malawi Population-based HIV Impact Assessment (MPHIA) Summary Sheet 2020-2021. 2022.

33. Kwan CK, Ernst JD. HIV and tuberculosis: a deadly human syndemic. Clin Microbiol Rev. 2011;24(2):351-76.
34. Corbett EL, Charalambous S, Moloi VM, Fielding K, Grant AD, Dye C, et al. Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners. Am J Respir Crit Care Med. 2004;170(6):673-9.
35. Law I, Floyd K. National tuberculosis prevalence surveys in Africa, 2008-2016: an overview of results and lessons learned. Trop Med Int Health. 2020;25(11):1308-27.
36. Marx FM, Hesseling AC, Martinson N, Theron G, Cohen T. National survey in South Africa reveals high tuberculosis prevalence among previously treated people. Lancet Infect Dis. 2022;22(9):1273.
37. Chikovore J, Hart G, Kumwenda M, Chipungu GA, Desmond N, Corbett L. Control, struggle, and emergent masculinities: a qualitative study of men's care-seeking determinants for chronic cough and tuberculosis symptoms in Blantyre, Malawi. BMC Public Health. 2014;14:1053.
38. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. Pulm Med. 2013;2013:828939.
39. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease. 2021.
40. Habib SS, Asad Zaidi SM, Jamal WZ, Azeemi KS, Khan S, Khowaja S, et al. Gender-based differences in community-wide screening for pulmonary tuberculosis in Karachi, Pakistan: an observational study of 311 732 individuals undergoing screening. Thorax. 2022;77(3):298-9.
41. Soko RN, Burke RM, Feasey HRA, Sibande W, Nliwasa M, Henrion MYR, et al. Effects of Coronavirus Disease Pandemic on Tuberculosis Notifications, Malawi. Emerg Infect Dis. 2021;27(7):1831-9.

Supplementary Material

Table S1: Clinical and microbiological characteristics of confirmed TB cases

Characteristics				Symptom screening						X-ray	Sputum results			
Sex	Age	HIV status	Previous TB?	Cough	Chronic cough	Night sweats	Weight loss	Fever	Any TB symptoms	Chest X-ray	Smear	Xpert	Culture result	Culture ID
Male	45	HIV negative	No	Yes	Yes	Yes	Yes	Yes	Yes	Abnormal	Negative	Positive	Negative	ND
Female	32	HIV positive	No	Yes	No	No	No	No	Yes	Normal	Negative	Negative	Positive	MTB
Female	34	HIV positive ART	No	Yes	Yes	Yes	Yes	No	Yes	Abnormal	Negative	Positive	Positive	MTB
Female	29	HIV negative	No	Yes	Yes	No	No	No	Yes	-	Negative	Positive	Positive	MTB
Male	25	HIV negative	No	Yes	Yes	No	No	No	Yes	Abnormal	Negative	Positive	Positive	MTB
Female	19	HIV negative	No	Yes	Yes	No	No	No	Yes	Abnormal	Positive	Positive	Positive	MTB
Female	26	HIV negative	No	Yes	Yes	No	No	Yes	Yes	Abnormal	Positive	Positive	Positive	MTB
Female	22	HIV negative	No	Yes	No	No	No	No	Yes	Normal	Negative	Negative	Positive	MTB
Male	33	HIV negative	Yes	Yes	No	Yes	No	Yes	Yes	Abnormal	Positive	Positive	Positive	MTB
Male	19	HIV negative	No	Yes	No	No	No	No	Yes	Abnormal	Negative	Negative	Positive	MTB
Male	56	HIV positive ART	No	Yes	Yes	No	No	Yes	Yes	Normal	Positive	Positive	Positive	MTB
Male	45	HIV positive ART	No	Yes	Yes	No	No	No	Yes	Abnormal	Negative	Positive	Negative	ND
Male	40	HIV negative	Yes	Yes	Yes	No	No	No	Yes	Normal	Positive	Positive	Positive	MTB
Female	61	HIV negative	No	No	No	No	No	No	No	Abnormal	Negative	Positive	Positive	MTB
Female	89	HIV negative	No	No	No	No	No	No	No	Abnormal	Negative	Positive	Negative	ND
Male	27	HIV negative	Yes	No	No	No	No	Yes	Yes	Abnormal	Negative	Positive	Contaminated	ND
Male	27	HIV negative	No	No	No	No	No	No	No	Abnormal	Negative	Negative	Positive	MTB
Male	33	HIV negative	Yes	No	No	No	No	No	No	Abnormal	Negative	Negative	Positive	MTB
Male	43	HIV negative	No	No	No	No	No	Yes	Yes	Abnormal	Negative	Positive	Positive	MTB
Male	30	HIV negative	No	No	No	Yes	No	No	Yes	Abnormal	Positive	Positive	Positive	MTB
Female	38	HIV negative	No	No	No	No	No	No	No	Abnormal	Negative	Negative	Positive	MTB
Male	30	HIV negative	No	No	No	Yes	No	Yes	Yes	Abnormal	Negative	Positive	Negative	ND
Female	19	HIV negative	No	No	No	No	No	No	No	-	Negative	Negative	Positive	MTB
Male	44	HIV negative	No	No	No	No	No	No	No	Normal	Positive	Positive	Positive	MTB
Male	36	HIV negative	No	No	No	Yes	No	No	Yes	Normal	Negative	Positive	Negative	ND
Male	54	HIV negative	No	No	No	No	No	No	No	Abnormal	Negative	Negative	Positive	MTB
Female	37	HIV positive ART	No	No	No	No	No	No	No	Abnormal	Negative	Positive	Positive	MTB
Male	22	HIV negative	No	No	No	No	No	No	No	Abnormal	Positive	Positive	Negative	ND

Table S2: Participants diagnosed with TB disaggregated by screening category and HIV status

			Participants diagnosed with TB		
Screening category	**Screen positive participants**	**Participants diagnosed with TB (%)**	**HIV-negative**	**HIV-positive on ART**	**HIV-positive (no ART)**
Symptom (cough) only	747	5* (17%)	3	1	1
Abnormal CXR only	406	12 (41%)	11	1	-
Symptom and abnormal CXR	241	9 (31%)	6	3	-
No symptom / CXR normal or not recorded	84	3 (10%)	3	-	-
Total	1,478	29	23	5	1

CXR: Chest X-ray

*One person identified with TB had cough recorded but no CXR record

Table S3: Prevalence of smear-positive TB disease per 100,000 adults with robust standard errors used to calculate 95% confidence intervals, from complete case and inverse probability weighting analysis

	Total (n)	Smear+ TB (n)	Prevalence (95% CI)	
			Complete case	Inverse weighting
All participants	15318	9	69 (36-133)	37 (9-169)
Sex				
Female	9423	2	25 (6-102)	18 (4-71)
Male	5895	9	136 (28-651)	84 (18-400)
Age				
18-24	5811	2	40 (10-159)	28 (7-112
25-49	4356	5	77 (15-398)	48 (9-250)
50+	582	2	130 (18-915)	141 (23-852)
HIV status				
HIV negative	15318	7	62 (30-130)	42 (20-88)
HIV positive	5895	2	115(24-550)	132 (33-520)
Previous diagnosis				
No previous TB	14895	25	55 (26-116)	42 (21-86
Previous TB	423	4	543 (113-2580)	349 (74-1640)

Table S4: Prevalence of TB disease per 100,000 adults with robust standard errors used to calculate 95% confidence intervals, using WHO-recommended expanded age and HIV groups

	Total (n)	TB (n)	Prevalence (95% CI)		
			Complete case	Fully imputed	Inverse weighting
All participants	15318	29	189 (132-272)	139 (71-272)	159 (78-324)
Sex					
Female	9423	11	117 (65-211)	97 (54-176)	97 (53-178)
Male	5895	18	305 (144-645)	198 (94-415)	259 (115-580)
Age					
18-24	5811	5	86 (36-207)	67 (29-165)	65 (27-158)
25-34	4356	11	253 (88-724)	184 (64-528)	220 (75-645)
35-44	2649	6	227 (69-739)	149 (46-489)	160 (48-537)
45-54	1205	4	332 (89-1228)	274 (79-940)	495 (119-2035)
55-64	710	2	282 (55-1440)	201 (40-1027)	195 (37-1032)
65+	582	1	172 (20-1459)	126 (15-1069)	124 (14-1055)
HIV status					
HIV negative	15318	23	179 (119-270)	132 (89-199)	177 (106-293)
HIV positive	9423	1	303 (115-795)	263 (107-643)	277 (105-731)
ART					
HIV positive	5895	5	439 (59-3198)	325 (44-2362)	443 (59-3272)
Previous diagnosis					
No previous TB	14895	25	168 (113-248)	128 (87-189)	164 (102-264)
Previous TB	423	4	946 (329-2687)	613 (214-1742)	702 (233-2096)

Notes:
HIV status as identified through testing in prevalence survey, or if no test as reported in individual survey
5 of complete cases no age recorded (3 HIV negative, 1 HIV positive & 1 HIV unknown)
626 participants with HIV unknown status but no TB cases amongst them
Previous TB includes one currently on TB treatment

Table S5: Risk factors for prevalent bacteriologically-confirmed TB using WHO recommended, expanded age and HIV categories with robust standard errors used to calculate 95% confidence intervals

		Multivariate analysis		
Variable	Univariate OR	Complete case OR (95% CI)	Fully imputed OR (95% CI)	Inverse weighting OR (95% CI)
Sex				
Female	1	1	1	1
Male	*2.62 (1.24-5.55)*	*2.76 (1.28-5.95)*	*2.06 (0.97-4.41)*	*2.38 (1.14-4.94)*
Age, years				
18-24	1	1	1	1
25-34	2.94 (1.02-8.47)	3.16 (1.09-9.15)	2.65 (0.86-8.22)	3.34 (1.09-10.27)
35-44	2.64 (0.80-8.65)	2.65 (0.76-9.20)	1.92 (0.55-6.78)	2.21 (0.60-8.18)
45-54	3.87 (1.04-14.43)	3.26 (0.83-12.80)	3.00 (1.05-8.62)	5.85 (1.24-27.49)
55-64	3.28 (0.63-16.97)	2.80 (0.53-14.77)	2.29 (0.42-12.40)	2.27 (0.43-12.14)
65+	2.00 (0.23-17.19)	1.83 (0.21-15.82)	1.69 (0.19-14.88)	1.81 (0.20-16.23)
HIV/ART status				
HIV-	1	1	1	1
HIV+ on ART	1.69 (0.64-4.46)	1.10 (0.30-4.07)	1.49 (0.55-4.03)	1.10 (0.37-3.24)
HIV+ not on ART	2.45 (0.33-18.38)	1.95 (0.22-17.09)	2.20 (0.27-18.09)	1.96 (0.21-18.14)
HIV unknown	0	0	0	0
Previous TB	5.68 (1.96-16.42)	4.25 (0.87-20.67)	3.41 (0.97-12.01)	3.10 (0.83-11.56)
TB contact (within 12 months)	1.59 (0.38-6.71)	1.33 (0.30-5.94)	1.29 (0.29-5.83)	1.23 (0.25-6.04)
Crowding, persons per room				
<1	1	1	1	1
1-2	1.50 (0.70-3.24)	1.65 (0.73-3.72)	1.67 (0.83-3.36)	2.16 (0.95-4.92)
>2	2.00 (0.44-9.04)	2.46 (0.44-13.58)	2.57 (0.48-13.60)	1.91 (0.37-9.96)
Wealth quartile				
1	1	1	1	1
2	0.66 (0.21-2.08)	0.64 (0.20-2.05)	0.58 (0.17-1.94)	0.59 (0.16-2.12)
3	1.24 (0.47-3.26)	1.10 (0.39-3.11)	1.04 (0.37-2.92)	1.26 (0.42-3.79)
4 (top)	0.81 (0.28-2.32)	0.67 (0.20-2.23)	0.63 (0.19-2.07)	0.70 (0.22-2.23)

Chapter 5

Do community-based active case-finding interventions have indirect impacts on wider TB case detection and determinants of subsequent TB testing behaviour? A systematic review

To determine whether TB active case-finding (ACF) has indirect as well as direct impact (beyond those directly diagnosed patients) I conducted a systematic review to identify and assess published TB ACF studies that reported proxy behavioural outcomes or effects on routine facility-based TB case-notifications. Publications from 1 January 1980 to 13 April 2020 were systematically searched for those reporting on community-based ACF interventions compared to a comparison group, together with review of linked manuscripts reporting knowledge, attitudes, and practices (KAP) outcomes or qualitative data on TB testing behaviour.

Just 12 studies were identified that reported routine notification rates separately from ACF intervention-attributed rates, enabling me to calculate case-notification rate (CNR) ratios and only one study reported any proxy behavioural outcomes. Two further linked qualitative studies were also identified. The main finding was the need for more evidence: I found mixed weak evidence that TB ACF may be effective at indirectly increasing routine TB case-notification

rates for non-bacteriologically confirmed TB, and insufficient evidence to conclude whether or not ACF impacts subsequent TB testing behaviour.

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Student ID Number	1806428	**Title**	Mrs
First Name(s)	Helena Rosemary Anne		
Surname/Family Name	Feasey		
Thesis Title	Investigating the potential impact and suitability of tuberculosis active case-finding approaches in the rapidly changing environment of urban Blantyre, Malawi		
Primary Supervisor	Prof Liz Corbett		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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SECTION E

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PLOS GLOBAL PUBLIC HEALTH

RESEARCH ARTICLE

Do community-based active case-finding interventions have indirect impacts on wider TB case detection and determinants of subsequent TB testing behaviour? A systematic review

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Abstract

Community-based active case-finding (ACF) may have important impacts on routine TB case-detection and subsequent patient-initiated diagnosis pathways, contributing "indirectly" to infectious diseases prevention and care. We investigated the impact of ACF beyond directly diagnosed patients for TB, using routine case-notification rate (CNR) ratios as a measure of indirect effect. We systematically searched for publications 01-Jan-1980 to 13-Apr-2020 reporting on community-based ACF interventions compared to a comparison group, together with review of linked manuscripts reporting knowledge, attitudes, and practices (KAP) outcomes or qualitative data on TB testing behaviour. We calculated CNR ratios of routine case-notifications (i.e. excluding cases identified directly through ACF) and compared proxy behavioural outcomes for both ACF and comparator communities. Full text manuscripts from 988 of 23,883 abstracts were screened for inclusion; 36 were eligible. Of these, 12 reported routine notification rates separately from ACF intervention-attributed rates, and one reported any proxy behavioural outcomes. Two further studies were identified from screening 1121 abstracts for linked KAP/qualitative manuscripts. 8/12 case-notification studies were considered at critical or serious risk of bias. 8/11 non-randomised studies reported bacteriologically-confirmed CNR ratios between 0.47 (95% CI:0.41–0.53) and 0.96 (95% CI:0.94–0.97), with 7/11 reporting all-form CNR ratios between 0.96 (95% CI:0.88–1.05) and 1.09 (95% CI:1.02–1.16). One high-quality randomised-controlled trial reported a ratio of 1.14 (95% CI 0.91–1.43). KAP/qualitative manuscripts provided

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Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: JEG, HA, and ELC are authors of trials included in this systematic review. HA and ELC are members of the WHO TB Screening Guideline Development Group, which CM co-ordinates. JEG, HA, ELC, and PM have received research grants to their institutions for projects evaluating community-based active case-finding. All other authors declare no competing interests.

insufficient evidence to establish the impact of ACF on subsequent TB testing behaviour. ACF interventions with routine CNR ratios >1 suggest an indirect effect on wider TB case-detection, potentially due to impact on subsequent TB testing behaviour through follow-up after a negative ACF test or increased TB knowledge. However, data on this type of impact are rarely collected. Evaluation of routine case-notification, testing and proxy behavioural outcomes in intervention and comparator communities should be included as standard methodology in future ACF campaign study designs.

Introduction

With over 1.4 million deaths per year [1], tuberculosis (TB) was second only to SARS-CoV-2 as an infectious cause of death globally in 2020. As many as three million people are living with undiagnosed TB disease [1]. Early diagnosis and treatment are fundamental to TB control efforts: the WHO End TB strategy includes targets of at least 90% of people who develop TB being notified and treated within one year by 2025 [2]. Innovative approaches are needed to accelerate progress towards this target from the current estimate of 71% [1].

WHO defines both patient-initiated care-seeking and provider-initiated systematic screening approaches to identify people living with undiagnosed TB [3, 4]. Screening pathways can be facility-based systematic screening or community-based "active case-finding" (ACF). Patient-initiated care-seeking can arise through people recognizing TB symptoms and presenting to a health facility (passive case-finding or PCF), or result from advocacy, communication and social mobilization activities (ACSM) that can prompt earlier care seeking for facility-based TB screening (enhanced case-finding or ECF).The key difference between ACF and ECF is that ACF implies individual interaction between a participant and healthcare worker in the community (e.g. where the participant completes a symptom screen, submits sputum for TB testing or undergoes a chest X-ray).

ACF interventions are designed to directly identify people living with undiagnosed TB in the community but may also have an indirect impact on wider TB case detection as seen in an 2011–14 ACF intervention in Blantyre, Malawi where routine facility-based case-notifications increased substantially over the intervention period [5]. Routine case notification rate (CNR) ratios with a comparison group (excluding those directly identified through the ACF) >1 would be an indication of indirect impact. This indirect impact could be due to enhanced diagnostics introduced through the intervention or an impact on subsequent community TB testing rates and behaviour. Enhanced diagnostics could increase routine case-notifications through improved test sensitivity, although this is likely to be limited to bacteriologically-confirmed TB and there may be a concurrent drop in clinically-diagnosed TB. Health workers could also offer more TB tests if aware of the enhanced diagnostic capacity, leading to higher testing rates. Higher TB testing rates could be due to changes in health worker or community behaviour.

ACF interventions can cover a wide range of activities including door-to-door visits or mobile clinics. They are almost invariably accompanied by ACSM activities, even if only to promote ACF participation and explain to the community the purpose of the intervention and the need for repeat testing if symptoms persist. As such, ACF could influence subsequent TB testing behaviour through the three elements of the COM-B behavioural theory (capacity, opportunity and motivation) and potentially increase TB case-notifications in health facilities through indirect effects (Fig 1). COM-B is a comprehensive model developed from a review of 19 existing behaviourial theories [6] that has been widely applied in assessing and developing

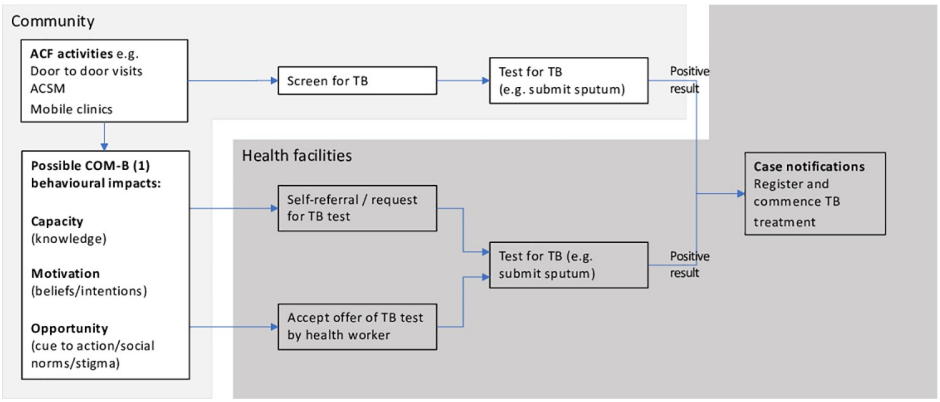

Fig 1. Conceptual framework for how tuberculosis active case finding may affect subsequent healthcare-seeking behaviour. Footnote: (1) Capacity, Opportunity and Motivation are the three domains of the COM-B behavioural theory [6].

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public health interventions [6–9] including those for Tuberculosis diagnosis and prevention [10–12].

The behavioural mechanisms by which ACSM delivered through ACF interventions may lead to increased knowledge about TB disease and services, or act as a prompt for symptomatic people to present to a health centre for TB testing, are not well understood. ACF interventions could affect knowledge, attitudes and practice (KAP), prompting more timely care-seeking and increasing levels of TB testing and case-notifications through health facilities. ACF interventions may also reduce TB stigma or change social norms and community perceptions around TB. These factors could influence the capacity, motivation and opportunity [6] for subsequent TB testing behaviour (Fig 1). The duration of any behaviour change from ACF is likely to be modified by characteristics of the target population, such as level of education, and ease of access to routine healthcare.

Previous systematic reviews by Kranzer et al (2013) [13], Mhimbira et al (2017) [14] and Burke et al (2021) [15] have shown that ACF interventions can initially increase TB case-notifications, but not invariably. The indirect effects of ACF on routine case-notifications however, has not previously been reviewed. We therefore aimed to systematically review the evidence of indirect effects of ACF on routine facility-based TB case-notifications and also accompanying quantitative proxy behavioural outcomes, such as KAP, that could inform the mechanisms underlying any effect on subsequent TB testing behaviour.

Methods

We conducted a systematic review of studies reporting the indirect effect of community ACF for TB on routinely-diagnosed TB case-notifications and quantitative proxy behavioural outcomes, such as self-reported TB testing behaviour and KAP of TB.

Definitions

Active case finding (ACF) was defined as systematic TB screening activities implemented in a specific population. The screening could take any form (e.g. symptom interview, radiology, microbiological testing, referral for specialist medical assessment, in any order) but required a personal interaction between a screener and the person being screened. Health promotion communication activities alone (e.g. leaflet delivery) were considered to be ECF and not ACF. Interventions based solely at a routine healthcare facility were considered systematic TB screening interventions, not ACF.

Routinely-diagnosed TB case-notifications were those identified through ongoing standard healthcare facility-based case-finding activities and excluding TB case-notifications identified through ACF activities (whether tested in the field or referred for testing after screening in the community).

Additionality represents the total increase above expected numbers in TB case-notifications following an active case-finding intervention. This captures all patients who would not have been identified during that time period in the absence of the intervention [16], and can be estimated from comparison of changes in case-notifications in the intervention population during the project compared to the control population or period [17].

Substitution represents the phenomenon of TB patients diagnosed by an active case-finding intervention who, in the absence of the intervention, would still have been identified through routine case-finding activities within the same time period. The extent to which substitution has occurred can be estimated from the number of patients directly diagnosed by ACF minus those identified as additional cases (additionality).

The quantitative proxy behavioural outcomes we examined were:

TB knowledge, attitudes and practices (KAP) were what is known, believed and done in relation to TB [18], typically assessed through pre- and post-intervention surveys.

Testing for TB was when a person who has TB symptoms or signs suggestive of TB has a diagnostic test (through submitting sputum for microbiological testing, radiology or specialist medical assessment).

TB stigma was defined as a dynamic process of devaluation that significantly discredits an individual in the eyes of others due to their known or suspected TB status. Within particular cultures or settings, certain attributes are defined by others as discreditable or unworthy [19]. TB stigma could be assessed through a validated scale or through qualitative data.

TB social norms were rules and standards that are understood by members of a group, and that guide or constrain social behaviours around TB, without the force of law [20]. Social norms could be assessed through quantitative data using validated domains or vignettes, or qualitative approaches.

Inclusion and exclusion criteria

We included studies evaluating an ACF intervention that compared epidemiological TB outcomes (TB case-notifications or TB prevalence) between populations exposed and not exposed to ACF and reported either routinely-diagnosed TB case-notifications or identified proxy behavioural outcomes. Routinely-diagnosed TB notification outcomes could either be directly reported or calculated if both direct ACF yield and overall case notifications were reported for the same period and relevant population. Applicable study designs included randomised controlled trials, studies with a parallel comparison group (controlled before-after studies) and studies with a time-based comparison (before-after studies). We included studies with adults aged 15 years or older that screened at least 1000 people (since the prevalence of active TB in a community will rarely exceed 1%). Interventions conducted in closed communities (e.g. prisons) and specific occupational groups (e.g. miners) were included but screening interventions for contacts of people with TB (contact tracing) were not. Studies published before 1 January 1980 and those not in English were excluded.

Search strategies

The literature search included all studies identified in a previous review by Kranzer et al in 2013 [13], covering the period 1 Jan 1980 to Oct 13 2010, and an additional search of PubMed, EMBASE, Scopus and the Cochrane Library for papers published between 1 Nov 2010 and 4

Feb 2020 (subsequently updated to 13 April 2020) (search strategy in S1 Text). Studies identified through the updated search were title and abstract double screened for initial eligibility (original research, where ACF had taken place, written in English, French or Spanish) by FN, AES and LHC. The full text of eligible studies and all studies from the Kranzer and colleagues review were reviewed by two of HRAF, RMB and MN. Inclusion decisions were resolved by consensus and discussion with ELC and PM. Reference lists from eligible manuscripts were examined and expert opinion on other available papers was sought from members of the WHO TB Screening Guideline Development Group for this and the accompanying review on TB ACF effectiveness [15]. Data was extracted from studies independently by two of HRAF, RMB and MN and entered into a spreadsheet.

Accompanying qualitative and KAP studies literature search

To increase the number of studies reporting proxy behavioural outcomes relevant to subsequent health seeking behaviour, a further search was conducted for additional secondary manuscripts on qualitative or KAP studies related to the ACF studies identified through the initial literature search (search strategy S2 Text). To be included, the study had to be part of the ACF intervention study identified through the main literature search and include qualitative or quantitative data on the impact of the ACF itself on community TB health seeking behaviour (KAP, TB testing behaviours, pathways to care, TB stigma or social norms). Studies not specifically demonstrating the impact of the ACF on these factors in the ACF target population were excluded, e.g. if the KAP measures were for a different population.

Access to healthcare

We classified studies according to level of healthcare access within the target population based on distance to and cost of care, as indicated by the reported context or assumed from knowledge of the local health system (S3 Table), on a scale of 'Standard' (routine free healthcare available within catchment area), 'Restricted' (access restricted due to distance and/or cost) or 'Hard to reach' (populations specifically selected as hard to reach).

Outcomes and risk of bias assessment

Outcomes were a comparison of routine case notification rates (excluding those identified through ACF) and a comparison of reported TB KAP scores (proxy behavioural measure) between groups exposed to and not exposed to the community-based ACF.

To establish routinely diagnosed case notification rates, person-years of follow-up and notified TB cases diagnosed only through routine screening activities were extracted or calculated from available data using simple arithmetic (see S3 Table for extracted data). Person-years were calculated for the target populations for which case-notifications were reported. For before-after studies if the size of the population was not reported separately for the pre- and post-intervention periods it was assumed the size of the population did not change. None of the studies presented case-notification ratios for routine diagnosis; we calculated these through subtracting the available ACF-specific case-notifications from the overall notification data. For randomised and before-after studies we calculated the CNR ratio (intervention vs control groups or baseline vs post-intervention populations) and for controlled before-after studies with a non-randomised comparison group the outcome measure was a comparison of the before to after TB CNR ratio in the two comparison groups: the ratio of the CNR ratios.

Where data was available confidence intervals were calculated using Stata. For studies affected by clustering, three possible values (0.01, 0.05 and 0.1) of the intra-cluster correlation coefficient (ICC) were used to calculate three possible 95% confidence intervals using the

Cochrane recommended method [21]. Only the narrowest intervals (ICC = 0.01) are presented in this text, with the others presented in Table 2. Confidence intervals for KAP scores are presented as reported by the authors.

For randomised studies, the Cochrane Risk of Bias (ROB) tool [22] was used to assess risk of bias. Non-randomised studies were assessed for risk of bias using ROBINS-I [23] and qualitative studies were assessed through the Critical Appraisal Skills Programme (CASP) checklist [24].

Ethical approval and data availability

Ethical approval was not required for this study. All data is available within the results and supplementary materials tables.

Results

From a total of 23,883 studies identified, full texts of 988 were assessed for inclusion (S1 Table), and 36 with a suitable community-based ACF study design for this review were identified, including 12 that reported case-notification data from both routine facilities and from ACF-identified notifications (Fig 2). Only one out of the 36 manuscripts reported any proxy behavioural outcomes [25], but the additional search identified 1121 manuscripts, of which four articles were eligible for inclusion as KAP/qualitative manuscripts after full text review, but two of these were excluded from full analysis following identification of additional documentation (S2 Table).

Routine TB case-notifications

Of the 12 studies identified for the review of ACF impact on routinely-identified case-notifications, one was a randomised controlled trial [26], six were controlled before-and-after studies (with a parallel comparison group) and five were before-after studies with no comparison group (Table 1). One of the controlled before-and-after studies (Cegielski 2013 [27]) was excluded from further analysis since no cases of TB were identified after the intervention period so meaningful case notification ratios could not be calculated. For all studies (except Miller 2010) the "after" or outcome notifications period was the period during the intervention and did not extend beyond.

Populations varied from urban high-density neighbourhoods to rural communities with long distances to healthcare. From the limited information available, three studies were classified as having been conducted in a setting with "standard" access to routine healthcare, two were classified as specifically "hard-to-reach" and the rest were classified as having restricted access to routine care due to remoteness and/or cost (see S3 Table for extracted data).

ACF interventions combined different strategies including door-to-door screening (eight studies), sputum collection by volunteers or community health workers (seven studies) and community mobilisation for mobile screening clinics (four studies) (Table 1). Of the 11 studies analysed, four reported only bacteriologically-confirmed TB, two reported data for all forms TB (including clinically-diagnosed TB) and five reported both. Only Datiko 2017 and Lorent 2014 reported improving routinely available TB diagnostics as part of the intervention.

The included RCT was conducted by Miller et al comparing door-to-door ACF with leaflet delivered ECF in a Brazilian favela, with a staggered intervention delivered serially in pairs of clusters [26]. The total trial period was 283 days, including the complete intervention time through 60 days after ending ACF in the final clusters. Using calendar time-period, the CNR ratio was 1.14 (95% CI: 0.94–1.40) implying a 14% relative increase in non-ACF-diagnosed case notification rate for ACF compared to ECF (Table 2). A before-during-after analysis,

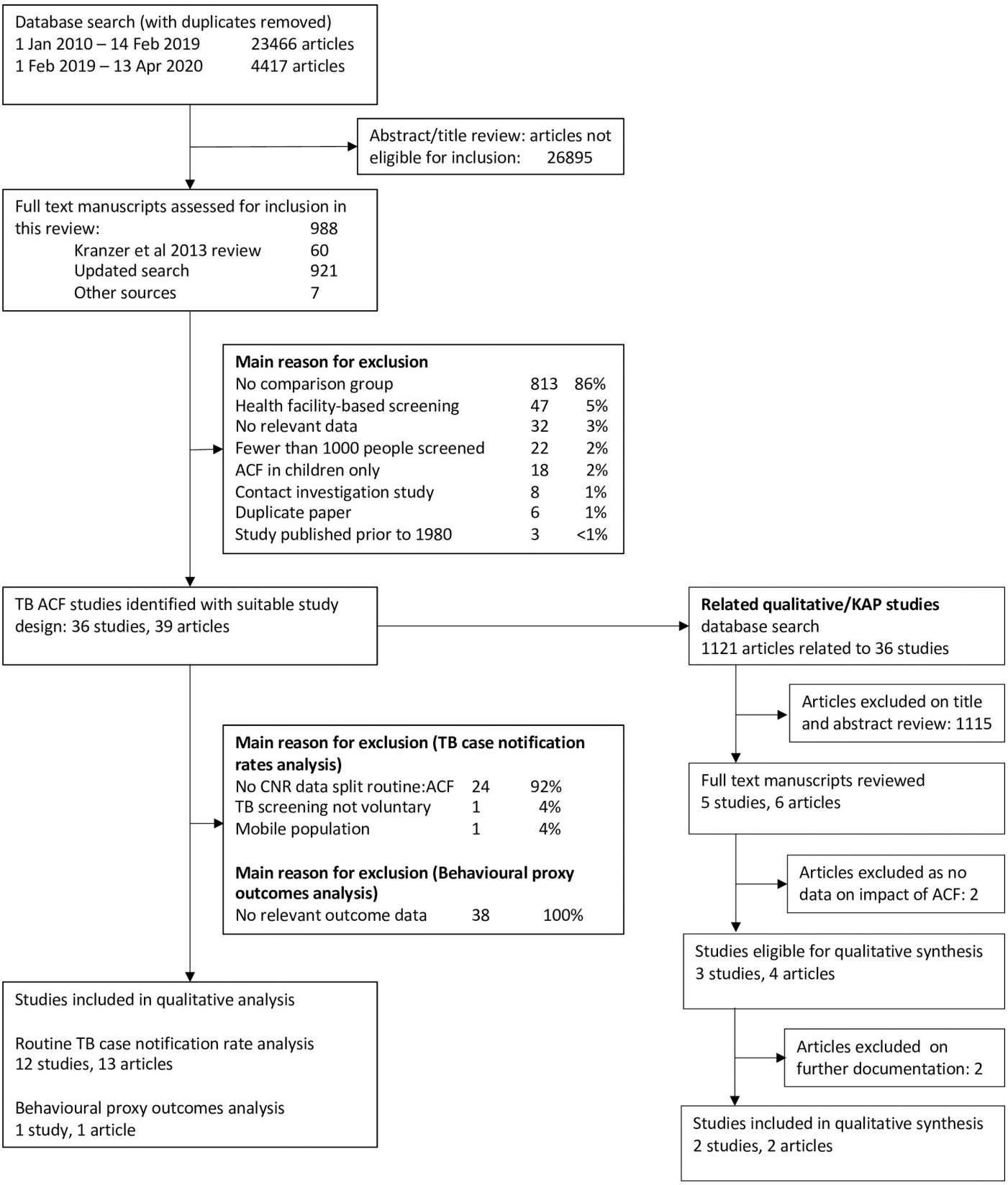
Database search (with duplicates removed)
1 Jan 2010 – 14 Feb 2019 23466 articles
1 Feb 2019 – 13 Apr 2020 4417 articles
Abstract/title review: articles not eligible for inclusion: 26895
Full text manuscripts assessed for inclusion in this review: 988
Kranzer et al 2013 review 60
Updated search 921
Other sources 7
Main reason for exclusion
No comparison group 813 86%
Health facility-based screening 47 5%
No relevant data 32 3%
Fewer than 1000 people screened 22 2%
ACF in children only 18 2%
Contact investigation study 8 1%
Duplicate paper 6 1%
Study published prior to 1980 3 <1%
TB ACF studies identified with suitable study design: 36 studies, 39 articles
Related qualitative/KAP studies database search
1121 articles related to 36 studies
Articles excluded on title and abstract review: 1115
Full text manuscripts reviewed
5 studies, 6 articles
Articles excluded as no data on impact of ACF: 2
Studies eligible for qualitative synthesis
3 studies, 4 articles
Articles excluded on further documentation: 2
Studies included in qualitative synthesis
2 studies, 2 articles
Main reason for exclusion (TB case notification rates analysis)
No CNR data split routine:ACF 24 92%
TB screening not voluntary 1 4%
Mobile population 1 4%
Main reason for exclusion (Behavioural proxy outcomes analysis)
No relevant outcome data 38 100%
Studies included in qualitative analysis
Routine TB case notification rate analysis
12 studies, 13 articles
Behavioural proxy outcomes analysis
1 study, 1 article

Fig 2. Modified PRISMA diagram showing articles reviewed and main reasons for exclusion.

https://doi.org/10.1371/journal.pgph.0000088.g002

however, accounting for the staggered cluster pair-by-pair initiation design, showed data consistent with a degree of "substitution" whereby patients who would otherwise have been diagnosed routinely during the intervention period and immediately afterwards were found though ACF. The CNR ratio for ACF compared to ECF clusters was, 0.65 (95% CI: 0.36–1.19) during the intervention and 0.80 (95% CI: 0.51–1.27) for the 60 days immediately after the intervention, but 1.42 (95% CI: 1.12–1.82) for days outside this period (both pre intervention and >60days to end of follow-up) which accounted for 68.5% of the 283-day total trial period (Fig 3). There were some concerns of bias due to missing data in this study.

Of the other included studies, the outcome measure of routinely-diagnosed CNR ratio or ratio of CNR ratios (depending on study design) ranged from 0.96 to 1.09 for all forms of TB and 0.47 to 0.96 for bacteriologically-confirmed TB (Table 2). These differences were only significant at the $p<0.05$ level for three of the seven studies reporting all forms of TB: Aye 2018 1.09 (95% CI: 1.02–1.16) [28], Fatima 2016 1.04 (95% CI: 1.03–1.05) [29] and Fatima 2014 1.06 (95% CI: 1.03–1.09) [30]. Confidence intervals were not calculated for Ford 2019 [31] due to

Table 1. Characteristics of included studies.

Study	Design	Country	Population	Healthcare access	ACF	Qualitative / KAP studies
Case-notifications outcomes						
Miller 2010	Cluster-randomised trial	Brazil	Urban slums	Standard	ACF (door to door) vs. usual case finding plus leafleting	
Aye 2018	Controlled before-after	Myanmar	Urban slums (& "neighbourhood contacts")	Standard	Door to door symptom screening and sputum collection for "neighbourhood contacts", community mobilisation and sputum collection for others	
Cegielski 2013	Controlled before-after	USA	General population—urban	Standard	Community mobilisation, TST screening, mobile clinic.	
Datiko 2017 (& Yassin 2013)	Controlled before-after	Ethiopia	Remote rural	Restricted	Community mobilisation, door to door symptom screening, sputum transport	Tulloch 2015
Kan 2012	Controlled before-after	China	General population—rural	Restricted	Schoolchildren reported symptoms in family members, home visits to symptomatic people, sputum transport.	
Parija 2014	Controlled before-after	India	General population—rural	Restricted	Community mobilisation, mobile clinic, community health workers	
Vyas 2019	Controlled before-after	India	Indigenous groups	Restricted	Door to door symptom screening, sputum collection	
Corbett 2010	Before-after	Zimbabwe	General population—urban	Standard	Community mobilisation, door to door symptom screening or mobile clinics	
Fatima 2016	Before-after	Pakistan	Urban slums "neighbourhood contacts"	Standard	Door to door, sputum collection.	
Fatima 2014	Before-after	Pakistan	Urban slums perceived high risk or hard to reach	Hard to reach	Community mobilisation, mobile clinics (microscopy)	
Ford 2019	Before-after	India	Remote rural	Restricted	Community mobilisation, mobile clinics (CxR).	
Lorent 2014	Before-after	Cambodia	Urban slums—perceived high risk or hard to reach	Hard to reach	Community health workers, door to door symptom screening, sputum collection	Lorent 2015
Behavioural outcomes (KAP)						
Adane 2019	RCT	Ethiopia	Prison	N/A	Peer educators in prisons. People in prison with identified TB symptoms in control and intervention transferred to clinic for physician review	

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Table 2. Routinely-diagnosed TB case-notifications outcome measures.

Study	Healthcare access	CNR Ratio / Ratio of CNR ratios*	95% CI† ICC = 0.01	95% CI ICC = 0.05	95%CI ICC = 0.10
Randomised controlled trial (RCT)					
Miller 2010	Standard	1.14	0.94–1.40	0.72–1.76	0.58–2.15
Controlled before-after trials–bacteriologically confirmed					
Datiko 2017	Restricted	0.47	0.41–0.53	-	-
Kan 2012	Restricted	0.81	0.66–0.99	0.52–1.32	0.42–1.61
Parija 2014	Restricted	0.85	0.77–0.94	0.67–1.06	0.60–1.15
Vyas 2019	Restricted	0.83	0.77–0.88	0.71–0.97	0.66–1.04
Controlled before-after trials–all forms					
Aye 2018	Standard	1.09	1.02–1.16	0.94–1.27	0.88–1.35
Datiko 2017	Restricted	0.96	0.88–1.05	-	-
Vyas 2019	Restricted	1.00	0.95–1.05	0.90–1.12	0.86–1.18
Before-after trials–bacteriologically confirmed					
Corbett 2010	Standard	0.75	0.63–0.89	-	-
Fatima 2016	Standard	0.96	0.94–0.97	-	-
Fatima 2014	Hard to reach	0.93	0.90–0.95	-	-
Lorent 2014	Hard to reach	0.83	0.77–0.89	-	-
Before-after trials–all forms					
Fatima 2016	Standard	1.04	1.03–1.05	-	-
Fatima 2014	Hard to reach	1.06	1.03–1.09	-	-
Ford 2019	Restricted	1.02	-	-	-
Lorent 2014	Hard to reach	0.93	0.89–0.97	-	-

†For studies not affected by clustering overall confidence interval presented.

ICC values are estimates not from primary study.

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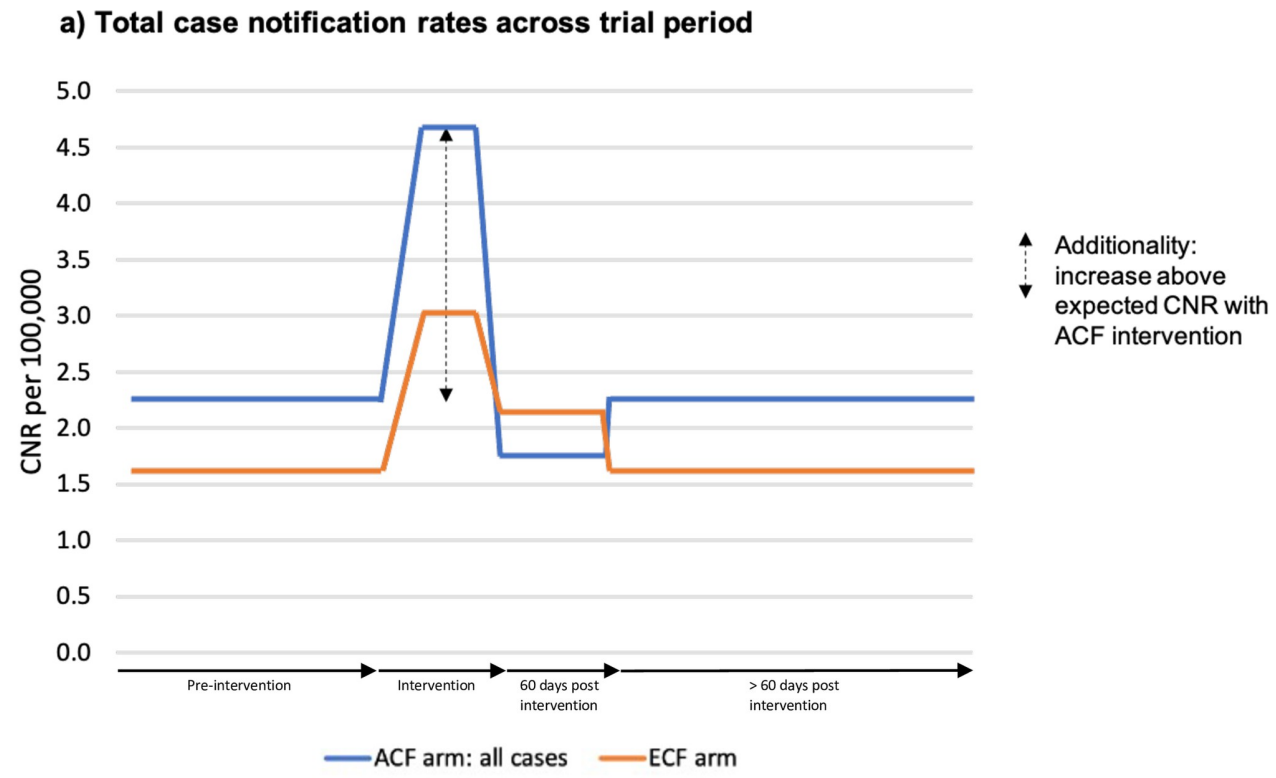
unavailability of data. Outcome measures did not appear to be associated with reported health-care accessibility.

For all five before-after studies, the during intervention overall (both ACF and routine) case notification rates increased but the routine CNR change for bacteriologically-confirmed TB ranged from a 25% reduction (Corbett 2010 [32]) to a 4% reduction (Fatima 2016) (Fig 4), consistent with a degree of substitution or accelerated diagnosis of patients who would otherwise been diagnosed routinely. For all forms of TB, however, the change ranged from a 7% reduction (Lorent 2014 [33]) to a 6% increase (Fatima 2016 [29]). Lorent 2014 was the only before-after study reporting a decrease in all form routine TB CNR during intervention implementation.

For the six controlled before-after studies increases or decreases in the routine TB CNR in the intervention group reflected the directional change in routine case notification rate in the control group for all studies except two bacteriologically-confirmed reports: Parija 2014 [34] (1% increase in control group and 14% reduction in intervention group) and Datiko 2017 [35] (8% increase in control group and 49% reduction in intervention group) (Fig 5). Both studies were conducted with remote rural communities and in Datiko 2017 participants with smear-negative ACF results were offered follow-up radiological TB diagnosis.

The majority of non-randomised studies were considered to be at critical (two studies) or serious risk of bias (6 studies) with three studies at moderate risk of bias (Corbett 2010 [32], Parija 2014 [34] and Vyas 2019 [36]) (Fig 6).


a) Total case notification rates across trial period
CNR per 100,000
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Pre-intervention
Intervention
60 days post intervention
> 60 days post intervention
ACF arm: all cases
ECF arm
Additionality: increase above expected CNR with ACF intervention

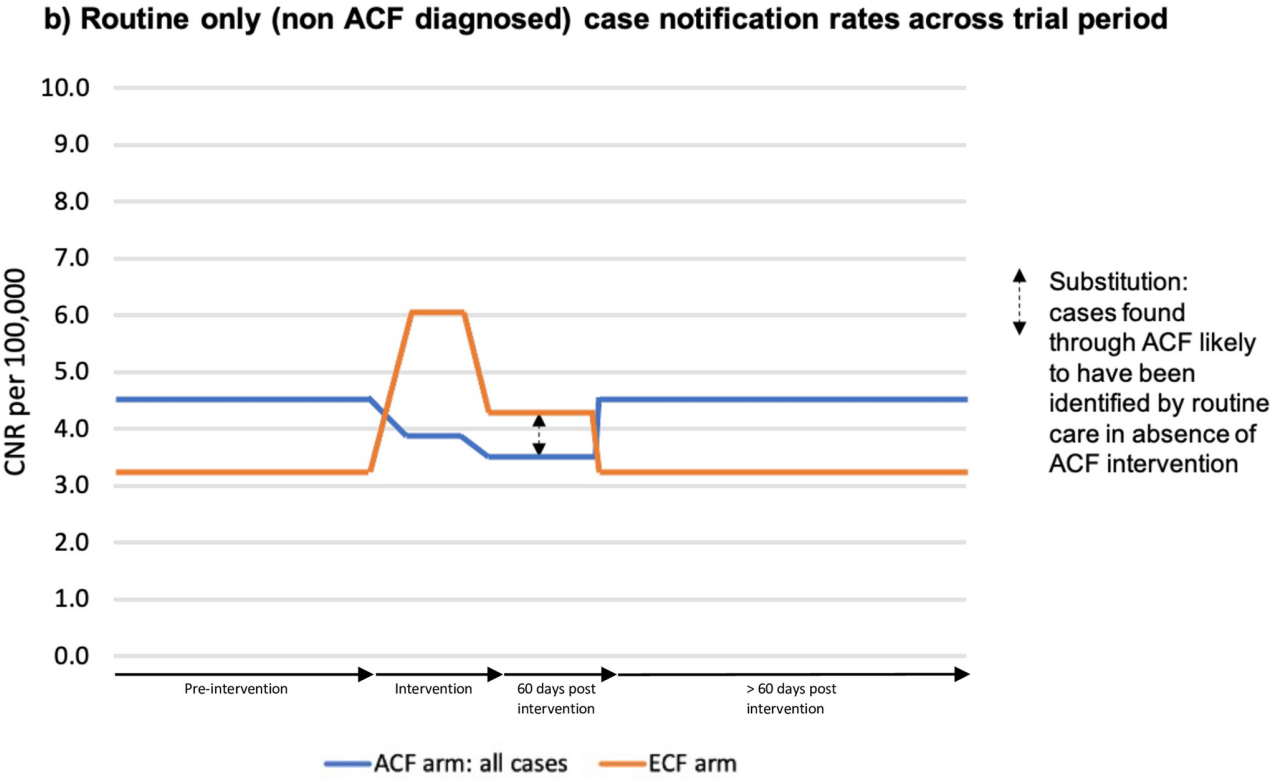

b) Routine only (non ACF diagnosed) case notification rates across trial period
CNR per 100,000
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Pre-intervention
Intervention
60 days post intervention
> 60 days post intervention
ACF arm: all cases
ECF arm
Substitution: cases found through ACF likely to have been identified by routine care in absence of ACF intervention

Fig 3. Case notification rates from Miller cluster-randomised trial in Brazil. Notes: ACF = Active case-finding; ECF = Enhanced case-finding. Relative CNR in days before intervention and >60 days after intervention unknown so presented as consistent.

https://doi.org/10.1371/journal.pgph.0000088.g003

Proxy behavioural outcomes

The included study from the search on proxy behavioural outcomes was a cluster-randomised trial of ACF provided through peer inmate educators in 16 selected prisons in Ethiopia that was classified to be at low risk of bias [25] (Fig 6). KAP scores were collected through a semi-structured post-intervention survey conducted with a randomly selected (process not reported) sample of 1218 inmates, using a pre-tested questionnaire detailed in a separate manuscript describing questionnaire development and baseline KAP survey results [37].

This study reported that the intervention group had higher levels of good TB knowledge and practice than the control group. Composite scores of overall knowledge ($p<0.0001$) and good practice ($p<0.0001$) were significantly higher for ACF compared to control prison respondents, even after adjustment for education, geographical location and cluster size in a generalised estimating equation (GEE) model (adjusted OR 2·54, 95% CI 1·93–3·94 for good knowledge, and adjusted OR 1·84, 1·17–2·96 for good practice). There was no significant

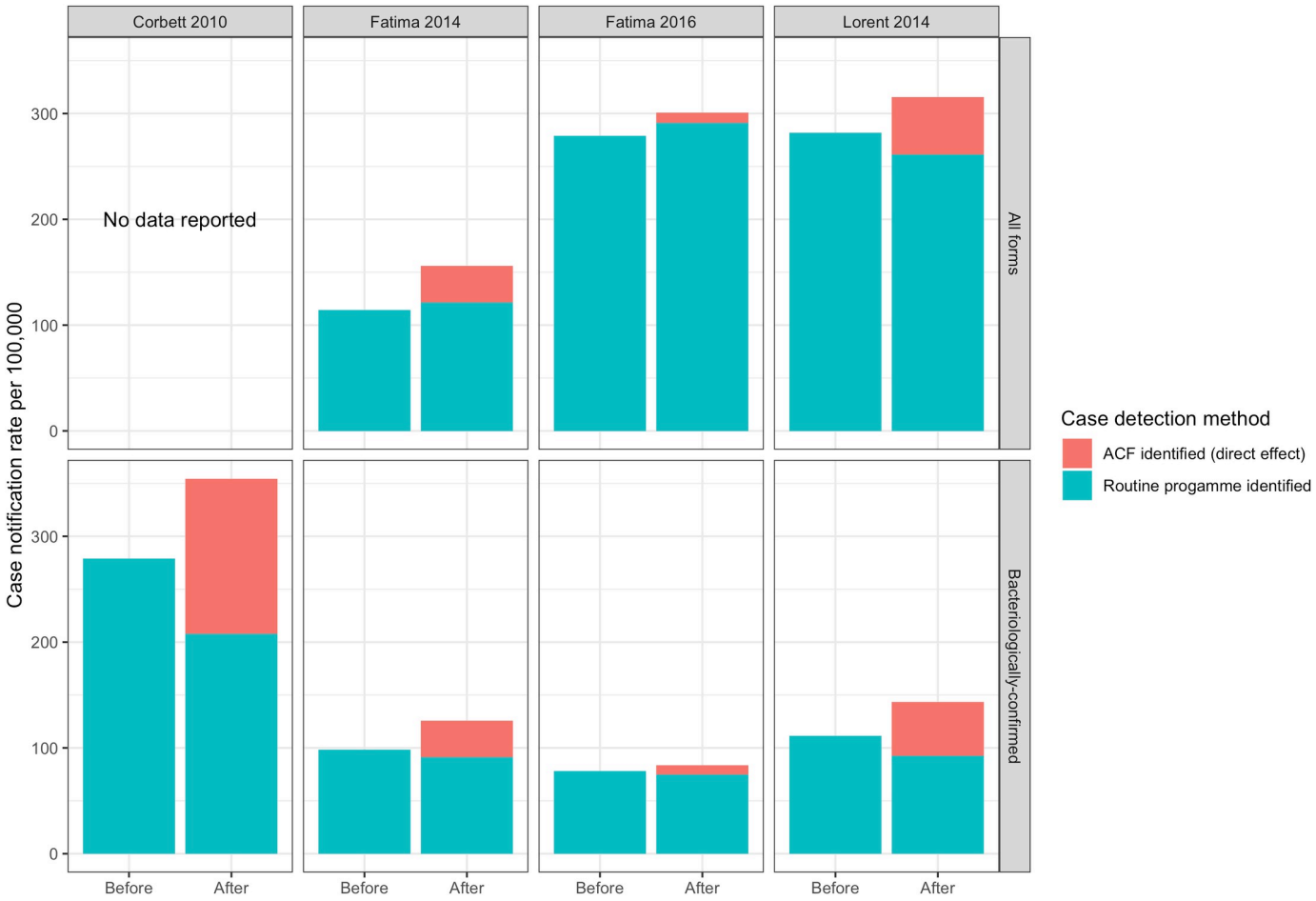


Fig 4. Routinely diagnosed case notification rates in non-randomised before-after studies.

https://doi.org/10.1371/journal.pgph.0000088.g004

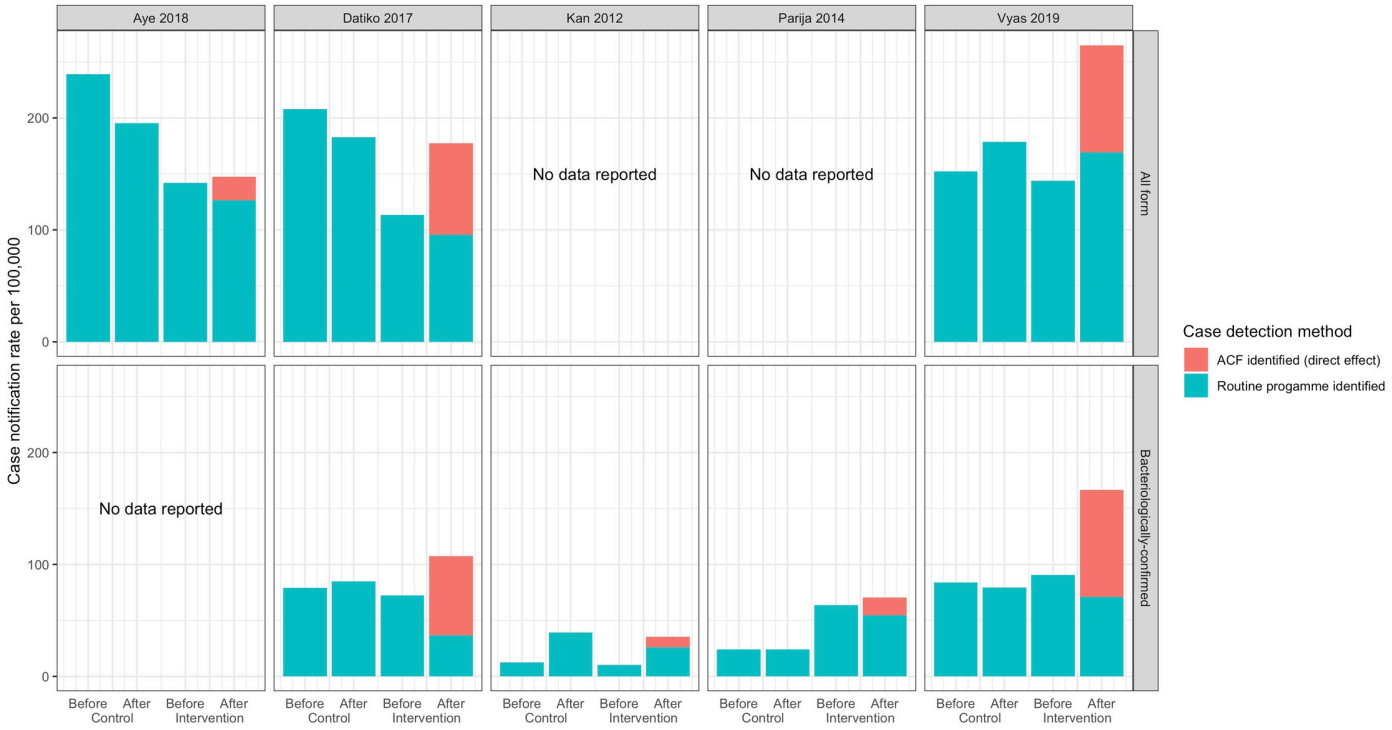


Fig 5. Routinely-diagnosed case notification rates in controlled before-after studies.

https://doi.org/10.1371/journal.pgph.0000088.g005

difference in the composite favourable attitude domain between the two groups (adjusted OR 0.80, 95% CI 0.52–1.25).

Linked KAP and qualitative studies

Of the four publications [38–41] initially identified, two were excluded from further analysis [38, 39] as additional documentation [42] demonstrated that KAP surveys were not aligned to the populations or timing of the ACF interventions. The two included qualitative studies provided insight into how ACF impacts subsequent TB testing and healthcare-seeking behaviours, although neither directly compared healthcare-seeking behaviours between ACF and routine diagnosis populations.

Tulloch *et al* conducted in-depth-interviews from May 2011 to February 2012 with participants in a door-to-door symptom screening ACF intervention in 19 districts of Sidama zone conducted in rural Ethiopia from Oct 2010 to 2015 [40, 43, 44]. From these data, researchers describe different healthcare-seeking pathways including those who have heard about TB services through the intervention activities, and then self-referred to a facility for testing. Some participants also acted as ongoing advocates: *"There are some who have not heard, if so I always tell them at any opportunity"* [40]. The study thus defines mechanisms through which an indirect effect of the ACF intervention could affect subsequent healthcare-seeking behaviour. In addition, the majority of undiagnosed participants were disappointed to have a negative result with an unresolved health problem: *"I feel much sorrow. I gave them my sputum and they said I was negative but still I feel pain inside. . . I am not happy about the result."* [40].

Lorent et al. 2015 conducted a survey and interviews with patients diagnosed with TB through door-to-door ACF among high-risk urban populations in Cambodia [33, 41]. Approximately 20% of TB patients diagnosed through the ACF intervention delayed treatment

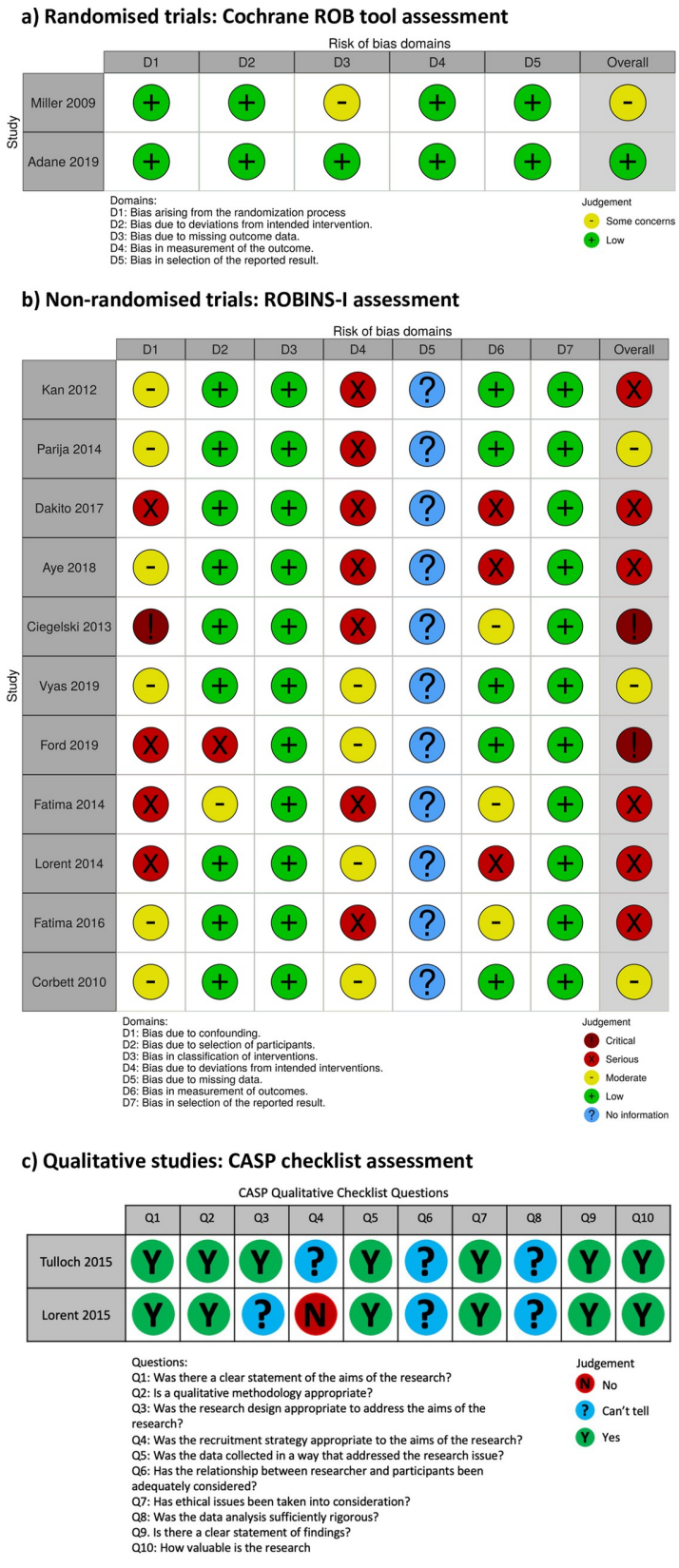


Fig 6. Risk of bias and quality assessments for included studies.

https://doi.org/10.1371/journal.pgph.0000088.g006

initiation so the main study focus was on exploring reasons for delayed or failed linkage to care, with a comparison of perspectives between those who delayed treatment initiation and those who started treatment without delay. Participants reported that ACF had removed barriers of access and cost and emphasised the need for health education on TB, including stronger peer-support networks.

Discussion

To our knowledge, the potential indirect impact of TB active case finding interventions on routine TB case-notifications and subsequent TB testing behaviour has not previously been reviewed. In this systematic review, which has direct relevance to ACF campaigns for other respiratory pathogens such as SARS-CoV-2, we aimed to synthesise evidence from evaluations of TB ACF interventions relating to this indirect, but potentially important, impact. Our main finding was the need for more evidence: we found mixed weak evidence that TB ACF may be effective at indirectly increasing routine TB case notification rates for non-bacteriologically confirmed TB, and insufficient evidence to conclude whether or not ACF impacts subsequent TB testing behaviour. The small number of published studies that specifically address this important issue were at risk of bias introduced by the design or completeness of evaluation, and critical differences in study design precluded meta-analysis as well as firm conclusions. Reaching consensus on how to approach and address this question, including published draft protocols, questionnaires, analysis plans, and key-word suggestions would facilitate the rapid accumulation of high-quality harmonised publications able to support meta-analysis in subsequent systematic reviews. ACF implementers should aim to routinely include prospective qualitative and quantitative assessment of indirect effects, given the critical importance of behavioural change as a key driver of respiratory disease care and prevention [45].

In this review a routine CNR ratio >1 gives an indication of an indirect effect of ACF on routine case-notifications. This was seen in the Miller 2010 RCT (1.14, CI:0.94–1.40) and four of the other studies for all form TB notifications: Aye 2018 (1.09, CI:1.02–1.16), Fatima 2016 (1.04, CI:1.03–1.05), Fatima 2014 (1.06, CI:1.03–1.09), and Ford 2019 (1.02, no CI) but not in any of the bacteriologically-confirmed TB reports. This suggests any indirect impact was unlikely to be due to improved diagnostics implemented through the ACF since this would be expected to be seen primarily in bacteriologically-confirmed rates, but instead may be due to increased TB testing rates and changes in TB testing behaviour. In addition, an indirect effect was not observed in the only two studies which did report improved diagnostics (Datiko 2017 & Lorent 2014). case-notifications. The limited evidence available suggests that there may be a difference in impact between the two forms of TB (Table 2, Figs 4 and 5).

Routine bacteriologically-confirmed TB notifications mostly decreased during the ACF, consistent with a degree of "substitution" (see Methods) whereby ACF identifies some patients who would otherwise have been identified by routine services–although they may have benefited through earlier diagnosis and treatment. Consequently, overall bacteriologically-confirmed CNR increased with ACF but the CNR for routinely diagnosed bacteriologically-confirmed cases decreased (CNR ratio range 0.47–0.96). However, for all forms of TB, routine TB CNRs tended to remain at a similar or slightly higher-level during the community ACF interventions (CNR ratio range 0.93–1.09), which could be explained either by ACF promoting early presentation for clinical diagnosis (when patients are not readily confirmed) or by false positive diagnoses, or a combination of the two.

This difference between bacteriologically-confirmed and all forms TB could be due to the desire identified in Tulloch et al. [40] for participants with negative bacteriological TB results from the ACF to have some resolution for their health problem. These participants could

subsequently attend a facility looking for a diagnosis and then be clinically diagnosed with either extra-pulmonary or pulmonary TB. Datiko et al. [35] and Lorent et al. [33] showed a decrease in routine all forms TB CNR but in the Datiko study, researchers actively followed up ACF participants with negative results by offering them further radiological examination and clinical diagnosis, whilst participants in the Lorent study were selected as the 'most hard-to-reach', suggesting they may have found it difficult to visit a facility for a later clinical diagnosis.

It should be noted that a CNR ratio of ≤ 1 in this review does not preclude an indirect impact of the ACF on case-notifications as this could still occur but be masked by the "substitution" effect, especially when the CNR ratio is 1 or only slightly below (as in Vyas 2019 (1.00, CI:0.95–1.05), Datiko 2017 (0.96, CI:0.88–1.05) and Lorent 2014 (0.93, CI:0.89–0.97) for all forms TB, and Fatima 2016 (0.96, CI:0.94–0.97) and Fatima 2014 (0.93, CI:0.90–0.95) for bacteriologically-confirmed TB). When the CNR ratio is substantially smaller (e.g. Datiko 2017 (0.47, CI:0.41–0.53) and Corbett 2010 (0.75, CI:0.63–0.89) for bacteriologically-confirmed TB) this suggests there is no indirect impact.

Where it occurs, the indirect impact of ACF on routine TB case-notifications could extend beyond the period of the ACF intervention itself. However, the Miller et al RCT [26] was the only study to specifically assess impact after the end of ACF in a study that reported bacteriologically-confirmed cases only and compared ACF with an ECF intervention. As expected, during the intervention period (mean 27 days) and the 60 days directly afterwards, ECF (leaflets) was associated with increased numbers of TB patients diagnosed through the routine health services. However, the ACF arm had total routine case-notifications beyond those seen with ECF. This could reflect a longer-lasting indirect ACF impact or could just reflect ongoing higher CNRs in the ACF arm since the relative contributions of the pre-intervention and >60 days post-intervention periods are unknown. Personal interaction has been shown to be more effective than purely written information in multiple disciplines [46–48] so temporary in-person community TB diagnosis services could potentially create a longer-term impression than providing literature alone.

We found no evidence that the nature of target populations and levels of healthcare access were important effect modifiers, but cannot conclude that these do not influence the indirect effectiveness of ACF due to the limited number of studies, lack of consistent reporting, and heterogeneity of both populations and interventions.

Disappointingly, we found no studies reporting TB testing rates which would have allowed us to distinguish whether increases in routine TB case-notifications were likely due to an increase in testing or enhanced sensitivity of improved diagnostics with a constant testing rate. In addition, only one study included proxy behavioural outcomes as an integral part of the study design. This Ethiopian cluster randomised trial set in prisons used KAP outcomes as a proxy for subsequent healthcare-seeking behaviour [25] and was assessed as being at low risk-of-bias. TB knowledge and intended care seeking for TB symptoms was improved among inmates provided with the peer-educator intervention, and the study protocol and outcome measures provide a template for subsequent similar interventions and evaluations. Two additional reports provided some qualitative insights supportive of possible impact of ACF on subsequent health seeking behaviour, but conclusions were limited by lack of non-ACF or before-after comparators.

There were several limitations to this review. Despite a literature search covering 40 years and $>25{,}000$ titles and abstracts, we found only 12 studies with suitable routine TB case notification data, all of which had very heterogenous interventions and study designs. Just one study specifically addressed outcomes related to subsequent TB testing behaviour following an ACF intervention. As such, we could not conduct meta-analysis, assess generalisability, or quantify the likely impact of behaviour change from ACF on key variables that define the reproduction

number for TB and drive epidemiology [49]. Due to resource and time constraints, we only included manuscripts published in English, and did not include unpublished data or grey literature. Notably, TB REACH (http://www.stoptb.org/global/awards/tbreach/) has funded numerous ACF projects since 2010 with reporting that meets many of our criteria, but we were unable to access unpublished data within the short time available for this review. In addition, the Kranzer et al review used for articles published between 1980 to 2010 did not focus on proxy behavioural outcomes so studies reporting on these could have been missed for this period, but as these outcomes are likely to always be secondary to core outcomes of TB notifications and epidemiology (which were included) the likelihood is low. Statistical limitations include limited availability to adjust for confounders as these data were not consistently reported. We also assumed that ACF diagnoses are a subset of the total notifications but an ACF diagnosis could then become a notification in another population for example through population movement, although this is not reported by any of the studies.

Our main recommendations are to strengthen the evidence regarding ACF and indirect effects on subsequent TB notifications and testing behaviour. Qualitative and quantitative assessment of the indirect effects of ACF should be conducted prospectively. Testing rates would be a better outcome measure than case-notifications to establish indirect impact on TB testing behaviour but these are not routinely collected. Case-notifications, and TB testing where available, from both ACF and routine diagnostic services should be reported separately, ideally including pre-ACF, during-ACF and post-ACF periods, evaluated against a comparator population. The inclusion of a comparator is critical, as this is what allows attribution of impact to the ACF intervention itself. To better understand the mechanisms through which ACF potentially impacts TB testing behaviour, relevant outcomes including TB KAP, test initiator (patient or health worker), stigma and norms should be investigated and reported, ideally through repeated cross-sectional sampling before and after implementation. Accompanying qualitative research would provide the rich detail needed to understand how the ACF intervention creates these indirect impacts on subsequent TB case detection.

Conclusions

In conclusion, the available literature is insufficient, providing only weak evidence for an indirect effect of ACF on clinically diagnosed routine TB case-notifications and insufficient quantitative evidence to assess whether or not ACF impacts subsequent TB testing behaviour. The few available data suggest that ACF can increase TB knowledge and intention to seek early TB diagnosis, together with a desire for diagnosis in those with negative bacteriological ACF results, with potential to impact on future TB testing and case detection rates. Future ACF intervention studies should incorporate assessment of any indirect impact of ACF on facility-based testing and notifications, and other factors with potential to influence TB testing behaviour including KAP, stigma and social norms.

Supporting information

S1 Checklist. PRISMA checklist for systematic review.
(PDF)

S1 Text. Main search strategy.
(PDF)

S2 Text. Accompanying qualitative and KAP studies search strategy.
(PDF)

S1 Table. List of papers about TB ACF reviewed at full text.
(PDF)

S2 Table. List of TB ACF studies identified with suitable study design and included in search for additional KAP or qualitative manuscripts.
(PDF)

S3 Table. Data extracted from and characteristics of included studies with routine case-notification outcomes.
(PDF)

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References

1. World Health Organisation. Global Tuberculosis Report 2020. 2020.
2. World Health Organisation. The End TB Strategy. 2015.
3. World Health Organisation. Early detection of Tuberculosis. An overview of approaches, guidelines and tools. 2011.
4. World Health Organisation. Systematic screening for active tuberculosis. Principles and recommendations. 2013.
5. MacPherson PW E.; Choko A.; Nliwasa M.; Mdolo A.; Chiume L.; Corbett E. Pre and post-intervention prevalence surveys will be conducted to establish whether the ACF leads to a reduction in TB prevalence World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union); Cape Town. South Africa2015.
6. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci. 2011; 6:42. https://doi.org/10.1186/1748-5908-6-42 PMID: 21513547

7. Kredo T, Cooper S, Abrams A, Muller J, Volmink J, Atkins S. Using the behavior change wheel to identify barriers to and potential solutions for primary care clinical guideline use in four provinces in South Africa. BMC Health Serv Res. 2018; 18(1):965. https://doi.org/10.1186/s12913-018-3778-2 PMID: 30547793

8. Leon N, Namadingo H, Bobrow K, Cooper S, Crampin A, Pauly B, et al. Intervention development of a brief messaging intervention for a randomised controlled trial to improve diabetes treatment adherence in sub-Saharan Africa. BMC Public Health. 2021; 21(1):147. https://doi.org/10.1186/s12889-020-10089-6 PMID: 33451308

9. Williams KN, Thompson LM, Sakas Z, Hengstermann M, Quinn A, Díaz-Artiga A, et al. Designing a comprehensive behaviour change intervention to promote and monitor exclusive use of liquefied petroleum gas stoves for the Household Air Pollution Intervention Network (HAPIN) trial. BMJ Open. 2020; 10(9):e037761. https://doi.org/10.1136/bmjopen-2020-037761 PMID: 32994243

10. Ayakaka I, Ackerman S, Ggita JM, Kajubi P, Dowdy D, Haberer JE, et al. Identifying barriers to and facilitators of tuberculosis contact investigation in Kampala, Uganda: a behavioral approach. Implement Sci. 2017; 12(1):33. https://doi.org/10.1186/s13012-017-0561-4 PMID: 28274245

11. Van Ginderdeuren E, Bassett J, Hanrahan C, Mutunga L, Van Rie A. Health system barriers to implementation of TB preventive strategies in South African primary care facilities. PLoS One. 2019; 14(2): e0212035. https://doi.org/10.1371/journal.pone.0212035 PMID: 30763378

12. Oliwa JN, Nzinga J, Masini E, van Hensbroek MB, Jones C, English M, et al. Improving case detection of tuberculosis in hospitalised Kenyan children-employing the behaviour change wheel to aid intervention design and implementation. Implement Sci. 2020; 15(1):102. https://doi.org/10.1186/s13012-020-01061-4 PMID: 33239055

13. Kranzer K, Afnan-Holmes H, Tomlin K, Golub JE, Shapiro AE, Schaap A, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. Int J Tuberc Lung Dis. 2013; 17(4):432–46. https://doi.org/10.5588/ijtld.12.0743 PMID: 23485377

14. Mhimbira FA, Cuevas LE, Dacombe R, Mkopi A, Sinclair D. Interventions to increase tuberculosis case detection at primary healthcare or community-level services. Cochrane Database Syst Rev. 2017; 11 (11):Cd011432. https://doi.org/10.1002/14651858.CD011432.pub2 PMID: 29182800

15. Burke RM, Nliwasa M, Feasey HRA, Chaisson LH, Golub JE, Naufal F, et al. Community-based active case-finding interventions for tuberculosis: a systematic review. Lancet Public Health. 2021. https://doi.org/10.1016/S2468-2667(21)00033-5 PMID: 33765456

16. Blok L, Creswell J, Stevens R, Brouwer M, Ramis O, Weil O, et al. A pragmatic approach to measuring, monitoring and evaluating interventions for improved tuberculosis case detection. International health. 2014; 6(3):181–8. https://doi.org/10.1093/inthealth/ihu055 PMID: 25100402

17. Creswell J, Sahu S, Blok L, Bakker MI, Stevens R, Ditiu L. A multi-site evaluation of innovative approaches to increase tuberculosis case notification: summary results. PLoS One. 2014; 9(4):e94465. https://doi.org/10.1371/journal.pone.0094465 PMID: 24722399

18. World Health Organisation. Advocacy, communication and social mobilization for TB Control / A Guide to Developing Knowledge, Attitude and Practice Surveys. 2008.

19. Challenge TB. TB Stigma Measurement Guidance. 2018.

20. Dempsey RC, McAlaney J, Bewick BM. A Critical Appraisal of the Social Norms Approach as an Interventional Strategy for Health-Related Behavior and Attitude Change. Frontiers in Psychology. 2018; 9 (2180). https://doi.org/10.3389/fpsyg.2018.02180 PMID: 30459694

21. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Chapter 23.1.4. Cochrane; 2020.

22. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019; 366:l4898. https://doi.org/10.1136/bmj.l4898 PMID: 31462531

23. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016; 355:i4919. https://doi.org/10.1136/bmj.i4919 PMID: 27733354

24. Critical Appraisal Skills Programme. CASP Qualitative Checklist. 2018.

25. Adane K, Spigt M, Winkens B, Dinant G-J. Tuberculosis case detection by trained inmate peer educators in a resource-limited prison setting in Ethiopia: a cluster-randomised trial. The Lancet Global Health. 2019; 7(4):e482–e91. https://doi.org/10.1016/S2214-109X(18)30477-7 PMID: 30824364

26. Miller AC, Golub JE, Cavalcante SC, Durovni B, Moulton LH, Fonseca Z, et al. Controlled trial of active tuberculosis case finding in a Brazilian favela. The international journal of tuberculosis and lung disease:

the official journal of the International Union against Tuberculosis and Lung Disease. 2010; 14(6):720–6.

27. Cegielski JP, Griffith DE, McGaha PK, Wolfgang M, Robinson CB, Clark PA, et al. Eliminating tuberculosis one neighborhood at a time. American journal of public health. 2013; 103(7):1292–300. https://doi.org/10.2105/AJPH.2012.300781 PMID: 23078465

28. Aye S, Majumdar SS, Oo MM, Tripathy JP, Satyanarayana S, Kyaw NTT, et al. Evaluation of a tuberculosis active case finding project in peri-urban areas, Myanmar: 2014–2016. Int J Infect Dis. 2018; 70:93–100. https://doi.org/10.1016/j.ijid.2018.02.012 PMID: 29476901

29. Fatima R, Qadeer E, Yaqoob A, Haq MU, Majumdar SS, Shewade HD, et al. Extending 'Contact Tracing' into the Community within a 50-Metre Radius of an Index Tuberculosis Patient Using Xpert MTB/RIF in Urban, Pakistan: Did It Increase Case Detection? PLoS One. 2016; 11(11):e0165813. https://doi.org/10.1371/journal.pone.0165813 PMID: 27898665

30. Fatima R, Qadeer E, Enarson DA, Creswell J, Stevens RH, Hinderaker SG, et al. Success of active tuberculosis case detection among high-risk groups in urban slums in Pakistan. Int J Tuberc Lung Dis. 2014; 18(9):1099–104. https://doi.org/10.5588/ijtld.14.0001 PMID: 25189559

31. Ford D, Datta B, Prakash AK, Tripathy JP, Goyal P, Singh S, et al. Fifth year of a public-private partnership to improve the case detection of tuberculosis in India: A role model for future action? Indian J Tuberc. 2019; 66(4):480–6. https://doi.org/10.1016/j.ijtb.2019.09.005 PMID: 31813435

32. Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): A cluster-randomised trial. The Lancet. 2010; 376(9748):1244–53. https://doi.org/10.1016/S0140-6736(10)61425-0 PMID: 20923715

33. Lorent N, Choun K, Thai S, Kim T, Huy S, Pe R, et al. Community-based active tuberculosis case finding in poor urban settlements of Phnom Penh, Cambodia: a feasible and effective strategy. PLoS One. 2014; 9(3):e92754. https://doi.org/10.1371/journal.pone.0092754 PMID: 24675985

34. Parija D, Patra TK, Kumar AMV, Swain BK, Satyanarayana S, Sreenivas A, et al. Impact of awareness drives and community-based active tuberculosis case finding in Odisha, India. International Journal of Tuberculosis and Lung Disease. 2014; 18(9):1105–7. https://doi.org/10.5588/ijtld.13.0918 PMID: 25189560

35. Datiko DG, Yassin MA, Theobald SJ, Blok L, Suvanand S, Creswell J, et al. Health extension workers improve tuberculosis case finding and treatment outcome in Ethiopia: a large-scale implementation study. BMJ Glob Health. 2017; 2(4):e000390. https://doi.org/10.1136/bmjgh-2017-000390 PMID: 29209537

36. Vyas A, Creswell J, Codlin AJ, Stevens R, Rao VG, Kumar B, et al. Community-based active case-finding to reach the most vulnerable: tuberculosis in tribal areas of India. Int J Tuberc Lung Dis. 2019; 23(6):750–5. https://doi.org/10.5588/ijtld.18.0741 PMID: 31315709

37. Adane K, Spigt M, Johanna L, Noortje D, Abera SF, Dinant GJ. Tuberculosis knowledge, attitudes, and practices among northern Ethiopian prisoners: Implications for TB control efforts. PLoS One. 2017; 12(3):e0174692. https://doi.org/10.1371/journal.pone.0174692 PMID: 28358877

38. Thapa B, Chadha SS, Das A, Mohanty S, Tonsing J. High and equitable tuberculosis awareness coverage in the community-driven Axshya TB control project in India. Public health action. 2015; 5(1):70–3. https://doi.org/10.5588/pha.14.0105 PMID: 26400604

39. Thapa B, Prasad BM, Chadha SS, Tonsing J. Serial survey shows community intervention may contribute to increase in knowledge of Tuberculosis in 30 districts of India. BMC public health. 2016; 16(1):1155–. https://doi.org/10.1186/s12889-016-3807-1 PMID: 27835999

40. Tulloch O, Theobald S, Morishita F, Datiko DG, Asnake G, Tesema T, et al. Patient and community experiences of tuberculosis diagnosis and care within a community-based intervention in Ethiopia: a qualitative study. BMC Public Health. 2015; 15(1):187. https://doi.org/10.1186/s12889-015-1523-x PMID: 25885789

41. Lorent N, Choun K, Malhotra S, Koeut P, Thai S, Khun KE, et al. Challenges from Tuberculosis Diagnosis to Care in Community-Based Active Case Finding among the Urban Poor in Cambodia: A Mixed-Methods Study. PLOS ONE. 2015; 10(7):e0130179. https://doi.org/10.1371/journal.pone.0130179 PMID: 26222545

42. Karuna DS, International Union Against Tuberculosis and Lung Disease. Knowledge, Attitude and Practice about Tuberculosis in India. A Midline Survey, 2013. 2014.

43. Datiko DG, Yassin MA, Theobald SJ, Blok L, Suvanand S, Creswell J, et al. Health extension workers improve tuberculosis case finding and treatment outcome in Ethiopia: a large-scale implementation study. BMJ global health. 2017; 2(4):e000390–e. https://doi.org/10.1136/bmjgh-2017-000390 PMID: 29209537

44. Yassin MA, Datiko DG, Tulloch O, Markos P, Aschalew M, Shargie EB, et al. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. PLoS One. 2013; 8(5):e63174. https://doi.org/10.1371/journal.pone.0063174 PMID: 23723975

45. Flaxman S, Mishra S, Gandy A, Unwin HJT, Mellan TA, Coupland H, et al. Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. Nature. 2020; 584(7820):257–61. https://doi.org/10.1038/s41586-020-2405-7 PMID: 32512579

46. Knopf-Amelung S, Gotham H, Kuofie A, Young P, Manney Stinson R, Lynn J, et al. Comparison of Instructional Methods for Screening, Brief Intervention, and Referral to Treatment for Substance Use in Nursing Education. Nurse Educ. 2018; 43(3):123–7. https://doi.org/10.1097/NNE.0000000000000439 PMID: 28817479

47. Ali N, Zahra T, Vosogh MN, Vosoghi N, Zare M, Mardi A, et al. Effectiveness Comparison of Mothers' In-person Versus Written Nutritional Education Intervention on Infant Growth in Iran. Int J MCH AIDS. 2015; 3(1):74–80. PMID: 27621988

48. Ramsaroop SD, Reid MC, Adelman RD. Completing an advance directive in the primary care setting: what do we need for success? J Am Geriatr Soc. 2007; 55(2):277–83. https://doi.org/10.1111/j.1532-5415.2007.01065.x PMID: 17302667

49. Houben RMGJ, Dowdy DW, Vassall A, Cohen T, Nicol MP, Granich RM, et al. How can mathematical models advance tuberculosis control in high HIV prevalence settings? The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease. 2014; 18(5):509–14. https://doi.org/10.5588/ijtld.13.0773 PMID: 24903784

Appendix 1: Main Search Strategy

Search strategy
Databases
PubMed, EMBASE, Scopus, Cochrane Library

PubMed

#1	"tuberculosis"[MeSH Terms]
#2	"tuberculosis"[tw] OR “Pulmonary Consumption”[tw] OR “Consumption, Pulmonary”[tw] OR Phthisis[tw] OR “Tuberculoses”[tw] OR “MDR-TB”[tw] OR “XDR-TB”[tw] OR “MDR TB”[tw] OR “XDR TB”[tw]
#3	#1 OR #2
#4	“Mass Screening”[MeSH Terms] OR “Mass Chest X-Ray”[MeSH Terms] OR "contact tracing"[MeSH Terms] OR “health surveys”[MeSH Terms] OR “Cross-Sectional Studies”[MeSH Terms] OR “Epidemiologic Studies”[MeSH Terms]
#5	“Mass Chest X Ray”[tw] OR “Mass Chest X-Rays”[tw] OR “screenings”[tw] OR “screening”[tw] OR “cross-sectional”[tw] OR “case-detection”[tw] OR “case finding”[tw] OR “contact tracing”[tw] OR “health survey”[tw] OR "prevalence survey"[tw] OR “prevalence studies”[tw] OR "mass radiography"[tw] OR "contact examination"[tw]
#6	#4 OR #5
#7	#3 AND #6
#8	("animals"[MeSH Terms] NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms]))
#9	#7 NOT #8
#10	("2010/11/01"[EDAT] : "3000/12/31"[EDAT] OR "2010/11/01"[CRDT] : "3000/12/31"[CRDT]) OR ("2010/11/01"[PDAT] : "3000/11/31"[PDAT])
#11	#9 AND #10

Embase

#1	'tuberculosis'/exp OR 'lung tuberculosis'/exp
#2	(‘tuberculosis’ OR ‘Pulmonary Consumption’ OR ‘Consumption, Pulmonary’ OR Phthisis OR ‘Tuberculoses’ OR “MDR-TB” OR “XDR-TB” OR “MDR TB” OR “XDR TB”):ab,ti,kw
#3	#1 OR #2
#4	'tuberculosis control'/exp OR 'case finding'/exp OR 'mass radiography'/exp OR 'mass screening'/exp OR 'contact examination'/exp OR 'screening'/exp
#5	(‘Mass Chest X Ray’ OR ‘Mass Chest X-Rays’ OR ‘Screenings’ OR ‘screening’ OR ‘Cross-Sectional Studies’ OR ‘Case-detection’ OR ‘case finding’ OR ‘contact tracing’ OR ‘mass radiography’ OR ‘contact examination’ OR ‘health survey’ OR ‘cross-sectional’ OR 'prevalence survey' OR ‘prevalence studies’):ab,ti,kw
#6	#4 OR #5
#7	#3 AND #6
#8	'animal'/exp NOT ('animal'/exp AND 'human'/exp)
#9	#7 NOT #8
#10	[1-11-2010]/sd
#11	#9 AND #10

Scopus

#1	TITLE-ABS-KEY (tuberculosis OR phthisis OR "pulmonary consumption" OR Tuberculoses OR “MDR-TB” OR “XDR-TB” OR “MDR TB” OR “XDR TB”)
#2	TITLE-ABS-KEY("mass chest x ray" OR "mass chest x-rays" OR screenings OR screening OR "health survey" OR "cross-sectional" OR "case-detection" OR "case finding" OR "contact tracing" OR "prevalence survey" OR "prevalence studies" OR "mass radiography" OR "contact examination")
#3	#1 AND #2
#4	PUBDATETXT (november 2010) OR PUBDATETXT (december 2010) OR PUBYEAR > 2010
#5	#3 AND #4

removed b/c redundant:
(mass screenings) OR (mass screening)
(cross-sectional studies)
(active case finding)
(intensified case-finding) OR (intensified case finding)
(contact screening)
(population screening)

Cochrane Library

#1 MeSH descriptor: [Tuberculosis] explode all trees
#2 "tuberculosis" OR (Pulmonary NEXT Consumption*) OR Phthisis OR Tuberculoses OR “MDR-TB” OR “XDR-TB” OR “MDR TB” OR “XDR TB”
#3 #1 OR #2
#4 MeSH descriptor: [Mass Screening] explode all trees
#5 MeSH descriptor: [Mass Chest X-Ray] explode all trees
#6 MeSH descriptor: [Contact Tracing] explode all trees
#7 MeSH descriptor: [Health Surveys] explode all trees
#8 MeSH descriptor: [Cross-Sectional Studies] explode all trees
#9 MeSH descriptor: [Epidemiologic Studies] explode all trees
#10 “Mass Chest X Ray” OR “Mass Chest X-Rays” OR “screenings” OR “screening” OR “cross-sectional” OR “case-detection” OR “case finding” OR “contact tracing” OR “health survey” OR "prevalence survey" OR “prevalence studies” OR "mass radiography" OR "contact examination"
#11 {OR #4-#10}
#12 #3 AND #11 with Cochrane Library publication date Between Nov 2010 and Mar 2019

Appendix 2: Accompanying qualitative and KAP studies search strategy

Pubmed

For each study in Appendix 4

#1	"any reported study name" (e.g. "DETECTB")
#2	Paper first author [Author] (e.g. Corbett EL[Author])
#3	Paper last author [Author] (e.g. Hayes RJ [Author])
#4	#2 OR #3
#5	"Tuberculosis"
#6	"study location" (e.g. "Zimbabwe")
#7	"year study completed/01/01"[Date - MeSH] : "3000"[Date - MeSH] (e.g. "2009/01/01"[Date - MeSH] : "3000"[Date - MeSH])
#8	#4 AND #5 AND #6 AND #7
#9	#1 OR #8

Chapter 6

Impact of active case-finding for tuberculosis on case-notifications in Blantyre, Malawi: a community-based cluster-randomised trial (SCALE)

To examine the direct and indirect population-level impact of community-based ACF on overall and routine facility-based TB case-notifications, I led a cluster-randomised trial of door-to-door TB ACF in urban Blantyre. Following the previously described pre-intervention prevalence survey, constrained randomisation was used to allocate 72 neighbourhoods to either door-to-door ACF (sputum microscopy for reported cough >2 weeks) or standard-of-care (SOC), with the ACF intervention delivered May 2019 to March 2020. Due to the COVID-19 pandemic interrupting the trial, the primary outcome changed from prevalence of undiagnosed TB to cluster-level bacteriologically-confirmed case-notification rate (CNR) ratio within 91 days of ACF, with a secondary outcome of 91-day CNR ratios comparing all non-ACF registrations to assess indirect impact . Of 1,192 ACF participants, 13 (1.09%) were smear-positive. Within 91 days, 113 (42 bacteriologically-confirmed) and 108 (33 bacteriologically-confirmed) tuberculosis patients were identified as ACF (58,944 person-years follow-up) or SOC (52,805 person-years) cluster residents, respectively. There was no difference by arm in CNR ratios and so no detectable impact of this previously successful approach targeting symptomatic disease, likely due to several previous years of ACF in this location and rapid declines in TB burden linked to improved management of HIV.

This paper was prepared for submission to PLoS Medicine and will be submitted in May 2023.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1806428	**Title**	Mrs
First Name(s)	Helena Rosemary Anne		
Surname/Family Name	Feasey		
Thesis Title	Investigating the potential impact and suitability of tuberculosis active case-finding approaches in the rapidly changing environment of urban Blantyre, Malawi		
Primary Supervisor	Prof Liz Corbett		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLos Medicine
Please list the paper's authors in the intended authorship order:	Helena R A Feasey, McEwen Khundi, Rebecca Nzawa Soko, Christian Bottomley, Lingstone Chiume, Helen E D Burchett, Marriott Nliwasa, Hussein H Twabi, James A Mpunga, Peter MacPherson, Elizabeth L Corbett

Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I developed the research question and redefined the outcomes as needed, I led the prevalence survey and ACF implementation including all CRFs and SOPs, I led data collection and analysis, and I led writing of the manuscript as first author.

SECTION E

Student Signature	Helena Feasey
Date	13 March 2023

Supervisor Signature	Elizabeth Corbett
Date	13 March 2023

Impact of active case-finding for tuberculosis on case-notifications in Blantyre, Malawi: a community-based cluster-randomised trial (SCALE)

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Abstract word count: 326
Tables: 2
Figures: 4

Abstract: 349 words

Background

Active case-finding (ACF) for tuberculosis can help find the "missing millions" with undiagnosed tuberculosis. In a cluster randomised trial, we investigated the impact of ACF on case-notifications in Blantyre, Malawi, where ACF has been intensively implemented following 2014 national survey estimates of ~1,000 per 100,000 adults with undiagnosed TB.

Methods

Following a pre-intervention prevalence survey in randomly selected households (May 2019 to March 2020), constrained randomisation was used to allocate neighbourhoods to either door-to-door ACF (sputum microscopy for reported cough >2 weeks) or standard-of-care (SOC). Implementation was interrupted by COVID-19. Cluster-level bacteriologically-confirmed case-notification rate (CNR) ratio within 91 days of ACF was our redefined primary outcome; comparison between arms used negative-binomial regression. Secondary outcomes were 91-day CNR ratios comparing all tuberculosis registrations and all non-ACF registrations, respectively. Investigators, but not participants or field-workers, were masked to allocation until final analysis. Interrupted time series (ITS) analysis of CNRs in the SOC arm examined prevalence survey impact.

(ISRCTN11400592)

Results

72 clusters served by 10 study-supported tuberculosis registration centres were publicly randomised to ACF (261,244 adults, 58,944 person-years follow-up) or SOC (256,713 adults, 52,805 person-years). Of 1,192 ACF participants, 13 (1.09%) were smear-positive. Within 91 days, 113 (42 bacteriologically-confirmed) and 108 (33 bacteriologically-confirmed) tuberculosis patients were identified as ACF or SOC cluster residents, respectively. There was no difference by arm, with adjusted 91-day CNR ratios 1.12 (95% CI: 0.61-2.07) for bacteriologically-confirmed tuberculosis (primary outcome); 0.93 (95% CI: 0.68-1.28) for all tuberculosis registrations; and 0.86 (95%CI: 0.63-1.16) for non-ACF (routinely) diagnosed. Of 7,905 ACF and 7,992 SOC pre-intervention survey participants, 12 (0.15%) and 17 (0.21%), respectively, had culture/Xpert-confirmed tuberculosis. ITS analysis showed no survey impact on SOC CNRs.

Conclusion

Despite residual undiagnosed tuberculosis of 150 per 100,000 population, there was no increase in tuberculosis notifications from this previously successful approach targeting symptomatic disease, likely due to several previous years of ACF and rapid declines in TB burden. In such settings, future ACF should focus on targeted outreach and demand creation, alongside optimised facility-based screening. Routine surveillance systems more attuned to rapidly changing TB epidemiology are urgently needed to meet TB elimination goals.

Introduction

Tuberculosis remains a major killer, with 1.6 million deaths from TB in 2021, second only to COVID-19 as an infectious cause of death [1]. People living with HIV (PLHIV) have greatly increased susceptibility to active TB disease and death from TB [2], especially if their HIV is untreated, reflected in much higher *per capita* TB incidence and mortality rates in sub-Saharan Africa than other global regions since the 1990s. During the last decade, concerted investment to diagnose and treat PLHIV [3, 4] and reduce barriers to TB diagnosis has led to substantial TB epidemiology improvements [1, 5], although with setbacks due to service disruptions during COVID-19 [1, 6]. Regional TB incidence declined in Africa by an estimated 21% during 2015-21, although an estimated 4.1million people (980,000 in the WHO Africa region) with incident TB went undiagnosed and untreated in 2021 [1], 40% more than in 2019 [1]. Closing this treatment gap is essential to meeting TB elimination targets defined in the WHO EndTB Strategy targets [7] and may require more intensive systematic screening in facilities and also active case-finding (ACF) providing community-level diagnosis with focus on men and HIV-negative TB patients who otherwise tend to have prolonged duration of infectiousness [8].

ACF has potential to increase TB diagnosis and rapidly reduce the prevalence of undiagnosed infectious TB [9, 10] and was widely implemented in the last century [11]. ACF approaches vary greatly in intensity and delivery aspects, but often use periodic outreach by mobile teams using combinations of symptom screening, chest X-ray and either microscopy or, more recently, rapid molecular tests [10]. Less intensive,

enhanced case-finding (ECF) uses health information or awareness campaigns to encourage health-seeking behaviour when people experience TB symptoms, with or without access to diagnostics at community-level [10]. Evidence of an indirect effect, for example health promotion, may be reflected in prolonged increased TB notifications due to a change in testing behaviour through increased knowledge of symptoms and diagnosis, reducing TB stigma, changing social norms, or providing a prompt for symptomatic people to attend a health facility for testing [12]. Because of the high cost, and risk of false-positive and false-negative screening results, community-wide ACF is conditionally recommended only for general populations with undiagnosed TB of 500 per 100,000 population or higher [10, 13]. Evaluating impact is technically difficult and costly, and a recent systematic review [9] identified just eight randomised controlled trials, only two of which had community TB infection incidence or prevalence outcomes [14, 15].

Sustainable Community Active-case finding for Lung Health (SCALE) was a cluster-randomised trial investigating the impact of ACF on underlying TB epidemiology in Blantyre city, Malawi. The primary outcome was modified from undiagnosed TB to recent TB testing and cluster-level case-notification rates after pre-intervention survey showing substantial reduction from 2013-14 estimates of 1,014 per 100,000 adults with undiagnosed infectious TB [16, 17], and then disruption due to COVID-19 [5]. We also investigated facility-based TB case-notifications following ACF in each cluster given potential to indirectly affect subsequent TB testing rates by health promotion [12].

Methods

We conducted a cluster-randomised trial (ISRCTN11400592) of TB ACF in high-density and peri-urban residential areas of Blantyre, Malawi with a pre-intervention prevalence survey implemented June 2019 to March 2020 [17]. 315 government community health worker catchment areas were aggregated to form the 72 trial clusters with an estimated 2015 population of ~4,400 adult (aged 15 years or older) residents in each cluster and an overall estimated population of 515,000 in 2019.

The trial was planned as a three-part study with pre- and post-intervention prevalence surveys to assess the effectiveness of three rounds of door-to-door community ACF delivered using brief door-to-door enquiry for prolonged cough with collection of two sputum specimens for microscopy [18, 19]. Blantyre city had an estimated prevalence of 1,014 per 100,000 adults with undiagnosed infectious TB in the 2013-14 Malawi national TB prevalence survey [20]. We had anticipated decline to 500 per 100,000 adults with undiagnosed TB due to previous ACF in Blantyre using the same approach by our team in 2011-14 [19] and national TB programme ACF 2015-2019, associated with declining TB notifications in Blantyre [5, 19].

The SCALE pre-intervention prevalence survey, however, showed a much greater than anticipated decline to 150-189 per 100,000 adults with undiagnosed TB [17], necessitating a change in primary outcome to recent TB testing and cluster-level TB case-notification rates. With the onset of the COVID-19 pandemic, the door-to-door intervention and household survey for recent testing became too risky to continue. The trial was therefore suspended after the pre-intervention prevalence survey and

one round of ACF, with the primary outcome changed from prevalence of undiagnosed TB to evaluating the impact on bacteriologically TB case notifications as described below.

Study population

We conducted a city-wide census household enumeration with the Blantyre District Health Office (DHO) in 2015. In 2008 and 2018 the Malawi National Statistical Office (NSO) additionally conducted Population and Household National Censuses [21]. Adult (18 years and older) population denominators for this trial were estimated by applying estimated weekly population growth rates for each neighbourhood using linear interpolation and projection from the 2015 and 2018 data.

Prevalence survey participants were identified through random selection of 115 households, from a sampling frame of all household GPS co-ordinates obtained from Google Earth, aiming to recruit 215 adults (aged 18 and above) per cluster. All adults from selected households who were willing and able to provide consent were included in the prevalence survey. For the ACF intervention, all adult residents (18 years and older) living in intervention clusters, with a cough of two weeks or more and not currently on TB treatment were eligible.

Procedures

A pre-intervention prevalence survey was conducted in all clusters (two clusters per week) and the ACF was conducted in the intervention arm the following week with staggered initiation over a period from 12 May 2019 until 2 March 2020. Local leaders

were engaged and study information meetings held in all clusters prior to the start of the prevalence survey. For the prevalence survey, participants from randomly selected households were invited to attend a study tent located in an accessible neighbourhood location for digital chest X-ray, interpreted by a trained radiographer (any abnormality versus normal), with assistance by computer aided diagnostic software (Qure.ai version 2). Participants reporting a cough of any duration or an abnormal X-ray were asked to provide two spot sputum samples for smear microscopy, Xpert MTB/RIF and Mycobacteria growth indicator tube (MGIT) culture. Confirmatory samples were requested from participants with positive TB test results, with support to register for TB treatment at their nearest health facility. HIV testing was offered to all participants using OraQuick (OraSure) and Determine (Alere) finger-prick rapid HIV diagnostic tests conducted in parallel, with Uni-Gold (Trinity Biotech) to confirm positive HIV results. Prevalence survey activities took five to six days per cluster.

Active-case finding

The ACF intervention commenced in intervention clusters two- to three-days after the prevalence survey, and lasted for a period of up to five days. Fieldworkers moved door-to-door leaving information leaflets and enquiring about symptoms of cough lasting two weeks or longer in any adult household member, including those not present at the time of ACF team visit. GPS coordinates were taken to document each household visit. Adults with cough were asked to provide a spot sputum and given a sputum pot for next-morning sputum collection. Information leaflets and two sputum pots were provided for reported symptomatic – but absent – household members, with a leaflet explaining how to collect sputum. Sputum samples were collected by the

ACF team the next-day and examined using smear microscopy. Up to three visits were made per household if no one was present, with information leaflets left at all households. Participants with positive microscopy results were contacted directly by telephone and household visit, asked for a confirmatory sample, and assisted to register for TB treatment at the nearest health facility. For participants with negative results, a neighbourhood tent was set up on a designated day in the following calendar week to issue results.

Standard of care

All public medical services are provided free at the point of care in Malawi. To provide an enhanced standard of care to all residents, study clinic assistants were assigned to each of 10 District Health Office (DHO) Blantyre primary health facilities between May 2019 to October 2020. These Clinic Assistants assisted the District Health TB officers in their duties and facilitated identification of outpatient clinic attendees with cough through triage and referral to clinical officers if eligible for TB investigations under National TB Programme (NTP) guidelines.

Outcomes

The primary outcome of the final protocol was the cluster-level case notification rate (CNR) of bacteriologically-confirmed TB (per 1000 adult residents) in the 91 days after the start of the prevalence survey. Secondary outcomes were the cluster-level CNR for all-form TB and CNRs for both bacteriologically-confirmed and all-form TB identified through routine diagnosis (excluding those identified through the ACF and prevalence survey) during the same period.

Case notifications were recorded through a tablet-based electronic TB database, established in 2011, delivered by DHO TB officers, and maintained jointly by Blantyre DHO and Malawi-Liverpool Wellcome Programme (MLW), which recorded details for all patients registering for TB treatment within urban Blantyre [5, 22], including place of residence GPS co-ordinates identified through a satellite map application (ePAL), which has previously been validated [22, 23]). All patients registering for TB treatment were asked for a spot sputum sample for smear microscopy and MGIT culture at the MLW/Kamuzu University of Health Sciences (KUHeS) TB Research Laboratory. The electronic registry was reconciled with NTP paper registers on a monthly basis and household GPS co-ordinates of 5% of participants were checked through home visits.

Data was censored from 23 March 2020 (date of declaration of Malawi COVID-19 state emergency) since COVID-19 led to a large reduction in TB case-notifications in Blantyre [5] and elsewhere. This was 21 days after the start of the prevalence survey in the final two clusters.

Randomisation and masking

Clusters were randomly assigned to receive either the door-to-door ACF intervention, or enhanced standard of care. Randomisation was conducted at a public meeting using random selection of one number from a previously prepared list of 999 randomly selected allocations generated by the trial statistician using a computer programme. Randomisation was constrained to provide balance on mean distance from cluster centres to the nearest health clinic, baseline TB case-notification rates, adult population, longitude and latitude of cluster centres, and referral health centre.

Participants and field-workers were not masked to the intervention, but laboratory work and clinical management were completed without reference to trial arm and analysis by trial arm was not undertaken until the final analysis.

Statistical methods

Sample sizes were initially calculated to provide ≥80% power to detect a 28 to 35% reduction in the original trial outcome of prevalence of undiagnosed TB. With the revised primary outcome the study was expected to provide 89% power to detect a 30% increase in bacteriologically-confirmed case-notifications, assuming a rate of 276 cases per 100,000 adults in the control arm, 91 days (13 weeks) of follow-up per cluster and an intra-cluster correlation of 0.3.

For the primary outcome (bacteriologically-confirmed TB CNRs), we calculated the cluster-specific number of people with bacteriologically-confirmed TB identified as initiating TB treatment by the ePAL system in the 91 days after the start of the prevalence survey in that cluster, and divided by the estimated person-years of follow-up in each cluster to give CNRs per 100,000 person-years. The CNR ratio, adjusted to account for the variables that randomisation was constrained by, was estimated through a Poisson regression model with random effects to account for clustering. Secondary outcomes were calculated similarly using the relevant numerators obtained from ePAL treatment registrations.

Time trends in CNRs were plotted, calculating the five-week rolling mean case notification rates, with 95% confidence intervals estimated through 1,000 bootstrap

239 replications, by arm and stratified by sex. In a further pre-planned analysis of impact of
240 the prevalence survey alone on case notification rate over time, an interrupted time
241 series analysis was conducted on the case notification rates over the 52 weeks before
242 and 13 weeks (91 days) after the start of the prevalence survey. The Poisson regression
243 model included a linear term to account for time trend and two indicators to model
244 the impact of the prevalence survey. One indicator was used to estimate impact in the
245 6-week period immediately following the survey and the other was used to estimate
246 long-term impact. Newey West confidence intervals were calculated to account for
247 over dispersion and auto-correlation [24].
248
249 All analyses were done with R version 4.2.1. This trial is registered (ISRCTN11400592).
250
251 *Data and reproducibility*
252 Data and code to reproduce this analysis is available from *https://osf.io/fvqtw/*
253
254 *Ethics*
255 Approval was granted by the research ethics committees of the Malawi College of
256 Medicine (now Kamuzu University of Health Sciences) and the London School of
257 Hygiene and Tropical Medicine. Written (or witnessed if illiterate) informed consent
258 was provided by all participants in the prevalence survey and active case-finding. Oral
259 consent was provided by people registering for TB treatment for electronic data
260 capture, including recording of household co-ordinates.

Results

Participant and cluster characteristics

36 clusters were randomised to each study arm with an estimated 2019 adult population (age 15+) of 261,244 in the ACF clusters and 256,713 in SOC clusters. Clusters were followed up for a median of 168 days (range 21-316) and people in ACF and SOC clusters contributed 58,944 and 52,805 person-years of follow-up, respectively (Table 1).

Of the 36 clusters in each arm, 29 of those in the ACF arm and 26 in the SOC arm completed 91 days after the start of the prevalence survey before 23 March 2020, when data was censored (Table 1). Baseline characteristics of the adult population are presented by arm in Table 1. Household characteristics and most individual characteristics (sex, age, HIV status, previous TB treatment and reported TB symptoms) were similar between arms.

Pre-intervention prevalence survey

Between 12 May 2019 and 13 March 2020, 15,897 participants were recruited to the pre-intervention prevalence survey (7,905 in the ACF arm and 7,992 in SOC clusters). Overall, 1,274/15,897 (8.0%) TB presumptive participants (cough and/or abnormal X-ray) and 29 (0.18%) bacteriologically-confirmed cases of TB were identified: 12 (151 per 100,000, 95% CI: 87-265) in the ACF arm and 17 (213 per 100,000, 95% CI: 133-340) in SOC clusters. All were supported to register for TB treatment locally except four in the SOC arm who moved out of Blantyre and registered in treatment sites outside of the city.

Table 1: Baseline characteristics table*

Unit	Variable	Unit / category	ACF	SOC
Community		clusters	36	36
	Completed 91 days FU**	clusters	29	26
	Adult population in 2015	(100)	1899	1821
	Previous CNR	(per 100 000 PYs)	262.0	275.9
	Adult population in 2019	(100)	2612	2567
	Adult person years ***	(PYs)	58944	52805
	Distance to health facility	Metres (mean)	889.8	938.7
Household				
	Crowding	persons per room (mean)	1.3	1.4
	SES indicators	bottom quartile (%)	24.3	25.7
Individual				
	Age	years (mean,range)	32.2	32.6
			(18-94)	(18-98)
	Sex	Male (%)	47.0	46.4
	HIV/ART status	HIV+ on ART (%)	10.5	11.1
		HIV+ not on ART (%)	1.5	1.7
		HIV unknown (%)	4.3	3.9
	TB contact (within 12 months)	Yes (%)	5.0	4.1
	Previous TB treatment	Yes (%)	2.8	2.9
	Reported TB symptoms	Cough (any duration) (%)	5.3	5.2
		Cough ≥ 2 weeks† (%)	3.4	3.3
		Night sweats (%)	5.7	5.1
		Weight loss (%)	5.8	5.0
		Fever (%)	3.4	2.8
		Any (cough any duration) (%)	15.5	14.4

* % for categorical data; mean (range) for quantitative data

** Number of clusters completed 91 days follow-up after prevalence survey before 23 March 2020

*** Person years of follow-up after prevalence survey

† Chronic cough

Clinical and microbiological details of the 29 bacteriologically-confirmed cases are presented in Supplementary Table 1.

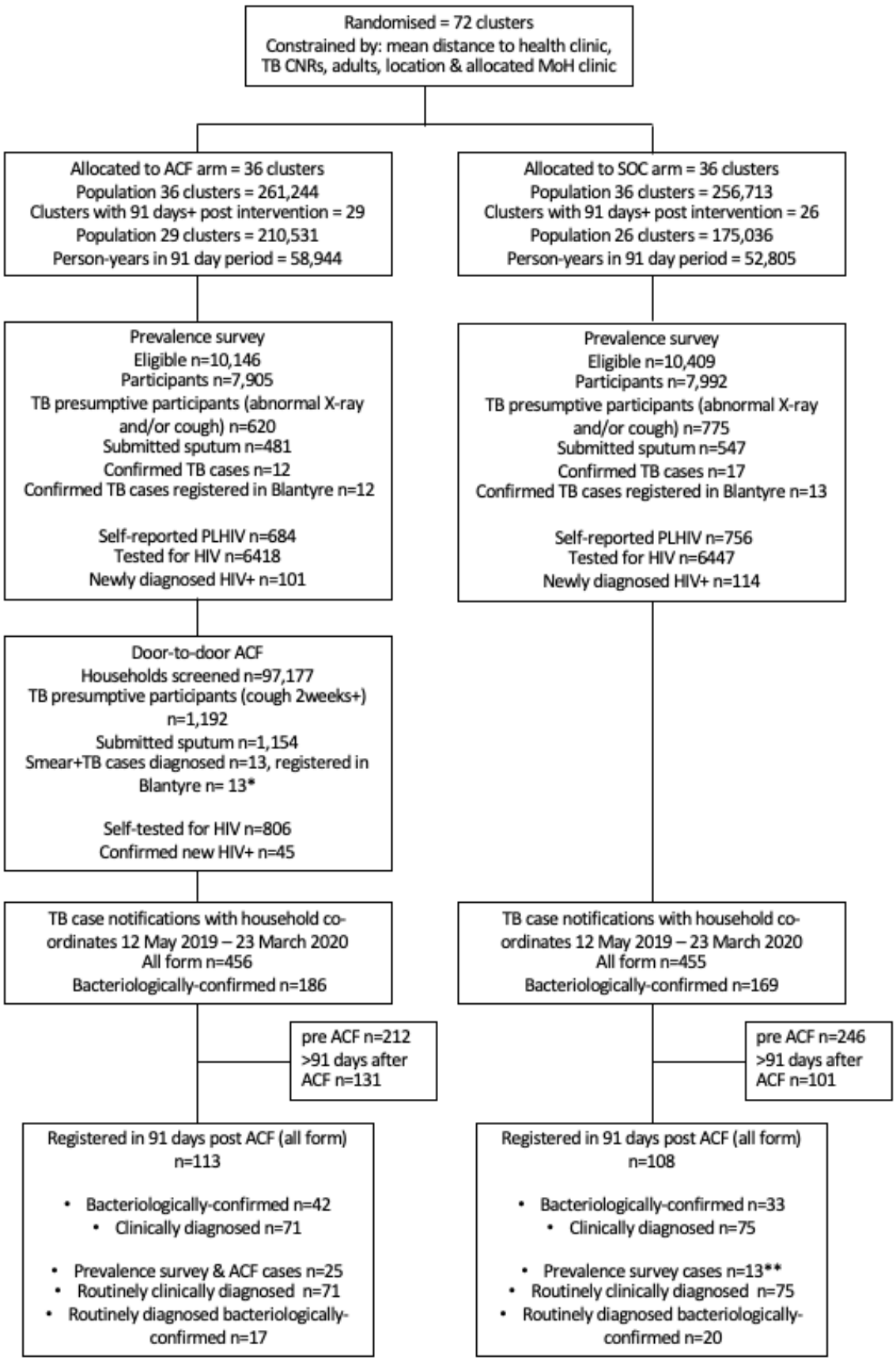
ACF intervention

Between 19 May 2019 and 14 March 2020 the door-to-door ACF intervention visited 97,177 households with 261,244 adult (15 years or older) residents. In total, 1,192 (0.5% (1,192/261,244) adults volunteered or were identified by household members as having chronic cough – substantially below the 3.4% of adults who reported cough of 2 weeks or longer on direct enquiry for symptoms in the pre-intervention prevalence survey (Table 1). Of these, 1,154 (96.8%) submitted sputum; 13/1,192 (1.1%) were smear positive (Figure 1). All participants were confirmed positive by Xpert and MGIT culture (Supplementary Table 2). The yield of the ACF intervention was therefore 5.0 new confirmed TB cases per 100,000 adult population.

During the study period, 1,475 adults aged 15 years or older registered for TB treatment through any diagnostic route at health facilities in urban Blantyre. Of these 911/1,475 (61.8%) were resident within SCALE clusters and had their household GPS co-ordinates recorded. 368/1,475 (25.0%) urban residents had no co-ordinates recorded (reason unknown) and of those with co-ordinates recorded, 196/1,475 (13.3%) were resident outside of SCALE clusters (i.e. lived in urban Blantyre, but not in a study cluster). Of these registering cases, 456/911 (50.1%) were resident in the ACF arm, (186 [40.8%] bacteriologically-confirmed), and 455/911 (49.9%) were resident in the SOC arm (169 [37.14%] bacteriologically confirmed) – Figure 1. In ACF clusters, 113 cases were registered in the 91 days after the start of the intervention (42 [37.2%]

316 bacteriologically-confirmed). For SOC clusters, 108 cases (with 33 [30.6%]
317 bacteriologically-confirmed) were registered in the same 91-day period.
318
319 Overall, across arms, of all cluster-residents registering for treatment for
320 bacteriologically-confirmed TB through any diagnostic route, 69.9% (248/355) were
321 male, 51.0% (181/355) were HIV positive (94.5% were taking ART), and mean age was
322 35 years (SD 12)
323
324 *Outcomes*
325 The case notification rate (CNR) for bacteriologically-confirmed TB registered through
326 any diagnostic route in the intervention arm during the 91 days after the start of the
327 intervention was 71.3 per 100,000 adults per year (42/58,944) and 62.5 per 100,000
328 adults per year in the SOC arm (33/52,805), giving an unadjusted rate ratio of 1.14
329 (95% CI: 0.72-1.80, p=0.58) – Table 2. The adjusted rate ratio was 1.12 (95% CI: 0.61-
330 2.07, p=0.71).
331
332 For the secondary outcome of all forms of TB, CNRs were 191.7 per 100,000 adults per
333 year in the ACF arm, and 204.5 per 100,000 adults in the SOC arm, with an adjusted
334 rate ratio of 0.93 (95% CI: 0.68-1.28, p=0.67) – Table 2. For routinely diagnosed all
335 forms of TB (excluding those detected by the prevalence survey and ACF
336 interventions), CNRs for the ACF arm and SOC arms were 149.3 per 100,000 adults per
337 year and 179.9 per 100,000 adults per year, respectively (adjusted rate ratio: 0.86,
338 95%CI: 0.63-1.16, p=0.33). Comparison of bacteriologically-confirmed routinely
339 diagnosed case notifications gave an adjusted CNR ratio of 0.73 (0.36-1.47, p=0.37).

340 **Figure 1 Consort diagram of trial participants**



341 *Of 13 ACF-identified smear+ TB cases 10 were HIV positive when registering for TB treatment

Table 2. Primary and secondary outcomes: TB case-notification rates (any diagnostic route) at 91 days*

Endpoint			Unadjusted			Adjusted**		
	ACF	SOC	Ratio+	95% CI	P-value	Ratio	95% CI	P-value
Adult CNRs (91 days)								
Bact-confirmed	42/58944†	33/52805	1.14	0.72-1.80	0.58	1.12	0.61-2.07	0.71
All TB registrations	113/58944	108/52805	0.94	0.72-1.22	0.63	0.93	0.68-1.28	0.67
All routinely diagnosed TB††	88/58944	95/52805	0.83	0.62-1.11	0.21	0.86	0.63-1.16	0.33
Other pre-set CNRs								
Bact-confirmed routinely diagnosed	17/58944	20/52805	0.76	0.40-1.45	0.41	0.73	0.36-1.47	0.37

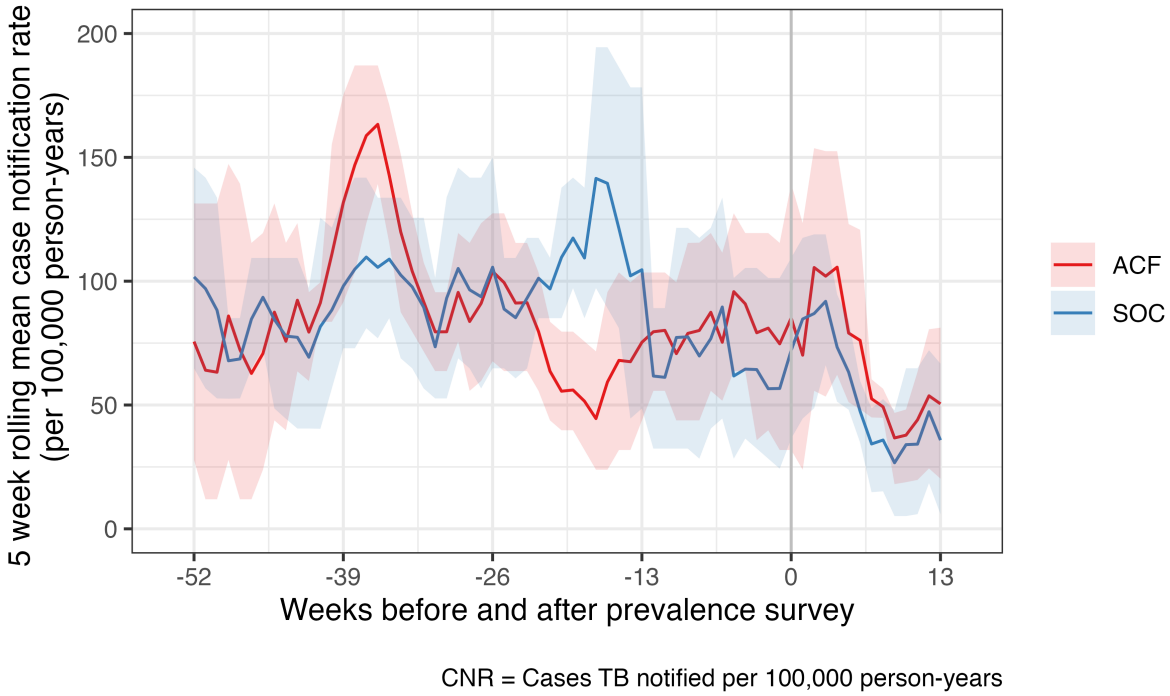
* CNR based on routine notification data using enhanced surveillance system (ePAL) for GPS data
+ Ratios obtained by fitting a negative binomial regression model to cluster-levels counts with the number of person years included as an offset.
** Adjusted for variables used to restrict randomisation: Previous CNR, number of adults, mean distance from cluster centres to the nearest health clinic, allocated health centre and longitude and latitude of cluster centre
† Number of notifications within 91 days / person-years follow-up
†† Routinely diagnosed TB excludes ACF and prevalence survey participants, aiming to measure "indirect effect" of ACF

Time trend analysis

In the period from 52 weeks before to 13 weeks after the intervention, the five-week rolling mean estimated annual bacteriologically-confirmed CNR varied from 36.6 (95% CI: 18.2 – 46.7) to 162.6 (95% CI: 135.4 - 187.1) per 100,000 adults in the ACF arm, and from 26.8 (95% CI: 5.2 – 46.5) to 141.3 (95% CI: 97.2 - 190.5) per 100,000 adult years in the SOC arm (Figure 2). Higher CNRs were observed among men (overall mean CNRs 105.9 [ACF arm] and 120.3 [SOC arm] per 100,000 person years) compared to women

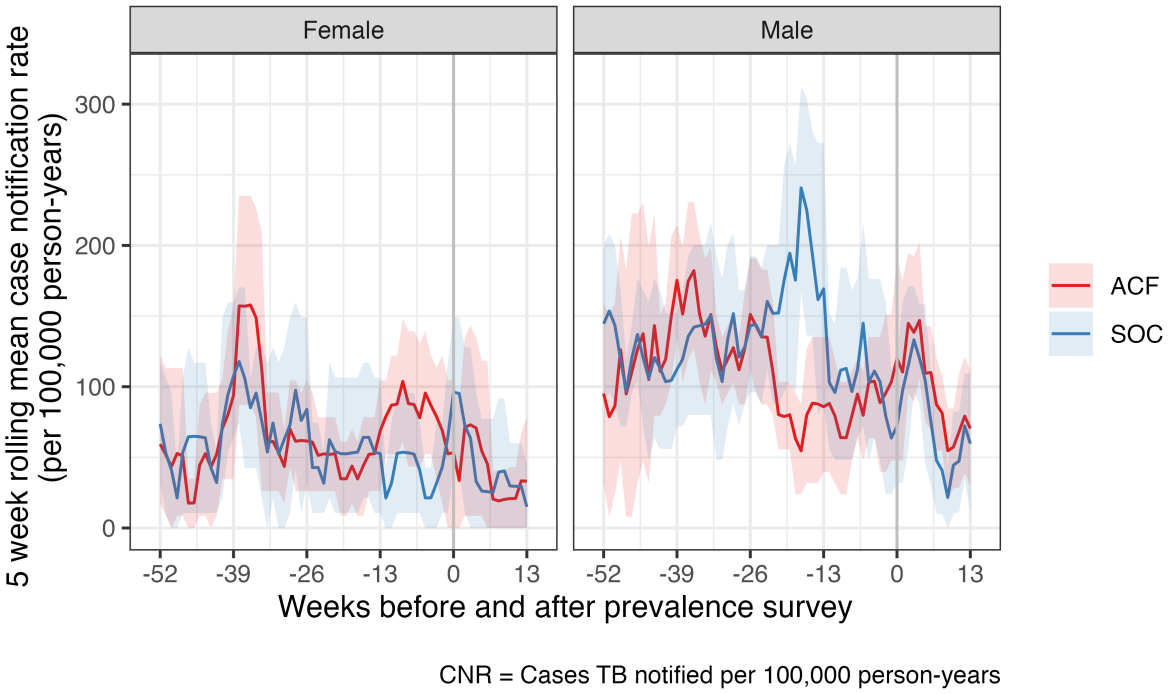
(overall mean CNRs 61.1 [ACF] and 55.6 [SOC] per 100,000 person years) during this period (Figure 3). Substantial week-to-week variation reflects small numbers of mean cases per arm per week. No overall time trends were observed for both bacteriologically-confirmed and all-forms of TB CNRs.

Figure 2 Rolling mean weekly case notification rate before and after prevalence survey



CNR = Cases TB notified per 100,000 person-years

Figure 3 Rolling mean weekly case notification rate before and after prevalence survey by sex

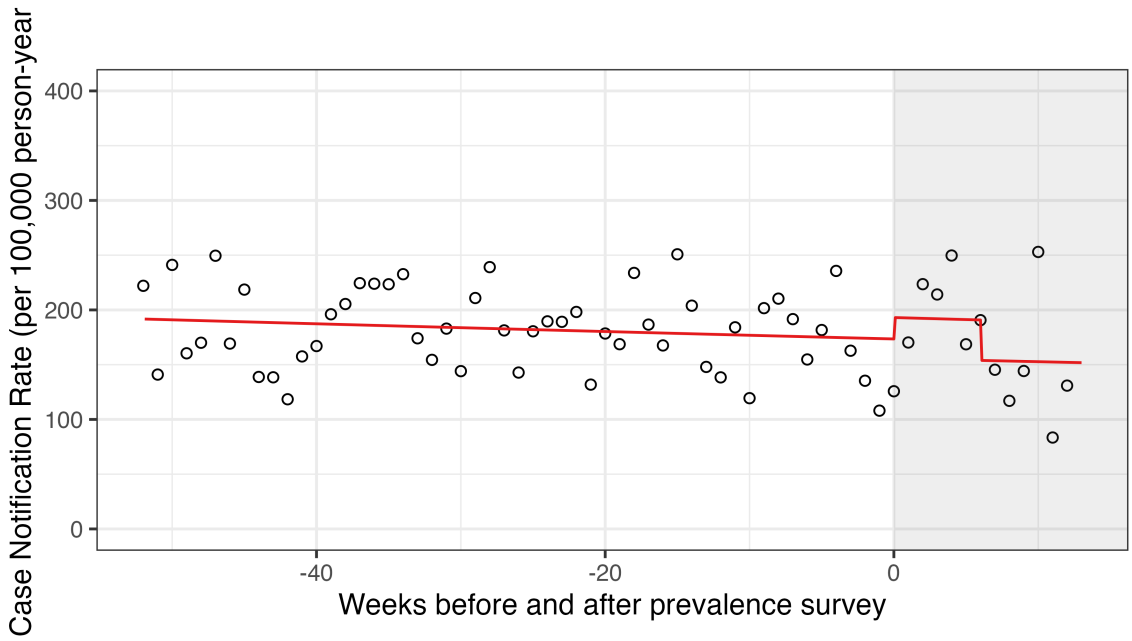


During the 52 weeks prior to the prevalence survey in the SOC clusters, 506 TB case notifications were recorded with GPS co-ordinates. In the 13 weeks after the prevalence survey started there were 109 notifications: 61 of these in the first 6 weeks and 48 in the subsequent 7 weeks. The mean weekly CNR pre-intervention was 186.5 (range 72.8-336.2) per 100,000 adult years before the intervention, 189.5 (range 108.4-287.0) per 100,000 adult years in the six weeks immediately after the survey started, and 163.5 (range 52.6-351.8) per 100,000 adult years in the subsequent 7 weeks.

The start of the prevalence survey was associated with a 4.9% (95% CI -20.5% to 38.5%, p-value =0.8) increase in TB notifications from cluster residents, which then

reduced to -9.2% (95% CI -33.5% to 23.8%), p-value=0.6) lower than the pre-intervention level after 6 weeks, until the end of the analysis period (Figure 4).

Figure 4 SOC arm case notification rate before and after prevalence survey



CNR = Cases TB notified per 100,000 person-years
Dots = observed case notification rate
Line = fitted model with both multiple step changes due to prevalence survey
Shaded area indicates time after prevalence survey

Discussion

In this cluster-randomised trial investigating the impact of ACF on case-notifications, we found no evidence of effectiveness of door-to-door enquiry for cough of 2 weeks or longer, an approach previously shown to increase case-notification rates when first implemented in the current trial setting of Blantyre, Malawi in 2011-14 [19] and in other African settings [18, 25]. The effectiveness of the intervention was likely limited by low participation and lower-than-expected prevalence. TB surveillance needs to diversify to allow programmes to track, adapt and better target interventions towards the remaining people with undiagnosed TB in a more precise and timely fashion. To achieve this, ACF interventions should have robust impact assessment, such as the geolocated case-notification approach used here, and future ACF in Blantyre should be more highly targeted to defined sub-populations such as working age men, as a complement to optimised health centre screening and laboratory strengthening.

Our ACF approach targeted symptomatic individuals as a less costly, but less sensitive, alternative to systematic screening regardless of symptoms, with targets based on population-level estimates of chronic cough. A critical limiting factor in SCALE, however, was low participation: only 17% of estimated ACF cluster residents with chronic cough submitted sputum, lower than for the same strategy in the same city in 2011-14 [19], despite undiagnosed infectious TB remaining well above TB elimination targets affecting 150-189 per 100,000 adults [17]. Declining ACF participation has been noted previously during prolonged or repeated implementation [15, 18] and may indicate community fatigue as ACF becomes less novel, or as TB becomes a less pressing community concern as true TB incidence and mortality rates fall. In addition,

since historical TB screening activity in Blantyre has often used a symptom screening approach similar to that used in this study, much of the TB responsive to this form of ACF (symptomatic or clinical) may have already been detected and the pool of undiagnosed people willing to participate in this type of intervention already depleted [26].

Undiagnosed infectious TB in Blantyre has been reduced from over 1,000 to 150-189 per 100,000 adults, associated with TB interventions focused on symptomatic disease, including ACF, decentralisation of TB diagnostic centres and more use of molecular diagnostics as well as scale up of HIV services. This decline is also reflected in decreasing case notifications and concurrent evidence of declining TB burden in primary care attendees [27, 28]. Blantyre is now below the threshold (500 per 100,000 adults) for which community-wide intervention is recommended [10], but remaining prevalence still suggests need for affordable and effective ways to focus case-detection, for example targeted spatially [29] or by target group [10], such as adult men, given their increased prevalence of undiagnosed TB [30].

ACF intensity can be increased by more systematic screening, more sensitive diagnostic algorithms based on molecular sputum tests and digital chest X-ray with computer-aided diagnostics (DCXR-CAD)[10, 31], or higher intensity intervention [9, 32]. High intensity ACF, notably annual sputum molecular testing, is effective [15, 33] but costly, and should only be considered in medium-burden settings when more efficient alternatives such as facility-based systematic screening [34, 35] and diagnostic cascades have been optimised [36] . Alternatively, national TB programmes in settings

444 such as Blantyre could start to explore community-led and peer-led approaches that
445 have been successfully used to target and obtain high participation by high-risk
446 populations for HIV testing, including men [37]. With potential for effective self-
447 sampling approaches, such as tongue swabs [38], programmes may have to choose
448 whether to maximise reach to previously untested high-risk individuals, at the cost of
449 sensitivity, or using more highly sensitive universal approaches in communities [15, 33]
450 despite the difficulties and cost of scale-up and maintenance [39].
451
452 To ensure we know which ACF approaches are the most effective we need to robustly
453 measure the impact of TB screening interventions, supported by digital technologies
454 such as the high-resolution surveillance of GPS locations of TB case notifications used
455 in SCALE. To our knowledge this is only the second published trial of ACF, after a study
456 by Miller et al in Brazilian favelas [40], to assess the impact on TB case notifications in
457 the period after – instead of only during – intervention implementation. In other
458 studies using impact of TB case-notifications as the outcome the time period of
459 analysis is the overall calendar period for the ACF intervention implementation even
460 though the interventions cover a large area and are usually implemented in a
461 staggered fashion [9]. Whether randomised controlled trials, before-after studies
462 (where the comparison is just over time) or controlled before-after (with a parallel
463 control group) studies they examine the impact during rather than after the ACF. Our
464 enhanced surveillance system, however, enabled us to identify the timing of each case
465 notification relative to when the ACF was conducted in that residential cluster,
466 providing the temporal component needed for casual inference. To strengthen

evidence generated, future trials should have robust assessment methodologies and report outcomes relative to the dates of the ACF intervention in that specific area.

We found no significant impact of the ACF intervention or community TB prevalence survey (which is also a form of ACF, since it aimed to identify undiagnosed TB) on TB case-notifications. Our analysis of time trends suggests that there may have been a small peak in TB case notification rate after the intervention/prevalence survey in both arms followed by a dip, as would be expected with the substitution effect, whereby patients who would otherwise have been diagnosed routinely during the intervention period and immediately afterwards are instead found though ACF [12].

Routine facility-based TB case notifications also showed no indication of any indirect effect (such as health promotion) during ACF. This result does not preclude an indirect impact though, as this could be masked by the substitution effect, but other outcome evaluations (TB testing, TB knowledge, attitudes and perceptions, qualitative research) are needed to identify if this occurs and future interventions should continue to monitor any indirect effects [10]. This lack of observed impact could also reflect previous ACF interventions having met the accumulated demand [41] and a subsequent lack of novelty for targeted populations.

Regardless of future ACF intervention choices, current TB surveillance is not providing the richness and timeliness of data needed to enable many national programmes to evaluate impact, change strategy as and when needed as local TB epidemics become

491 increasingly concentrated [26]. Surveys of TB immunoreactivity were used for
492 surveillance of TB epidemics [42], and could be reintroduced with newer tests [43].
493 National programmes in countries lacking formal address systems can consider digital
494 clinic-based systems such as those in SCALE to provide sufficiently precise
495 spatiotemporal resolution of diagnosed TB patients to evaluate geographically-
496 targeted ACF interventions from TB registration clinics. Extending these systems to TB
497 testing, tracking positivity, and including questions on TB testing in Demographic
498 Health Surveys would, first, allow underserved communities to be identified for ACF,
499 ideally with simultaneous investment into strengthening routine services, and,
500 secondly, provide guidance for when to stop.
501
502 Limitations of the study include the lower than anticipated prevalence, reduced
503 intervention intensity (one instead of three rounds) and reduced data available due to
504 censoring from March 2020 due to the impact of COVID-19. In addition, 25% of
505 Blantyre-resident TB case-notifications during the relevant period had no co-ordinates
506 recorded in our digital TB system (ePAL), a potential cause of ascertainment bias. It is
507 also possible that the enhanced standard of care provided by the study clinic assistants
508 at all primary facilities within Blantyre could have increased TB testing, and hence,
509 caused the small increase in case notifications corresponding to our prevalence survey
510 and intervention. We consider this unlikely, however, as facilities were staffed by study
511 clinic assistants for more than 91 days before the start of the intervention in 56 of 72
512 clusters. Linkage to care and treatment was high though at 100% of those remaining
513 within Blantyre City.
514

Conclusions

Community-wide ACF can lead to substantial and rapid declines in TB burden following initial deployment in settings with high undiagnosed TB burdens, but well-implemented ACF interventions can fail to impact underlying TB epidemiology for a variety of reasons. Here we show evidence of diminishing returns and no remaining epidemiological impact from a previously effective ACF strategy in a high HIV prevalence city following several years of ACF and rapid declines in TB burden. In such settings, choices now lie between greatly increasing investment to provide highly sensitive screening to every individual or instead changing focus to targeted outreach and demand creation, alongside optimised facility-based and TB contact screening. Our data also show need for routine surveillance systems more attuned to rapidly changing TB epidemiology to meet TB elimination goals by 2035.

References

1. World Health Organization. Global Tuberculosis Report 2022. 2022.
2. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G. Tuberculosis and HIV co-infection. PLoS Pathog. 2012;8(2):e1002464.
3. World Health Organization. Key facts HIV. 2022.
4. Joint United Nations Programme on HIV/AIDS (UNAIDS). Ending AIDS, Progress towards the 90-90-90 targets; Global AIDS update 2017. 2017.
5. Soko RN, Burke RM, Feasey HRA, Sibande W, Nliwasa M, Henrion MYR, et al. Effects of Coronavirus Disease Pandemic on Tuberculosis Notifications, Malawi. Emerg Infect Dis. 2021;27(7):1831-9.
6. Arega B, Negesso A, Taye B, Weldeyohhans G, Bewket B, Negussie T, et al. Impact of COVID-19 pandemic on TB prevention and care in Addis Ababa, Ethiopia: a retrospective database study. BMJ Open. 2022;12(2):e053290.
7. World Health Organisation. The End TB Strategy. 2015.
8. Ku C-C, MacPherson P, Khundi M, Nzawa Soko RH, Feasey HRA, Nliwasa M, et al. Durations of asymptomatic, symptomatic, and care-seeking phases of tuberculosis disease with a Bayesian analysis of prevalence survey and notification data. BMC Medicine. 2021;19(1):298.
9. Burke RM, Nliwasa M, Feasey HRA, Chaisson LH, Golub JE, Naufal F, et al. Community-based active case-finding interventions for tuberculosis: a systematic review. Lancet Public Health. 2021.
10. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease. 2021.
11. Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. Int J Tuberc Lung Dis. 2005;9(11):1183-203.
12. Feasey HRA, Burke RM, Nliwasa M, Chaisson LH, Golub JE, Naufal F, et al. Do community-based active case-finding interventions have indirect impacts on wider TB case detection and determinants of subsequent TB testing behaviour? A systematic review. PLOS Global Public Health. 2021;1(12):e0000088.
13. World Health Organization. Systematic screening for active tuberculosis. Principles and recommendations. 2013.
14. Ayles H, Muyoyeta M, Du Toit E, Schaap A, Floyd S, Simwinga M, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. Lancet. 2013;382(9899):1183-94.
15. Marks GB, Nguyen NV, Nguyen PTB, Nguyen TA, Nguyen HB, Tran KH, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. N Engl J Med. 2019;381(14):1347-57.
16. World Health Organization. National Tuberculosis Prevalence Surveys 2007-2016. 2021.
17. Feasey HRA, Khundi M, Soko RN, Nightingale E, Burke RM, Henrion MYR, et al. Prevalence of Bacteriologically-Confirmed Tuberculosis in Urban Blantyre, Malawi 2019-20: Substantial Decline Compared to 2013-14 National Survey. medRxiv. 2023:2023.04.20.23288872.

18. Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): A cluster-randomised trial. The Lancet. 2010;376(9748):1244-53.
19. Burke RMN, M.; Dodd, P. J.; Feasey, H. R. A.; Khundi, M.; Choko, A.; Nzawa-Soko, R.; Mpunga, J.; Webb, E. L.; Fielding K.; MacPherson P.; Corbett E. L. Impact of community-wide tuberculosis active case finding and HIV testing on tuberculosis trends in Malawi. Clinical Infectious Diseases. 2023.
20. Banda R. Results from the national TB prevalence survey of Malaw In: 45th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease. Barcelona. 2014.
21. National Statistical Office (NSO). 2018 Malawi Population and Housing Census Main Report.
22. MacPherson P, Khundi M, Nliwasa M, Choko AT, Phiri VK, Webb EL, et al. Disparities in access to diagnosis and care in Blantyre, Malawi, identified through enhanced tuberculosis surveillance and spatial analysis. BMC Medicine. 2019;17(1):21.
23. MacPherson P, Choko AT, Webb EL, Thindwa D, Squire SB, Sambakunsi R, et al. Development and validation of a global positioning system-based "map book" system for categorizing cluster residency status of community members living in high-density urban slums in Blantyre, Malawi. Am J Epidemiol. 2013;177(10):1143-7.
24. Bottomley C, Scott JAG, Isham V. Analysing Interrupted Time Series with a Control. Epidemiologic Methods. 2019;8(1).
25. Yassin MA, Datiko DG, Tulloch O, Markos P, Aschalew M, Shargie EB, et al. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. PLoS One. 2013;8(5):e63174.
26. Yaesoubi R, Cohen T. Identifying dynamic tuberculosis case-finding policies for HIV/TB coepidemics. Proceedings of the National Academy of Sciences. 2013;110(23):9457-62.
27. MacPherson P, Webb EL, Kamchedzera W, Joekes E, Mjoli G, Lalloo DG, et al. Computer-aided X-ray screening for tuberculosis and HIV testing among adults with cough in Malawi (the PROSPECT study): A randomised trial and cost-effectiveness analysis. PLoS Med. 2021;18(9):e1003752.
28. Divala TH, Fielding KL, Kandulu C, Nliwasa M, Sloan DJ, Gupta-Wright A, et al. Utility of broad-spectrum antibiotics for diagnosing pulmonary tuberculosis in adults: a systematic review and meta-analysis. Lancet Infect Dis. 2020;20(9):1089-98.
29. Khundi M, Carpenter JR, Nliwasa M, Cohen T, Corbett EL, MacPherson P. Effectiveness of spatially targeted interventions for control of HIV, tuberculosis, leprosy and malaria: a systematic review. BMJ Open. 2021;11(7):e044715.
30. Horton KC, MacPherson P, Houben RM, White RG, Corbett EL. Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. PLoS Med. 2016;13(9):e1002119.
31. Moodley N, Velen K, Saimen A, Zakhura N, Churchyard G, Charalambous S. Digital Chest Radiography Enhances Screening Efficiency for Pulmonary Tuberculosis in Primary Health Clinics in South Africa. Clin Infect Dis. 2022;74(9):1650-8.
32. Dodd PJ, White RG, Corbett EL. Periodic Active Case Finding for TB: When to Look? PLOS ONE. 2011;6(12):e29130.

33. Kendall EA, Kitonsa PJ, Nalutaaya A, Robsky KO, Erisa KC, Mukiibi J, et al. Decline in prevalence of tuberculosis following an intensive case-finding campaign and the COVID-19 pandemic in an urban Ugandan community. medRxiv. 2023:2023.03.03.23286745.
34. Hanrahan CF, Nonyane BAS, Mmolawa L, West NS, Siwelana T, Lebina L, et al. Contact tracing versus facility-based screening for active TB case finding in rural South Africa: A pragmatic cluster-randomized trial (Kharitode TB). PLoS Med. 2019;16(4):e1002796.
35. Shapiro AE, Chakravorty R, Akande T, Lonnroth K, Golub JE. A systematic review of the number needed to screen to detect a case of active tuberculosis in different risk groups. World Health Organization. 2013:86.
36. Feasey HRA, Corbett EL, Nliwasa M, Mair L, Divala TH, Kamchedzera W, et al. Tuberculosis diagnosis cascade in Blantyre, Malawi: a prospective cohort study. BMC Infect Dis. 2021;21(1):178.
37. Indravudh PP, Fielding K, Chilongosi R, Nzawa R, Neuman M, Kumwenda MK, et al. Effect of door-to-door distribution of HIV self-testing kits on HIV testing and antiretroviral therapy initiation: a cluster randomised trial in Malawi. BMJ Glob Health. 2021;6(Suppl 4).
38. Wood RC, Andama A, Hermansky G, Burkot S, Asege L, Job M, et al. Characterization of oral swab samples for diagnosis of pulmonary tuberculosis. PLoS One. 2021;16(5):e0251422.
39. Sohn H, Sweeney S, Mudzengi D, Creswell J, Menzies NA, Fox GJ, et al. Determining the value of TB active case-finding: current evidence and methodological considerations. Int J Tuberc Lung Dis. 2021;25(3):171-81.
40. Miller AC, Golub JE, Cavalcante SC, Durovni B, Moulton LH, Fonseca Z, et al. Controlled trial of active tuberculosis case finding in a Brazilian favela. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2010;14(6):720-6.
41. MacPherson PW, E.; Choko, A.; Nliwasa, M.; Mdolo, A.; Chiume, L.; Corbett, E. Pre and post-intervention prevalence surveys will be conducted to establish whether the ACF leads to a reduction in TB prevalence World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union); Cape Town. South Africa2015.
42. Rieder HL, Chadha VK, Nagelkerke NJ, van Leth F, van der Werf MJ. Guidelines for conducting tuberculin skin test surveys in high-prevalence countries. Int J Tuberc Lung Dis. 2011;15 Suppl 1:S1-25.
43. Hamada Y, Cirillo DM, Matteelli A, Penn-Nicholson A, Rangaka MX, Ruhwald M. Tests for tuberculosis infection: landscape analysis. Eur Respir J. 2021;58(5).

Supplementary Table 1: Clinical and microbiological characteristics of confirmed TB cases from pre-intervention prevalence survey

Characteristics				Symptom screening						X-ray	Sputum results			
Sex	Age	HIV status	Previous TB?	Cough	Chronic cough	Night sweats	Weight loss	Fever	Any TB symptoms	Chest X-ray	Smear	Xpert	Culture result	Culture ID
Male	45	HIV negative	No	Yes	Yes	Yes	Yes	Yes	Yes	Abnormal	Negative	Positive	Negative	ND
Female	32	HIV positive	No	Yes	No	No	No	No	Yes	Normal	Negative	Negative	Positive	MTB
Female	34	HIV positive ART	No	Yes	Yes	Yes	Yes	No	Yes	Abnormal	Negative	Positive	Positive	MTB
Female	29	HIV negative	No	Yes	Yes	No	No	No	Yes	-	Negative	Positive	Positive	MTB
Male	25	HIV negative	No	Yes	Yes	No	No	No	Yes	Abnormal	Negative	Positive	Positive	MTB
Female	19	HIV negative	No	Yes	Yes	No	No	No	Yes	Abnormal	Positive	Positive	Positive	MTB
Female	26	HIV negative	No	Yes	Yes	No	No	Yes	Yes	Abnormal	Positive	Positive	Positive	MTB
Female	22	HIV negative	No	Yes	No	No	No	No	Yes	Normal	Negative	Negative	Positive	MTB
Male	33	HIV negative	Yes	Yes	No	Yes	No	Yes	Yes	Abnormal	Positive	Positive	Positive	MTB
Male	19	HIV negative	No	Yes	No	No	No	No	Yes	Abnormal	Negative	Negative	Positive	MTB
Male	56	HIV positive ART	No	Yes	Yes	No	No	Yes	Yes	Normal	Positive	Positive	Positive	MTB
Male	45	HIV positive ART	No	Yes	Yes	No	No	No	Yes	Abnormal	Negative	Positive	Negative	ND
Male	40	HIV negative	Yes	Yes	Yes	No	No	No	Yes	Normal	Positive	Positive	Positive	MTB
Female	61	HIV negative	No	No	No	No	No	No	No	Abnormal	Negative	Positive	Positive	MTB
Female	89	HIV negative	No	No	No	No	No	No	No	Abnormal	Negative	Positive	Negative	ND
Male	27	HIV negative	Yes	No	No	No	No	Yes	Yes	Abnormal	Negative	Positive	Contaminated	ND
Male	27	HIV negative	No	No	No	No	No	No	No	Abnormal	Negative	Negative	Positive	MTB
Male	33	HIV negative	Yes	No	No	No	No	No	No	Abnormal	Negative	Negative	Positive	MTB
Male	43	HIV negative	No	No	No	No	No	Yes	Yes	Abnormal	Negative	Positive	Positive	MTB
Male	30	HIV negative	No	No	No	Yes	No	No	Yes	Abnormal	Positive	Positive	Positive	MTB
Female	38	HIV negative	No	No	No	No	No	No	No	Abnormal	Negative	Negative	Positive	MTB
Male	30	HIV negative	No	No	No	Yes	No	Yes	Yes	Abnormal	Negative	Positive	Negative	ND
Female	19	HIV negative	No	No	No	No	No	No	No	-	Negative	Negative	Positive	MTB
Male	44	HIV negative	No	No	No	No	No	No	No	Normal	Positive	Positive	Positive	MTB
Male	36	HIV negative	No	No	No	Yes	No	No	Yes	Normal	Negative	Positive	Negative	ND
Male	54	HIV negative	No	No	No	No	No	No	No	Abnormal	Negative	Negative	Positive	MTB
Female	37	HIV positive ART	No	No	No	No	No	No	No	Abnormal	Negative	Positive	Positive	MTB
Male	22	HIV negative	No	No	No	No	No	No	No	Abnormal	Positive	Positive	Negative	ND

Supplementary Table 2: Demographic and microbiological characteristics of confirmed TB cases from ACF intervention

Demographics		Initial results				Confirmatory results				
Sex	Age	Smear 1		Smear 2		Smear		GeneXpert		Culture
Male	47	Negative	No AAFB	Positive	1+ AAFB	Negative	No AAFB	Positive	Very low	MTB
Male	38	Positive	3+ AAFB	Positive	3+ AAFB	Positive	3+ AAFB	Positive	High	MTB
Male	37	Positive	3+ AAFB	Positive	2+ AAFB	Positive	Scanty AAFB	Positive	Very low	MTB
Female	42	Positive	3+ AAFB	Positive	3+ AAFB	Positive	3+ AAFB	Positive	Medium	MTB
Female	56	Positive	3+ AAFB	Positive	3+ AAFB	Positive	3+ AAFB	Positive	High	MTB
Male	26	Positive	3+ AAFB	Positive	3+ AAFB	Positive	1+ AAFB	Positive	Very low	MTB
Male	53	Positive	3+ AAFB	-	-	Positive	3+ AAFB	Positive	Medium	MTB
Male	41	Positive	3+ AAFB	Positive	3+ AAFB	Positive	3+ AAFB	Positive	Medium	MTB
Male	34	Positive	Scanty AAFB	Positive	Scanty AAFB	Positive	Scanty AAFB	Positive	Low	MTB
Male	35	Negative	No AAFB	Positive	Scanty AAFB	Negative	No AAFB	Negative	Not detected	MTB
Female	38	Positive	2+ AAFB	Positive	2+ AAFB	Positive	2+ AAFB	Positive	Medium	MTB
Male	42	Positive	1+ AAFB	Positive	Scanty AAFB	Positive	1+ AAFB	Positive	Low	MTB
Female	31	Positive	3+ AAFB	Positive	3+ AAFB	Positive	3+ AAFB	Positive	Medium	MTB

AAFB = Acid-alcohol-fast-bacilli , number (e.g. 3+) indicates number of bacilli seen
MTB=Mycobacterium Tuberculosis detected
Note: All ACF participants reported a cough of two weeks or more

Chapter 7

Discussion

7.1 Summary of research

The research presented in this thesis provides new evidence to inform future case-finding strategies and improve access to TB diagnosis both in Blantyre and similar high HIV-prevalence, urban locations in low-and-middle income countries.

The studies on the facility-based TB diagnosis cascade (Chapter 3) and community prevalence of undiagnosed TB (Chapter 4) demonstrate the local context: an environment where previous case-finding activities and improvements in HIV management have likely led to a substantial decline in TB prevalence, despite ongoing sub-optimal case-finding in facilities. Although there could be indirect effects of community-based ACF, such as from health promotion, my systematic review (Chapter 5) found a lack of current evidence for this and no additional supporting evidence was found in the SCALE trial. SCALE (Chapter 6) showed no remaining impact of a previously successful door-to-door ACF approach, likely due to the rapid declines in TB burden demonstrated by the prevalence survey and low rates of participation in the ACF, consistent with diminishing interest after a period of repeated TB case-finding activities. In settings such as Blantyre, choices now lie between greatly increasing investment to provide highly sensitive screening to every individual or instead changing focus, at least for the time being, to targeted outreach and demand creation, alongside optimised facility-based and TB household screening. Ideally, changes in case-finding would be accompanied by a suitable surveillance strategy able to provide indicators of when a switch back to community-wide ACF might be once again be needed.

The TB prevalence survey estimate for Blantyre city of 150–189 per 100,000 in 2019-20 (Chapter 4) was more than 80% lower than previous estimates from the 2013-14 Malawi National Prevalence survey of 1,016 per 100,000 in urban adults [1]. This is likely due to the combined effects of previous ACF efforts in Blantyre, and the rapid scale up of HIV testing and treatment services to reach high coverage of ART treatment for people living with HIV (PLHIV) [2]. Our 2019-20 survey, however, showed that undiagnosed TB prevalence remained higher amongst men, PLHIV, and those reporting previous TB, as well as among people aged 50 years and over. Continued investment in targeted case-finding amongst these groups is required to meet the EndTB goals. As is typical for TB prevalence surveys, more than half of survey participants (52%) diagnosed with active pulmonary TB disease, had subclinical TB that would not have been identified through the symptom screen alone. These data provide evidence to inform future local, adaptive, targeted case-finding strategies.

The substantial decline in local TB burden has been achieved despite sub-optimal facility-based case-finding, demonstrated in my assessment of the local TB diagnosis cascade (Chapter 3). Same-day sputum submission for TB testing following all steps of the diagnosis cascade was achieved in only 4.7% of those clinically indicated in the Malawi national guidelines, with patients lost at every stage of the TB diagnosis cascade. Requesting sputum after eliciting symptoms is the key point of the cascade to intervene, since failure to do so led to the biggest single gap in the diagnosis cascade. TB screening guidelines should be optimised, including giving important epidemiological groups such as men similar priority to PLHIV, and interventions to increase guideline adherence implemented. However, if guideline adherence is improved, novel high-throughput triage testing approaches will also be needed to reach the required capacity for same-day diagnosis at primary health clinics. There is clearly potential to reach many of the remaining undiagnosed people with TB through optimised facility-based case-finding .

My systematic review, presented in Chapter 5, synthesised evidence on the potential indirect impact of TB active case-finding interventions on routine TB case-notifications and subsequent TB testing behaviour. I found the currently available literature to be insufficient, providing only weak evidence for an indirect effect of ACF on clinically diagnosed routine TB case-notifications with insufficient quantitative evidence to assess whether or not ACF impacts subsequent TB testing behaviour. The few available data suggest that ACF can increase TB knowledge and intention to seek early TB diagnosis, which together with a desire for a diagnosis and resolution in those with negative bacteriological ACF results, could impact on future TB testing and case-detection rates. This important evidence gap can be filled by providing better

guidance to encourage routinely implementing teams to document indirect as well as direct notifications, coinciding in time and place with ACF, and guidance on how to conduct and analyse the relevant qualitative and quantitative sub-studies alongside ACF in future intervention studies.

The SCALE cluster-randomised trial (Chapter 6) of door-to-door community-based ACF found no quantitative direct or indirect impact of ACF on TB case-notifications, despite using a previously successful approach, with effectiveness of the intervention likely limited by low participation and lower-than-expected prevalence of undiagnosed TB. The geolocation case-notification approach used here provided robust assessment and could help TB programmes track, adapt and better target interventions towards the remaining people with undiagnosed TB in a more precise and timely fashion. Although highly-sensitive universal TB screening approaches have been shown to be effective elsewhere [3], the required investment may not be justified in Blantyre, where instead future ACF should focus on highly targeted outreach and demand creation to defined sub-populations such as working age men. This should be implemented as a complement to the optimised facility screening and diagnostic capacity strengthening recommended by the facility-based TB diagnosis cascade analysis.

7.2 Implications for policy and implementation

As detailed below, my research has had demonstrable implications for future policy and practice for the Malawi National TB Programme (NTP) as well as international TB case-finding policy and recommendations.

Most clearly, my systematic review identifying the lack of data regarding indirect effects of TB ACF informed the updated 2021 WHO guidelines on TB screening, with indirect effects of ACF identified as a significant research gap [4]. These WHO guidelines recommend studies of screening interventions should incorporate both qualitative and quantitative assessment of the indirect effects of screening, given the importance of health-seeking behaviour in TB care engagement and the potential impact of population-wide screening to change it.

The Malawi NTP guidelines are currently being updated, and will now include greater emphasis on the need for interventions able to reach and diagnose men and updated national recommendations for case-finding interventions. Men can be targeted both through adding them as a designated priority epidemiological group to facility screening guidelines, and through ACF interventions designed specifically to maximise reach to men. My prevalence survey results have contributed clear evidence that there is still a disproportionate burden of undiagnosed

TB in men, despite declining TB case-notification rates. This adds to a considerable body of complementary data from colleagues in MLW and London School, with past projects and an ongoing FCDO project (LIGHT) in MLW, Malawi, aiming to provide new evidence on the effectiveness of different approaches for reaching men with TB and HIV interventions in urban, HIV-prevalent settings [4].

The new Malawi NTP guidelines will also reflect updated WHO guidance on which communities to conduct general ACF within – which changed from communities with a prevalence greater than 1% (or 1000 per 100,000 population) in the 2013 guidelines to 0.5% in 2021 [5]. This decision was informed by the new systematic review of the effectiveness of ACF [6], which I contributed to. The SCALE trial is also likely to be included in any future systematic reviews and thus shape future recommendations on how and where to conduct ACF. Now that the extent of decline of undiagnosed TB prevalence in Blantyre, to 150 per 100,000 from the SCALE prevalence survey is known, and the clear negative finding of the SCALE trial reported here, generalised ACF is no longer appropriate in Blantyre. Instead, more targeted activities are required in future, which is likely to be reflected in NTP guidelines and policy. Given the importance of men and the ongoing LIGHT project, which is working with the Malawi Ministry of Gender and other stakeholders as well as NTP to assess gender-sensitive ACF strategies, the new NTP Guidelines are likely to include recommendations to evaluate, implement and scale up case-finding strategies targeted to men.

Case notification rates have been declining in Blantyre and Malawi over the last 10 years but it took the prevalence survey reported here to distinguish between the two possible causes of this – either routine services becoming less effective – thereby reducing the case-detection rate - or a genuine fall in the TB epidemiological burden. The prevalence survey also demonstrates the rapidly changing TB and HIV epidemiology in Malawi, highlighting the need for timely subdistrict surveillance. Following this demonstration, the NTP is intending to introduce an adaptation of the electronic geolocation surveillance system used for my project into other priority areas across Malawi. More effective subdistrict surveillance and other investments are required to build on previous successes in order to eliminate TB in Malawi and meet the EndTB goals.

7.3 Recommendations for future work

7.3.1 Optimising facility-based screening

Facility-based case-finding, through either passive case-finding or systematic screening, has been a cornerstone of WHO recommendations to reach and diagnose those with TB since 1974 [7]. However, this straightforward approach is still not being applied to its full potential in Malawi, leading to many missed opportunities for TB testing and likely substantial under diagnosis. WHO recommends systematic screening for TB disease may be conducted among people with a risk factor for TB who are either seeking health care or who are already in care, in settings where the TB prevalence in the general population is 100 per 100,000 population or higher [5]. Following this I would recommend that all outpatient clinic attendees in Blantyre who have one or more of the following characteristics should be systematically screened for TB (with DXR if available and otherwise symptom screens): male, aged over 50, PLHIV or have had previous TB.

Facility-based screening is technically less challenging to implement for a number of reasons. In facility-based testing participants are actively seeking care so are unlikely to decline to participate in symptom screening and testing. In addition, since resources such as clinical expertise, laboratory facilities and potentially X-ray machines, are already located in the facility, testing can be brought much closer to the point of care, and linkage to care is also easier to achieve than in community-based ACF. In addition, the prevalence of TB disease is higher in those attending health facilities than the general population [8]. Consequently, higher yields are seen in facility-based than community-based case-finding interventions, making them more likely to be cost-effective [9]. We should therefore ensure that facility-based testing is working optimally - both diagnostic enquiry amongst acute care clinic attendees and screening in HIV clinics - as a first priority before focusing on community-based case finding. Supporting this, one of the clear lessons from active case-finding studies in low-income settings in the 1980s was it is incongruous to provide more sophisticated TB diagnostic services as part of community ACF than are available at clinic-level [10, 11].

Once all high-risk groups are appropriately highlighted in guidelines and policy, pathways to diagnosis and care should be established and interventions developed with NTP to increase adherence to guidelines after first identifying the relevant barriers and enablers. This research is vital to understand the reasons behind the widely acknowledged ‘know-do gap’ in TB, and how this can be addressed [12]. The interventions can then be trialled and subsequent quality of care delivery assessed through further entry and exit interview cohorts or the use of

standardised patients [13].

In my facility-based study, I also identified a lack of laboratory diagnostic capacity as a critical bottleneck to full scale up of existing recommendations. If guideline adherence increases and all those clinically-indicated to provide sputum for a TB test do so, there is currently insufficient Xpert testing capacity in Blantyre to process all these samples. Additional resources should therefore be allocated to securing investment for high capacity Xpert machines.

To increase yields from facility-based case finding further and identify those with subclinical TB (approximately 50% of those with TB disease [14]) the NTP could locate their available digital X-rays in health clinics instead of mobile vans. Digital X-rays with CAD could then be properly incorporated into the screening algorithm with for example, all men attending outpatient clinics (high-risk group who rarely attend clinics) receiving a chest X-ray screen (see Table 1). This digital CXR CAD could be used for triage for both TB and other diseases (such as cardiomegaly) and has the significant advantage of capturing those with subclinical TB who would otherwise be missed with a symptom screen.

People previously diagnosed with TB are another high-risk group who should receive targeted screening. At present once someone in Malawi, or indeed the UK, successfully completes TB treatment they are 'discharged' with no further contact but this could be changed to a systematic screening system. A 12-monthly review clinic with digital CXR, symptom screen and molecular tests for all patients, would effectively screen this high-risk group (Table 7.1). However, since digital X-ray and CAD have lower specificity amongst those who have had previous treatment [15], review of change from previous X-rays should be used to reveal progression, and since molecular tests can also remain positive for many years after cure [16], potential for false positives should be considered. Mouth swab or face mask sampling would mean even those who cannot produce sputum can still receive a molecular test. These return screening visits could also enable assessment and treatment of post-TB lung disease – the extent of which has recently started to be revealed [17].

7.3.2 Targeted active case-finding (ACF) in the community

As TB prevalence declines, TB ACF approaches need to be more targeted in order to cost-effectively reach those remaining people with undiagnosed TB. TB prevalence in Blantyre is now below the 0.5% (or 500 per 100,000 population) recommended by the WHO for ACF in the general population [5] so future ACF should be targeted at high-risk groups or location hotspots, with higher yield reported from ACF targeted at high-risk populations [8]. Surveil-

lance and prevalence surveys can identify these high-risk groups and, if geospatial data is available, location hotspots as well. Working age to older men are identified as a key high-risk group in Blantyre, who have been underserved by previous ACF approaches.

ACF can be targeted at men through choice of venue (e.g. workplace or sports club), timing (e.g. outside working hours) and male-friendly practices (e.g. peer-delivery). Venues where men congregate include workplaces such as factories, building sites and minibus stations, leisure venues like sports clubs or bars, and lifestyle sites like churches and barbershops. Barbershops have successfully been used as venues for health promotion targeting African-American men for cancer, diabetes and HIV prevention [18, 19], and as distribution points for condoms [20]. Female beauty salons have similarly supported contraceptive distribution in South Africa [21]. Venues like barbers could be combined with peer-delivery and community-based outreach approaches, such as those successfully used to deliver HIV self-testing [22]. Peer delivery would likely reduce the technical knowledge and ability of those delivering the intervention, so using new, more straightforward sample collection methods, such as mouth swabs [23, 24], would be particularly applicable. However, unlike HIV self-testing, sample transportation to laboratories for running diagnostic tests would still be required, so a robust system for this linkage to laboratories and then into care, where applicable, would be vital.

Different ACF implementation options offer varying screening algorithm sensitivity and require different levels of resource. Universal testing approaches, such as that used by ACT3 in Vietnam [3], are highly sensitive, identifying both subclinical and clinical TB disease, but very resource intensive. Molecular tests can be offered to all, irrespective of symptoms but this results in high numbers of tests being run and therefore substantial resource investment (Table 7.1 compares likely yield and resources required of different case-finding methods).

An alternative option is universal screening with X-rays and CAD, followed by diagnostic tests for those with abnormal X-rays. This would still identify the approximately 50% without symptoms (sub-clinical TB), whilst requiring fewer molecular tests than universal testing, but does require access to X-ray equipment and expertise. X-rays can also support diagnosis and access to care for non-TB health problems [25]. Combining X-ray with other screening tests, such as for HIV and diabetes, could offer a more comprehensive health check which may appeal more to men [26], and would work well in a workplace intervention (Table 7.1), where space is available for the X-rays. Working collaboratively and expanding case-finding to a more horizontal rather than vertical, disease-specific approach would make it more cost-effective overall, and likely to result in better linkage to care.

Finally, symptom screening followed by diagnostic tests could continue to be a useful and low-resource algorithm if combined with sufficient community outreach and demand creation – for example through peer-delivery in churches or barbershops [19]. Although this approach would not capture subclinical TB, diagnosis of disease at the subclinical stage does not appear to be essential to achieving rapid declines in TB burden, as seen in Malawi with the >80% decline in undiagnosed prevalent TB seen in Blantyre in this thesis. Within this targeted group the prevalence remains high enough that a symptom-based approach could still be effective.

This type of potentially complementary approach needs to be explored in Blantyre, starting with assessment of acceptability and feasibility, modelling potential impact and then trials of proposed interventions. Discussions with the TB/HIV Community Scientific Advisory Board at MLW have already suggested a high acceptability for mouth swab sample collection and interventions targeting men, but further research is needed. Qualitative and quantitative assessment of any indirect effects of these case-finding interventions should also be included.

Table 7.1: Potential case-finding methods for future investigation and implementation in Blantyre indicating likely yield and resource level required

Location	**Case-finding method**	**Screening algorithm**	**Sensitivity / Yield**	**Resource level**
Facility	Full adherence to guidelines in acute care clinics, inc men as priority group	Symptom screening + sputum / mouth swab sampling for Xpert	++	+
	All male attendees of acute care outpatient clinics	Digital X-ray with CAD + sputum / mouth swab sampling for Xpert	+++*	++
	Those with previous TB at 12-month intervals	Serial digital X-ray review + symptom enquiry + sputum / mouth swab sampling for universal testing with Xpert	+++*	+
Community	Venues where men congregate with peer delivery – e.g. barbershops, sports clubs, church groups	Mouth swab sampling for universal testing with Xpert	+++*	+++
		Symptom screening + mouth swab sampling for Xpert	+	+
	Workplace general healthcare screening – e.g. factories, building sites	Digital X-Ray with CAD + sputum / mouth swab sampling for Xpert	++*	++

Notes: *Identifies sub-clinical as well as clinical TB

7.3.3 TB surveillance

TB surveillance is required to estimate the disease burden, identify high-risk populations and geographical areas, and target and evaluate interventions to reduce TB incidence and mortality. In Malawi and many other LMICs, this is conducted through collecting case-notification data in paper registers and then transferring this data to an electronic system before submission to the WHO. However, as the epidemiology of HIV and TB is rapidly changing, this TB surveillance is not providing the richness and timeliness of data to allow programmes to track, adapt and better target interventions towards the remaining people with undiagnosed TB. An electronic system would provide better timeliness and, in countries lacking formal address systems, a clinic-based geolocation system, such as that used in Blantyre, would provide the level of spatiotemporal detail required to target and assess interventions as local epidemics become increasingly concentrated. Such systematic surveillance, together with real-time information on resource availability, would allow policymakers to better understand when to intensify case-finding methods, how best to target them, and provide robust intervention assessment [27]. If data is specified by where people were diagnosed (e.g. through facilities or community ACF), this would also enable comparative assessment of indirect impacts of ACF interventions.

Extending surveillance systems to TB testing as well as TB case-notifications would provide data on access to diagnosis and allow underserved communities to be identified for ACF. This data would also enable further quantitative assessment of the potential indirect impact of ACF and its influence on health-seeking behaviour. A greater range of more informative questions on TB testing should also be included in national Demographic Health Surveys providing further data on which communities and population subgroups are accessing services, and which are underserved.

TB programmes and the WHO should also consider adding TB surveillance further upstream and re-introducing TB infection or immunoreactivity surveillance with newer, more specific tests [28], adapting methods routinely used in the last century. As undiagnosed active TB prevalence falls, the numbers of people needed to identify differences between populations and geographic areas is increasing
dramatically, but Mtb immunoreactivity can be 11- to 55-times more prevalent than the prevalence of undiagnosed TB disease [28], providing power to track trends and provide geospatial resolution. In addition, since it can take many months or even years for TB infection to develop into TB disease, case-notifications are far removed from the dynamics of TB transmission.

Tracking infection can therefore provide both a pragmatic proxy indicator of disease in the population, and also reveal variations in TB transmission between groups and over short time periods, helping to better inform prevention activities. Convenience sampling strategies, such as including Mtb immunoreactivity screening in childhood vaccination or antenatal clinic attendees, and screening of high-exposure occupational groups, such as health workers, could provide good sentinel populations for TB infection surveillance, but further research is needed to establish the acceptability, feasibility and public health utility of this approach in settings such as Blantyre.

7.4 Limitations

Although the work in this thesis is likely to have impact on both future policy and research, I acknowledge limitations to this work including limited generalisability, and the suboptimal recruitment and participation of men in some sub-studies. The relatively low numbers of prevalence survey and active case-finding participants diagnosed with active TB disease limited my ability to draw strong conclusions, as did issues raised by the COVID-19 pandemic.

The setting for the studies in this thesis was Blantyre, Malawi. Blantyre has had both a high HIV and TB burden and Malawi is classed as one of the least developed countries in the world [29]. For my findings to be applicable elsewhere the location would need to have a similar HIV and TB burden and social-economic situation. The situation is likely to be more similar in other low-income sub-Saharan African countries such as Zambia and Mozambique than in the highest TB burden middle-income countries in Asia, Europe and South America where determinants of TB and available health systems are likely to be different compared to Blantyre. Malawi has also made substantial progress towards meeting the 95-95-95 UNAIDS goals [30] with greatly improved management of HIV [2], but this differs from some of the other high HIV-associated TB burden countries such as South Africa [31]. This will impact TB epidemiology, with likely continued high TB prevalence where HIV is less well managed, and therefore reduced applicability of the case-finding methods discussed here.

The recruitment and participation of men was sub-optimal in both the prevalence survey and the SCALE ACF intervention due to difficulties in finding them at home during working hours. Lower rates of male participation are common in prevalence surveys throughout Africa [32], and I used recommended imputation and modelling techniques to minimise the resulting selection bias. The lower than desired participation of men in the ACF intervention underscores the need to carefully target future interventions specifically towards this high-risk group.

The small numbers diagnosed with TB in both the prevalence survey and ACF intervention give wide confidence intervals and limit the power to draw conclusions from multivariable analysis and subgroup analyses, but reflects the lower-than-expected prevalence of TB. The systematic review also identified few studies reporting relevant data, again limiting conclusions but highlighting the need for further research and focus on the potential indirect impacts of TB ACF.

The COVID-19 pandemic had a significant impact on this PhD. The pandemic led to the curtailment of the ACF intervention after only one round, the removal of a post-intervention survey to assess rates of TB testing and also led to the censuring of data in the analysis of the TB case-notifications outcome. My team at MLW conducted a study on the impact of the pandemic and COVID-19 restrictions on TB case notifications in Blantyre, for which I led the qualitative element of in-depth interviews with District TB Officers. This study found a 35.9% reduction in TB case-notifications following the declaration of the state of emergency in Malawi due to COVID-19, likely driven by fear of COVID-19 infection, temporary facility closures, inadequate personal protective equipment and COVID-19 stigma because of similar symptoms to TB. However, TB case-notifications recovered to near pre-pandemic numbers by December 2020 [33].

Finally, I acknowledge that this PhD focuses on earlier diagnosis of TB aiming to interrupt or reduce future transmission. This is one of the current priorities of the WHO EndTB strategy, but does not explicitly incorporate preventive approaches that address the underlying upstream social determinants of TB. History has shown that the most dramatic reductions in TB burden have occurred when economic and social advances proceed alongside medical innovations [34], meaning working collaboratively towards poverty reduction at both a national and international level will be needed to reach TB elimination goals.

7.5 Final conclusions

This thesis shows substantial progress towards TB elimination goals, with major reductions in undiagnosed TB disease in Blantyre, likely achieved through substantial improvements in HIV management and previous symptom-based TB screening interventions. This changing TB and HIV epidemiology should then prompt changing priorities for future TB case-finding policy and practice.

Comprehensive TB surveillance, ideally including geolocation, is vital to understand and provide a more timely response to this changing epidemiology, identify target groups and track

progress to meeting TB elimination goals. Surveillance can help direct and evaluate future case-finding efforts, allowing these to be more effectively targeted. National TB Programmes in Malawi, and low-income countries with similar TB and HIV epidemiology, need to invest in efficient facility-based testing with higher throughput, potentially by integrating of digital chest X-ray with CAD screening in acute care clinic attendees and other high risk outpatient groups. Future community ACF should be more targeted, for instance to older men, and could draw on the experience of HIV by taking advantage of new sampling techniques and peer-delivery systems, with a need to balance between highly sensitive approaches and feasibility and affordability in resource limited settings.

There is potential indirect impact of TB ACF but further evidence is needed with qualitative and quantitative assessment of this included in trials of future ACF interventions.

7.6 References

1. World Health Organization. National Tuberculosis Prevalence Surveys 2007-2016. 2021.
2. PHIA Project. Malawi Population-based HIV Impact Assessment (MPHIA) Summary Sheet 2020-2021. 2022.
3. Marks GB, Nguyen NV, Nguyen PTB, Nguyen TA, Nguyen HB, Tran KH, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. N Engl J Med. 2019;381(14):1347-57.
4. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease. 2021.
5. Luke Banda MLW. We Can End TB! Leaving no-one behInd: Transforming Gendered pathways to Health for TB (LIGHT) 2023 [Available from: https://www.mlw.mw/news_and_events/we-can-end-tb/].
6. Burke RM, Nliwasa M, Feasey HRA, Chaisson LH, Golub JE, Naufal F, et al. Community-based active case-finding interventions for tuberculosis: a systematic review. Lancet Public Health. 2021.
7. WHO Expert Committee on Tuberculosis. WHO Expert Committee on Tuberculosis Ninth Report. World Health Organisation (WHO); 1974.
8. Deya RW, Masese LN, Jaoko W, Muhwa JC, Mbugua L, Horne DJ, et al. Yield and Coverage of Active Case Finding Interventions for Tuberculosis Control:A Systematic Review and Meta-analysis. Tuberc Res Treat. 2022;2022:9947068.
9. Sekandi JN, Dobbin K, Oloya J, Okwera A, Whalen CC, Corso PS. Cost-Effectiveness Analysis of Community Active Case Finding and Household Contact Investigation for Tuberculosis Case Detection in Urban Africa. PLOS ONE. 2015;10(2):e0117009.
10. Fox W. Tuberculosis case-finding and treatment programmes in the developing countries. British Medical Bulletin. 1988;44(3):717-37.
11. Aluoch JA, Edwards EA, Stott H, Fox W, Sutherland I. A fourth study of case-finding methods for pulmonary tuberculosis in Kenya. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1982;76(5):679-91.
12. Madhu PK. The Know-Do Gap in Tuberculosis Care. The Stephen Lawn Memorial Lecture 2023. 2023.

13. Das J, Kwan A, Daniels B, Satyanarayana S, Subbaraman R, Bergkvist S, et al. Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study. Lancet Infect Dis. 2015;15(11):1305-13.

14. Frascella B, Richards AS, Sossen B, Emery JC, Odone A, Law I, et al. Subclinical Tuberculosis Disease—A Review and Analysis of Prevalence Surveys to Inform Definitions, Burden, Associations, and Screening Methodology. Clinical Infectious Diseases. 2021;73(3):e830-e41.

15. Mungai B, Ong'angò J, Ku CC, Henrion MYR, Morton B, Joekes E, et al. Accuracy of computer-aided chest X-ray in community-based tuberculosis screening: Lessons from the 2016 Kenya National Tuberculosis Prevalence Survey. PLOS Glob Public Health. 2022;2(11):e0001272.

16. Theron G, Venter R, Calligaro G, Smith L, Limberis J, Meldau R, et al. Xpert MTB/RIF Results in Patients With Previous Tuberculosis: Can We Distinguish True From False Positive Results? Clin Infect Dis. 2016;62(8):995-1001.

17. Maleche-Obimbo E, Odhiambo MA, Njeri L, Mburu M, Jaoko W, Were F, et al. Magnitude and factors associated with post-tuberculosis lung disease in low- and middle-income countries: A systematic review and meta-analysis. PLOS Global Public Health. 2022;2(12):e0000805.

18. Linnan LA, D'Angelo H, Harrington CB. A literature synthesis of health promotion research in salons and barbershops. Am J Prev Med. 2014;47(1):77-85.

19. Wilson TE, Gousse Y, Joseph MA, Browne RC, Camilien B, McFarlane D, et al. HIV Prevention for Black Heterosexual Men: The Barbershop Talk with Brothers Cluster Randomized Trial. Am J Public Health. 2019;109(8):1131-7.

20. UNFPA W, PATH,. Condom Programming for HIV Prevention. An Operations Manual for Programme Managers. 2005.

21. Wara NJ, Psaros C, Govere S, Dladla N, Stuckwisch A, Zionts D, et al. Hair salons and stylist–client social relationships as facilitators of community-based contraceptive uptake in KwaZulu-Natal, South Africa: a qualitative analysis. Reproductive Health. 2021;18(1):178.

22. Indravudh PP, Fielding K, Chilongosi R, Nzawa R, Neuman M, Kumwenda MK, et al. Effect of door-to-door distribution of HIV self-testing kits on HIV testing and antiretroviral

therapy initiation: a cluster randomised trial in Malawi. BMJ Glob Health. 2021;6(Suppl 4).

23. Luabeya AK, Wood RC, Shenje J, Filander E, Ontong C, Mabwe S, et al. Noninvasive Detection of Tuberculosis by Oral Swab Analysis. J Clin Microbiol. 2019;57(3).

24. Wood RC, Andama A, Hermansky G, Burkot S, Asege L, Job M, et al. Characterization of oral swab samples for diagnosis of pulmonary tuberculosis. PLoS One. 2021;16(5):e0251422.

25. Twabi HH, Semphere R, Mukoka M, Chiume L, Nzawa R, Feasey HRA, et al. Pattern of abnormalities amongst chest X-rays of adults undergoing computer-assisted digital chest X-ray screening for tuberculosis in Peri-Urban Blantyre, Malawi: A cross-sectional study. Trop Med Int Health. 2021;26(11):1427-37.

26. Chikovore J, Hart G, Kumwenda M, Chipungu G, Desmond N, Corbett EL. TB and HIV stigma compounded by threatened masculinity: implications for TB health-care seeking in Malawi. Int J Tuberc Lung Dis. 2017;21(11):26-33.

27. Yaesoubi R, Cohen T. Identifying dynamic tuberculosis case-finding policies for HIV/TB coepidemics. Proceedings of the National Academy of Sciences. 2013;110(23):9457-62.

28. Rickman HM, Kamchedzera W, Schwalb A, Phiri MD, Ruhwald M, Shanaube K, et al. Know your tuberculosis epidemic–Is it time to add Mycobacterium tuberculosis immunoreactivity back into global surveillance? PLOS Global Public Health. 2022;2(10):e0001208.

29. Development UNCoTa. UN list of least developed countries 2022 [Available from: https://unctad.org/topic/least-developed-countries/list].

30. Relief PUSPsEPfA. Malawi Country Operational Plan 2022. Strategic Direction Summary. 2022.

31. UNAIDS. Country factsheets. South Africa 2021 HIV and AIDS estimates 2021 [Available from: https://www.unaids.org/en/regionscountries/countries/southafrica].

32. Law I, Floyd K. National tuberculosis prevalence surveys in Africa, 2008-2016: an overview of results and lessons learned. Trop Med Int Health. 2020;25(11):1308-27.

33. Soko RN, Burke RM, Feasey HRA, Sibande W, Nliwasa M, Henrion MYR, et al. Effects of Coronavirus Disease Pandemic on Tuberculosis Notifications, Malawi. Emerg Infect

Dis. 2021;27(7):1831-9.

34. World Health Organization EbEBaASK. Equity, social determinants and public health programmes. 2010.

Appendices

A Systematic Review (Chapter 5) Supplementary Materials 3-6: lists of studies reviewed, data extracted and PRISMA checklist

Appendix 3

List of papers about TB ACF reviewed at full text.

Author	Year	Journal	Title	Decision	mainreason	Which review?
Abascal et. al	2020	Sci Rep	Screening of inmates transferred to Spain reveals a Peruvian prison as a reservoir of persistent Mycobacterium tuberculosis MDR strains and mixed infections	exclude	No comparison group	NA
Abbara et. al	2020	Int J Infect Dis	The challenges of tuberculosis control in protracted conflict: The case of Syria	exclude	No relevant data / not an ACF intervention	NA
Abdulkareem et. al	2020	Int J Infect Dis	First insight into latent tuberculosis infection among household contacts of tuberculosis patients in Duhok, Iraqi Kurdistan: using tuberculin skin test and QuantiFERON-TB Gold Plus test	exclude	No comparison group	NA
Abdurrahman et. al	2017	New microbes and new infections	Are patients with pulmonary tuberculosis who are identified through active case finding in the community different than those identified in healthcare facilities?	exclude	No comparison group	NA
Abebe et. al	2011	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Prevalence of pulmonary tuberculosis and associated risk factors in Eastern Ethiopian prisons	exclude	No comparison group	NA
Abebe et. al	2012	BMC public health	Tuberculosis lymphadenitis in Southwest Ethiopia: a community based cross-sectional study	exclude	No comparison group	NA
Abera et. al	2018	The open microbiology journal	Pulmonary Tuberculosis and Associated Factors Among Diabetic Patients Attending Hawassa Adare Hospital, Southern Ethiopia	exclude	No comparison group	NA
Abseno et. al	2014	Ethiopian medical journal	Tuberculosis among Addis Ababa city bus drivers and cash collectors	exclude	No comparison group	NA
Abubakar et. al	2011	Eurosurveillance	Assessing the efect of foreign travel and protection by BCG vaccination on the spread of tuberculosis in a low incidence country, United Kingdom, October 2008 to December 2009	exclude	No comparison group	NA
Abuogi et. al	2013	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Impact of expanded antiretroviral use on incidence and prevalence of tuberculosis in children with HIV in Kenya	exclude	Healthcare based screening	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Accinelli et. al	2015	American journal of respiratory and critical care medicine	Sustained Benefit of Community-based Tuberculosis Interventions after 30 Years	exclude	NA	NA
Ackermann et. al	2018	Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin	Screening for infectious diseases among newly arrived asylum seekers, Bavaria, Germany, 2015	exclude	No comparison group	NA
Adams et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	High completion rates of isoniazid preventive therapy among persons living with HIV in Swaziland	exclude	No comparison group	NA
Adams et. al	2014	The Pediatric infectious disease journal	Diagnosis and treatment of tuberculosis among children at an HIV care program in Dar es Salaam, Tanzania	exclude	No comparison group	NA
Adane et. al	2020	Tuberc Res Treat	Prevalence and Associated Factors of Tuberculosis among Adult Household Contacts of Smear Positive Pulmonary Tuberculosis Patients Treated in Public Health Facilities of Haramaya District, Oromia Region, Eastern Ethiopia	exclude	No comparison group	NA
Adane et. al	2016	PloS one	Half of Pulmonary Tuberculosis Cases Were Left Undiagnosed in Prisons of the Tigray Region of Ethiopia: Implications for Tuberculosis Control	exclude	No comparison group	NA
Adane et. al	2019	Lancet Glob Health	Tuberculosis case detection by trained inmate peer educators in a resource-limited prison setting in Ethiopia: a cluster-randomised trial	include	NA	CNR review
Addis et. al	2015	Asian Pacific journal of tropical medicine	Prevalence of smear positive pulmonary tuberculosis in Gondar prisoners, North West Ethiopia	exclude	No comparison group	NA
Adelman et. al	2015	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Intensified tuberculosis case finding among HIV-infected persons using a WHO symptom screen and Xpert((R)) MTB/RIF	exclude	No comparison group	NA
Adesokan et. al	2014	African journal of medicine and medical sciences	Prevalence of previously undetected tuberculosis and underlying risk factors for transmission in a prison setting in Ibadan, south-western Nigeria	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Adesokan et. al	2012	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Mycobacterium bovis infection in livestock workers in Ibadan, Nigeria: evidence of occupational exposure	exclude	No comparison group	NA
Adetifa et. al	2016	Bulletin of the World Health Organization	A tuberculosis nationwide prevalence survey in Gambia, 2012	exclude	No comparison group	NA
Adetifa et. al	2017	American Journal of Tropical Medicine and Hygiene	Mycobacterium tuberculosis infection in close childhood contacts of adults with pulmonary tuberculosis is increased by secondhand exposure to tobacco	exclude	No comparison group	NA
Adetunji et. al	2019	J Immunoassay Immunochem	Rifampicin-resistant tuberculosis among known HIV-infected patients in Oyo State, Nigeria	exclude	No comparison group	NA
Adinarayanan et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Role of bacille Calmette-Guerin in preventing tuberculous infection	exclude	No comparison group	NA
Adjobimey et. al	2016	International Journal of Tuberculosis and Lung Disease	Implementation of isoniazid preventive therapy in children aged under 5 years exposed to tuberculosis in Benin	exclude	No comparison group	NA
Adler-Shohet et. al	2014	The Pediatric infectious disease journal	Management of latent tuberculosis infection in child contacts of multidrug-resistant tuberculosis	exclude	No comparison group	NA
Adler et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis in HIV-infected South African children with complicated severe acute malnutrition	exclude	No comparison group	NA
Agarwal et. al	2018	Gastroenterology	VERY HIGH RATE OF TUBERCULOSIS COMPLICATING INFLIXIMAB THERAPY FOR INFLAMMATORY BOWEL DISEASE DESPITE TUBERCULOSIS SCREENING IN INDIA	exclude	No comparison group	NA
Agaya et. al	2015	Tropical medicine & international health : TM & IH	Tuberculosis and latent tuberculosis infection among healthcare workers in Kisumu, Kenya	exclude	No comparison group	NA
Aggarwal et. al	2015	PLoS ONE	Prevalence of pulmonary tuberculosis among adults in a north Indian district	exclude	No comparison group	NA
Agizew T.B. et. al	2010	International Journal of Tuberculosis and Lung Disease	Tuberculosis in asymptomatic HIV-infected adults with abnormal chest radiographs screened for tuberculosis prevention	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Agizew et. al	2017	PloS one	Higher-than-expected prevalence of non-tuberculous mycobacteria in HIV setting in Botswana: Implications for diagnostic algorithms using Xpert MTB/RIF assay	exclude	No comparison group	NA
Agizew et. al	2019	BMC Infect Dis	Tuberculosis treatment outcomes among people living with HIV diagnosed using Xpert MTB/RIF versus sputum-smear microscopy in Botswana: a stepped-wedge cluster randomised trial	exclude	Healthcare based screening	NA
Aguilera et. al	2016	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis in prisoners and their contacts in Chile: estimating incidence and latent infection	exclude	No comparison group	NA
Aguirre et. al	2017	Mem. Inst. Oswaldo Cruz	Prevalence of tuberculosis respiratory symptoms and associated factors in the indigenous populations of Paraguay (2012)	exclude	No comparison group	NA
Ahmad Khan et. al	2014	AIDS (London, England)	Performance of symptom-based tuberculosis screening among people living with HIV: not as great as hoped	exclude	No comparison group	NA
Ahmed et. al	2020	Pediatrics	Interferon-gamma Release Assays in Children <15 Years of Age	exclude	No comparison group	NA
Ahmed et. al	2020	Pediatrics	Interferon-γ Release Assays in Children <15 Years of Age	exclude	No comparison group	NA
Ahmed et. al	2019	Indian J. Public Health Res. Dev.	Epidemiology character of tuberculosis among internally displaced persons in Tikrit City	exclude	No comparison group	NA
Ahmed et. al	2017	International journal of mycobacteriology	Association between pulmonary tuberculosis and Type 2 diabetes in Sudanese patients	exclude	No comparison group	NA
Ahn et. al	2015	American Journal of Infection Control	Nosocomial exposure to active pulmonary tuberculosis in a neonatal intensive care unit	exclude	No comparison group	NA
Aia et. al	2018	Western Pacific surveillance and response journal : WPSAR	Epidemiology of tuberculosis in Papua New Guinea: analysis of case notification and treatment-outcome data, 2008-2016	exclude	No comparison group	NA
Aibana et. al	2016	PloS one	Nutritional Status and Tuberculosis Risk in Adult and Pediatric Household Contacts	exclude	No comparison group	NA
Aibana et. al	2018	The Journal of nutrition	Vitamin E Status Is Inversely Associated with Risk of Incident Tuberculosis Disease among Household Contacts	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Aibana et. al	2017	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	Impact of Vitamin A and Carotenoids on the Risk of Tuberculosis Progression	exclude	No comparison group	NA
Akanbi et. al	2017	BMC pulmonary medicine	Evaluation of gene xpert for routine diagnosis of HIV-associated tuberculosis in Nigeria: A prospective cohort study	exclude	No comparison group	NA
Akanbi et. al	2013	AIDS research and human retroviruses	Tuberculosis after one year of combination antiretroviral therapy in Nigeria: a retrospective cohort study	exclude	No comparison group	NA
Akkerman et. al	2016	The European respiratory journal	Implementing tuberculosis entry screening for asylum seekers: the Groningen experience	exclude	No comparison group	NA
Aksenova et. al	2020	Int J Infect Dis	Latent tuberculosis infection in children and adolescents in Russia	exclude	ACF in children only	NA
Aksenova et. al	2018	European Respiratory Journal	TB detection in children in Moscow (Russia) as in low TB incidence region	exclude	ACF in children only	NA
Al Hajoj et. al	2016	PloS one	Interferon Gamma Release Assay versus Tuberculin Skin Testing among Healthcare Workers of Highly Diverse Origin in a Moderate Tuberculosis Burden Country	exclude	No comparison group	NA
Al Hosani et. al	2013	Journal of epidemiology and global health	Prevalence of pulmonary tuberculosis among expatriates subjected to medical visa screening in Abu Dhabi, United Arab Emirates	exclude	No comparison group	NA
Al Wakeel et. al	2014	Nephrology Dialysis Transplantation	The use of quantiferon TB gold in-tube test in screening latent and active tuberculosis among saudi dialysis patients	exclude	No comparison group	NA
Al-Darraji et. al	2013	PloS one	The diagnostic performance of a single GeneXpert MTB/RIF assay in an intensified tuberculosis case finding survey among HIV-infected prisoners in Malaysia	exclude	No comparison group	NA
Al-Darraji et. al	2016	Tropical medicine & international health : TM & IH	Undiagnosed pulmonary tuberculosis among prisoners in Malaysia: an overlooked risk for tuberculosis in the community	exclude	No comparison group	NA
Al-Darraji et. al	2015	Respirology	Factors limiting the scale up of isoniazid preventive therapy among hiv-infected prisoners in Malaysia	exclude	No comparison group	NA
Alamo et. al	2012	Tropical medicine & international health : TM & IH	Performance of the new WHO diagnostic algorithm for smear-negative pulmonary tuberculosis in HIV prevalent settings: a multisite study in Uganda	exclude	Healthcare based screening	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Alawdah et. al	2017	Open Forum Infectious Diseases	Improving patient and employee safety through implementation of an infection risk screening process for international patients at boston children's hospital-the airship protocol	exclude	No comparison group	NA
Aldridge et. al	2015	BMJ open	Effectiveness of peer educators on the uptake of mobile X-ray tuberculosis screening at homeless hostels: a cluster randomised controlled trial	exclude	NA	NA
Aldridge et. al	2016	The Lancet. Infectious diseases	Prevalence of and risk factors for active tuberculosis in migrants screened before entry to the UK: a population-based cross-sectional study	exclude	No comparison group	NA
Aldridge et. al	2016	Lancet (London, England)	Tuberculosis in migrants moving from high-incidence to low-incidence countries: a population-based cohort study of 519 955 migrants screened before entry to England, Wales, and Northern Ireland	exclude	No comparison group	NA
Alekseev et. al	2018	European Respiratory Journal	The efficacy of screening for tuberculosis infection in paediatric population in the Republic of Tatarstan	exclude	ACF in children only	NA
Alelign et. al	2019	PLoS One	Smear positive tuberculosis and genetic diversity of M. tuberculosis isolates in individuals visiting health facilities in South Gondar Zone, northwest Ethiopia	exclude	No comparison group	NA
Alelign et. al	2019	Tuberc Res Treat	Tuberculosis at Farmer-Cattle Interface in the Rural Villages of South Gondar Zone of Northwest Ethiopia	exclude	No comparison group	NA
Alemayehu et. al	2014	International journal of mycobacteriology	Active tuberculosis case finding and detection of drug resistance among HIV-infected patients: A cross-sectional study in a TB endemic area, Gondar, Northwest Ethiopia	exclude	No comparison group	NA
Alemu et. al	2016	PloS one	High Incidence of Tuberculosis in the Absence of Isoniazid and Cotrimoxazole Preventive Therapy in Children Living with HIV in Northern Ethiopia: A Retrospective Follow-Up Study	exclude	No comparison group	NA
Ali et. al	2019	Transactions of the Royal Society of Tropical Medicine and Hygiene	A descriptive analysis of screening and treatment of tuberculosis in pregnant women in urban tertiary care hospitals in Pakistan	exclude	No comparison group	NA
Ali et. al	2015	PloS one	Prevalence of Pulmonary Tuberculosis among Prison Inmates in Ethiopia, a Cross-Sectional Study	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Almufty et. al	2019	Trop Med Infect Dis	Latent Tuberculosis Infection among Healthcare Workers in Duhok Province: From Screening to Prophylactic Treatment	exclude	No comparison group	NA
Alsayed Hasanain et. al	2019	Trop Med Int Health	Predictors of therapeutic failure among patients with acute brucellosis treated by dual therapy with doxycycline-rifampin	exclude	No relevant data / not an ACF intervention	NA
Alsharif et. al	2020	Ann Thorac Med	Incidence of latent tuberculosis infection among health science students during clinical training	exclude	No comparison group	NA
Alshukairi et. al	2020	J Infect Public Health	Family cluster of multi-drug resistant tuberculosis in Kingdom of Saudi Arabia	exclude	No comparison group	NA
Altet et. al	2015	Annals of the American Thoracic Society	Predicting the Development of Tuberculosis with the Tuberculin Skin Test and QuantiFERON Testing	exclude	No comparison group	NA
Alvarez-Alvarez et. al	2013	Anales de pediatria (Barcelona, Spain : 2003)	[Description of tuberculosis outbreak and usefulness of mediastinal ultrasound]	exclude	No comparison group	NA
Alvarez et. al	2014	PloS one	Taima (stop) TB: the impact of a multifaceted TB awareness and door-to-door campaign in residential areas of high risk for TB in Iqaluit, Nunavut	exclude	Fewer than 1000 people screened	NA
Amanullah et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	High tuberculosis prevalence in children exposed at home to drug-resistant tuberculosis	exclude	No comparison group	NA
Amare D. et. al	2010	Int J Tuberc Lung Dis	Prevalence of pulmonary tb and hiv among tb suspects in rural community in southwest ethiopia. 41st world conference on lung health of the international union against tuberculosis and lung disease, berlin, germany, 11-15 november 2010	exclude	No comparison group	NA
Aminzadeh et. al	2011	International journal of preventive medicine	A six months follow-up on children less than 6 years old in contact with smear positive tuberculosis patients, varamin city, tehran, iran	exclude	No comparison group	NA
Amiri et. al	2014	PloS one	Vulnerability of homeless people in Tehran, Iran, to HIV, tuberculosis and viral hepatitis	exclude	No comparison group	NA
An and et. al	2018	Cureus	Improving Screening for Latent Tuberculosis Infection in a Student-run Free Clinic	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
An der Heiden et. al	2017	Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin	Contact investigation after a fatal case of extensively drug-resistant tuberculosis (XDR-TB) in an aircraft, Germany, July 2013	exclude	No comparison group	NA
Anaraki et. al	2018	Epidemiology and infection	Expected background rates of latent TB infection in London inner city schools: lessons from a TB contact investigation exercise in a secondary school	exclude	No comparison group	NA
Andama et. al	2020	Diagn. Microbiol. Infect. Dis.	Accuracy and incremental yield of urine Xpert MTB/RIF Ultra versus Determine TB-LAM for diagnosis of pulmonary tuberculosis	exclude	Healthcare based screening	NA
Andre et. al	2018	Bulletin of the World Health Organization	Patient-led active tuberculosis case-finding in the Democratic Republic of the Congo	exclude	No comparison group	NA
Andrews et. al	2015	American journal of respiratory and critical care medicine	The dynamics of QuantiFERON-TB gold in-tube conversion and reversion in a cohort of South African adolescents	exclude	No comparison group	NA
Andrews et. al	2017	The Lancet. Respiratory medicine	Serial QuantiFERON testing and tuberculosis disease risk among young children: an observational cohort study	exclude	No comparison group	NA
Aneja K.S. et. al	1984	Indian Journal of Tuberculosis	Active case finding in tuberculosis as a component of primary health care	exclude	NA	NA
Anger et. al	2012	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	Active case finding and prevention of tuberculosis among a cohort of contacts exposed to infectious tuberculosis cases in New York City	exclude	No comparison group	NA
Anigilaje et. al	2016	PloS one	Tuberculosis, before and after Antiretroviral Therapy among HIV-Infected Children in Nigeria: What Are the Risk Factors?	exclude	No comparison group	NA
Anih et. al	2019	Journal of Acquired Immune Deficiency Syndromes	Implementation of tuberculosis service integration into ANC and PMTCT programs in northern nigeria	exclude	No comparison group	NA
Aquino et. al	2015	Cadernos de saude publica	Factors associated with treatment for latent tuberculosis in persons living with HIV/AIDS	exclude	No comparison group	NA
Ar-Karachaiphong et. al	2019	Journal of the Medical Association of Thailand	Agreement of tuberculin skin test and quantiFERON®-TB gold-in-tube for screening Mycobacterium tuberculosis infection in healthcare workers in a university hospital	exclude	Fewer than 1000 people screened	NA
Araujo et. al	2020	Int J Infect Dis	Determinants of losses in the latent tuberculosis cascade of care in Brazil: A retrospective cohort study	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Armstrong-Hough et. al	2017	PloS one	Drop-out from the tuberculosis contact investigation cascade in a routine public health setting in urban Uganda: A prospective, multi-center study	exclude	No comparison group	NA
Arnedo-Pena et. al	2020	Int J Tuberc Lung Dis	Vitamin D status and latent tuberculosis infection: conversion in nursing homes, Spain	exclude	No comparison group	NA
Arnold et. al	2016	The Journal of infection	XDR-TB transmission in London: Case management and contact tracing investigation assisted by early whole genome sequencing	exclude	Fewer than 1000 people screened	NA
Arroyave et. al	2017	Epidemiology and infection	Negative latent tuberculosis at time of incarceration: identifying a very high-risk group for infection	exclude	No comparison group	NA
Arroyave et. al	2017	Epidemiology and infection	Negative latent tuberculosis at time of incarceration: identifying a very high-risk group for infection	exclude	No comparison group	NA
Arroyave et. al	2019	J Immigr Minor Health	Guards in Prisons: A Risk Group for Latent Tuberculosis Infection	exclude	No comparison group	NA
Arscott-Mills et. al	2014	Journal of tropical pediatrics	Yield of screening for TB and HIV among children failing to thrive in Botswana	exclude	Healthcare based screening	NA
Asemahagn et. al	2017	Tuberculosis research and treatment	Are Shopkeepers Suffering from Pulmonary Tuberculosis in Bahir Dar City, Northwest Ethiopia: A Cross-Sectional Survey	exclude	No comparison group	NA
Assefa et. al	2019	BMC Infectious Diseases	Missed pulmonary tuberculosis: A cross sectional study in the general medical inpatient wards of a large referral hospital in Ethiopia 11 Medical and Health Sciences 1117 Public Health and Health Services Julian Tang	exclude	No comparison group	NA
Attah et. al	2018	Alexandria Journal of Medicine	Risk factors associated with paediatric tuberculosis in an endemic setting	exclude	No comparison group	NA
Auld et. al	2020	BMC Med	Effect of tuberculosis screening and retention interventions on early antiretroviral therapy mortality in Botswana: a stepped-wedge cluster randomized trial	exclude	Healthcare based screening	NA
Auld et. al	2016	PloS one	Wide Variations in Compliance with Tuberculosis Screening Guidelines and Tuberculosis Incidence between Antiretroviral Therapy Facilities - Cote d'Ivoire	exclude	No comparison group	NA
Aunsborg et. al	2020	Int J Infect Dis	A clinical score has utility in tuberculosis case-finding among patients with HIV: A feasibility study from Bissau	exclude	No relevant data / not an ACF intervention	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Aye et. al	2018	International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases	Evaluation of a tuberculosis active case finding project in peri-urban areas, Myanmar: 2014-2016	include	NA	CNR review
Aye et. al	2018	International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases	Evaluation of a tuberculosis active case finding project in peri-urban areas, Myanmar: 2014-2016	include but duplicate	NA	NA
Ayles H. et. al	2012	19th Conference of Retroviruses and Opportunistic Infections	A household-based hiv and tb intervention increases hiv testing in households and reduces prevalence of tb at the community level: The zamstar community randomized trial	include but duplicate	NA	NA
Ayles et. al	2013	Lancet (London, England)	Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial	include	NA	Prevelance review
Azit et. al	2019	BMC Public Health	Factors associated with tuberculosis disease among children who are household contacts of tuberculosis cases in an urban setting in Malaysia	exclude	No comparison group	NA
Bacha et. al	2019	Journal of the International AIDS Society	Actively contributing to a cascade of change: Analysis of the TB treatment cascade among children and adolescents living with HIV in six high TB/HIV burden countries	exclude	No comparison group	NA
Baghaei et. al	2018	The clinical respiratory journal	Diagnosing active and latent tuberculosis among Iranian HIV-infected patients	exclude	No comparison group	NA
Baghaie et. al	2012	Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit	Contact tracing of a 15-year-old girl with smear-negative pulmonary tuberculosis in Tehran	exclude	No comparison group	NA
Bah et. al	2012	Revue de Medecine Legale	Prevalence of tuberculosis in the prison population of Conakry, Guinea Republic	exclude	No comparison group	NA
Bailey et. al	2016	BMC infectious diseases	The association of hyperglycaemia with prevalent tuberculosis: a population-based cross-sectional study	exclude	No comparison group	NA
Bajema et. al	2019	BMC infectious diseases	Subclinical tuberculosis among adults with HIV: clinical features and outcomes in a South African cohort	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Bakeera-Kitaka et. al	2011	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis in human immunodeficiency virus infected Ugandan children starting on antiretroviral therapy	exclude	ACF in children only	NA
Bakeera-Kitaka et. al	2011	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis in human immunodeficiency virus infected Ugandan children starting on antiretroviral therapy	exclude	Healthcare based screening	NA
Balasubramanian R. et. al	2004	International Journal of Tuberculosis and Lung Disease	Gender disparities in tuberculosis: Report from a rural DOTS programme in south India	exclude	No comparison group	NA
Balcells et. al	2016	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	M. tuberculosis DNA detection in nasopharyngeal mucosa can precede tuberculosis development in contacts	exclude	No comparison group	NA
Balcells et. al	2016	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	M. tuberculosis DNA detection in nasopharyngeal mucosa can precede tuberculosis development in contacts	exclude	No comparison group	NA
Balcha et. al	2015	Global health action	Outcome of tuberculosis treatment in HIV-positive adults diagnosed through active versus passive case-finding	exclude	Fewer than 1000 people screened	NA
Balcha et. al	2014	PloS one	Intensified tuberculosis case-finding in HIV-positive adults managed at Ethiopian health centers: diagnostic yield of Xpert MTB/RIF compared with smear microscopy and liquid culture	exclude	No comparison group	NA
Baldassari et. al	2019	Mult Scler J Exp Transl Clin	Tuberculosis screening in multiple sclerosis: effect of disease-modifying therapies and lymphopenia on the prevalence of indeterminate TB screening results in the clinical setting	exclude	No comparison group	NA
Baliashvili et. al	2018	Public health action	A population-based tuberculosis contact investigation in the country of Georgia	exclude	No comparison group	NA
Balmelli et. al	2014	Swiss medical weekly	Contact tracing investigation after professional exposure to tuberculosis in a Swiss hospital using both tuberculin skin test and IGRA	exclude	No comparison group	NA

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Banfield et. al	2012	PloS one	Factors associated with the performance of a blood-based interferon-gamma release assay in diagnosing tuberculosis	exclude	No comparison group	NA
Banfield et. al	2012	PLoS ONE	Factors associated with the performance of a blood-based interferon-?_ release assay in diagnosing tuberculosis	exclude	No comparison group	NA
Banjara et. al	2015	Transactions of the Royal Society of Tropical Medicine and Hygiene	Feasibility of a combined camp approach for vector control together with active case detection of visceral leishmaniasis, post kala-azar dermal leishmaniasis, tuberculosis, leprosy and malaria in Bangladesh, India and Nepal: an exploratory study	exclude	No comparison group	NA
Banu et. al	2013	PloS one	Epidemiology of tuberculosis in an urban slum of Dhaka City, Bangladesh	exclude	No comparison group	NA
Banu et. al	2015	PloS one	Effect of active case finding on prevalence and transmission of pulmonary tuberculosis in Dhaka Central Jail, Bangladesh	exclude	No comparison group	NA
Barcellini et. al	2019	PLoS One	App-based symptoms screening with Xpert MTB/RIF Ultra assay used for active tuberculosis detection in migrants at point of arrivals in Italy: The E-DETECT TB intervention analysis	exclude	NA	NA
Basham et. al	2019	Can J Public Health	Tuberculosis among northern Manitoba First Nations, 2008-2012: program performance on- and off-reserve	exclude	No comparison group	NA
Basir et. al	2019	BMC Health Serv Res	Operationalization of bi-directional screening for tuberculosis and diabetes in private sector healthcare clinics in Karachi, Pakistan	exclude	Healthcare based screening	NA
Bassett et. al	2019	BMC infectious diseases	Test and Treat TB: a pilot trial of GeneXpert MTB/RIF screening on a mobile HIV testing unit in South Africa	exclude	No comparison group	NA
Bates et. al	2012	PloS one	Evaluation of the burden of unsuspected pulmonary tuberculosis and co-morbidity with non-communicable diseases in sputum producing adult inpatients	exclude	No comparison group	NA
Batra et. al	2012	PloS one	Childhood tuberculosis in household contacts of newly diagnosed TB patients	exclude	No comparison group	NA
Becerra et. al	2011	Lancet (London, England)	Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Becerra et. al	2013	The Pediatric infectious disease journal	Tuberculosis in children exposed at home to multidrug-resistant tuberculosis	exclude	No comparison group	NA
Becerra et. al	2019	Bmj	Transmissibility and potential for disease progression of drug resistant Mycobacterium tuberculosis: prospective cohort study	exclude	No comparison group	NA
Bedell et. al	2012	PloS one	High prevalence of tuberculosis and serious bloodstream infections in ambulatory individuals presenting for antiretroviral therapy in Malawi	exclude	No comparison group	NA
Bedoya et. al	2015	Iatreia	Study and clinical management of child household contacts of tuberculosis patients, medellin 2010-2011	exclude	No comparison group	NA
Bekken et. al	2020	BMC Infect Dis	Identification of subclinical tuberculosis in household contacts using exposure scores and contact investigations	exclude	No comparison group	NA
Bekker et. al	2012	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	High tuberculosis exposure among neonates in a high tuberculosis and human immunodeficiency virus burden setting	exclude	No comparison group	NA
Belizario et. al	2014	Pathogens and global health	Integrated surveillance of pulmonary tuberculosis and paragonimiasis in Zamboanga del Norte, the Philippines	exclude	No comparison group	NA
Benjamin et. al	2019	PLoS One	Accuracy of Determine TB-LAM Ag to detect TB in HIV infected patients associated with diagnostic methods used in Brazilian public health units	exclude	No comparison group	NA
Benjumea-Bedoya et. al	2019	Front Public Health	Integrated Care for Latent Tuberculosis Infection (LTBI) at a Primary Health Care Facility for Refugees in Winnipeg, Canada: A Mixed-Methods Evaluation	exclude	No comparison group	NA
Bennet et. al	2017	Infectious diseases (London, England)	Tuberculosis infection and disease in the 2015 cohort of unaccompanied minors seeking asylum in Northern Stockholm, Sweden	exclude	No comparison group	NA
Bennet et. al	2019	Pediatr Infect Dis J	Effective Tuberculosis Contact Investigation Using Interferon-Gamma Release Assays	exclude	No comparison group	NA
Berhane et. al	2019	Clin Lab	The Role of Neutrophil to Lymphocyte Count Ratio in the Differential Diagnosis of Pulmonary Tuberculosis and Bacterial Community-Acquired Pneumonia: a Cross-Sectional Study at Ayder and Mekelle Hospitals, Ethiopia	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Berhe et. al	2013	BMC infectious diseases	Population-based prevalence survey of tuberculosis in the Tigray region of Ethiopia	exclude	No comparison group	NA
Berju et. al	2019	Int J Microbiol	Smear-Positive Tuberculosis Prevalence and Associated Factors among Pregnant Women Attending Antinatal Care in North Gondar Zone Hospitals, Ethiopia	exclude	No comparison group	NA
Berkowitz et. al	2018	Diabetes research and clinical practice	The prevalence and determinants of active tuberculosis among diabetes patients in Cape Town, South Africa, a high HIV/TB burden setting	exclude	No comparison group	NA
Berraies et. al	2016	Revue de pneumologie clinique	[Results of tuberculosis screening in children with household contact]	exclude	No comparison group	NA
Bettelli et. al	2019	Haematologica	Latent tuberculosis infection in adults with acute leukemia and aplastic anemia: A retrospective single center experience	exclude	No comparison group	NA
Beyanga et. al	2018	BMC infectious diseases	Investigation of household contacts of pulmonary tuberculosis patients increases case detection in Mwanza City, Tanzania	exclude	No comparison group	NA
Bharara et. al	2019	Sexually Transmitted Infections	Integration of HIV testing with tuberculosis and sexually transmitted infections at a tertiary care hospital in Delhi	exclude	No comparison group	NA
Bhat et. al	2013	PloS one	Intensified tuberculosis case finding among malnourished children in nutritional rehabilitation centres of Karnataka, India: missed opportunities	exclude	No comparison group	NA
Bhatnagar et. al	2019	PLoS One	Intensified tuberculosis and HIV surveillance in a prison in Northeast India: Implementation research	exclude	Fewer than 1000 people screened	NA
Bhatti et. al	2014	Medical Channel	Predisposing factors of HIV and its co-infection with Tuberculosis in the metropolitan city of Karachi	exclude	Fewer than 1000 people screened	NA
Bhatti et. al	2014	Medical Channel	Predisposing factors of HIV and its co-infection with Tuberculosis in the metropolitan city of Karachi	exclude	No comparison group	NA
Bigogo et. al	2018	BMC infectious diseases	Tuberculosis case finding using population-based disease surveillance platforms in urban and rural Kenya	exclude	No comparison group	NA
Binepal et. al	2015	Public health action	Screening difficult-to-reach populations for tuberculosis using a mobile medical unit, Punjab India	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Bjerregaard-Andersen M. et. al	2010	BMC Infectious Diseases	Tuberculosis burden in an urban population: A cross sectional tuberculosis survey from Guinea Bissau	exclude	No comparison group	NA
Bjerrum et. al	2015	BMC infectious diseases	Diagnostic accuracy of the rapid urine lipoarabinomannan test for pulmonary tuberculosis among HIV-infected adults in Ghana-findings from the DETECT HIV-TB study	exclude	No comparison group	NA
Bjerrum et. al	2016	Tropical medicine & international health : TM & IH	Tuberculosis and non-tuberculous mycobacteria among HIV-infected individuals in Ghana	exclude	No comparison group	NA
Bloss et. al	2012	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Lessons learned during tuberculosis screening in public medical clinics in Francistown, Botswana	exclude	No comparison group	NA
Blount et. al	2016	BMC public health	Tuberculosis progression rates in U.S. Immigrants following screening with interferon-gamma release assays	exclude	No comparison group	NA
Bobbio et. al	2019	BMJ Open	Focused ultrasound to diagnose HIV-associated tuberculosis (FASH) in the extremely resource-limited setting of South Sudan: a cross-sectional study	exclude	No comparison group	NA
Bodena et. al	2019	Risk Manag Healthc Policy	Trend Analysis And Seasonality Of Tuberculosis Among Patients At The Hiwot Fana Specialized University Hospital, Eastern Ethiopia: A Retrospective Study	exclude	No comparison group	NA
Bogorodskaya et. al	2018	European Respiratory Journal	Results of TB prophylactics and early detection in HIV-positive people in Moscow, Russia	exclude	Healthcare based screening	NA
Bonnet et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Prospective cohort study of the feasibility and yield of household child tuberculosis contact screening in Uganda	exclude	No comparison group	NA
Bonsu et. al	2020	Int J Tuberc Lung Dis	National population-based tuberculosis prevalence survey in Ghana, 2013	exclude	No comparison group	NA
Bonvicini et. al	2018	International journal of environmental research and public health	Compliance with Tuberculosis Screening in Irregular Immigrants	exclude	No comparison group	NA
Bonvicini et. al	2019	International Journal of Environmental Research and Public Health	Compliance with tuberculosis screening in irregular immigrants	exclude	No comparison group	NA

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Borgdorff M.W. et. al	2004	Emerging Infectious Diseases	New measurable indicator for tuberculosis case detection	exclude	No comparison group	NA
Borraccino et. al	2014	The Journal of infection	Yield of tuberculosis contact investigation in a low-incidence country	exclude	No comparison group	NA
Borroto Guti?rrez et. al	2015	Rev. Cuba. Med. Trop.	Tuberculosis risk in the staff of three clinical surgical hospitals at Havana city	exclude	No comparison group	NA
Borroto et. al	2019	Transactions of the Royal Society of Tropical Medicine and Hygiene	Latent tuberculosis infection in health care workers of Cuban health facilities: Risk assessing and results of an intervention	exclude	No comparison group	NA
Bosa et. al	2017	Mediterranean journal of hematology and infectious diseases	Feasibility and Effectiveness of Tuberculosis Active Case-Finding among Children Living with Tuberculosis Relatives: a Cross-Sectional Study in Guinea-Bissau	exclude	No comparison group	NA
Bourgarit et. al	2015	Annals of the American Thoracic Society	Latent Tuberculosis Infection Screening and 2-Year Outcome in Antiretroviral-Naive HIV-Infected Patients in a Low-Prevalence Country	exclude	No comparison group	NA
Bua et. al	2016	Journal of public health (Oxford, England)	Tuberculosis screening among asylum seekers in Sardinia	exclude	No comparison group	NA
Bunyasi et. al	2019	Int J Tuberc Lung Dis	Temporal trends in the prevalence of Mycobacterium tuberculosis infection in South African adolescents	exclude	No comparison group	NA
Buonsenso et. al	2020	J Clin Microbiol	Accuracy of QuantiFERON-TB Gold-PLUS Test for the Diagnosis of Mycobacterium tuberculosis infection in Children	exclude	No comparison group	NA
Busatto et. al	2017	Revista brasileira de enfermagem	Tuberculosis among prison staff in Rio Grande do Sul	exclude	No comparison group	NA
Butt et. al	2013	Journal of Pakistan Association of Dermatologists	Frequency of pulmonary tuberculosis in patients with skin diseases requiring high dose long-term systemic steroid therapy	exclude	No comparison group	NA
Bwana et. al	2011	Tanzania journal of health research	Smear positive pulmonary tuberculosis among HIV patients receiving highly active antiretroviral therapy in Dar es Salaam, Tanzania	exclude	No comparison group	NA
Byashalira et. al	2019	Int J Mycobacteriol	Clinical outcomes of new algorithm for diagnosis and treatment of Tuberculosis sepsis in HIV patients	exclude	Healthcare based screening	NA
Cadmus et. al	2018	Journal of preventive medicine and hygiene	Isolation of Mycobacterium tuberculosis from livestock workers and implications for zooanthroponotic transmission in Ibadan, South-western Nigeria	exclude	No comparison group	NA

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Calligaro et. al	2017	The Lancet. Infectious diseases	Effect of new tuberculosis diagnostic technologies on community-based intensified case finding: a multicentre randomised controlled trial	exclude	NA	NA
Camargos et. al	2019	Pediatric Pulmonology	Agreement between tuberculin skin test and interferon-gamma release assay for the diagnosis of latent tb infection among under fifteen-year-olds	exclude	No comparison group	NA
Camelique et. al	2019	Int J Tuberc Lung Dis	Mobile community-based active case-finding for tuberculosis among older populations in rural Cambodia	exclude	No comparison group	NA
Campbell et. al	2019	American journal of kidney diseases : the official journal of the National Kidney Foundation	Screening for Latent Tuberculosis Infection in Migrants With CKD: A Cost-effectiveness Analysis	exclude	No comparison group	NA
Cao et. al	2019	BMC Infect Dis	The association between tuberculin skin test result and active tuberculosis risk of college students in Beijing, China: a retrospective cohort study	exclude	No comparison group	NA
Capewell S. et. al	1986	Tubercle	The diagnosis and management of tuberculosis in common hostel dwellers	exclude	NA	NA
Capewell S. et. al	1984	British Journal of Diseases of the Chest	The value of contact procedures for tuberculosis in Edinburgh	exclude	No comparison group	NA
Carbone Ada et. al	2015	BMC infectious diseases	Active and latent tuberculosis in Brazilian correctional facilities: a cross-sectional study	exclude	No comparison group	NA
Carrizales-Luna et. al	2019	Annals of the Rheumatic Diseases	Quantiferon gold-plus and tuberculin skin test reactivity predictors in patients with rheumatoid arthritis	exclude	No comparison group	NA
Casas et. al	2011	Tropical medicine & international health : TM & IH	Burden and outcome of HIV infection and other morbidities in health care workers attending an Occupational Health Program at the Provincial Hospital of Tete, Mozambique	exclude	No comparison group	NA
Cassels A. et. al	1982	Tubercle	Tuberculosis case-finding in Eastern Nepal	exclude	No comparison group	NA
Castells Carrillo et. al	2019	Enferm Infecc Microbiol Clin	Diagnostic delay as main contributing factor to a large outbreak of tuberculosis in a university	exclude	No comparison group	NA
Cates et. al	2016	Journal of public health management and practice : JPHMP	Contact Investigations Around Mycobacterium tuberculosis Patients Without Positive Respiratory Culture	exclude	Fewer than 1000 people screened	NA
Cavalcante S.C. et. al	2010	International Journal of Tuberculosis and Lung Disease	Community-randomized trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil	exclude	Contact tracing	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Cegielski et. al	2013	Revista panamericana de salud publica = Pan American journal of public health	[Eliminating tuberculosis one neighborhood at a time]	include	NA	CNR review
Ch and ra et. al	2018	Indian Journal of Tuberculosis	Tuberculosis and other chronic morbidity profile of sewage workers of Delhi	exclude	No comparison group	NA
Chadha et. al	2019	PLoS One	Sub-national TB prevalence surveys in India, 2006-2012: Results of uniformly conducted data analysis	exclude	No comparison group	NA
Chadha et. al	2019	Indian J Tuberc	Sensitivity and specificity of screening tools and smear microscopy in active tuberculosis case finding	exclude	No relevant data / not an ACF intervention	NA
Chadha et. al	2012	PloS one	Prevalence of pulmonary tuberculosis among adults in a rural sub-district of South India	exclude	No comparison group	NA
Chan et. al	2019	Southeast Asian J. Trop. Med. Public Health	A cross sectional survey of pulmonary tuberculosis among elderly diabetics attending primary care clinics in Penang, Malaysia	exclude	No comparison group	NA
Chancellor et. al	2019	N Z Med J	Infectious pulmonary tuberculosis in a New Zealand cancer centre	exclude	No comparison group	NA
Chandra et. al	2019	Indian J Tuberc	Tuberculosis and other chronic morbidity profile of sewage workers of Delhi	exclude	No comparison group	NA
Chandrasekaran et. al	2016	Open Forum Infectious Diseases	Household contact tracing of adult pulmonary tuberculosis (TB) patients in India: Prevalence of TB disease and infection	exclude	No comparison group	NA
Charles et. al	2016	PLoS ONE	Implementation of tuberculosis intensive case finding, isoniazid preventive therapy, and infection control ("Three I's") and HIV-tuberculosis service integration in lower income countries	exclude	Healthcare based screening	NA
Charoensook et. al	2018	Journal of Infection in Developing Countries	Pulmonary tuberculosis screening and quality of life among migrant workers, Northern Thailand	exclude	No comparison group	NA
Chatla et. al	2018	The Indian journal of tuberculosis	Active case finding of rifampicin sensitive and resistant TB among household contacts of drug resistant TB patients in Andhra Pradesh and Telangana states of India - A systematic screening intervention	exclude	No comparison group	NA
Chatterjee et. al	2014	PloS one	Incidence of active pulmonary tuberculosis in patients with coincident filarial and/or intestinal helminth infections followed longitudinally in South India	include	No comparison group	Prevelance review

Author	Year	Journal	Title	Decision	mainreason	Which review?
Chauhan et. al	2013	Indian journal of pediatrics	Tuberculin Skin Test, chest radiography and contact screening in children </=5 y: relevance in Revised National Tuberculosis Control Programme (RNTCP)	exclude	No comparison group	NA
Chemeda et. al	2019	J. Clin. Tuberc. Other Microbact. Dis.	Utility of urine as a clinical specimen for the diagnosis of pulmonary tuberculosis in people living with HIV in Addis Ababa, Ethiopia	exclude	No comparison group	NA
Chen et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Community-based active case finding for tuberculosis in rural western China: a cross-sectional study	exclude	NA	NA
Chen et. al	2019	Infect Dis Poverty	Role of community-based active case finding in screening tuberculosis in Yunnan province of China	include	NA	CNR review
Chen et. al	2012	The Journal of international medical research	A tuberculosis outbreak among senior high school students in China in 2011	exclude	No comparison group	NA
Cheng et. al	2020	Infect Dis Poverty	Incidence and risk factors of tuberculosis among the elderly population in China: a prospective cohort study	exclude	No comparison group	NA
Cheng et. al	2018	Journal of occupational medicine and toxicology (London, England)	Evaluating a framework for tuberculosis screening among healthcare workers in clinical settings, Inner Mongolia, China	exclude	No comparison group	NA
Cheong et. al	2017	International Journal of Antimicrobial Agents	Prevalence and epidemiologic characteristics of latent tuberculosis infection among healthcare workers at a hospital in Seoul, South Korea	exclude	No comparison group	NA
Chheng et. al	2015	Clinical epidemiology	Tuberculosis case finding in first-degree relative contacts not living with index tuberculosis cases in Kampala, Uganda	exclude	No comparison group	NA
Chiappini et. al	2018	Acta paediatrica (Oslo, Norway : 1992)	Italian multicentre study found infectious and vaccine-preventable diseases in children adopted from Africa and recommends prompt medical screening	exclude	No comparison group	NA
Chinnakali et. al	2016	Annals of Tropical Medicine and Public Health	Active screening for tuberculosis among slum dwellers in selected urban slums of Puducherry, South India	exclude	No comparison group	NA
Chisti et. al	2014	PloS one	A prospective study of the prevalence of tuberculosis and bacteraemia in Bangladeshi children with severe malnutrition and pneumonia including an evaluation of Xpert MTB/RIF assay	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Chopra et. al	2019	Indian Journal of Tuberculosis	Cough of more than two weeks – Time to think beyond pulmonary TB	exclude	No comparison group	NA
Choun et. al	2019	Glob Health Action	Performance of algorithms for tuberculosis active case finding in underserved high-prevalence settings in Cambodia: a cross-sectional study	exclude	No comparison group	NA
Churchyard G.J. et. al	2000	International Journal of Tuberculosis and Lung Disease	Factors associated with an increased case-fatality rate in HIV-infected and non-infected South African gold miners with pulmonary tuberculosis	exclude	No relevant data / not an ACF intervention	NA
Churchyard et. al	2011	Thorax	Twelve-monthly versus six-monthly radiological screening for active case-finding of tuberculosis: a randomised controlled trial	include	NA	CNR review
Churchyard et. al	2010	AIDS (London, England)	Symptom and chest radiographic screening for infectious tuberculosis prior to starting isoniazid preventive therapy: yield and proportion missed at screening	exclude	No relevant data / not an ACF intervention	NA
Coffman et. al	2017	BMC public health	Tuberculosis among older adults in Zambia: burden and characteristics among a neglected group	exclude	No comparison group	NA
Coit et. al	2019	International Journal of Tuberculosis and Lung Disease	Performance of a household tuberculosis exposure survey among children in a Latin American setting	exclude	No comparison group	NA
Colgan et. al	2019	J Paediatr Child Health	Latent tuberculosis may be missed by current screening practices: Analysis of interferon-gamma release assay results from a paediatric refugee clinic	exclude	No comparison group	NA
Collins et. al	2019	Am J Public Health	QuantiFERON-TB Gold Versus Tuberculin Screening and Care Retention Among Persons Experiencing Homelessness: Georgia, 2015-2017	exclude	NA	NA
Coppeta et. al	2019	Open Respir Med J	Prevalence and Risk Factors for Latent Tuberculosis Infection among Healthcare Workers in a Low Incidence Country	exclude	No comparison group	NA
Corbett E.L. et. al	2009	International Journal of Tuberculosis and Lung Disease	Prevalent infectious tuberculosis in Harare, Zimbabwe: Burden, risk factors and implications for control	exclude	No comparison group	NA
Corbett et. al	2010	The Lancet	Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): A cluster-randomised trial	include	NA	Both CNR and prevelance

Author	Year	Journal	Title	Decision	mainreason	Which review?
Costa et. al	2011	Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia	Active tuberculosis among health care workers in Portugal	exclude	No comparison group	NA
Costa et. al	2010	Revista Portuguesa de Pneumologia	Comparison of interferon-Î³ release assay and tuberculin test for screening in healthcare workers	exclude	No comparison group	NA
Costa et. al	2019	European Respiratory Journal	Tuberculosis screening at social solidarity institutions	exclude	No comparison group	NA
Costenaro et. al	2016	Journal of acquired immune deficiency syndromes (1999)	Implementation and Operational Research: Implementation of the WHO 2011 Recommendations for Isoniazid Preventive Therapy (IPT) in Children Living With HIV/AIDS: A Ugandan Experience	exclude	No comparison group	NA
Cowger et. al	2017	Journal of acquired immune deficiency syndromes (1999)	Programmatic Evaluation of an Algorithm for Intensified Tuberculosis Case Finding and Isoniazid Preventive Therapy for People Living With HIV in Thailand and Vietnam	exclude	No comparison group	NA
Crampin et. al	2011	Tropical medicine & international health : TM & IH	Married to M. tuberculosis: risk of infection and disease in spouses of smear-positive tuberculosis patients	exclude	No comparison group	NA
Cranmer et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Integrating tuberculosis screening in Kenyan Prevention of Mother-To-Child Transmission programs	exclude	No comparison group	NA
Crawshaw et. al	2018	BMC medicine	Infectious disease testing of UK-bound refugees: a population-based, cross-sectional study	exclude	No comparison group	NA
Crepet et. al	2016	International health	Lessons learnt from TB screening in closed immigration centres in Italy	exclude	No comparison group	NA
Creswell et. al	2014	PloS one	An evaluation of systematic tuberculosis screening at private facilities in Karachi, Pakistan	exclude	No comparison group	NA
Cuomo et. al	2018	Journal of infection and public health	Migration and health: A retrospective study about the prevalence of HBV, HIV, HCV, tuberculosis and syphilis infections amongst newly arrived migrants screened at the Infectious Diseases Unit of Modena, Italy	exclude	No comparison group	NA
Cuomo et. al	2019	Journal of Infection and Public Health	Migration and health: A retrospective study about the prevalence of HBV, HIV, HCV, tuberculosis and syphilis infections amongst newly arrived migrants screened at the Infectious Diseases Unit of Modena, Italy	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Da Costa et. al	2010	Revista Portuguesa de Pneumologia	Tuberculosis - Risk of continued transmission in healthcare workers	exclude	No comparison group	NA
Dahiwale et. al	2011	Indian pediatrics	Significance of family survey of index case for detection of tuberculosis	exclude	No comparison group	NA
Datiko D.G. et. al	2009	PLoS ONE	Health extension workers improve tuberculosis case detection and treatment success in southern Ethiopia: A community randomized trial	include	NA	CNR review
Datiko et. al	2017	BMJ global health	Health extension workers improve tuberculosis case finding and treatment outcome in Ethiopia: a large-scale implementation study	include	NA	CNR review
Datiko et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	A community-based isoniazid preventive therapy for the prevention of childhood tuberculosis in Ethiopia	exclude	No comparison group	NA
Davarpanah et. al	2015	Galen Medical Journal	Incidence of active tuberculosis among human immunodeficiency virus (HIV)-positive patients and evaluation of their responses to usual anti-tuberculosis medications in shiraz, south west of Iran	exclude	No comparison group	NA
Davis et. al	2019	American Journal of Respiratory and Critical Care Medicine	Diagnostic accuracy of c-reactive protein for active TB in adults without HIV: A cross-sectional study	exclude	No comparison group	NA
Davis et. al	2019	ERJ open research	Home-based tuberculosis contact investigation in uganda: a household randomised trial	exclude	Fewer than 1000 people screened	NA
De Francisco et. al	2019	Journal of Crohn's and Colitis	Risk of tuberculosis in patients with inflammatory bowel disease receiving biologics using two interferon-γ release assays as monitoring	exclude	No comparison group	NA
de Glanville et. al	2019	Sci Rep	Household socio-economic position and individual infectious disease risk in rural Kenya	exclude	No comparison group	NA
De Vries G. et. al	2007	American Journal of Respiratory and Critical Care Medicine	Impact of mobile radiographic screening on tuberculosis among drug users and homeless persons	include	NA	CNR review
Debulpaep et. al	2019	Front Pediatr	Contribution of QuantiFERON-TB Gold-in-Tube to the Diagnosis of Mycobacterium tuberculosis Infection in Young Children in a Low TB Prevalence Country	exclude	No comparison group	NA
Debulpaep et. al	2020	Front Pediatr	Tuberculosis Transmission in a Primary School and a Private Language School. An Estimation of Infectivity	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Deery et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	A home tracing program for contacts of people with tuberculosis or HIV and patients lost to care	exclude	No comparison group	NA
Degner et. al	2016	Journal of correctional health care : the official journal of the National Commission on Correctional Health Care	Comparison of Digital Chest Radiography to Purified Protein Derivative for Screening of Tuberculosis in Newly Admitted Inmates	include	NA	CNR review
Degner et. al	2016	Journal of correctional health care : the official journal of the National Commission on Correctional Health Care	Comparison of Digital Chest Radiography to Purified Protein Derivative for Screening of Tuberculosis in Newly Admitted Inmates	include but duplicate	NA	NA
Del Portillo-Mustieles et. al	2013	Tuberculosis research and treatment	Active Case Finding of Pulmonary Tuberculosis through Screening of Respiratory Symptomatics Using Sputum Microscopy: Is It Time to Change the Paradigm?	exclude	No comparison group	NA
Delva et. al	2016	Tuberculosis research and treatment	Active Tuberculosis Case Finding in Port-au-Prince, Haiti: Experiences, Results, and Implications for Tuberculosis Control Programs	include	NA	CNR review
Den boon S. et. al	2008	Epidemiology and Infection	Comparison of symptoms and treatment outcomes between actively and passively detected tuberculosis cases: The additional value of active case finding	exclude	No comparison group	NA
Deng et. al	2019	Epidemiol Infect	Isolation measures and protection awareness are significant for latent tuberculosis infection: a cross-sectional study based on T-SPOT.TB among health care workers in China	exclude	No comparison group	NA
Deribew et. al	2011	PloS one	Investigation outcomes of tuberculosis suspects in the health centers of Addis Ababa, Ethiopia	exclude	No comparison group	NA
Derseh et. al	2017	BMC infectious diseases	Smear positive pulmonary tuberculosis and associated risk factors among tuberculosis suspects attending spiritual holy water sites in Northwest Ethiopia	exclude	No comparison group	NA
Desilva et. al	2018	Open Forum Infectious Diseases	An outbreak of multidrug-resistant tuberculosis, Minnesota 2016-2017	exclude	No comparison group	NA
Dey A et. al	2019	Trop Med Infect Dis	Active Case Finding for Tuberculosis through TOUCH Agents in Selected High TB Burden Wards of Kolkata, India: A Mixed Methods Study on Outcomes and Implementation Challenges	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Dey et. al	2019	Trop Med Infect Dis	Active Case Finding for Tuberculosis through TOUCH Agents in Selected High TB Burden Wards of Kolkata, India: A Mixed Methods Study on Outcomes and Implementation Challenges	exclude	No comparison group	NA
Dhanaraj et. al	2015	PloS one	Prevalence and risk factors for adult pulmonary tuberculosis in a metropolitan city of South India	exclude	No comparison group	NA
Dhungana et. al	2013	Nepal Medical College journal : NMCJ	Surveillance of tuberculosis among HIV infected persons in three different regions of Nepal	exclude	No comparison group	NA
Di Naso et. al	2018	Biochimica Clinica	The molecular laboratory in the infectious disease emergency: The model “diagnosi in banchina”	exclude	No comparison group	NA
Diendere et. al	2011	Medecine tropicale : revue du Corps de sante colonial	[Prevalence and risk factors associated with infection by human immunodeficiency virus, hepatitis B virus, syphilis and bacillary pulmonary tuberculosis in prisons in Burkina Faso]	exclude	Fewer than 1000 people screened	NA
Dierberg et. al	2016	Emerging infectious diseases	Improved Detection of Tuberculosis and Multidrug-Resistant Tuberculosis among Tibetan Refugees, India	exclude	No comparison group	NA
Dion et. al	2018	Can Commun Dis Rep	Results of a population screening intervention for tuberculosis in a Nunavik village, Quebec, 2015-2016	exclude	No comparison group	NA
Dolla et. al	2017	Transactions of the Royal Society of Tropical Medicine and Hygiene	Tuberculosis among the homeless in Chennai city, South India	exclude	No comparison group	NA
Dolla et. al	2018	Indian Journal of Tuberculosis	Burden of pulmonary tuberculosis in modern prison: A cross sectional prevalence survey from south India	exclude	No comparison group	NA
Dolla et. al	2019	Indian J Tuberc	Burden of pulmonary tuberculosis in modern prison: A cross sectional prevalence survey from south India	exclude	No comparison group	NA
Dolla et. al	2019	Transactions of the Royal Society of Tropical Medicine and Hygiene	Age-specific prevalence of TB infection among household contacts of pulmonary TB: Is it time for TB preventive therapy?	exclude	No comparison group	NA
Dorjee et. al	2018	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	High Prevalence of Active and Latent Tuberculosis in Children and Adolescents in Tibetan Schools in India: The Zero TB Kids Initiative in Tibetan Refugee Children	exclude	No comparison group	NA
Dorjee et. al	2019	Clin Infect Dis	High Prevalence of Active and Latent Tuberculosis in Children and Adolescents in Tibetan Schools in India: The Zero TB Kids Initiative in Tibetan Refugee Children	exclude	No comparison group	NA

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Drain et. al	2016	BMC pulmonary medicine	Rapid urine lipoarabinomannan assay as a clinic-based screening test for active tuberculosis at HIV diagnosis	exclude	No comparison group	NA
Drain et. al	2017	Open forum infectious diseases	Clinic-Based Urinary Lipoarabinomannan as a Biomarker of Clinical Disease Severity and Mortality Among Antiretroviral Therapy-Naive Human Immunodeficiency Virus-Infected Adults in South Africa	exclude	No comparison group	NA
Drain et. al	2014	BMC infectious diseases	Diagnostic accuracy of a point-of-care urine test for tuberculosis screening among newly-diagnosed HIV-infected adults: a prospective, clinic-based study	exclude	No comparison group	NA
Dravid et. al	2019	BMC Infect Dis	Incidence of tuberculosis among HIV infected individuals on long term antiretroviral therapy in private healthcare sector in Pune, Western India	exclude	No comparison group	NA
Drevno et. al	2020	Gastroenterology	IMPROVING TUBERCULOSIS RE SCREENING IN INFLAMMATORY BOWEL DISEASE PATIENTS RECEIVING BIOLOGIC THERAPY: A SINGLE CENTER QUALITY IMPROVEMENT INITIATIVE	exclude	No comparison group	NA
Du et. al	2017	Journal of occupational health	Prevalence of tuberculosis among health care workers in tuberculosis specialized hospitals in China	exclude	No comparison group	NA
Duarte et. al	2018	European Respiratory Journal	Tuberculosis contact investigation-5-year experience of a Portuguese ambulatory center	exclude	No comparison group	NA
Duarte et. al	2018	Multiple Sclerosis Journal	Tuberculosis screening in patients with multiple sclerosis who are candidates for natalizumab and fingolimod in a Portuguese tertiary centre	exclude	No comparison group	NA
Dur and o et. al	2016	BMJ open	Prevalence and predictors of latent tuberculosis infection among Italian State Policemen engaged in assistance to migrants: a national cross-sectional study	exclude	No comparison group	NA
Durovni et. al	2013	The Lancet. Infectious diseases	Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial	exclude	Healthcare based screening	NA
Dutta et. al	2018	PLoS ONE	Impact of involvement of non-formal health providers on TB case notification among migrant slum-dwelling populations in Odisha, India	exclude	Healthcare based screening	NA

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Eang et. al	2012	BMC public health	Early detection of tuberculosis through community-based active case finding in Cambodia	exclude	Contact tracing	NA
Ebrahimi et. al	2013	Iranian journal of psychiatry	Frequency of latent and smear positive tuberculosis in chronic psychotic disorders	exclude	No comparison group	NA
Egere et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Identifying children with tuberculosis among household contacts in The Gambia	exclude	No comparison group	NA
Ekeke et. al	2020	Adv Respir Med	Screening diabetes mellitus patients for tuberculosis in Southern Nigeria: A pilot study	exclude	No comparison group	NA
El Jihad et. al	2019	Turkish Journal of Gastroenterology	Screening for latent and patent tuberculosis in patients with cirrhosis	exclude	No comparison group	NA
Elden et. al	2011	BMC health services research	Integrating intensified case finding of tuberculosis into HIV care: an evaluation from rural Swaziland	exclude	No comparison group	NA
Endo et. al	2019	Epidemiology and Infection	A tuberculosis outbreak at an insecure, temporary housing facility, manga café, Tokyo, Japan, 2016–2017	exclude	No comparison group	NA
Enos et. al	2018	PloS one	Kenya tuberculosis prevalence survey 2016: Challenges and opportunities of ending TB in Kenya	exclude	No relevant data / not an ACF intervention	NA
Epstein et. al	2019	Int J Tuberc Lung Dis	QuantiFERON((R))-TB Gold In-Tube reliability for immigrants with parasitic infections in Boston, USA	exclude	No comparison group	NA
Epstein et. al	2019	International Journal of Tuberculosis and Lung Disease	QuantiFERON®-TB Gold In-Tube reliability for immigrants with parasitic infections in Boston, USA	exclude	No comparison group	NA
Erawati et. al	2020	J Multidiscip Healthc	The Prevalence and Demographic Risk Factors for Latent Tuberculosis Infection (LTBI) Among Healthcare Workers in Semarang, Indonesia	exclude	No comparison group	NA
Erme et. al	2017	Open Forum Infectious Diseases	A collaborative response by public health and Local Hospitals to a NICU tuberculosis exposure	exclude	No comparison group	NA
Estevan et. al	2013	Revista da Sociedade Brasileira de Medicina Tropical	Active and latent tuberculosis in prisoners in the Central-West Region of Brazil	exclude	No comparison group	NA
Faccini et. al	2013	Emerging infectious diseases	Tuberculosis outbreak in a primary school, Milan, Italy	exclude	No comparison group	NA
Fang et. al	2018	The Lancet. Public health	Travel-related infections in mainland China, 2014-16: an active surveillance study	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Fang et. al	2013	Journal of epidemiology	Outbreak of pulmonary tuberculosis in a Chinese high school, 2009-2010	exclude	No comparison group	NA
Fang et. al	2013	Journal of epidemiology	Outbreak of pulmonary tuberculosis in a Chinese high school, 2009-2010	exclude	No comparison group	NA
Farazi et. al	2015	The Pan African medical journal	Silico-tuberculosis and associated risk factors in central province of Iran	exclude	No comparison group	NA
Farhoudi et. al	2019	Infectious Disorders - Drug Targets	Prevalence of tuberculosis in a prison in tehran by active case finding	exclude	No comparison group	NA
Farhoudi et. al	2018	Infectious disorders drug targets	Prevalence of Tuberculosis in a Prison in Tehran by Active Case Finding	exclude	NA	NA
Fatima et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Success of active tuberculosis case detection among high-risk groups in urban slums in Pakistan	include	NA	CNR review
Fatima et. al	2016	PloS one	Extending 'Contact Tracing' into the Community within a 50-Metre Radius of an Index Tuberculosis Patient Using Xpert MTB/RIF in Urban, Pakistan: Did It Increase Case Detection?	include	NA	CNR review
Feasey et. al	2013	Journal of clinical microbiology	Evaluation of Xpert MTB/RIF for detection of tuberculosis from blood samples of HIV-infected adults confirms Mycobacterium tuberculosis bacteremia as an indicator of poor prognosis	exclude	No comparison group	NA
Feasey et. al	2013	Journal of clinical microbiology	Evaluation of Xpert MTB/RIF for detection of tuberculosis from blood samples of HIV-infected adults confirms Mycobacterium tuberculosis bacteremia as an indicator of poor prognosis	exclude	No comparison group	NA
Firanescu et. al	2019	Romanian Journal of Diabetes, Nutrition and Metabolic Diseases	Pulmonary Tuberculosis Screening in Patients with Diabetes Mellitus	exclude	No comparison group	NA
Floridia et. al	2017	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	Tuberculosis Case Finding With Combined Rapid Point-of-Care Assays (Xpert MTB/RIF and Determine TB LAM) in HIV-Positive Individuals Starting Antiretroviral Therapy in Mozambique	exclude	No comparison group	NA
Ford et. al	2019	Indian J Tuberc	Fifth year of a public-private partnership to improve the case detection of tuberculosis in India: A role model for future action?	include	NA	CNR review

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Fortunato et. al	2011	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Screening and follow-up of children exposed to tuberculosis cases, Luanda, Angola	exclude	No comparison group	NA
Fox et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Latent tuberculous infection in household contacts of multidrug-resistant and newly diagnosed tuberculosis	exclude	No comparison group	NA
Fox et. al	2019	The Lancet Infectious Diseases	Household contact investigation to improve tuberculosis control	exclude	Contact tracing	NA
Fox et. al	2012	PloS one	Contact investigation in households of patients with tuberculosis in Hanoi, Vietnam: a prospective cohort study	exclude	No comparison group	NA
Freeman et. al	2012	The New Zealand medical journal	Screening for Mycobacterium tuberculosis infection among healthcare workers in New Zealand: prospective comparison between the tuberculin skin test and the QuantiFERON-TB Gold In-Tube assay	exclude	No comparison group	NA
Fröberg et. al	2020	European Respiratory Journal	Screening and treatment of tuberculosis among pregnant women in Stockholm, Sweden, 2016–2017	exclude	No comparison group	NA
Fuge et. al	2016	BMC research notes	Prevalence of smear positive pulmonary tuberculosis and associated risk factors among prisoners in Hadiya Zone prison, Southern Ethiopia	exclude	No comparison group	NA
Gadallah et. al	2019	J Prev Med Hyg	Multicenter screening of diabetic patients for detecting new cases of tuberculosis: an approach to intensify the case detection rate of tuberculosis in developing countries with high prevalence of diabetes	exclude	No comparison group	NA
Ganmaa et. al	2019	BMC Infect Dis	Risk factors for active tuberculosis in 938 QuantiFERON-positive schoolchildren in Mongolia: a community-based cross-sectional study	exclude	No comparison group	NA
Ganmaa et. al	2019	Clin Infect Dis	Prevalence and Determinants of QuantiFERON-Diagnosed Tuberculosis Infection in 9810 Mongolian Schoolchildren	exclude	No comparison group	NA
Gao et. al	2017	The Lancet. Infectious diseases	Incidence of active tuberculosis in individuals with latent tuberculosis infection in rural China: follow-up results of a population-based, multicentre, prospective cohort study	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Gao et. al	2017	The Lancet. Infectious diseases	Incidence of active tuberculosis in individuals with latent tuberculosis infection in rural China: follow-up results of a population-based, multicentre, prospective cohort study	exclude	No comparison group	NA
GarcÃa-GarcÃa Ma.D.L. et. al	2000	International Journal of Tuberculosis and Lung Disease	The role of core groups in transmitting Mycobacterium tuberculosis in a high prevalence community in Southern Mexico	exclude	No comparison group	NA
Garrido et. al	2012	Pediatric pulmonology	Usefulness of thoracic CT to diagnose tuberculosis disease in patients younger than 4 years of age	exclude	No comparison group	NA
Gashu et. al	2016	PloS one	The Yield of Community-Based "Retrospective" Tuberculosis Contact Investigation in a High Burden Setting in Ethiopia	exclude	No comparison group	NA
Gebrecherkos et. al	2019	Transactions of the Royal Society of Tropical Medicine and Hygiene	Prevalence, HIV co-infection and multi-drug resistance of smear positive pulmonary tuberculosis in prison settings of Northwest Ethiopia	exclude	No comparison group	NA
Gebrecherkos et. al	2016	BMC public health	Smear positive pulmonary tuberculosis and HIV co-infection in prison settings of North Gondar Zone, Northwest Ethiopia	exclude	No comparison group	NA
Gebrecherkos et. al	2016	BMC public health	Smear positive pulmonary tuberculosis and HIV co-infection in prison settings of North Gondar Zone, Northwest Ethiopia	exclude	No comparison group	NA
Gebreegziabiher et. al	2017	International journal of mycobacteriology	A survey on undiagnosed active pulmonary tuberculosis among pregnant mothers in mekelle and surrounding Districts in Tigray, Ethiopia	exclude	No comparison group	NA
Gedfew et. al	2020	Diabetes Metab Syndr Obes	Incidence and Predictors of Tuberculosis among Adult Diabetic Patients, Debre Markos Referral Hospital, Northwest Ethiopia, 2018: A Retrospective Cohort Study	exclude	No comparison group	NA
Gijón et. al	2016	Open Forum Infectious Diseases	Tuberculosis outbreak in a nursery school: A process developed during three years	exclude	No comparison group	NA
Gizachew Beza et. al	2017	International journal of bacteriology	Prevalence and Associated Factors of Tuberculosis in Prisons Settings of East Gojjam Zone, Northwest Ethiopia	exclude	No comparison group	NA
Gizachew Beza et. al	2017	International journal of bacteriology	Prevalence and Associated Factors of Tuberculosis in Prisons Settings of East Gojjam Zone, Northwest Ethiopia	exclude	No comparison group	NA
Glynn J.R. et. al	1998	Bulletin of the World Health Organization	Measurement and determinants of tuberculosis outcome in Karonga District, Malawi	exclude	No relevant data / not an ACF intervention	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Godfrey-Faussett et. al	1995	Transactions of the royal society of tropical medicine and hygiene	Recruitment to a trial of tuberculosis preventive therapy from a voluntary HIV testing centre in Lusaka: relevance to implementation	exclude	No comparison group	NA
Goletti et. al	2020	Int J Infect Dis	Latent tuberculosis infection screening in persons newly-diagnosed with HIV infection in Italy: A multicentre study promoted by the Italian Society of Infectious and Tropical Diseases	exclude	No comparison group	NA
Golla et. al	2017	BMC infectious diseases	The impact of drug resistance on the risk of tuberculosis infection and disease in child household contacts: a cross sectional study	exclude	No comparison group	NA
GonzÃ¡lez-Ochoa E. et. al	2009	Tropical Medicine and International Health	Pulmonary tuberculosis case detection through fortuitous cough screening during home visits	exclude	NA	NA
Gopi P.G. et. al	2005	Indian J Tuberc	Failure to initiate treatment for tuberculosis patients diagnosed in a community survey and at health facilities under a DOTS programme in a district of South India	exclude	No comparison group	NA
Gopi P.G. et. al	2006	International Journal of Tuberculosis and Lung Disease	Yield of pulmonary tuberculosis cases by employing two screening methods in a community survey	exclude	No comparison group	NA
Gounder et. al	2011	Journal of acquired immune deficiency syndromes (1999)	Diagnostic accuracy of a urine lipoarabinomannan enzyme-linked immunosorbent assay for screening ambulatory HIV-infected persons for tuberculosis	exclude	No comparison group	NA
Gounder et. al	2011	Journal of acquired immune deficiency syndromes (1999)	Active tuberculosis case-finding among pregnant women presenting to antenatal clinics in Soweto, South Africa	exclude	No comparison group	NA
Govindasamy et. al	2013	PloS one	Linkage to HIV, TB and non-communicable disease care from a mobile testing unit in Cape Town, South Africa	exclude	No comparison group	NA
Gr and jean et. al	2011	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis in household contacts of multidrug-resistant tuberculosis patients	exclude	No comparison group	NA
Graves et. al	2019	BMC Infect Dis	Tuberculosis infection risk, preventive therapy care cascade and incidence of tuberculosis disease in healthcare workers at Maputo Central Hospital	exclude	No comparison group	NA
Gray et. al	2020	J Public Health (Oxf)	Investigating the prevalence of latent Tuberculosis infection in a UK remand prison	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Guerra et. al	2019	PloS one	Active and latent tuberculosis among inmates in La Esperanza prison in Guaduas, Colombia	exclude	No comparison group	NA
Guillen et. al	2019	European Respiratory Journal	TB status in a dynamic cohort of patients with inflammatory bowel disease receiving immunosuppression treatment, with up to 8 years of follow-up	exclude	No comparison group	NA
Gunasekera et. al	2020	Int J Tuberc Lung Dis	Smoking and HIV associated with subclinical tuberculosis: analysis of a population-based prevalence survey	exclude	No comparison group	NA
Guo et. al	2019	BMC Infect Dis	High incidence and low case detection rate among contacts of tuberculosis cases in Shanghai, China	exclude	No comparison group	NA
Guo et. al	2020	Epidemiology and Infection	An office building outbreak: The changing epidemiology of tuberculosis in Shenzhen, China	exclude	No comparison group	NA
Gupta-Wright et. al	2018	Lancet (London, England)	Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial	exclude	No comparison group	NA
Gupta et. al	2011	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	Symptom screening among HIV-infected pregnant women is acceptable and has high negative predictive value for active tuberculosis	exclude	No comparison group	NA
Gupta et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Active case finding for tuberculosis among people who inject drugs on methadone treatment in Dar es Salaam, Tanzania	exclude	No comparison group	NA
Gupta et. al	2019	N Engl J Med	Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women	exclude	Fewer than 1000 people screened	NA
Gupta et. al	2020	Clinical Infectious Diseases	Feasibility of identifying household contacts of rifampinand multidrug-resistant tuberculosis cases at high risk of progression to tuberculosis disease	exclude	No comparison group	NA
Gupta et. al	2016	Lung India : official organ of Indian Chest Society	Household symptomatic contact screening of newly diagnosed sputum smears positive tuberculosis patients - An effective case detection tool	exclude	No comparison group	NA
Gupta et. al	2015	Journal of human reproductive sciences	Should men with idiopathic obstructive azoospermia be screened for genitourinary tuberculosis?	exclude	No comparison group	NA

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Gupta et. al	2018	Thorax	Yield and cost of screening for active and latent tuberculosis among high-risk groups attending London emergency departments	exclude	No comparison group	NA
Gupta et. al	2013	JK Practitioner	Prevalence of tuberculosis in a rural population aged 15 years and above in R.S. pura block of district JAMMU	exclude	No comparison group	NA
Gurjav et. al	2019	Int. J. Tuberc. Lung Dis.	Vitamin D deficiency is associated with tuberculosis infection among household contacts in Ulaanbaatar, Mongolia	exclude	No comparison group	NA
Gurung et. al	2019	Infect Dis Poverty	The role of active case finding in reducing patient incurred catastrophic costs for tuberculosis in Nepal	exclude	Fewer than 1000 people screened	NA
Guwatudde D. et. al	2003	Bulletin of the World Health Organization	Burden of tuberculosis in Kampala, Uganda	exclude	No comparison group	NA
Gyawali et. al	2012	Nepal Medical College journal : NMCJ	Prevalence of tuberculosis in household contacts of sputum smears positive cases and associated demographic risk factors	exclude	No comparison group	NA
Gyawali et. al	2013	Nepal Medical College journal : NMCJ	Tobacco and alcohol: the relation to pulmonary tuberculosis in household contacts	exclude	Contact tracing	NA
Habib et. al	2019	European Respiratory Journal	Utilizing chest X-ray based active case finding approach for early tuberculosis case detection in Pakistan	exclude	No comparison group	NA
Habte et. al	2016	International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases	The additional yield of GeneXpert MTB/RIF test in the diagnosis of pulmonary tuberculosis among household contacts of smear positive TB cases	exclude	No comparison group	NA
Hamdi et. al	2019	European Respiratory Journal	How to conduct a screening of tuberculosis in children with a household contact	exclude	No comparison group	NA
Hamusse et. al	2017	BMC infectious diseases	Prevalence and Incidence of Smear-Positive Pulmonary Tuberculosis in the Hetosa District of Arsi Zone, Oromia Regional State of Central Ethiopia	exclude	NA	NA
Han et. al	2019	BMC infectious diseases	Epidemiology survey of infectious diseases in North Korean travelers, 2015-2017	exclude	No comparison group	NA
Han et. al	2019	BMC infectious diseases	Epidemiology survey of infectious diseases in North Korean travelers, 2015-2017	exclude	No comparison group	NA
Han et. al	2019	PLoS One	Evaluation and treatment of latent tuberculosis infection among healthcare workers in Korea: A multicentre cohort analysis	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Hanifa et. al	2012	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis among adults starting antiretroviral therapy in South Africa: the need for routine case finding	exclude	No comparison group	NA
Hanifa et. al	2016	PloS one	Diagnostic Accuracy of Lateral Flow Urine LAM Assay for TB Screening of Adults with Advanced Immunosuppression Attending Routine HIV Care in South Africa	exclude	No comparison group	NA
Hanifa et. al	2015	PloS one	The diagnostic accuracy of urine lipoarabinomannan test for tuberculosis screening in a South African correctional facility	exclude	No comparison group	NA
Hanrahan et. al	2019	Paediatr Int Child Health	Diagnostic strategies for childhood tuberculosis in the context of primary care in a high burden setting: the value of alternative sampling methods	exclude	No comparison group	NA
Hanrahan et. al	2019	PLoS Med	Contact tracing versus facility-based screening for active TB case finding in rural South Africa: A pragmatic cluster-randomized trial (Kharitode TB)	exclude	Healthcare based screening	NA
Hansen et. al	2019	European Respiratory Journal	Benefits of a municipality tuberculosis screening program among socially vulnerable citizens	exclude	No comparison group	NA
Hargreaves et. al	2020	Travel Med Infect Dis	Delivering multi-disease screening to migrants for latent TB and blood-borne viruses in an emergency department setting: A feasibility study	exclude	No comparison group	NA
Harper I. et. al	1996	Tubercle and Lung Disease	Tuberculosis case finding in remote mountainous areas - Are microscopy camps of any value? Experience from Nepal	exclude	No comparison group	NA
Harries A.D. et. al	2004	International Journal of Tuberculosis and Lung Disease	Tuberculosis control in Malawian prisons: From research to policy and practice	exclude	NA	NA
Harstad et. al	2010	BMC public health	The role of entry screening in case finding of tuberculosis among asylum seekers in Norway	exclude	No comparison group	NA
Haynie et. al	2017	Open Forum Infectious Diseases	Interdisciplinary public health intervention in a multigenerational tuberculosis (TB) outbreak in harris county, Texas: A case study with implications for disease control process improvement and transmission cycle interruption	exclude	No comparison group	NA
Hazard et. al	2016	Infection control and hospital epidemiology	Hidden Reservoir: An Outbreak of Tuberculosis in Hospital Employees with No Patient Contact	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Hazra et. al	2019	Journal of Pure and Applied Microbiology	Same day sputum microscopy for screening of pulmonary tuberculosis: Its accuracy and usefulness in comparison with conventional method	exclude	Healthcare based screening	NA
He et. al	2010	BMC Infectious Diseases	Infection control and the burden of tuberculosis infection and disease in health care workers in china: A cross-sectional study	exclude	No comparison group	NA
He et. al	2017	Infectious diseases of poverty	Use of low-dose computed tomography to assess pulmonary tuberculosis among healthcare workers in a tuberculosis hospital	exclude	No comparison group	NA
Henostroza et. al	2016	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	High prevalence of tuberculosis in newly enrolled HIV patients in Zambia: need for enhanced screening approach	exclude	No comparison group	NA
Henostroza et. al	2013	PloS one	The high burden of tuberculosis (TB) and human immunodeficiency virus (HIV) in a large Zambian prison: a public health alert	exclude	No comparison group	NA
Herchline et. al	2018	Open Forum Infectious Diseases	Treatment of latent tuberculosis infection in a refugee population	exclude	No comparison group	NA
Hermans et. al	2012	BMC public health	Implementation and effect of intensified case finding on diagnosis of tuberculosis in a large urban HIV clinic in Uganda: a retrospective cohort study	exclude	Healthcare based screening	NA
Hern and ez Sarmiento et. al	2013	Journal of immigrant and minority health	Tuberculosis among homeless population from Medellin, Colombia: associated mental disorders and socio-demographic characteristics	exclude	No comparison group	NA
Hern and ez Sarmiento et. al	2013	Journal of immigrant and minority health	Tuberculosis in indigenous communities of Antioquia, Colombia: epidemiology and beliefs	exclude	No comparison group	NA
Hern and ez-Leon et. al	2012	Salud publica de Mexico	[Active tuberculosis in a cohort of HIV-infected inmates in a prison in Mexico City: clinical and epidemiological characteristics]	exclude	Fewer than 1000 people screened	NA
Hernan Garcia et. al	2016	Archivos de bronconeumologia	Outbreak of isoniazid-resistant tuberculosis in an immigrant community in Spain	exclude	No comparison group	NA
Hiruy et. al	2018	International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases	Comparison of the yield of tuberculosis among contacts of multidrug-resistant and drug-sensitive tuberculosis patients in Ethiopia using GeneXpert as a primary diagnostic test	exclude	Fewer than 1000 people screened	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Hladun et. al	2014	Journal of travel medicine	Results from screening immigrants of low-income countries: data from a public primary health care	exclude	No comparison group	NA
Ho et. al	2016	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	The role of macroscopic sputum quality assessments to optimise sputum testing for tuberculosis	exclude	No comparison group	NA
Ho et. al	2016	The Lancet. Infectious diseases	Reassessment of the positive predictive value and specificity of Xpert MTB/RIF: a diagnostic accuracy study in the context of community-wide screening for tuberculosis	exclude	No relevant data / not an ACF intervention	NA
Hoa N.B. et. al	2010	Bulletin of the World Health Organization	National survey of tuberculosis prevalence in Viet Nam [EnquÃªte nationale sur la prÃ©valence de la tuberculose au Viet Nam]	exclude	No comparison group	NA
Hoang et. al	2019	BMC Public Health	Active contact tracing beyond the household in multidrug resistant tuberculosis in Vietnam: a cohort study	exclude	Fewer than 1000 people screened	NA
Hoffmann et. al	2013	PloS one	High prevalence of pulmonary tuberculosis but low sensitivity of symptom screening among HIV-infected pregnant women in South Africa	exclude	No comparison group	NA
Hom et. al	2012	PloS one	Drug-resistant tuberculosis among HIV-infected patients starting antiretroviral therapy in Durban, South Africa	exclude	No comparison group	NA
Honarvar et. al	2013	Journal of addiction medicine	Pulmonary and latent tuberculosis screening in opiate drug users: an essential and neglected approach for harm-reduction facilities	exclude	No comparison group	NA
Honarvar et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Pulmonary tuberculosis in migratory nomadic populations: the missing link in Iran's National Tuberculosis Programme	exclude	No comparison group	NA
Hong Y.P. et. al	2000	International Journal of Tuberculosis and Lung Disease	Twenty-year trend of chronic excretors of tubercle bacilli based on the nationwide tuberculosis prevalence surveys in Korea, 1975-1995	exclude	No relevant data / not an ACF intervention	NA
Hong Y.P. et. al	1993	Tubercle and Lung Disease	The sixth Nationwide Tuberculosis Prevalence Survey in Korea, 1990	exclude	No relevant data / not an ACF intervention	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Honjepari et. al	2019	Public Health Action	Implementation of screening and management of household contacts of tuberculosis cases in Daru, Papua New Guinea	exclude	No comparison group	NA
Hopkins et. al	2019	BMJ Open	Demographics and health profile on precursors of non-communicable diseases in adults testing for HIV in Soweto, South Africa: a cross-sectional study	exclude	No comparison group	NA
Horton et. al	2019	Open Forum Infectious Diseases	Public health at the United States/Mexico Border: evaluation of the county of San Diego health and human services agency's health screening assessment of asylum-seeking families at The San Diego rapid response network shelter	exclude	No comparison group	NA
Hoseinpoor et. al	2017	Int. J. Pediatr.	Evaluation of active case finding (ACF) of tuberculosis in slums population in North of Iran	exclude	No comparison group	NA
Hosten et. al	2018	Conflict and health	Tuberculosis contact-tracing among Syrian refugee populations: lessons from Jordan	exclude	No comparison group	NA
Hou et. al	2020	Am J Trop Med Hyg	Outbreak of Mycobacterium tuberculosis Beijing Strain in a High School in Yunnan, China	exclude	No comparison group	NA
Hsieh et. al	2019	Respir Care	The Risk of Latent Tuberculosis Infection in Respiratory Therapists in a Country with Intermediate Incidence	exclude	No comparison group	NA
Htet et. al	2018	BMC infectious diseases	Improving detection of tuberculosis among household contacts of index tuberculosis patients by an integrated approach in Myanmar: a cross-sectional study	exclude	No comparison group	NA
Huang et. al	2019	J Infect Dev Ctries	Enhanced directly-observed treatment short-course for tuberculosis control program in mountain areas of Taiwan	exclude	Contact tracing	NA
Huerga et. al	2019	Arch Dis Child	High prevalence of infection and low incidence of disease in child contacts of patients with drug-resistant tuberculosis: a prospective cohort study	exclude	No comparison group	NA
Humphreys et. al	2018	Thorax	Screening contacts of patients with extrapulmonary TB for latent TB infection	exclude	No comparison group	NA
Hussain et. al	2019	Indian Journal of Public Health Research and Development	Associated factors of latent tuberculosis among diabetics in Urban Health Clinics	exclude	No comparison group	NA
Hussain et. al	2020	PLoS One	Prevalence, risk factors and health seeking behaviour of pulmonary tuberculosis in four tribal dominated districts of Odisha: Comparison with studies in other regions of India	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Hwang et. al	2019	Pediatric Infection and Vaccine	Childhood tuberculosis contact investigation and treatment of latent tuberculosis infection: A single center study, 2014–2017	exclude	No comparison group	NA
Igari et. al	2019	J Infect Chemother	Positivity rate of interferon-gamma release assays for estimating the prevalence of latent tuberculosis infection in renal transplant recipients in Japan	exclude	No comparison group	NA
Igari et. al	2019	Journal of Infection and Chemotherapy	Positivity rate of interferon-γ release assays for estimating the prevalence of latent tuberculosis infection in renal transplant recipients in Japan	exclude	No comparison group	NA
Imsanguan et. al	2020	Bull World Health Organ	Contact tracing for tuberculosis, Thailand	exclude	No comparison group	NA
Ines et. al	2018	European Respiratory Journal	Evaluation of Tuberculin skin test size and risk of tuberculosis in children household contact	exclude	No comparison group	NA
Iqbal et. al	2019	J. Pak. Med. Assoc.	Mycobacterium tuberculosis infection and resistance to rifampicin with GeneXpert®MTB/RIF: A single-center experience on bronchoalveolar lavage samples in renal failure patients	exclude	No comparison group	NA
Iqbal et. al	2019	Journal of Postgraduate Medical Institute	Causes and outcome of pleural effusion in children in a tertiary care hospital of Peshawar, Pakistan	exclude	No comparison group	NA
Iqbal et. al	2019	European Respiratory Journal	Validity of Pleural Fluid Protein in differentiating Tuberculous from Malignant Pleural Effusion	exclude	Healthcare based screening	NA
Iroezindu et. al	2016	Annals of medical and health sciences research	Factors Associated with Prevalent Tuberculosis Among Patients Receiving Highly Active Antiretroviral Therapy in a Nigerian Tertiary Hospital	exclude	No comparison group	NA
Isaakidis et. al	2014	PloS one	Alarming levels of drug-resistant tuberculosis in HIV-infected patients in metropolitan Mumbai, India	exclude	No comparison group	NA
Izumi et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Evaluation of tuberculosis contact investigations in Japan	exclude	No comparison group	NA
Jacob et. al	2013	PloS one	Mycobacterium tuberculosis bacteremia in a cohort of hiv-infected patients hospitalized with severe sepsis in uganda-high frequency, low clinical suspicion [corrected] and derivation of a clinical prediction score	exclude	No comparison group	NA

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Jada et. al	2015	Research Journal of Pharmaceutical, Biological and Chemical Sciences	A comparison of clinical, laboratory and radiological imaging in assessing prevalence of pulmonary tuberculosis among adults in rural Kancheepuram, Tamil Nadu, India	exclude	No comparison group	NA
Jaganath et. al	2013	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	Contact investigation for active tuberculosis among child contacts in Uganda	exclude	No comparison group	NA
Jain et. al	2015	Asian Pacific Journal of Tropical Disease	Surveillance of tuberculosis co-infection among HIV infected patients and their CD4+ cell count profile	exclude	No comparison group	NA
Jamal et. al	2019	European Respiratory Journal	Active case finding for tuberculosis among prisoners in Karachi, Pakistan	exclude	No comparison group	NA
Jana et. al	2019	American Journal of Respiratory and Critical Care Medicine	Role of loop mediated isothermal amplification assay in detecting mycobacterium tuberculosis	exclude	No comparison group	NA
Janagond et. al	2017	International journal of mycobacteriology	Screening of health-care workers for latent tuberculosis infection in a Tertiary Care Hospital	exclude	No comparison group	NA
Janda et. al	2020	PLoS Med	Comprehensive infectious disease screening in a cohort of unaccompanied refugee minors in Germany from 2016 to 2017: A cross-sectional study	exclude	No comparison group	NA
Janssens et. al	2017	BMC infectious diseases	Screening for tuberculosis in an urban shelter for homeless in Switzerland: a prospective study	exclude	No comparison group	NA
Jasper et. al	2020	J Postgrad Med	Is routine pre-entry chest radiograph necessary in a high tuberculosis prevalence country?	exclude	No comparison group	NA
Javaid et. al	2016	Asian Pacific journal of tropical medicine	Screening outcomes of household contacts of multidrug-resistant tuberculosis patients in Peshawar, Pakistan	exclude	No comparison group	NA
Jayasooriya et. al	2019	Transactions of the Royal Society of Tropical Medicine and Hygiene	The hidden burden of chronic respiratory disease in patients attending tb clinics in the Gambia	exclude	No comparison group	NA
Jensen et. al	2016	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Impact of contact investigation and tuberculosis screening among high-risk groups in Denmark	exclude	No comparison group	NA
Jensen et. al	2015	Thorax	Screening for TB by sputum culture in high-risk groups in Copenhagen, Denmark: a novel and promising approach	exclude	No comparison group	NA

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Jenum et. al	2018	BMJ open respiratory research	Incidence of tuberculosis and the influence of surveillance strategy on tuberculosis case-finding and all-cause mortality: a cluster randomised trial in Indian neonates vaccinated with BCG	exclude	ACF in children only	NA
Jereb J. et. al	2003	International Journal of Tuberculosis and Lung Disease	Tuberculosis contact investigations: Outcomes in selected areas of the United States, 1999	exclude	No comparison group	NA
Jerene et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis along the continuum of HIV care in a cohort of adolescents living with HIV in Ethiopia	exclude	No comparison group	NA
Jerene et. al	2017	International health	The yield and feasibility of integrated screening for TB, diabetes and HIV in four public hospitals in Ethiopia	exclude	No comparison group	NA
Jerene et. al	2015	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	The yield of a tuberculosis household contact investigation in two regions of Ethiopia	exclude	No comparison group	NA
Ji et. al	2020	Int J Infect Dis	Screening for pulmonary tuberculosis in high-risk groups of diabetic patients	exclude	No comparison group	NA
Jia et. al	2014	BMC infectious diseases	Tuberculosis burden in China: a high prevalence of pulmonary tuberculosis in household contacts with and without symptoms	exclude	No comparison group	NA
Jimenez-Fuentes et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Screening for active tuberculosis in high-risk groups	exclude	No comparison group	NA
John et. al	2015	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis among nomads in Adamawa, Nigeria: outcomes from two years of active case finding	include	NA	CNR review
Jordan et. al	2019	Int J Tuberc Lung Dis	Prevalence and risk factors of tuberculosis disease in South African correctional facilities in 2015	exclude	No comparison group	NA
Josaphat et. al	2014	Revista portuguesa de pneumologia	Tuberculosis: which patients do not identify their contacts?	exclude	No comparison group	NA

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Joshi et. al	2015	Public health action	Impact of intensified case-finding strategies on childhood TB case registration in Nepal	exclude	ACF in children only	NA
Joshi et. al	2017	Bulletin of the World Health Organization	Peer-led active tuberculosis case-finding among people living with HIV: lessons from Nepal	exclude	No comparison group	NA
Kaiser et. al	2015	MMWR. Morbidity and mortality weekly report	Rapid large-scale deployment of tuberculosis testing in a high school - Riverside County, California, 2013-2014	exclude	No comparison group	NA
Kakar et. al	2018	Pak. J. Zool.	Study on accuracy and efficiency of molecular diagnostic techniques used for tuberculosis and analysis of associated risk factors for tuberculosis in jail inmates of Quetta, Pakistan	exclude	No comparison group	NA
Kakinda et. al	2016	BMC public health	A comparision of the yield of three tuberculosis screening modalities among people living with HIV: a retrospective quasi-experiemental study	exclude	Healthcare based screening	NA
Kall et. al	2012	BMC infectious diseases	Latent and subclinical tuberculosis in HIV infected patients: a cross-sectional study	exclude	No comparison group	NA
Kalonji et. al	2016	Tropical medicine and health	Prevalence of tuberculosis and associated risk factors in the Central Prison of Mbuji-Mayi, Democratic Republic of Congo	exclude	No comparison group	NA
Kambali et. al	2015	Journal of community health	A workplace tuberculosis case investigation in the presence of immigrant contacts from high prevalence countries	exclude	No comparison group	NA
Kamenska et. al	2019	J Infect Dev Ctries	Strategies for active detection of tuberculosis in Ukraine: Comparative effectiveness amongst key populations (2014-2018)	exclude	NA	NA
Kan et. al	2012	Public health action	Mobilising elementary and secondary school students for tuberculosis case finding in Anhui, China	include	NA	CNR review
Kancheya et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Integrating active tuberculosis case finding in antenatal services in Zambia	exclude	No comparison group	NA
Kapadiya et. al	2018	Indian journal of community medicine : official publication of Indian Association of Preventive & Social Medicine	Assessment of Tuberculosis Prevalence in Newly Diagnosed Human Immunodeficiency Virus-Infected Adults Attending Care and Treatment Center in Gujarat, India	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Kapata et. al	2016	PloS one	The Prevalence of Tuberculosis in Zambia: Results from the First National TB Prevalence Survey, 2013-2014	exclude	No comparison group	NA
Karamagi et. al	2018	BMC health services research	Improving TB case notification in northern Uganda: evidence of a quality improvement-guided active case finding intervention	include	NA	CNR review
Karki et. al	2017	Asia-Pacific journal of public health	Active Community-Based Case Finding for Tuberculosis With Limited Resources	exclude	No comparison group	NA
Kaswa et. al	2015	Tropical Medicine and International Health	Outbreak investigation of tuberculosis and multidrugresistant tuberculosis in the central prison of Mbuji-Mayi the diamond capital of the Democratic Republic of Congo	exclude	No comparison group	NA
Katelaris et. al	2020	J Infect Dis	Effectiveness of BCG Vaccination Against Mycobacterium tuberculosis Infection in Adults: A Cross-sectional Analysis of a UK-Based Cohort	exclude	No comparison group	NA
Kato-Maeda et. al	2019	Int J Tuberc Lung Dis	Magnitude of Mycobacterium tuberculosis transmission among household and non-household contacts of TB patients	exclude	No comparison group	NA
Keane V.P. et. al	1995	The Southeast Asian journal of tropical medicine and public health	Prevalence of tuberculosis in Vietnamese migrants: the experience of the Orderly Departure Program.	exclude	No comparison group	NA
Kebede et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	The first population-based national tuberculosis prevalence survey in Ethiopia, 2010-2011	exclude	No comparison group	NA
Kempker et. al	2012	Journal of immigrant and minority health	Quality improvement of tuberculosis screening in foreign-born patients	exclude	No comparison group	NA
Kempker et. al	2019	Open Forum Infect Dis	High Yield of Active Tuberculosis Case Finding Among HIV-Infected Patients Using Xpert MTB/RIF Testing	exclude	No comparison group	NA
Kerkhoff et. al	2020	N Engl J Med	Community-wide Screening for Tuberculosis	exclude	No relevant data / not an ACF intervention	NA
Kerkhoff et. al	2013	PLoS ONE	Blood Neutrophil Counts in HIV-Infected Patients with Pulmonary Tuberculosis: Association with Sputum Mycobacterial Load	exclude	No comparison group	NA
Khan A.J. et. al	2012	The Lancet Infectious Diseases	Engaging the private sector to increase tuberculosis case detection: An impact evaluation study	exclude	Healthcare based screening	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Khan et. al	2016	Annals of global health	Active Case Finding of Tuberculosis: Randomized Evaluation of Simple and Infotainment Chest Camps	exclude	No relevant data / not an ACF intervention	NA
Khanal et. al	2016	Public health action	Yield of intensified tuberculosis case-finding activities using Xpert((R)) MTB/RIF among risk groups in Nepal	exclude	No comparison group	NA
Khaparde et. al	2015	Tuberculosis research and treatment	Evaluation of TB Case Finding through Systematic Contact Investigation, Chhattisgarh, India	exclude	No comparison group	NA
Khatana et. al	2019	Journal of Clinical Tuberculosis and Other Mycobacterial Diseases	Effectiveness, acceptance and feasibility of home-based intervention model for tuberculosis contact tracing in Kashmir	exclude	No comparison group	NA
Khatana et. al	2017	The Indian journal of tuberculosis	Factors affecting applicability of "home-based interventional model" for active case finding among household contacts of index cases of pulmonary tuberculosis in Kashmir	exclude	Fewer than 1000 people screened	NA
Khonelidze et. al	2019	Journal of Hepatology	Piloting of integrated HCV, TB and HIV screening model at primary care level in Georgia	exclude	No comparison group	NA
Kiertiburanakul et. al	2012	The Journal of hospital infection	Five-year prospective study of tuberculin skin testing among new healthcare personnel at a university hospital in Thailand	exclude	No comparison group	NA
Kigozi et. al	2019	BMC Public Health	Yield of systematic household contact investigation for tuberculosis in a high-burden metropolitan district of South Africa	exclude	No comparison group	NA
Kim et. al	2019	Tuberc Respir Dis (Seoul)	Experiences of Latent Tuberculosis Infection Treatment for the North Korean Refugees	exclude	No comparison group	NA
Kim et. al	2019	Tuberc Respir Dis (Seoul)	A Pilot Project of Systematic Tuberculosis Screening in the Elderly in a South Korean Province	exclude	No comparison group	NA
Kim et. al	2020	Tuberc Respir Dis (Seoul)	One Step toward a Low Tuberculosis-Burden Country: Screening for Tuberculosis Infection among the Immigrants and Refugees	exclude	No relevant data / not an ACF intervention	NA
Kim et. al	2020	Int J Tuberc Lung Dis	Symptom and digital chest X-ray TB screening in South African prisons: yield and cost-effectiveness	exclude	No comparison group	NA
Kim et. al	2012	Journal of Acquired Immune Deficiency Syndromes	Symptom screen for identification of highly infectious tuberculosis in people living with HIV in Southeast Asia	exclude	No comparison group	NA
Kim et. al	2020	Korean Journal of Internal Medicine	Quantiferon-tb gold plus versus quantifer-on-tb gold in-tube test for diagnosing tuberculosis infection	exclude	Fewer than 1000 people screened	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Kim et. al	2017	Archives of environmental & occupational health	In-hospital contact investigation among health care workers after exposure to pulmonary tuberculosis in an intermediate tuberculosis prevalence area: A prospective study	exclude	No comparison group	NA
Kinikar et. al	2019	PLoS One	High risk for latent tuberculosis infection among medical residents and nursing students in India	exclude	No comparison group	NA
Kirkpatrick et. al	2006	Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin	Investigation of a tuberculosis cluster at a job centre in Manchester, United Kingdom	exclude	No comparison group	NA
Kisa et. al	2016	Tuberkuloz ve toraks	Tuberculosis screening and efficacy of prophylaxis in contacts of patients with pulmonary tuberculosis	exclude	No comparison group	NA
Kliner et. al	2013	Public health action	Development and testing of models of tuberculosis contact tracing in rural southern Africa	exclude	No comparison group	NA
Koenig et. al	2015	Bulletin of the World Health Organization	Tuberculosis in the aftermath of the 2010 earthquake in Haiti	exclude	No comparison group	NA
Koenig et. al	2015	Bulletin of the World Health Organization	Tuberculosis in the aftermath of the 2010 earthquake in Haiti	exclude	No comparison group	NA
Koesoemadinata et. al	2018	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Computer-assisted chest radiography reading for tuberculosis screening in people living with diabetes mellitus	exclude	No comparison group	NA
Koffi N. et. al	1997	International Journal of Tuberculosis and Lung Disease	Smear positive pulmonary tuberculosis in a prison setting: Experience in the penal camp of BouakÃ©, Ivory Coast	exclude	No comparison group	NA
Kolappan et. al	2013	The Indian journal of tuberculosis	Trends in the prevalence of pulmonary tuberculosis over a period of seven and half years in a rural community in south India with DOTS	include but duplicate	NA	Prevelance review
Kortas et. al	2017	Public health	Screening for infectious diseases among asylum seekers newly arrived in Germany in 2015: a systematic single-centre analysis	exclude	No comparison group	NA
Kosgei et. al	2011	Public health action	Symptom screen: diagnostic usefulness in detecting pulmonary tuberculosis in HIV-infected pregnant women in Kenya	exclude	No comparison group	NA
Kosgei et. al	2013	Public health action	Screening for tuberculosis in pregnancy: do we need more than a symptom screen? Experience from western Kenya	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Krain et. al	2019	Journal of Investigative Dermatology	571 Comparing the performance of two interferon-gamma release assays in autoimmune skin disease patients: A prospective study	exclude	Healthcare based screening	NA
Kranzer et. al	2012	PLoS medicine	Feasibility, yield, and cost of active tuberculosis case finding linked to a mobile HIV service in Cape Town, South Africa: a cross-sectional study	exclude	No comparison group	NA
Kristensen et. al	2019	European Respiratory Journal	Long-term incidence of tuberculosis among migrants according to migrant status: A cohort study	exclude	No comparison group	NA
Krivinka R. et. al	1974	Bulletin of the World Health Organization	Epidemiological and clinical study of tuberculosis in the district of Kolin, Czechoslovakia. Second report (1965-1972)	exclude	NA	NA
Kuan et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis among newly arrived foreign spouses before obtaining citizenship, Taiwan, 2006-2011	exclude	No comparison group	NA
Kubiak et. al	2018	International Journal of Tuberculosis and Lung Disease	Urinary LAM grade, culture positivity, and mortality among HIV-infected South African out-patients	exclude	No comparison group	NA
Kuehne et. al	2018	Eurosurveillance	Screening and prevention of infectious diseases in newly arrived migrants. Find and treat or find and lose? Tuberculosis treatment outcomes among screened newly arrived asylum seekers in Germany 2002 to 2014	exclude	No relevant data / not an ACF intervention	NA
Kuehne et. al	2018	Eurosurveillance	Screening and prevention of infectious diseases in newly arrived migrants. Find and treat or find and lose? Tuberculosis treatment outcomes among screened newly arrived asylum seekers in Germany 2002 to 2014	exclude	No comparison group	NA
Kufa et. al	2012	Journal of acquired immune deficiency syndromes (1999)	Undiagnosed tuberculosis among HIV clinic attendees: association with antiretroviral therapy and implications for intensified case finding, isoniazid preventive therapy, and infection control	exclude	No comparison group	NA
Kumar et. al	2020	PLoS Med	Health of Special Immigrant Visa holders from Iraq and Afghanistan after arrival into the United States using Domestic Medical Examination data, 2014-2016: A cross-sectional analysis	exclude	No comparison group	NA
Kumpatla et. al	2013	Public health action	Characteristics of patients with diabetes screened for tuberculosis in a tertiary care hospital in South India	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Kundu et. al	2013	International Medical Journal	TB/HIV co-infection profile and impact of RNTCP and NACP liaison in the setting of free home based antiretroviral therapy in a rural tertiary teaching hospital in India	exclude	No comparison group	NA
Kunwipakorn et. al	2019	Journal of the Medical Association of Thailand	Community active case finding for pulmonary tuberculosis	exclude	Fewer than 1000 people screened	NA
Kurtz et. al	2019	Int J Tuberc Lung Dis	Effect of neonatal bacille Calmette-Guerin on the tuberculin skin test reaction in the first 2 years of life	exclude	No comparison group	NA
Kushner et. al	2019	Open Forum Infectious Diseases	Use of interferon-gamma release assays (IGRAs) reduced latent tuberculosis infection (LTBI) diagnosis in refugee and immigrant children	exclude	No comparison group	NA
Kyaw et. al	2019	Trop Med Infect Dis	Outcomes of Community-Based Systematic Screening of Household Contacts of Patients with Multidrug-Resistant Tuberculosis in Myanmar	exclude	No comparison group	NA
LaCourse et. al	2016	Journal of acquired immune deficiency syndromes (1999)	Tuberculosis Case Finding in HIV-Infected Pregnant Women in Kenya Reveals Poor Performance of Symptom Screening and Rapid Diagnostic Tests	exclude	No comparison group	NA
Laghari et. al	2019	BMC Public Health	Contact screening and risk factors for TB among the household contact of children with active TB: a way to find source case and new TB cases	exclude	No comparison group	NA
Lassausaie et. al	2015	Epidemiology and infection	Tuberculosis in Laos, who is at risk: the mahouts or their elephants?	exclude	No comparison group	NA
Law et. al	2015	Tropical medicine & international health : TM & IH	The first national tuberculosis prevalence survey of Lao PDR (2010-2011)	exclude	No comparison group	NA
Lawn et. al	2011	PLoS medicine	Screening for HIV-associated tuberculosis and rifampicin resistance before antiretroviral therapy using the Xpert MTB/RIF assay: a prospective study	exclude	No comparison group	NA
Lawn et. al	2017	BMC medicine	Diagnostic accuracy, incremental yield and prognostic value of Determine TB-LAM for routine diagnostic testing for tuberculosis in HIV-infected patients requiring acute hospital admission in South Africa: a prospective cohort	exclude	No comparison group	NA
Lawn et. al	2015	BMC medicine	Rapid microbiological screening for tuberculosis in HIV-positive patients on the first day of acute hospital admission by systematic testing of urine samples using Xpert MTB/RIF: a prospective cohort in South Africa	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Lawn et. al	2012	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Diagnostic yield of tuberculosis using sputum induction in HIV-positive patients before antiretroviral therapy	exclude	No comparison group	NA
Lawn et. al	2012	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	Characteristics and early outcomes of patients with Xpert MTB/RIF-negative pulmonary tuberculosis diagnosed during screening before antiretroviral therapy	exclude	No comparison group	NA
Lawn et. al	2012	AIDS (London, England)	Clinical significance of lipoarabinomannan detection in urine using a low-cost point-of-care diagnostic assay for HIV-associated tuberculosis	exclude	No comparison group	NA
Lawn et. al	2013	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Diagnostic and prognostic value of serum C-reactive protein for screening for HIV-associated tuberculosis	exclude	No comparison group	NA
Lawn et. al	2013	BMC medicine	HIV-associated tuberculosis: relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays	exclude	No comparison group	NA
Lawn et. al	2012	The Lancet. Infectious diseases	Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study	exclude	No comparison group	NA
Lebina et. al	2016	Tuberculosis research and treatment	The Use of Xpert MTB/Rif for Active Case Finding among TB Contacts in North West Province, South Africa	exclude	No comparison group	NA
Ledda et. al	2019	Future Microbiol	Tuberculosis screening among healthcare workers in Sicily, Italy	exclude	No comparison group	NA
Lee M.S.-N. et. al	2008	International Journal of Tuberculosis and Lung Disease	Early and late tuberculosis risks among close contacts in Hong Kong	exclude	No comparison group	NA
Lee et. al	2017	The Korean journal of internal medicine	Comparing tuberculin skin test and interferon gamma release assay (T-SPOT.TB) to diagnose latent tuberculosis infection in household contacts	exclude	No comparison group	NA
Lee et. al	2019	BMC Infect Dis	Impact of metformin use among tuberculosis close contacts with diabetes mellitus in a nationwide cohort study	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Lee et. al	2019	Tuberc Res Treat	The Presence of Cough and Tuberculosis: Active Case Finding Outcomes in the Philippines	exclude	No comparison group	NA
Lee et. al	2019	Int J Tuberc Lung Dis	Long-term performance of the IGRA to predict and prevent active tuberculosis development in HIV-infected patients	exclude	No comparison group	NA
Lee et. al	2018	Tuberculosis and respiratory diseases	Pre-immigration Screening for Tuberculosis in South Korea: A Comparison of Smear- and Culture-Based Protocols	exclude	No comparison group	NA
Lee et. al	2019	Tuberc Respir Dis (Seoul)	Pre-immigration Screening for Tuberculosis in South Korea: A Comparison of Smear- and Culture-Based Protocols	exclude	NA	NA
Lee et. al	2019	Tuberc Respir Dis (Seoul)	Active Case Finding in the Elderly Tuberculosis in South Korea	exclude	No relevant data / not an ACF intervention	NA
Lee et. al	2015	PloS one	A Clinical Algorithm to Identify HIV Patients at High Risk for Incident Active Tuberculosis: A Prospective 5-Year Cohort Study	exclude	No comparison group	NA
Legesse et. al	2013	International journal of mycobacteriology	Community-based prevalence of undiagnosed mycobacterial diseases in the Afar Region, north-east Ethiopia	exclude	No comparison group	NA
Leung et. al	2013	The European respiratory journal	Transmission of multidrug-resistant and extensively drug-resistant tuberculosis in a metropolitan city	exclude	No comparison group	NA
Lewis et. al	2013	PloS one	Eligibility for isoniazid preventive therapy in South African gold mines	exclude	No comparison group	NA
Li et. al	2019	Int J Tuberc Lung Dis	Prevalence of pulmonary tuberculosis in Tibet Autonomous Region, China, 2014	exclude	No comparison group	NA
Li et. al	2018	European Respiratory Journal	Occupational tuberculosis screening for healthcare workers in a UK centre	exclude	No comparison group	NA
Liang et. al	2015	BMC public health	USA's expanded overseas tuberculosis screening program: a retrospective study in China	exclude	No comparison group	NA
Liang et. al	2019	J Interferon Cytokine Res	Comparison of Three Cellular Immunoassays to Detect Tuberculosis Infection in 876 Healthy Recruits	exclude	Fewer than 1000 people screened	NA
Liaquat et. al	2015	Pakistan journal of medical sciences	Concomitant presence of culture-proven active pulmonary tuberculosis in patients with chronic obstructive pulmonary disease - A hospital based study	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Lim et. al	2016	Canadian respiratory journal	Is Universal Screening Necessary? Incidence of Tuberculosis among Tibetan Refugees Arriving in Calgary, Alberta	exclude	No comparison group	NA
Lin et. al	2010	BMC public health	"Cough officer screening" improves detection of pulmonary tuberculosis in hospital in-patients	exclude	No comparison group	NA
Lin et. al	2015	Tropical medicine & international health : TM & IH	Screening of patients with diabetes mellitus for tuberculosis in community health settings in China	exclude	No comparison group	NA
Lin et. al	2012	Tropical medicine & international health : TM & IH	Screening patients with diabetes mellitus for tuberculosis in China	exclude	Healthcare based screening	NA
Lin et. al	2015	BMC public health	Screening for pulmonary tuberculosis in type 2 diabetes elderly: a cross-sectional study in a community hospital	exclude	No comparison group	NA
Little et. al	2018	BMC infectious diseases	Yield of household contact tracing for tuberculosis in rural South Africa	exclude	No comparison group	NA
Liu et. al	2019	Int J Infect Dis	Assessment of active tuberculosis findings in the eastern area of China: A 3-year sequential screening study	include	NA	Prevelance review
Liu et. al	2015	Annals of internal medicine	Effect of a culture-based screening algorithm on tuberculosis incidence in immigrants and refugees bound for the United States: a population-based cross-sectional study	exclude	NA	NA
Lo et. al	2016	Global health action	Tuberculosis among transhumant pastoralist and settled communities of south-eastern Mauritania	exclude	No comparison group	NA
LoBue P.A. et. al	2004	Chest	Screening of immigrants and refugees for pulmonary tuberculosis in San Diego County, California	exclude	No comparison group	NA
Lohmann et. al	2012	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Grading of a positive sputum smear and the risk of Mycobacterium tuberculosis transmission	exclude	No comparison group	NA
Lopes et. al	2019	J Bras Pneumol	Diagnosis and treatment of latent tuberculosis infection in patients undergoing treatment with immunobiologic agents: a four-year experience in an endemic area	exclude	No comparison group	NA
Lopez-Varela et. al	2015	The Pediatric infectious disease journal	Incidence of Tuberculosis Among Young Children in Rural Mozambique	exclude	ACF in children only	NA
Lopez-Varela et. al	2015	The Pediatric infectious disease journal	Incidence of Tuberculosis Among Young Children in Rural Mozambique	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Lopez-Varela et. al	2019	J Acquir Immune Defic Syndr	High Yield of Home-Based TB Diagnosis Among Newly Diagnosed Patients With HIV	exclude	No comparison group	NA
Loredo et. al	2014	BMC pulmonary medicine	Yield of close contact tracing using two different programmatic approaches from tuberculosis index cases: a retrospective quasi-experimental study	exclude	No comparison group	NA
Lorent et. al	2015	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Is frontloaded sputum microscopy an option in active tuberculosis case finding?	exclude	No comparison group	NA
Lorent et. al	2014	PloS one	Community-based active tuberculosis case finding in poor urban settlements of Phnom Penh, Cambodia: a feasible and effective strategy	include	NA	CNR review
Lowther et. al	2011	Public health reports (Washington, D.C. : 1974)	Outbreak of tuberculosis among Guatemalan immigrants in rural Minnesota, 2008	exclude	No comparison group	NA
Lu et. al	2019	Global Health	Tuberculosis among migrant workers in Taiwan	exclude	No comparison group	NA
Luabeya et. al	2015	The Pediatric infectious disease journal	Risk of Disease After Isoniazid Preventive Therapy for Mycobacterium tuberculosis Exposure in Young HIV-uninfected Children	exclude	No comparison group	NA
Lupisan et. al	2019	Int J Infect Dis	Etiology and epidemiology of community-acquired pneumonia in adults requiring hospital admission: A prospective study in rural Central Philippines	exclude	No comparison group	NA
Ly et. al	2019	J Epidemiol Glob Health	Preliminary Feasibility Study of Questionnaire-based Active Pulmonary Tuberculosis Screening in Marseille Sheltered Homeless People, Winter 2018	exclude	No comparison group	NA
M and alakas et. al	2017	PloS one	BUTIMBA: Intensifying the Hunt for Child TB in Swaziland through Household Contact Tracing	exclude	No comparison group	NA
Mabuto et. al	2015	BMC public health	Tuberculosis active case finding: uptake and diagnostic yield among minibus drivers in urban South Africa	exclude	No comparison group	NA
Machekera et. al	2019	Public Health Action	A comparison of the yield and relative cost of active tuberculosis case-finding algorithms in Zimbabwe	exclude	No comparison group	NA
Maggard et. al	2015	Bulletin of the World Health Organization	Screening for tuberculosis and testing for human immunodeficiency virus in Zambian prisons	include	NA	CNR review

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Mahomed et. al	2013	Tuberculosis (Edinburgh, Scotland)	Screening for TB in high school adolescents in a high burden setting in South Africa	exclude	No comparison group	NA
Mahomed et. al	2013	PloS one	TB incidence in an adolescent cohort in South Africa	exclude	No comparison group	NA
Majumder et. al	2016	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Screening for active tuberculosis in a diabetes mellitus clinic in Soweto, South Africa	exclude	No comparison group	NA
Makay et. al	2019	Annals of the Rheumatic Diseases	Latent tuberculosis infection in children with pediatric rheumatologic diseases treated with canakinumab	exclude	Healthcare based screening	NA
Malacarne et. al	2019	J Bras Pneumol	Performance of diagnostic tests for pulmonary tuberculosis in indigenous populations in Brazil: the contribution of Rapid Molecular Testing	exclude	No comparison group	NA
Malik et. al	2018	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Improving childhood tuberculosis detection and treatment through facility-based screening in rural Pakistan	exclude	No comparison group	NA
Mallick G et. al	2017	Public Health Action	Enhanced tuberculosis case finding through advocacy and sensitisation meetings in prisons of Central India	include	NA	CNR review
Mama et. al	2018	The open microbiology journal	Prevalence of Pulmonary Tuberculosis and Associated Factors Among HIV Positive Patients Attending Antiretroviral Therapy Clinic at Arba Minch General Hospital, Southern Ethiopia	exclude	No comparison group	NA
Mamani et. al	2016	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Prevalence and incidence rates of latent tuberculous infection in a large prison in Iran	exclude	No comparison group	NA
Mamani et. al	2013	Iranian Red Crescent medical journal	Latent and active tuberculosis: evaluation of injecting drug users	exclude	No comparison group	NA
Manalo F. et. al	1990	American Review of Respiratory Disease	Community-based short-course treatment of pulmonary tuberculosis in a developing nation: Initial report of an eight-month, largely intermittent regimen in a population with a high prevalence of drug resistance	exclude	No comparison group	NA

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Mani et. al	2019	Lung India : official organ of Indian Chest Society	Is it feasible to carry out active case finding for tuberculosis in community-based settings?	exclude	No comparison group	NA
Mao et. al	2014	Bulletin of the World Health Organization	Cross-sectional studies of tuberculosis prevalence in Cambodia between 2002 and 2011	exclude	No comparison group	NA
Maokola et. al	2019	Front Public Health	Performance of and Factors Associated With Tuberculosis Screening and Diagnosis Among People Living With HIV: Analysis of 2012-2016 Routine HIV Data in Tanzania	exclude	No comparison group	NA
Maokola et. al	2020	Front. Public Health	Performance of and Factors Associated With Tuberculosis Screening and Diagnosis Among People Living With HIV: Analysis of 2012–2016 Routine HIV Data in Tanzania	exclude	No comparison group	NA
Margolis et. al	2013	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Prevalence of tuberculosis symptoms and latent tuberculous infection among prisoners in northeastern Malaysia	exclude	No comparison group	NA
Marks et. al	2019	N Engl J Med	Community-wide Screening for Tuberculosis in a High-Prevalence Setting	include	NA	Prevelance review
Martinez et. al	2018	American Journal of Respiratory and Critical Care Medicine	A prospective validation of a clinical algorithm to detect tuberculosis in child contacts	exclude	No comparison group	NA
Martinez et. al	2018	The Lancet. Respiratory medicine	Effectiveness of WHO's pragmatic screening algorithm for child contacts of tuberculosis cases in resource-constrained settings: a prospective cohort study in Uganda	exclude	No comparison group	NA
Martinez et. al	2018	South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde	Tuberculin conversion and tuberculosis disease in infants and young children from the Drakenstein Child Health Study: A call to action	exclude	No comparison group	NA
Martinez et. al	2018	South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde	Tuberculin conversion and tuberculosis disease in infants and young children from the Drakenstein Child Health Study: A call to action	exclude	ACF in children only	NA
Masood-Us-Syed et. al	2012	Pakistan Paediatric Journal	Screening of childhood tuberculosis with Pakistan pediatric association scoring chart system	exclude	No comparison group	NA
Masood et. al	2016	Pakistan Journal of Medical and Health Sciences	Prevalence of Tuberculosis Among Patients having Diabetes Mellitis -A Cross-Sectional Study	exclude	Healthcare based screening	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Mastrolia et. al	2018	Travel medicine and infectious disease	Utility of tuberculin skin test and IGRA for tuberculosis screening in internationally adopted children: Retrospective analysis from a single center in Florence, Italy	exclude	No comparison group	NA
Mastrolia et. al	2019	Travel Medicine and Infectious Disease	Utility of tuberculin skin test and IGRA for tuberculosis screening in internationally adopted children: Retrospective analysis from a single center in Florence, Italy	exclude	No comparison group	NA
Masur et. al	2017	The American journal of tropical medicine and hygiene	Active Tuberculosis Case Finding in Haiti	exclude	No comparison group	NA
Masur et. al	2017	The American journal of tropical medicine and hygiene	Active Tuberculosis Case Finding in Haiti	exclude	No comparison group	NA
Maung et. al	2017	Infectious Diseases of Poverty	The contribution of a non-governmental organisation's Community Based Tuberculosis Care Programme to case finding in Myanmar: trend over time	exclude	No comparison group	NA
Mave et. al	2017	BMC infectious diseases	Tuberculosis screening among persons with diabetes mellitus in Pune, India	exclude	No comparison group	NA
Mazahir et. al	2017	Egyptian Pediatric Association Gazette	Burden of tuberculosis among household children of adult multi drug resistant patients and their response to first line anti tubercular drugs	exclude	No comparison group	NA
Mbatchou Ngahane et. al	2019	American Journal of Respiratory and Critical Care Medicine	Prevalence of tuberculosis and its factors among patients on maintenance dialysis in Douala, Cameroon	exclude	No comparison group	NA
Mbu et. al	2018	PloS one	Tuberculosis in people newly diagnosed with HIV at a large HIV care and treatment center in Northwest Cameroon: Burden, comparative screening and diagnostic yields, and patient outcomes	exclude	No comparison group	NA
McAllister et. al	2017	Public health action	Feasibility of two active case finding approaches for detection of tuberculosis in Bandung City, Indonesia	exclude	No comparison group	NA
McAllister et. al	2020	Transactions of the Royal Society of Tropical Medicine and Hygiene	High tuberculosis incidence among people living with diabetes in Indonesia	exclude	No comparison group	NA
McBryde et. al	2012	The Medical journal of Australia	Risk of active tuberculosis in immigrants: effects of age, region of origin and time since arrival in a low-exposure setting	exclude	No comparison group	NA

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Mehari et. al	2019	Can J Infect Dis Med Microbiol	Prevalence and Factors Associated with Multidrug-Resistant Tuberculosis (MDR-TB) among Presumptive MDR-TB Patients in Tigray Region, Northern Ethiopia	exclude	No comparison group	NA
Meier et. al	2020	Pneumologie	[Latent Tuberculosis Infection (LTBI) among Medical Personnel after Foreign Assignments]	exclude	No comparison group	NA
Meier et. al	2016	International journal of hygiene and environmental health	Tuberculosis in newly arrived asylum seekers: A prospective 12 month surveillance study at Friedland, Germany	exclude	No comparison group	NA
Meijer J. et. al	1971	Bulletin of the International Union against Tuberculosis	Identification of sources of infection [Identification des sources d'infection.]	exclude	NA	NA
Mekonnen et. al	2018	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Prevalence of pulmonary tuberculosis among students in three eastern Ethiopian universities	exclude	NA	NA
Melsew et. al	2019	BMC Infect Dis	The role of super-spreading events in Mycobacterium tuberculosis transmission: evidence from contact tracing	exclude	No comparison group	NA
Memish et. al	1995	The Canadian journal of infectious diseases = Journal canadien des maladies infectieuses	Evaluation and follow-up of infectious tuberculosis at the University of Ottawa	exclude	No comparison group	NA
Menzato et. al	2018	Blood	Successful simultaneous screening of sickle cell disease, hiv and tuberculosis in rural guinea bissau, west africa through rapid tests and a standardized clinical questionnaire: An outreach program due to a public-private partnership	exclude	No comparison group	NA
Merid et. al	2019	Int J Infect Dis	Population-based screening for pulmonary tuberculosis utilizing community health workers in Ethiopia	exclude	No comparison group	NA
Merid et. al	2018	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	High utility of active tuberculosis case finding in an Ethiopian prison	exclude	No comparison group	NA
Middelkoop K. et. al	2011	Journal of Acquired Immune Deficiency Syndromes	Antiretroviral therapy and TB notification rates in a high HIV prevalence South African community	exclude	Healthcare based screening	NA
Middelkoop K. et. al	2010	American Journal of Respiratory and Critical Care Medicine	Antiretroviral program associated with reduction in untreated prevalent tuberculosis in a South African township	exclude	No comparison group	NA

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Mijiti et. al	2016	The Lancet. Global health	Prevalence of pulmonary tuberculosis in western China in 2010-11: a population-based, cross-sectional survey	exclude	No relevant data / not an ACF intervention	NA
Miller A.C. et. al	2010	International Journal of Tuberculosis and Lung Disease	Controlled trial of active tuberculosis case finding in a Brazilian favela	include	NA	CNR review
Miller et. al	2010	International journal of tuberculosis and lung disease	Controlled trial of active tuberculosis case finding in a Brazilian favela	include but duplicate	NA	NA
Mirembe et. al	2019	Transactions of the Royal Society of Tropical Medicine and Hygiene	Strengthening tuberculosis diagnosis and notification through tb surge: Experience of Uganda protestant medical bureau	exclude	Healthcare based screening	NA
Miyahara et. al	2019	BMC Infect Dis	Predicting the risk of pulmonary tuberculosis based on the neutrophil-to-lymphocyte ratio at TB screening in HIV-infected individuals	exclude	No comparison group	NA
Modi et. al	2016	PloS one	Performance of Clinical Screening Algorithms for Tuberculosis Intensified Case Finding among People Living with HIV in Western Kenya	exclude	No comparison group	NA
Moges et. al	2012	BMC infectious diseases	Prevalence of smear positive pulmonary tuberculosis among prisoners in North Gondar Zone Prison, northwest Ethiopia	exclude	No comparison group	NA
Moh et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Screening for active tuberculosis before isoniazid preventive therapy among HIV-infected West African adults	exclude	No comparison group	NA
Mohammed et. al	2020	J Clin Tuberc Other Mycobact Dis	Burden of tuberculosis and challenges related to screening and diagnosis in Ethiopia	exclude	No comparison group	NA
Mohareb et. al	2017	Open Forum Infectious Diseases	Latent tuberculosis infection in a cohort of refugee patients resettling in New England	exclude	Fewer than 1000 people screened	NA
Monegal et. al	2007	FMC formacion medica continuada en atencion primaria	Educational intervention to promote the screening of tuberculosis in primary care: randomized clinical trial with assigned clusters	exclude	Healthcare based screening	NA
Moosazadeh et. al	2015	Iranian journal of medical sciences	The prevalence of latent tuberculosis infection and smear positive pulmonary tuberculosis in people with household close contact with tuberculosis in north of iran	exclude	No comparison group	NA
Mor et. al	2012	Respiratory care	Chest radiography validity in screening pulmonary tuberculosis in immigrants from a high-burden country	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Mor et. al	2015	The Israel Medical Association journal : IMAJ	The yield of tuberculosis screening of undocumented migrants from the Horn of Africa based on chest radiography	exclude	No comparison group	NA
Mor et. al	2015	The Israel Medical Association journal : IMAJ	The yield of tuberculosis screening of undocumented migrants from the Horn of Africa based on chest radiography	exclude	No comparison group	NA
Morano et. al	2013	Journal of community health	Latent tuberculosis infection: screening and treatment in an urban setting	exclude	No comparison group	NA
Morasert et. al	2018	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Prevalence and risk factors associated with tuberculosis disease in Suratthani Central Prison, Thailand	exclude	No comparison group	NA
Morishita et. al	2016	PLoS One	Increased Case Notification through Active Case Finding of Tuberculosis among Household and Neighbourhood Contacts in Cambodia	exclude	No relevant data / not an ACF intervention	NA
Morishita et. al	2017	PloS one	Bringing state-of-the-art diagnostics to vulnerable populations: The use of a mobile screening unit in active case finding for tuberculosis in Palawan, the Philippines	exclude	No comparison group	NA
Moucaut et. al	2013	Journal of occupational medicine and toxicology (London, England)	The effect of introducing IGRA to screen French healthcare workers for tuberculosis and potential conclusions for the work organisation	exclude	No comparison group	NA
Moyo et. al	2015	Public health action	Evaluation of tuberculin skin testing in tuberculosis contacts in Victoria, Australia, 2005-2013	exclude	No comparison group	NA
Moyo et. al	2012	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis case finding for vaccine trials in young children in high-incidence settings: a randomised trial	exclude	ACF in children only	NA
Mtwangambate et. al	2014	Diabetic medicine : a journal of the British Diabetic Association	'Cough-triggered' tuberculosis screening among adults with diabetes in Tanzania	exclude	No comparison group	NA
Mueller-Hermelink et. al	2018	Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin	Universal screening for latent and active tuberculosis (TB) in asylum seeking children, Bochum and Hamburg, Germany, September 2015 to November 2016	exclude	No comparison group	NA

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Mulder et. al	2011	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Coverage and yield of tuberculosis contact investigations in the Netherlands	exclude	Contact tracing	NA
Munoz et. al	2018	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	QuantiFERON-TB Gold In-Tube as a Confirmatory Test for Tuberculin Skin Test in Tuberculosis Contact Tracing: A Noninferiority Clinical Trial	exclude	No comparison group	NA
Mupfumi et. al	2014	Open forum infectious diseases	Impact of Xpert MTB/RIF on Antiretroviral Therapy-Associated Tuberculosis and Mortality: A Pragmatic Randomized Controlled Trial	exclude	No comparison group	NA
Murray et. al	2019	Emerg Infect Dis	Prevalence of Tuberculosis in Children After Natural Disasters, Bohol, Philippines	exclude	No comparison group	NA
Muyoyeta et. al	2017	BMC infectious diseases	Digital CXR with computer aided diagnosis versus symptom screen to define presumptive tuberculosis among household contacts and impact on tuberculosis diagnosis	exclude	No comparison group	NA
Mwansa-Kambafwile et. al	2013	PloS one	Tuberculosis case finding: evaluation of a paper slip method to trace contacts	exclude	No comparison group	NA
Myint et. al	2017	Infectious diseases of poverty	Active case-finding for tuberculosis by mobile teams in Myanmar: yield and treatment outcomes	exclude	No comparison group	NA
Myint et. al	2019	Public Health Action	Additional active tuberculosis cases detected and costs incurred by a second household contact investigation	exclude	No comparison group	NA
Naidoo et. al	2014	Journal of acquired immune deficiency syndromes (1999)	High rates of tuberculosis in patients accessing HAART in rural South Africa	exclude	No comparison group	NA
Naidoo et. al	2014	Journal of acquired immune deficiency syndromes (1999)	High rates of tuberculosis in patients accessing HAART in rural South Africa	exclude	Healthcare based screening	NA
Nair et. al	2016	PloS one	Household Contact Screening and Yield of Tuberculosis Cases-A Clinic Based Study in Chennai, South India	exclude	No comparison group	NA
Narang et. al	2015	Journal of epidemiology and global health	Prevalence of pulmonary tuberculosis in Wardha district of Maharashtra, Central India	exclude	No comparison group	NA
Nasehi et. al	2017	Epidemiology and health	Prevalence of latent tuberculosis infection among tuberculosis laboratory workers in Iran	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Nathavitharana et. al	2017	International Journal of Tuberculosis and Lung Disease	FAST implementation in Bangladesh: High frequency of unsuspected tuberculosis justifies challenges of scale-up	exclude	No comparison group	NA
Navarro et. al	2016	Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia	Prevalence of latent Mycobacterium tuberculosis infection in prisoners	exclude	No comparison group	NA
Nduba et. al	2015	International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases	Prevalence of tuberculosis in adolescents, western Kenya: implications for control programs	exclude	No comparison group	NA
Nduba et. al	2018	The Pediatric infectious disease journal	Incidence of Active Tuberculosis and Cohort Retention Among Adolescents in Western Kenya	exclude	No comparison group	NA
Nduba et. al	2018	The Pediatric infectious disease journal	Incidence of Active Tuberculosis and Cohort Retention Among Adolescents in Western Kenya	exclude	No comparison group	NA
Ndwiga et. al	2013	BMC health services research	Feasibility and effect of integrating tuberculosis screening and detection in postnatal care services: an operations research study	exclude	Healthcare based screening	NA
Nguyen et. al	2016	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Yield of chest radiograph in tuberculosis screening for HIV-infected persons at a district-level HIV clinic	exclude	Healthcare based screening	NA
Nguyen et. al	2011	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Improving the diagnosis of pulmonary tuberculosis in HIV-infected individuals in Ho Chi Minh City, Viet Nam	exclude	No comparison group	NA
Nguyen et. al	2012	Tuberculosis research and treatment	Performance of Clinical Algorithms for Smear-Negative Tuberculosis in HIV-Infected Persons in Ho Chi Minh City, Vietnam	exclude	No comparison group	NA
Ngwira et. al	2018	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	Screening for tuberculosis with Xpert MTB/RIF versus fluorescent microscopy among adults newly diagnosed with HIV in rural Malawi: a cluster randomized trial (CHEPETSA)	exclude	No comparison group	NA
Ngwira et. al	2019	Clin Infect Dis	Screening for Tuberculosis With Xpert MTB/RIF Assay Versus Fluorescent Microscopy Among Adults Newly Diagnosed With Human Immunodeficiency Virus in Rural Malawi: A Cluster Randomized Trial (Chepetsa)	exclude	Healthcare based screening	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Nienhaus et. al	2013	Journal of occupational medicine and toxicology (London, England)	Screening for tuberculosis and the use of a borderline zone for the interpretation of the interferon-gamma release assay (IGRA) in Portuguese healthcare workers	exclude	No comparison group	NA
Nienhaus et. al	2014	Journal of occupational medicine and toxicology (London, England)	Tuberculosis screening at the Sainte-Anne Hospital in Paris - results of first and second IGRA	exclude	No comparison group	NA
Njau et. al	2010	East African journal of public health	Tuberculosis in HIV-infected Tanzanian children below 14 years	exclude	No comparison group	NA
Noeske et. al	2011	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Controlling tuberculosis in prisons against confinement conditions: a lost case? Experience from Cameroon	exclude	No comparison group	NA
Nogueira et. al	2018	Revista de saude publica	Tuberculosis and latent infection in employees of different prison unit types	exclude	No comparison group	NA
Ntinginya et. al	2012	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Performance of the Xpert(R) MTB/RIF assay in an active case-finding strategy: a pilot study from Tanzania	exclude	No comparison group	NA
Nuzzo et. al	2015	American journal of public health	Postarrival Tuberculosis Screening of High-Risk Immigrants at a Local Health Department	exclude	No comparison group	NA
O'Grady et. al	2012	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	Evaluation of the Xpert MTB/RIF assay at a tertiary care referral hospital in a setting where tuberculosis and HIV infection are highly endemic	exclude	No comparison group	NA
Ogbudebe et. al	2015	International journal of mycobacteriology	Reaching the underserved: Active tuberculosis case finding in urban slums in southeastern Nigeria	exclude	No comparison group	NA
Okada K. et. al	2012	International Journal of Tuberculosis and Lung Disease	Epidemiological impact of mass tuberculosis screening: A 2-year follow-up after a national prevalence survey	exclude	No comparison group	NA
Okelloh et. al	2019	Public Health Action	Lessons learned from community-based tuberculosis case-finding in western Kenya	exclude	NA	NA
Oliveira-Cortez et. al	2019	Am J Trop Med Hyg	Low Prevalence of Latent Tuberculosis Infection among Contacts of Smear-Positive Adults in Brazil	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Oliwa et. al	2019	PLoS One	Diagnostic practices and estimated burden of tuberculosis among children admitted to 13 government hospitals in Kenya: An analysis of two years' routine clinical data	exclude	No comparison group	NA
Oloyede et. al	2013	East African medical journal	PREVALENCE, CO-PREVALENCE AND RISK FACTORS OF PULMONARY PARAGONIMIASIS AND PULMONARY TUBERCULOSIS IN NIGERIAN CHILDREN IN THE NIGER DELTA AREA	exclude	No comparison group	NA
Ongen et. al	2013	Tuberkuloz ve toraks	Pulmonary tuberculosis incidence in Turkish prisons: importance of screening and case finding strategies	exclude	No comparison group	NA
Oni et. al	2011	Thorax	High prevalence of subclinical tuberculosis in HIV-1-infected persons without advanced immunodeficiency: implications for TB screening	exclude	No comparison group	NA
Ormerod L.P. et. al	1993	Respiratory Medicine	Results of tuberculosis contact tracing: Blackburn 1982-1990	exclude	No comparison group	NA
Ortiz-Rico et. al	2015	Salud publica de Mexico	Conformance contrast testing between rates of pulmonary tuberculosis in Ecuadorian border areas	exclude	No comparison group	NA
Oshi et. al	2016	International journal of mycobacteriology	Does intensified case finding increase tuberculosis case notification among children in resource-poor settings? A report from Nigeria	exclude	ACF in children only	NA
Oshi et. al	2017	International journal of mycobacteriology	An evaluation of innovative community-based approaches and systematic tuberculosis screening to improve tuberculosis case detection in Ebonyi State, Nigeria	exclude	No relevant data / not an ACF intervention	NA
Ottmani S. et. al	2009	Eastern Mediterranean Health Journal	TB contact investigations: 12 years of experience in the National TB Programme, Morocco 1993-2004	exclude	No comparison group	NA
Owiti et. al	2019	BMC public health	Screening and testing for tuberculosis among the HIV-infected: outcomes from a large HIV programme in western Kenya	exclude	No comparison group	NA
Owokuhaisa et. al	2014	Advances in research	Prevalence of Pulmonary Tuberculosis among Prison Inmates at Mbarara Central Prison, South Western Uganda	exclude	No comparison group	NA
Pace-Asciak et. al	2013	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis among undocumented boat migrants to Malta: implications for a migrant tuberculosis policy	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Pacifici et. al	2010	Giornale Italiano di Medicina Tropicale	Screening for tuberculosis among asylum seekers: Experience from an immigration centre in Central Italy and literature review	exclude	No comparison group	NA
Padmapriyadarsini et. al	2016	The National medical journal of India	Effectiveness of symptom screening and incidence of tuberculosis among adults and children living with HIV infection in India	exclude	No comparison group	NA
Paiao et. al	2016	BMC infectious diseases	Impact of mass-screening on tuberculosis incidence in a prospective cohort of Brazilian prisoners	exclude	NA	NA
Pan et. al	2019	International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases	Adolescent tuberculosis associated with tuberculosis exposure in classrooms and dorm rooms in Guangxi, China	exclude	No comparison group	NA
Parija et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Impact of awareness drives and community-based active tuberculosis case finding in Odisha, India	include	NA	CNR review
Park et. al	2020	Sci Rep	Risk of active tuberculosis development in contacts exposed to infectious tuberculosis in congregate settings in Korea	exclude	No comparison group	NA
Pelissari et. al	2018	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Prevalence and screening of active tuberculosis in a prison in the South of Brazil	exclude	No comparison group	NA
Perez-Porcuna et. al	2012	The Pediatric infectious disease journal	Evaluation of new strategies for the diagnosis of tuberculosis among pediatric contacts of tuberculosis patients	exclude	No comparison group	NA
Perry et. al	2012	Archives de pediatrie : organe officiel de la Societe francaise de pediatrie	[Neonatal exposure to active pulmonary tuberculosis in a maternity ward: screening and clinical course of a cohort of exposed infants]	exclude	No comparison group	NA
Pevzner et. al	2010	American journal of public health	Tuberculosis transmission and use of methamphetamines in Snohomish County, WA, 1991-2006	exclude	No comparison group	NA
Phanuphak et. al	2012	Journal of acquired immune deficiency syndromes (1999)	Using tuberculin skin test as an entry point to screen for latent and active tuberculosis in Thai people living with HIV	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Philipsen et. al	2019	Int J Tuberc Lung Dis	Automated chest X-ray reading for tuberculosis in the Philippines to improve case detection: a cohort study	exclude	No comparison group	NA
Phipps et. al	2019	Journal of Pediatric Infectious Diseases	Screening Young Children for Latent Tuberculosis in England: Lessons Learned from the Field	exclude	ACF in children only	NA
Phuanukoonnon S. et. al	2010	Int J Tuberc Lung Dis	Burden of tuberculosis and health seeking behaviours of people with prolonged cough in rural png. 41st world conference on lung health of the international union against tuberculosis and lung disease, berlin, germany, 11-15 november 2010	exclude	No comparison group	NA
Phyo et. al	2019	Trop Med Infect Dis	Contact Investigation of Multidrug-Resistant Tuberculosis Patients: A Mixed-Methods Study from Myanmar	exclude	No comparison group	NA
Phyo et. al	2019	Int J Tuberc Lung Dis	High prevalence and incidence of tuberculosis in people living with the HIV in Mandalay, Myanmar, 2011-2017	exclude	No comparison group	NA
Pontarelli et. al	2019	Travel medicine and infectious disease	Screening for active and latent tuberculosis among asylum seekers in Italy: A retrospective cohort analysis	exclude	No comparison group	NA
Popovici et. al	2018	Epidemiology and infection	Cross-border outbreak of extensively drug-resistant tuberculosis linked to a university in Romania	exclude	No comparison group	NA
Pothukuchi et. al	2011	PloS one	Tuberculosis contact screening and isoniazid preventive therapy in a South Indian district: operational issues for programmatic consideration	exclude	No comparison group	NA
Pourakbari et. al	2019	Infectious Disorders - Drug Targets	Evaluation of the QuantiFERON®-TB gold in-tube assay and tuberculin skin test for the diagnosis of latent tuberculosis infection in an iranian referral hospital	exclude	No comparison group	NA
Powell et. al	2012	Public health reports (Washington, D.C. : 1974)	Passenger contact investigation associated with a transport driver with pulmonary tuberculosis	exclude	No comparison group	NA
Prasad BM et. al	2016	Indian J Tuberc	Lessons learnt from active tuberculosis case finding in an urban slum setting of Agra city, India.	exclude	No comparison group	NA
Prasad et. al	2016	Public health action	Experience of active tuberculosis case finding in nearly 5 million households in India	exclude	No comparison group	NA
Prasad et. al	2017	International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases	Status of Tuberculosis services in Indian Prisons	exclude	No comparison group	NA

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Puryear et. al	2013	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Yield of contact tracing from pediatric tuberculosis index cases in Gaborone, Botswana	exclude	No comparison group	NA
Putra et. al	2019	J Epidemiol Glob Health	The Implementation of Early Detection in Tuberculosis Contact Investigation to Improve Case Finding	exclude	No comparison group	NA
Qadeer et. al	2017	Journal of Clinical Tuberculosis and Other Mycobacterial Diseases	Yield of facility-based verbal screening amongst household contacts of patients with multi-drug resistant tuberculosis in Pakistan	exclude	No comparison group	NA
Qader et. al	2019	Int J Infect Dis	Prevalence of tuberculosis among mentally ill patients in conflict-stricken Afghanistan: A cross-sectional study	exclude	No comparison group	NA
Rafiei et. al	2019	Nephrology (Carlton)	Mycobacterium tuberculosis: Active disease and latent infection in a renal transplant cohort	exclude	No comparison group	NA
Ramos et. al	2013	International journal of mycobacteriology	Screening for tuberculosis in family and household contacts in a rural area in Ethiopia over a 20-month period	exclude	No comparison group	NA
Rangaka et. al	2012	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	Effect of antiretroviral therapy on the diagnostic accuracy of symptom screening for intensified tuberculosis case finding in a South African HIV clinic	exclude	No comparison group	NA
Ranganath et. al	2018	Indian Journal of Public Health Research and Development	Child contact screening and chemoprophylaxis against tuberculosis in South Indian districts-situation analysis	exclude	No comparison group	NA
Rao et. al	2015	The Indian journal of tuberculosis	Yield of pulmonary tuberculosis cases by symptoms: Findings from a community survey in Madhya Pradesh, central India	exclude	No comparison group	NA
Rao et. al	2015	The Indian journal of medical research	Pulmonary tuberculosis - a health problem amongst Saharia tribe in Madhya Pradesh	exclude	No comparison group	NA
Rao et. al	2019	BMC Infect Dis	Declining tuberculosis prevalence in Saharia, a particularly vulnerable tribal community in Central India: evidences for action	include	NA	Prevelance review
Rao et. al	2010	International journal of infectious diseases	Pulmonary tuberculosis: a public health problem amongst the Saharia, a primitive tribe of Madhya Pradesh, Central India	exclude	No comparison group	NA

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Ratnawati and Burhan et. al	2019	J. Nat. Sci. Biol. Med.	Comparison of tuberculin skin test and interferon-gamma release assay in the diagnosis of latent tuberculosis infection among Indonesian health-care workers	exclude	Fewer than 1000 people screened	NA
Ratovoson et. al	2014	PloS one	Increase in the number of tuberculosis cases treated following tuberculin skin testing in first-year schoolchildren in Madagascar	exclude	No comparison group	NA
Rauf et. al	2018	Open Public Health J.	Low body mass index and trends of tuberculosis infection: A cohort study of orphan children in Azad Jammu and Kashmir Pakistan	exclude	No comparison group	NA
Reddy et. al	2015	Public health action	Intensified tuberculosis case finding amongst vulnerable communities in southern India	include	NA	CNR review
Reepalu et. al	2016	PloS one	Factors Associated with Early Mortality in HIV-Positive Men and Women Investigated for Tuberculosis at Ethiopian Health Centers	exclude	No comparison group	NA
Reichler et. al	2018	Journal of Infectious Diseases	Risk and timing of tuberculosis among close contacts of persons with infectious tuberculosis	exclude	No comparison group	NA
Reid et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Screening for tuberculosis in a diabetes clinic in Gaborone, Botswana	exclude	No comparison group	NA
Rekha Devi et. al	2013	Pathogens and global health	Active detection of tuberculosis and paragonimiasis in the remote areas in North-Eastern India using cough as a simple indicator	exclude	No comparison group	NA
Rekha et. al	2013	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Improving screening and chemoprophylaxis among child contacts in India's RNTCP: a pilot study	exclude	No comparison group	NA
Rendleman N.J. et. al	1999	American Journal of Preventive Medicine	Mandated tuberculosis screening in a community of homeless people	include	NA	CNR review
Reviono et. al	2019	J Korean Med Sci	Good Agreement between an Interferon Gamma Release Assay and Tuberculin Skin Tests in Testing for Latent Tuberculosis Infection among HIV-Infected Patients in Indonesia	exclude	No comparison group	NA
Ringshausen et. al	2013	PloS one	Frequent detection of latent tuberculosis infection among aged underground hard coal miners in the absence of recent tuberculosis exposure	exclude	No comparison group	NA

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Ritter et. al	2012	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Prevalence of positive tuberculosis skin tests during 5 years of screening in a Swiss remand prison	exclude	No comparison group	NA
Rivera et. al	2017	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Diagnostic yield of active case finding for tuberculosis and HIV at the household level in slums in Haiti	exclude	No comparison group	NA
Rivera et. al	2019	Int J Tuberc Lung Dis	Diagnostic yield of active case finding for tuberculosis at human immunodeficiency virus testing in Haiti	exclude	No comparison group	NA
Ross J.D. et. al	1977	Update	Pulmonary tuberculosis in the common hostel population	exclude	NA	NA
Roy et. al	2016	Journal of Acquired Immune Deficiency Syndromes	Use of symptom screening and sputum microscopy testing for active tuberculosis case detection among HIV-infected patients in real-world clinical practice in Uganda	exclude	No comparison group	NA
Roy et. al	2016	Journal of acquired immune deficiency syndromes (1999)	Implementation and Operational Research: Use of Symptom Screening and Sputum Microscopy Testing for Active Tuberculosis Case Detection Among HIV-Infected Patients in Real-World Clinical Practice in Uganda	exclude	No comparison group	NA
Rozhana et. al	2019	Kuwait Medical Journal	Clinico-microbiological study on 100 HIV seropositive patients from bangladesh	exclude	No comparison group	NA
Sabri et. al	2019	PLoS One	Prevalence and risk factors for latent tuberculosis infection among healthcare workers in Morocco	exclude	No comparison group	NA
Sah et. al	2016	Public health action	Dotting the Three I's for collaborative TB-HIV activities: evaluation of a pilot programme in Kathmandu, Nepal	exclude	No comparison group	NA
Said et. al	2019	Pediatr Infect Dis J	Immunologic-based Diagnosis of Latent Tuberculosis Among Children Younger Than 5 Years of Age Exposed and Unexposed to Tuberculosis in Tanzania	exclude	No comparison group	NA
Salas-Coronas et. al	2018	The American journal of tropical medicine and hygiene	Newly Arrived African Migrants to Spain: Epidemiology and Burden of Disease	exclude	No comparison group	NA
Salazar-Austin et. al	2019	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	Improving TPT Uptake: A Cluster-Randomized Trial of Symptom-Based Versus Tuberculin Skin Test-Based Screening of Household Tuberculosis Contacts Less than 5 Years of Age	exclude	ACF in children only	NA

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Salazar-Austin et. al	2020	Clin Infect Dis	Improving Tuberculosis Preventive Therapy Uptake: A Cluster-randomized Trial of Symptom-based Versus Tuberculin Skin Test-based Screening of Household Tuberculosis Contacts Less Than 5 Years of Age	exclude	ACF in children only	NA
Saleh et. al	2019	International Journal of Cancer Management	Association of lung cancer and tuberculosis: A cross sectional study from northwest of Iran	exclude	No comparison group	NA
Salinas et. al	2015	Medicina clinica	[Tuberculosis screening program for undocumented immigrant teenagers using the QuantiFERON((R))-TB Gold In-Tube test]	exclude	No comparison group	NA
Samayoa et. al	2020	Open Forum Infect Dis	The Diagnostic Laboratory Hub: A New Health Care System Reveals the Incidence and Mortality of Tuberculosis, Histoplasmosis, and Cryptococcosis of PWH in Guatemala	exclude	No comparison group	NA
Sanaie et. al	2016	PloS one	An Evaluation of Passive and Active Approaches to Improve Tuberculosis Notifications in Afghanistan	include	NA	CNR review
Sanchez et. al	2012	Epidemiology and infection	Extensive Mycobacterium tuberculosis circulation in a highly endemic prison and the need for urgent environmental interventions	include	NA	Prevelance review
Sanchez et. al	2013	BMC public health	X ray screening at entry and systematic screening for the control of tuberculosis in a highly endemic prison	include but duplicate	NA	NA
Sander et. al	2019	J Clin Tuberc Other Mycobact Dis	Systematic screening for tuberculosis among hospital outpatients in Cameroon: The role of screening and testing algorithms to improve case detection	exclude	No comparison group	NA
Sandhu et. al	2020	Int J STD AIDS	Implementation of routine interferon-gamma release assay testing in a South London HIV cohort	exclude	No comparison group	NA
Sane Schepisi et. al	2013	BMC public health	Tuberculosis case finding based on symptom screening among immigrants, refugees and asylum seekers in Rome	exclude	No comparison group	NA
Santha T. et. al	2003	International Journal of Tuberculosis and Lung Disease	Are community surveys to detect tuberculosis in high prevalence areas useful? Results of a comparative study from Tiruvallur District, South India	exclude	No comparison group	NA
Santos et. al	2020	Clin Infect Dis	Yield, Efficiency and Costs of Mass Screening Algorithms for Tuberculosis in Brazilian Prisons	exclude	No comparison group	NA
Sarin et. al	2018	The Indian journal of tuberculosis	Prevalence of pulmonary tuberculosis among adults in selected slums of Delhi city	exclude	No comparison group	NA

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Saunders et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Predictors of contact tracing completion and outcomes in tuberculosis: a 21-year retrospective cohort study	exclude	No comparison group	NA
Saunders et. al	2019	Lancet Infect Dis	Active and passive case-finding in tuberculosis-affected households in Peru: a 10-year prospective cohort study	exclude	Contact tracing	NA
Sawka et. al	2019	Respirology	Five-year impact of a targeted screening program for latent tuberculosis infection in a high-risk population	exclude	No comparison group	NA
Sawry et. al	2018	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Evaluation of the intensified tuberculosis case finding guidelines for children living with HIV	exclude	No comparison group	NA
Sayyahfar et. al	2020	Transpl Infect Dis	Comparison of tuberculin skin test and interferon gamma release assay in pediatric candidates of heart transplantation and a 2-year follow-up	exclude	Healthcare based screening	NA
Schechner et. al	2015	The Journal of hospital infection	Preventing tuberculosis transmission at a maternity hospital by targeted screening radiography of migrants	exclude	No comparison group	NA
Schepisi et. al	2016	Infectious disease reports	Active Tuberculosis Case Finding Interventions Among Immigrants, Refugees and Asylum Seekers in Italy	exclude	No comparison group	NA
Schneeberger Geisler et. al	2010	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Screening for tuberculosis in asylum seekers: comparison of chest radiography with an interview-based system	exclude	NA	NA
Scotto et. al	2019	East Mediterr Health J	Screening for infectious diseases in newly arrived asymptomatic immigrants in southern Italy	exclude	No comparison group	NA
Sek and i J.N. et. al	2009	International Journal of Tuberculosis and Lung Disease	Active case finding of undetected tuberculosis among chronic coughers in a slum setting in kampala, uganda	exclude	No comparison group	NA
Sek and i et. al	2014	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Yield of undetected tuberculosis and human immunodeficiency virus coinfection from active case finding in urban Uganda	exclude	No comparison group	NA

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Sellami et. al	2019	Egypt. Rheumatol.	Screening for latent tuberculosis infection prior to biologic therapy in patients with chronic immune-mediated inflammatory diseases (IMID): Interferon-gamma release assay (IGRA) versus tuberculin skin test (TST)	exclude	Healthcare based screening	NA
Sema Baltazar et. al	2020	PLoS One	HIV prevalence and TB in migrant miners communities of origin in Gaza Province, Mozambique: The need for increasing awareness and knowledge	exclude	No comparison group	NA
Semitala et. al	2019	J Acquir Immune Defic Syndr	Brief Report: Yield and Efficiency of Intensified Tuberculosis Case-Finding Algorithms in 2 High-Risk HIV Subgroups in Uganda	exclude	Healthcare based screening	NA
Semunigus et. al	2016	Annals of clinical microbiology and antimicrobials	Smear positive pulmonary tuberculosis and associated factors among homeless individuals in Dessie and Debre Birhan towns, Northeast Ethiopia	exclude	No comparison group	NA
Semunigus et. al	2016	Annals of clinical microbiology and antimicrobials	Smear positive pulmonary tuberculosis and associated factors among homeless individuals in Dessie and Debre Birhan towns, Northeast Ethiopia	exclude	No comparison group	NA
Sengai et. al	2019	Public Health Action	Mobile targeted screening for tuberculosis in Zimbabwe: diagnosis, linkage to care and treatment outcomes	exclude	No comparison group	NA
Seri et. al	2017	PloS one	Prevalence of pulmonary tuberculosis among prison inmates: A cross-sectional survey at the Correctional and Detention Facility of Abidjan, Cote d'Ivoire	exclude	No comparison group	NA
Sethuraman et. al	2018	Open Forum Infectious Diseases	Community prevalence of bacteriologically confirmed pulmonary tuberculosis: A 7-year retrospective study	exclude	No comparison group	NA
Seyedalinaghi et. al	2018	Archives of Clinical Infectious Diseases	Comparing tuberculosis incidence in a prison with the society, tehran, iran	exclude	No comparison group	NA
Shah et. al	2020	Lung India	Comparison of tuberculin skin test and QuantiFERON-TB Gold In-Tube test in Bacillus Calmette-Guerin-vaccinated children	exclude	ACF in children only	NA
Shah et. al	2013	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Active contact investigation and treatment support: an integrated approach in rural and urban Sindh, Pakistan	exclude	No comparison group	NA
Shahryar et. al	2012	Life Sci. J.	Screening tuberculosis in the Sistan region of Iran: A population-based study	exclude	No comparison group	NA

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Shapiro et. al	2018	AIDS (London, England)	C-reactive protein as a screening test for HIV-associated pulmonary tuberculosis prior to antiretroviral therapy in South Africa	exclude	Healthcare based screening	NA
Shapiro et. al	2012	American journal of respiratory and critical care medicine	Community-based targeted case finding for tuberculosis and HIV in household contacts of patients with tuberculosis in South Africa	exclude	No comparison group	NA
Shargie E.B. et. al	2006	Bulletin of the World Health Organization	Tuberculosis case-finding through a village outreach programme in a rural setting in southern Ethiopia: Community randomized trial	include	NA	CNR review
Shargie E.B. et. al	2006	International Journal of Tuberculosis and Lung Disease	Prevalence of smear-positive pulmonary tuberculosis in a rural district of Ethiopia	exclude	No comparison group	NA
Sharma et. al	2018	Indian Journal of Tuberculosis	Tuberculosis (TB) intervention model targeting mobile population of truckers in Delhi, India	exclude	No comparison group	NA
Sharma et. al	2019	Indian J Tuberc	Tuberculosis (TB) intervention model targeting mobile population of truckers in Delhi, India	exclude	No comparison group	NA
Sharma et. al	2015	The Indian journal of medical research	Prevalence of tuberculosis in Faridabad district, Haryana State, India	exclude	No comparison group	NA
Shayo et. al	2014	Tropical medicine & international health : TM & IH	Symptom-based screening tool in ruling out active tuberculosis among HIV-infected patients eligible for isoniazid preventive therapy in Tanzania	exclude	No comparison group	NA
Shenoi et. al	2013	Public health action	'Cough officer' nurses in a general medical clinic successfully detect drug-susceptible and -resistant tuberculosis	exclude	No comparison group	NA
Shenoi et. al	2017	Open forum infectious diseases	Integrated Tuberculosis/Human Immunodeficiency Virus Community-Based Case Finding in Rural South Africa: Implications for Tuberculosis Control Efforts	exclude	No comparison group	NA
Shetty P.V.D. et. al	2008	International Journal of Tuberculosis and Lung Disease	Cross-referral between voluntary HIV counselling and testing centres and TB services, Maharashtra, India, 2003-2004	exclude	No comparison group	NA
Shewade et. al	2019	J Epidemiol Glob Health	Impact of Advocacy, Communication, Social Mobilization and Active Case Finding on TB Notification in Jharkhand, India	include	NA	CNR review
Shewade et. al	2018	Global health action	Active case finding among marginalised and vulnerable populations reduces catastrophic costs due to tuberculosis diagnosis	exclude	No relevant data / not an ACF intervention	NA

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Shinohara et. al	2020	Journal of Allergy and Clinical Immunology	Sex-difference In Associations Between Skin Responses To Purified Protein Derivative And Family Size During Infancy in Japan	exclude	No comparison group	NA
Shivakumar et. al	2016	Open Forum Infectious Diseases	Tuberculosis (TB) infection prevalence, incidence and risk factors among child and adult household contacts of adult TB cases in India	exclude	No comparison group	NA
Shrestha et. al	2019	Tuberc Res Treat	Pulmonary Tuberculosis among Male Inmates in the Largest Prison of Eastern Nepal	exclude	No comparison group	NA
Shriraam et. al	2020	Indian J Tuberc	Active case finding for Tuberculosis among migrant brick kiln workers in South India	exclude	No comparison group	NA
Shrivastava et. al	2013	Journal of research in health sciences	Tuberculosis: active case finding survey in an urban area of India, in 2012	exclude	No comparison group	NA
Silva et. al	2019	Rev Soc Bras Med Trop	Prevalence of coinfections in women living with human immunodeficiency virus in Northeast Brazil	exclude	No comparison group	NA
Silva et. al	2014	PloS one	Active case finding of tuberculosis (TB) in an emergency room in a region with high prevalence of TB in Brazil	exclude	No comparison group	NA
Singh et. al	2013	PloS one	Incidence and prevalence of tuberculosis among household contacts of pulmonary tuberculosis patients in a peri-urban population of South Delhi, India	exclude	No comparison group	NA
Singla et. al	2011	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Tuberculosis among household contacts of multidrug-resistant tuberculosis patients in Delhi, India	exclude	No comparison group	NA
Sireesha et. al	2018	Infectious disorders drug targets	Surreptitious TB infections with recently identified DM people: A cross-sectional study	exclude	No comparison group	NA
Sireesha et. al	2019	Infectious Disorders - Drug Targets	Surreptitious TB infections with recently identified DM people: A cross-sectional study	exclude	Healthcare based screening	NA
Sismanidis C. et. al	2008	Clinical Trials	Restricted randomization of ZAMSTAR: A 2 Ã 2 factorial cluster randomized trial	include but duplicate	NA	NA
So-Ngern et. al	2019	Annals of the Rheumatic Diseases	Tuberculin skin test for detection of tuberculosis in systemic sclerosis	exclude	No comparison group	NA
Soares et. al	2011	American Journal of Respiratory and Critical Care Medicine	Community-based respiratory symptom evaluation in a Brazilian favela	exclude	No comparison group	NA

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Soe et. al	2017	Infectious Diseases of Poverty	International non-governmental organizations' provision of community-based tuberculosis care for hard-to-reach populations in Myanmar, 2013–2014	exclude	No comparison group	NA
Solari et. al	2019	Rev Peru Med Exp Salud Publica	[Respiratory symptoms in people attended in health facilities of the Ministry of Health in Lima, Peru]	exclude	No comparison group	NA
Sollai et. al	2017	Medicine	Infectious diseases prevalence, vaccination coverage, and diagnostic challenges in a population of internationally adopted children referred to a Tertiary Care Children's Hospital from 2009 to 2015	exclude	No comparison group	NA
Sookaromdee et. al	2019	Neurology Asia	Tuberculosis screening among the bed ridden patients after stroke: A note from a study in a rural province in Thailand	exclude	No comparison group	NA
Sotelo et. al	2019	Journal of the International AIDS Society	National study: Prevalence of HIV, hepatitis B and C, syphilis and tuberculosis in people deprived of liberty in federal prisons in Argentina	exclude	No comparison group	NA
Sousa et. al	2018	European Respiratory Journal	Cost-effectiveness of two latent tuberculosis infection screening strategies	exclude	No comparison group	NA
Spruijt et. al	2019	PLoS One	Implementation of latent tuberculosis infection screening and treatment among newly arriving immigrants in the Netherlands: A mixed methods pilot evaluation	exclude	No comparison group	NA
Sridhar et. al	2014	The Pediatric infectious disease journal	Increased risk of Mycobacterium tuberculosis infection in household child contacts exposed to passive tobacco smoke	exclude	No comparison group	NA
Ssemmondo et. al	2016	Journal of acquired immune deficiency syndromes (1999)	Implementation and Operational Research: Population-Based Active Tuberculosis Case Finding During Large-Scale Mobile HIV Testing Campaigns in Rural Uganda	exclude	No comparison group	NA
Story A. et. al	2008	Int J Tuberc Lung Dis	Targeted mobile digital radiography to reduce diagnostic delay for tuberculosis among hard to reach groups 39th world conference on lung health of the international union against tuberculosis and lung disease	exclude	No comparison group	NA
Subramani et. al	2016	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Trend in the incidence of smear-positive tuberculosis in a district in South India after DOTS implementation	include	NA	Prevelance review

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Suh et. al	2018	Open Forum Infectious Diseases	2013-2015 nationwide tuberculosis contact investigation in childcare centers and schools in Korea	exclude	No comparison group	NA
Sulis et. al	2016	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Active tuberculosis case finding among pregnant women: a pilot project in Burkina Faso	exclude	No comparison group	NA
Sun et. al	2019	Br J Dermatol	Screening for hepatitis B virus and tuberculosis infection in patients with moderate-to-severe psoriasis recruiting for biological therapy in China	exclude	No comparison group	NA
Swindells et. al	2018	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Resource utilization for multidrug-resistant tuberculosis household contact investigations (A5300/I2003)	exclude	No comparison group	NA
Swindells et. al	2013	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Screening for pulmonary tuberculosis in HIV-infected individuals: AIDS Clinical Trials Group Protocol A5253	exclude	No comparison group	NA
Szkwarko et. al	2016	Public health action	Implementing intensified tuberculosis case-finding among street-connected youth and young adults in Kenya	exclude	No comparison group	NA
Szkwarko et. al	2018	Public health action	Implementation of an active, clinic-based child tuberculosis contact management strategy in western Kenya	exclude	No comparison group	NA
Tabuchi et. al	2011	BMC infectious diseases	Tuberculosis infection among homeless persons and caregivers in a high-tuberculosis-prevalence area in Japan: a cross-sectional study	exclude	No comparison group	NA
Tadesse et. al	2011	PloS one	Two-thirds of smear-positive tuberculosis cases in the community were undiagnosed in Northwest Ethiopia: population based cross-sectional study	exclude	No comparison group	NA
Tadesse et. al	2013	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Incidence of smear-positive tuberculosis in Dabat, northern Ethiopia	exclude	No comparison group	NA

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Tadesse et. al	2016	PloS one	Uptake of Isoniazid Preventive Therapy among Under-Five Children: TB Contact Investigation as an Entry Point	exclude	No comparison group	NA
Tafuri et. al	2011	American journal of infection control	Tuberculosis screening in migrant reception centers: results of a 2009 Italian survey	exclude	No comparison group	NA
Tagarro et. al	2011	Enfermedades infecciosas y microbiologia clinica	[Tuberculosis outbreak in a primary school: description and reflections on the value of gastric juice in the management of micro-epidemics]	exclude	No comparison group	NA
Tahseen et. al	2018	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Systematic case finding for tuberculosis in HIV-infected people who inject drugs: experience from Pakistan	exclude	No comparison group	NA
Targowski et. al	2016	International Review of Allergology and Clinical Immunology in Family Medicine	Assessment of annual risk of tuberculosis infection (ARTI) based on Styblo's formula as well as on tuberculin (TST) and gamma-interferon (IGRA) tests results	exclude	No comparison group	NA
Tasaka et. al	2020	Epidemiol Infect	A tuberculosis outbreak in a psychiatric hospital: Kanagawa, Japan, 2012	exclude	No comparison group	NA
Tefera et. al	2019	BMC Health Serv Res	Evaluation of facility and community-based active household tuberculosis contact investigation in Ethiopia: a cross-sectional study	exclude	Contact tracing	NA
Telisinghe et. al	2014	PloS one	High tuberculosis prevalence in a South African prison: the need for routine tuberculosis screening	exclude	No comparison group	NA
Tewes et. al	2020	BMC Public Health	Tuberculosis screening during the 2015 European refugee crisis	exclude	No comparison group	NA
Thanh et. al	2014	BMC public health	A household survey on screening practices of household contacts of smear positive tuberculosis patients in Vietnam	exclude	No comparison group	NA
Thapa B et. al	2017	Indian J Tuberc	Adding sputum collection and transportation services for early identification TB cases in hard-to-reach difficult terrain—Will it help?	exclude	NA	NA
Thee et. al	2019	PLoS One	Screening and treatment for tuberculosis in a cohort of unaccompanied minor refugees in Berlin, Germany	exclude	ACF in children only	NA
Thibeault et. al	2012	Aviation, space, and environmental medicine	A case of active tuberculosis in a cabin crew: the results of contact tracing	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Thind et. al	2012	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	An evaluation of 'Ribolola': a household tuberculosis contact tracing programme in North West Province, South Africa	exclude	No comparison group	NA
Thu et. al	2020	Tropical Medicine and Infectious Disease	An innovative public–private mix model for improving tuberculosis care in Vietnam: How well are we doing?	exclude	Healthcare based screening	NA
Tibbetts et. al	2020	Emerg Infect Dis	Public Health Response to Tuberculosis Outbreak among Persons Experiencing Homelessness, Minneapolis, Minnesota, USA, 2017-2018	exclude	No comparison group	NA
Titiyos et. al	2015	BMC research notes	The yield of screening symptomatic contacts of multidrug-resistant tuberculosis cases at a tertiary hospital in Addis Ababa, Ethiopia	exclude	No comparison group	NA
Tong et. al	2019	Am J Trop Med Hyg	Epidemic Situation of Tuberculosis in Prisons in the Central Region of China	exclude	No comparison group	NA
Torres Costa et. al	2011	Journal of occupational medicine and toxicology (London, England)	Screening for tuberculosis and prediction of disease in Portuguese healthcare workers	exclude	No comparison group	NA
Townes et. al	2016	Open Forum Infectious Diseases	Resource-intensive contact investigation resulting from an unrecognized pulmonary tuberculosis case at a rheumatology clinic	exclude	Healthcare based screening	NA
Trachanatzi et. al	2019	Acta Paediatr	Evaluating a 24-year tuberculosis screening in first-grade elementary schoolers in a low-burden area	exclude	ACF in children only	NA
Triasih et. al	2015	Tropical medicine & international health : TM & IH	Risk of infection and disease with Mycobacterium tuberculosis among children identified through prospective community-based contact screening in Indonesia	exclude	No comparison group	NA
Triasih et. al	2015	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	A prospective evaluation of the symptom-based screening approach to the management of children who are contacts of tuberculosis cases	exclude	No comparison group	NA
Trinidad et. al	2016	Journal of Clinical Tuberculosis and Other Mycobacterial Diseases	Tuberculosis screening at a diabetes clinic in the Republic of the Marshall Islands	exclude	No comparison group	NA
Tsegaye Sahle et. al	2019	PLoS One	Bacteriologically-confirmed pulmonary tuberculosis in an Ethiopian prison: Prevalence from screening of entrant and resident prisoners	include	NA	Prevelance review

Author	Year	Journal	Title	Decision	mainreason	Which review?
Tsuyuzaki et. al	2020	J Infect Chemother	Role of CD8 T-cell in immune response to tuberculosis-specific antigen in QuantiFERON-TB Gold Plus	exclude	No comparison group	NA
Tufa et. al	2017	Open Forum Infectious Diseases	Detecting TB cases among household contacts of patients with pulmonary tb through active contact tracing in The Arsi Zone, Ethiopia	exclude	No comparison group	NA
Tupasi T.E. et. al	1999	International Journal of Tuberculosis and Lung Disease	The 1997 nationwide tuberculosis prevalence survey in the Philippines	exclude	No comparison group	NA
Turinawe et. al	2016	PloS one	Operating Characteristics of a Tuberculosis Screening Tool for People Living with HIV in Out-Patient HIV Care and Treatment Services, Rwanda	exclude	No comparison group	NA
Uppada et. al	2016	BMC public health	Incidence of tuberculosis among school-going adolescents in South India	exclude	ACF in children only	NA
Usemann et. al	2019	Int J Tuberc Lung Dis	Cost-effectiveness of tuberculosis screening for migrant children in a low-incidence country	exclude	No comparison group	NA
Usemann et. al	2018	European Respiratory Journal	Cost-Effectiveness of Tuberculosis Screening for Migrant Children in Low-Incidence countries	exclude	No comparison group	NA
Usman et. al	2017	Pakistan Journal of Medical and Health Sciences	Tuberculin and sputum smear positivity among doctors and paramedics of a tertiary care hospital	exclude	No comparison group	NA
Usman et. al	2019	Sexually Transmitted Infections	Diagnostic accuracy of XPERT MTB/RIF in detecting pulmonary tuberculosis among people living with HIV in Western Nigeria	exclude	Healthcare based screening	NA
Ustero et. al	2017	PloS one	School and household tuberculosis contact investigations in Swaziland: Active TB case finding in a high HIV/TB burden setting	exclude	No comparison group	NA
Uwinkindi et. al	2014	Journal of acquired immune deficiency syndromes (1999)	Scaling up intensified tuberculosis case finding in HIV clinics in Rwanda	exclude	Healthcare based screening	NA
Valenca et. al	2015	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Prevalence of tuberculosis in prisons: risk factors and molecular epidemiology	exclude	No comparison group	NA
van der Westhuizen et. al	2018	Southern African Journal of Infectious Diseases	Evaluation of a screening chest X-ray programme for the detection of pulmonary tuberculosis in asymptomatic military members???	exclude	No comparison group	NA
van Hest et. al	2016	The European respiratory journal	Active tuberculosis case-finding among drug users and homeless persons: after the outbreak	include but duplicate	NA	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Van Hoving et. al	2020	J Acquir Immune Defic Syndr	Point-of-Care Ultrasound Predictors for the Diagnosis of Tuberculosis in HIV-Positive Patients Presenting to an Emergency Center	exclude	Healthcare based screening	NA
Van't Hoog A.H. et. al	2011	American Journal of Respiratory and Critical Care Medicine	High prevalence of pulmonary tuberculosis and inadequate case finding in rural Western Kenya	exclude	No relevant data / not an ACF intervention	NA
van't Hoog et. al	2011	American journal of respiratory and critical care medicine	High prevalence of pulmonary tuberculosis and inadequate case finding in rural western Kenya	exclude	No comparison group	NA
Vanino et. al	2017	Clinical infectious diseases : an official publication of the Infectious Diseases Society of America	Systematic Tuberculosis Screening in Asylum Seekers in Italy	exclude	No comparison group	NA
Varghese et. al	2019	Lung India	Prevalence of LTBI in patients with RA and AS	exclude	No comparison group	NA
Velasco-Arnaiz et. al	2018	Pediatric Infectious Disease Journal	Performance of Tuberculin Skin Tests and Interferon-γ Release Assays in Children Younger Than 5 Years	exclude	No comparison group	NA
Velasquez et. al	2012	Revista panamericana de salud publica = Pan American journal of public health	Tuberculosis testing among populations with high HIV risk in Tijuana, Baja California, Mexico	exclude	No comparison group	NA
Vella et. al	2011	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Household contact investigation of multidrug-resistant and extensively drug-resistant tuberculosis in a high HIV prevalence setting	exclude	No comparison group	NA
Verdier et. al	2012	Infectious disease reports	Risk factors for tuberculosis in contact investigations in Rotterdam, the Netherlands	exclude	No comparison group	NA
Verma et. al	2012	Journal of Nepal Health Research Council	Prevalence of pulmonary tuberculosis among HIV infected persons in Pokhara, Nepal	exclude	No comparison group	NA
Verso et. al	2019	Int J Environ Res Public Health	Latent Tuberculosis Infection among Healthcare Students and Postgraduates in a Mediterranean Italian Area: What Correlation with Work Exposure?	exclude	No comparison group	NA
Verver S. et. al	2001	International Journal of Tuberculosis and Lung Disease	Screening for pulmonary tuberculosis among immigrants: Estimated effect on severity of disease and duration of infectiousness	exclude	No comparison group	NA
Verver et. al	2017	BMC public health	Feasibility of district wide screening of health care workers for tuberculosis in Zambia	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Vieira et. al	2010	Revista brasileira de epidemiologia = Brazilian journal of epidemiology	Prevalence of patients with respiratory symptoms through active case finding and diagnosis of pulmonary tuberculosis among prisoners and related predictors in a jail in the city of Carapicuiba, Brazil	exclude	No comparison group	NA
Vijayageetha et. al	2019	Glob Health Action	Tuberculosis screening among pregnant women attending a tertiary care hospital in Puducherry, South India: is it worth the effort?	exclude	No comparison group	NA
Villa et. al	2019	Transactions of the Royal Society of Tropical Medicine and Hygiene	Tuberculosis risk among asylum-seekers and yield of interventions in Milan, Italy	exclude	No comparison group	NA
Villa et. al	2019	Eur Respir J	Tuberculosis among asylum seekers in Milan, Italy: epidemiological analysis and evaluation of interventions	exclude	No comparison group	NA
Villa et. al	2019	COPD: Journal of Chronic Obstructive Pulmonary Disease	[182] tuberculosis and latent tuberculosis infection screening among asylum seekers in Milan, Italy	exclude	No comparison group	NA
Visser et. al	2019	Western Pac Surveill Response J	Screening for latent tuberculosis infection by an Aboriginal Community Controlled Health Service, New South Wales, Australia, 2015	exclude	No comparison group	NA
von Streit et. al	2019	PLoS One	Prevalence of latent tuberculosis in homeless persons: A single-centre cross-sectional study, Germany	exclude	No comparison group	NA
Vyas et. al	2019	International Journal of Tuberculosis and Lung Disease	Community-based active case-finding to reach the most vulnerable: Tuberculosis in tribal areas of India	include	NA	CNR review
Waako et. al	2013	BMC infectious diseases	Burden of tuberculosis disease among adolescents in a rural cohort in Eastern Uganda	exclude	No comparison group	NA
Wali et. al	2019	BMC Public Health	Prevalence of tuberculosis, HIV/AIDS, and hepatitis; in a prison of Balochistan: a cross-sectional survey	exclude	No comparison group	NA
Wang P.D. et. al	2000	Journal of Infection	Tuberculosis transmission in the family	exclude	No comparison group	NA
Wang et. al	2014	Therapeutics and clinical risk management	Frequency of tuberculosis among diabetic patients in the People's Republic of China	exclude	Healthcare based screening	NA
Wang et. al	2012	The Journal of infection	Interferon-gamma release assay and Rifampicin therapy for household contacts of tuberculosis	exclude	No comparison group	NA
Wang et. al	2010	Journal of immigrant and minority health	Lessons learned from two school tuberculosis investigations	exclude	ACF in children only	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Wang et. al	2017	PloS one	ESMPE: A combined strategy for school tuberculosis prevention and control proposed by Dalian, China	exclude	No comparison group	NA
Wardhani et. al	2019	Indian Journal of Public Health Research and Development	Relationship between diabetes mellitus and tuberculosis in Indonesia	exclude	No comparison group	NA
Warria et. al	2020	Trop Med Int Health	Tuberculosis disease and infection among household contacts of bacteriologically confirmed and non-confirmed tuberculosis patients	exclude	No comparison group	NA
Warrington et. al	2018	Canadian journal of public health = Revue canadienne de sante publique	Prevalence of latent tuberculosis infection in Syrian refugees to Canada	exclude	No comparison group	NA
Wei et. al	2014	BMC infectious diseases	Changes in pulmonary tuberculosis prevalence: evidence from the 2010 population survey in a populous province of China	exclude	No comparison group	NA
Wei et. al	2015	Transactions of the Royal Society of Tropical Medicine and Hygiene	An intervention of active TB case finding among smokers attending routine primary care facilities in China: an exploratory study	exclude	Healthcare based screening	NA
Weinrich et. al	2017	European radiology	Yield of chest X-ray tuberculosis screening of immigrants during the European refugee crisis of 2015: a single-centre experience	exclude	No comparison group	NA
Whalen et. al	2011	PloS one	Secondary attack rate of tuberculosis in urban households in Kampala, Uganda	exclude	No comparison group	NA
Wigg et. al	2019	Transpl Infect Dis	High rates of indeterminate interferon-gamma release assays for the diagnosis of latent tuberculosis infection in liver transplantation candidates	exclude	No comparison group	NA
Williams G. et. al	2007	Best practice for the care of patients with tuberculosis: A guide for low-income countries	[No title available]	exclude	No relevant data / not an ACF intervention	NA
Williams et. al	2020	Arch Dis Child	Screening for infection in unaccompanied asylum-seeking children and young people	exclude	No comparison group	NA
Williams et. al	2019	Archives of Disease in Childhood	Infection screening in unaccompanied asylum-seeking children	exclude	No comparison group	NA
Williams et. al	2016	Journal of public health (Oxford, England)	The need to implement effective new entrant tuberculosis screening in children: evidence from school 'outbreak'	exclude	No comparison group	NA
Winetsky et. al	2014	PloS one	Prevalence, risk factors and social context of active pulmonary tuberculosis among prison inmates in Tajikistan	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Winetsky et. al	2012	PLoS medicine	Screening and rapid molecular diagnosis of tuberculosis in prisons in Russia and Eastern Europe: a cost-effectiveness analysis	exclude	No relevant data / not an ACF intervention	NA
Wingfield et. al	2018	Thorax	High prevalence of TB disease in contacts of adults with extrapulmonary TB	exclude	No comparison group	NA
Woldesemayat et. al	2015	PloS one	Follow-up of chronic coughers improves tuberculosis case finding: results from a community-based cohort study in southern Ethiopia	exclude	No comparison group	NA
Wong et. al	2020	ERJ Open Res	Prevalence of latent tuberculosis among refugee children in Malaysia	exclude	No comparison group	NA
Wood R. et. al	2007	American Journal of Respiratory and Critical Care Medicine	Undiagnosed tuberculosis in a community with high HIV prevalence: Implications for tuberculosis control	exclude	Fewer than 1000 people screened	NA
Wu et. al	2019	BMC Infect Dis	Diagnostic value of the interferon-gamma release assay for tuberculosis infection in patients with Behcet's disease	exclude	Healthcare based screening	NA
Xu et. al	2019	PLoS One	An outbreak of tuberculosis in a middle school in Henan, China: Epidemiology and risk factors	exclude	No comparison group	NA
Yadav et. al	2010	The Indian journal of tuberculosis	Prevalence of pulmonary tuberculosis amongst the Baigas--a primitive tribe of Madhya Pradesh, Central India	exclude	NA	NA
Yagi T. et. al	2006	Kekkaku	Clinical review of patients with pulmonary tuberculosis who were detected by the screening of homeless persons admitted in the shelter facilities	exclude	No comparison group	NA
Yasseen et. al	2019	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Paediatric tuberculosis among the foreign-born: utility of the Canadian TB immigration medical surveillance programme	exclude	No comparison group	NA
Yassin et. al	2019	Current Women's Health Reviews	Prevalence of latent tuberculosis (LTB) among pregnant women in a high burden setting in Sudan using interferon gamma (IFN- γ) releasing assay (IGRA)	exclude	No comparison group	NA
Yassin et. al	2013	PloS one	Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia	include but duplicate	NA	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Yeon et. al	2018	Scientific reports	Prevalence and risk factors of latent tuberculosis among Korean healthcare workers using whole-blood interferon-γ release assay	exclude	No comparison group	NA
Yezli et. al	2017	The American journal of tropical medicine and hygiene	Undiagnosed Active Pulmonary Tuberculosis among Pilgrims during the 2015 Hajj Mass Gathering: A Prospective Cross-sectional Study	exclude	No comparison group	NA
Yezli et. al	2017	The American journal of tropical medicine and hygiene	Undiagnosed Active Pulmonary Tuberculosis among Pilgrims during the 2015 Hajj Mass Gathering: A Prospective Cross-sectional Study	exclude	No comparison group	NA
Yimer S. et. al	2009	International Journal of Tuberculosis and Lung Disease	Evaluating an active case-fi nding strategy to identify smear-positive tuberculosis in rural Ethiopia	exclude	No comparison group	NA
Yoon et. al	2019	Am J Respir Crit Care Med	Yield and Efficiency of Novel Intensified Tuberculosis Case-Finding Algorithms for People Living with HIV	exclude	No comparison group	NA
Yoon et. al	2017	The Lancet. Infectious diseases	Point-of-care C-reactive protein-based tuberculosis screening for people living with HIV: a diagnostic accuracy study	exclude	No comparison group	NA
Yoon et. al	2019	Tuberculosis and Respiratory Diseases	The infectivity of pulmonary tuberculosis in Korean army units: Evidence from outbreak investigations	exclude	No comparison group	NA
You et. al	2019	Epidemiol Infect	A tuberculosis school outbreak in China, 2018: reaching an often overlooked adolescent population	exclude	No comparison group	NA
Young et. al	2016	MMWR. Morbidity and mortality weekly report	Tuberculosis Contact Investigations--United States, 2003-2012	exclude	No comparison group	NA
Yuen et. al	2019	Int J Tuberc Lung Dis	Optimizing the efficiency of tuberculosis active case-finding in health facilities and communities	exclude	NA	NA
Yuen et. al	2019	PLoS One	Tuberculosis household accompaniment to improve the contact management cascade: A prospective cohort study	exclude	Fewer than 1000 people screened	NA
Zaeh et. al	2013	Journal of Investigative Medicine	Improving tuberculosis screening and isoniazid preventative therapy in an HIV clinic in Addis Ababa, Ethiopia	exclude	Healthcare based screening	NA
Zaman et. al	2012	Epidemiology and infection	Prevalence of smear-positive tuberculosis in persons aged >/= 15 years in Bangladesh: results from a national survey, 2007-2009	exclude	No comparison group	NA
Zarnuzi and Wahyono et. al	2019	Indian Journal of Public Health Research and Development	Body mass index and lung tuberculosis in Indonesia: A cross-sectional in Indonesia	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Zawedde-Muyanja et. al	2018	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Decentralisation of child tuberculosis services increases case finding and uptake of preventive therapy in Uganda	exclude	Healthcare based screening	NA
Zenhausern et. al	2019	S Afr Med J	Tuberculosis transmission in a hospitalised neonate: Need for optimised tuberculosis screening of pregnant and postpartum women	exclude	Fewer than 1000 people screened	NA
Zhang et. al	2019	PLoS One	Findings from a pilot project to assess the feasibility of active tuberculosis case finding among seniors in rural Sichuan Province, China, 2017	exclude	No comparison group	NA
Zhang et. al	2019	Infectious diseases of poverty	Prevalence and risk factors of active pulmonary tuberculosis among elderly people in China: a population based cross-sectional study	exclude	No comparison group	NA
Zhang et. al	2020	Emerg Infect Dis	High Prevalence of and Risk Factors for Latent Tuberculosis Infection among Prisoners, Tianjin, China	exclude	No comparison group	NA
Zhang et. al	2019	Int J Tuberc Lung Dis	Serial T-SPOT.TB in household contacts of tuberculosis patients: a 6-year observational study in China	exclude	No comparison group	NA
Zhang et. al	2011	Tropical medicine & international health : TM & IH	Evaluation of active tuberculosis case finding through symptom screening and sputum microscopy of close contacts in Shandong, China	exclude	No comparison group	NA
Zhang et. al	2011	Tropical medicine & international health : TM & IH	Evaluation of active tuberculosis case finding through symptom screening and sputum microscopy of close contacts in Shandong, China	exclude	No comparison group	NA
Zhang et. al	2015	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Integrating tuberculosis screening into annual health examinations for the rural elderly improves case detection	exclude	No comparison group	NA
Zhang et. al	2010	Chinese medical journal	Diagnosis of pulmonary tuberculosis among asymptomatic HIV+ patients in Guangxi, China	exclude	No comparison group	NA
Zhang et. al	2010	Chinese medical journal	Diagnosis of pulmonary tuberculosis among asymptomatic HIV+ patients in Guangxi, China	exclude	No comparison group	NA
Zhou et. al	2020	Radiology of Infectious Diseases	Outbreak of pulmonary tuberculosis in lodging high school, should X-ray be replaced by CT?	exclude	No comparison group	NA
Zimba et. al	2019	Pan Afr Med J	The effect of sputum quality and volume on the yield of bacteriologically-confirmed TB by Xpert MTB/RIF and smear	exclude	No comparison group	NA

Author	Year	Journal	Title	Decision	mainreason	Which review?
Zishiri et. al	2015	Open forum infectious diseases	Implementing a large-scale systematic tuberculosis screening program in correctional facilities in South Africa	exclude	No comparison group	NA
NA et. al	2011	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease	Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases	exclude	No comparison group	NA
NA et. al	2013	Tropical medicine & international health : TM & IH	Screening of patients with diabetes mellitus for tuberculosis in India	exclude	No comparison group	NA
NA et. al	2019	Lancet	Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study	exclude	Healthcare based screening	NA

Appendix 4: List of TB ACF studies identified with suitable study design and included in search for additional KAP or qualitative manuscripts

Author	Year	Title	Decision	Main reason	Additional KAP/qualitative search
Adane et al (1)	2019	Tuberculosis case detection by trained inmate peer educators in a resource-limited prison setting in Ethiopia: a cluster-randomised trial	Proxy behavioural outcomes review		• 5 results • 4 excluded on abstract • Adane et al 2017 (2) excluded on full text as no data on impact of ACF
Aye et al (3)	2018	Evaluation of a tuberculosis active case finding project in peri-urban areas, Myanmar: 2014-2016	Routine CNR outcomes review		• 116 results • All excluded on abstract
Ayles et al (4)	2013	Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial	Exclude	No CNR data split routine : ACF	• 79 results • 78 excluded on abstract • Bond et al 2010 (5) excluded on full text as no data on impact of ACF
Cegielski et al (6)	2013	Eliminating tuberculosis one neighborhood at a time	Routine CNR outcomes review		• 12 results • All excluded on abstract
Chatterjee et al (7)	2014	Incidence of Active Pulmonary Tuberculosis in Patients with Coincident Filarial and/or Intestinal Helminth Infections Followed Longitudinally in South India	Exclude	No CNR data split routine : ACF	• 80 results • All excluded on abstract
Chen et al (8)	2019	Role of community-based active case finding in screening tuberculosis in Yunnan province of China	Exclude	No CNR data split routine : ACF	• 16 results • All excluded on abstract
Churchyard et al (9)	2011	Twelve-monthly versus six-monthly radiological screening for active case-finding of tuberculosis: A randomised controlled trial	Exclude	TB screening not voluntary	• 127 results • All excluded on abstract
Corbett et al (10)	2010	Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): A cluster-randomised trial	Routine CNR outcomes review		• 16 results • All excluded on abstract
Dakito et al (11) + Yassin et al (12)	2017 2013	Health extension workers improve tuberculosis case finding and treatment outcome in Ethiopia: a large-scale implementation study. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia	Routine CNR outcomes review		• 32 results • 31 excluded on abstract • Tulloch et al 2015 (13) included
Dakito et al (14)	2009	Health extension workers improve tuberculosis case detection and treatment success in southern Ethiopia: A community randomized trial	Exclude	No CNR data split routine : ACF	• 49 results • All excluded on abstract
Degner et al (15)	2016	Comparison of Digital Chest Radiography to Purified Protein Derivative for Screening of Tuberculosis in Newly Admitted Inmates	Exclude	No CNR data split routine : ACF	• 1 result • Excluded on abstract
Delva et al (16)	2016	Active Tuberculosis Case Finding in Port-au-Prince, Haiti: Experiences, Results, and Implications for Tuberculosis Control Programs	Exclude	No CNR data split routine : ACF	• 1 result • Excluded on abstract

de Vries et al (17) + van Hest et al (18)	2007 2016	Impact of mobile radiographic screening on tuberculosis among drug users and homeless persons Active tuberculosis case-finding among drug users and homeless persons: after the outbreak	Exclude	No CNR data split routine : ACF	• 82 results • All excluded on abstract
Fatima et al (19)	2014	Success of active tuberculosis case detection among high-risk groups in urban slums in Pakistan	Routine CNR outcomes review		• 34 results • All excluded on abstract
Fatima et al (20)	2016	Extending 'Contact Tracing' into the Community within a 50-Metre Radius of an Index Tuberculosis Patient Using Xpert MTB/RIF in Urban, Pakistan: Did It Increase Case Detection?	Routine CNR outcomes review		• 29 results • All excluded on abstract
Ford et al (21)	2019	Fifth year of a public-private partnership to improve the case detection of tuberculosis in India: A role model for future action?	Routine CNR outcomes review		• 3 results • All excluded on abstract
John et al (22)	2015	Tuberculosis among nomads in Adamawa, Nigeria: outcomes from two years of active case finding	Exclude	Mobile population	• 5 results • All excluded on abstract
Kan et al (23)	2012	Mobilising elementary and secondary school students for tuberculosis case finding in Anhui, China	Routine CNR outcomes review		• 30 results • All excluded on abstract
Karamagi et al (24)	2018	Improving TB case notification in northern Uganda: evidence of a quality improvement-guided active case finding intervention	Exclude	No CNR data split routine : ACF	• 3 results • All excluded on abstract
Kolappan et al (25)	2013	Trends in the prevalence of pulmonary tuberculosis over a period of seven and half years in a rural community in south India with DOTS	Exclude	No CNR data split routine : ACF	• 22 results • All excluded on abstract
Liu et al (26)	2019	Assessment of active tuberculosis findings in the eastern area of China: A 3-year sequential screening study	Exclude	No CNR data split routine : ACF	• 81 results • All excluded on abstract
Lorent et al (27)	2014	Community-based active tuberculosis case finding in poor urban settlements of Phnom Penh, Cambodia: a feasible and effective strategy	Routine CNR outcomes review		• 10 results • 9 excluded on abstract • 1 Lorent et al 2015 (28) included
Maggard et al (29)	2014	Screening for tuberculosis and testing for human immunodeficiency virus in Zambian prisons	Exclude	No CNR data split routine : ACF	• 16 results • All excluded on abstract
Mallick et al (30)	2017	Enhanced tuberculosis case finding through advocacy and sensitisation meetings in prisons of Central India	Exclude	No CNR data split routine : ACF	• 88 results • 86 excluded on abstract • Thapa et al 2015 (31) & 2016 (32) excluded on further review due to misalignment of KAP surveys and ACF populations or timing
Marks et al (33)	2019	Community-wide Screening for Tuberculosis in a High-Prevalence Setting	Exclude	No CNR data split routine : ACF	• 21 results • All excluded on abstract
Miller et al (34)	2009	Controlled trial of active tuberculosis case finding in a Brazilian favela	Routine CNR outcomes review		• 9 results • All excluded on abstract
Parija et al (35)	2014	Impact of awareness drives and community-based active tuberculosis case finding in Odisha, India.	Routine CNR outcomes review		• 12 results • All excluded on abstract

Rao et al (36)	2019	Declining tuberculosis prevalence in Saharia, a particularly vulnerable tribal community in Central India: evidences for action	Exclude	No CNR data split routine : ACF	• 36 results • All excluded on abstract
Reddy et al (37)	2015	Intensified tuberculosis case finding amongst vulnerable communities in southern India	Exclude	No CNR data split routine : ACF	• 19 results • 17 excluded on abstract • Thapa et al 2015 (31) & 2016 (32) excluded on further review due to misalignment of KAP surveys and ACF populations or timing
Rendleman (38)	1999	Mandated tuberculosis screening in a community of homeless people	Exclude	No CNR data split routine : ACF	• 1 result • Excluded on abstract
Sanaie et al (39)	2016	An Evaluation of Passive and Active Approaches to Improve Tuberculosis Notifications in Afghanistan	Exclude	No CNR data split routine : ACF	• 1 result • Excluded on abstract
Sanchez et al (40)	2013	X ray screening at entry and systematic screening for the control of tuberculosis in a highly endemic prison	Exclude	No CNR data split routine : ACF	• 13 results • All excluded on abstract
Shargie et al (41)	2006	Tuberculosis case-finding through a village outreach programme in a rural setting in southern Ethiopia: Community randomized trial	Exclude	No CNR data split routine : ACF	• 31 results • All excluded on abstract
Shewade et al (42)	2019	Impact of Advocacy, Communication, Social Mobilization and Active Case Finding on TB Notification in Jharkhand, India	Exclude	No CNR data split routine : ACF	• 9 results • 7 excluded on abstract • Thapa et al 2015 (31) & 2016 (32) excluded on further review due to misalignment of KAP surveys and ACF populations or timing
Tsegaye Sahle et al (43)	2019	Bacteriologically-confirmed pulmonary tuberculosis in an Ethiopian prison: Prevalence from screening of entrant and resident prisoners	Exclude	No CNR data split routine : ACF	• 1 result • Excluded on abstract
Vyas et al (44)	2018	Community-based active case-finding to reach the most vulnerable: tuberculosis in tribal areas of India	Routine CNR outcomes review		• 31 results • All excluded on abstract

Reference list

1. Adane K, Spigt M, Winkens B, Dinant G-J. Tuberculosis case detection by trained inmate peer educators in a resource-limited prison setting in Ethiopia: a cluster-randomised trial. The Lancet Global Health. 2019;7(4):e482-e91.
2. Adane K, Spigt M, Johanna L, Noortje D, Abera SF, Dinant GJ. Tuberculosis knowledge, attitudes, and practices among northern Ethiopian prisoners: Implications for TB control efforts. PLoS One. 2017;12(3):e0174692.
3. Aye S, Majumdar SS, Oo MM, Tripathy JP, Satyanarayana S, Kyaw NTT, et al. Evaluation of a tuberculosis active case finding project in peri-urban areas, Myanmar: 2014-2016. Int J Infect Dis. 2018;70:93-100.
4. Ayles H, Muyoyeta M, Du Toit E, Schaap A, Floyd S, Simwinga M, et al. Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial. Lancet. 2013;382(9899):1183-94.

5. Bond V, Chilikwela L, Simwinga M, Reade Z, Ayles H, Godfrey-Faussett P, et al. Children's role in enhanced case finding in Zambia. Int J Tuberc Lung Dis. 2010;14(10):1280-7.
6. Cegielski JP, Griffith DE, McGaha PK, Wolfgang M, Robinson CB, Clark PA, et al. Eliminating tuberculosis one neighborhood at a time. American journal of public health. 2013;103(7):1292-300.
7. Chatterjee S, Kolappan C, Subramani R, Gopi PG, Chandrasekaran V, Fay MP, et al. Incidence of active pulmonary tuberculosis in patients with coincident filarial and/or intestinal helminth infections followed longitudinally in South India. PLoS One. 2014;9(4):e94603.
8. Chen JO, Qiu YB, Rueda ZV, Hou JL, Lu KY, Chen LP, et al. Role of community-based active case finding in screening tuberculosis in Yunnan province of China. Infect Dis Poverty. 2019;8(1):92.
9. Churchyard GJ, Fielding K, Roux S, Corbett EL, Chaisson RE, De Cock KM, et al. Twelve-monthly versus six-monthly radiological screening for active case-finding of tuberculosis: a randomised controlled trial. Thorax. 2011;66(2):134-9.
10. Corbett EL, Bandason T, Duong T, Dauya E, Makamure B, Churchyard GJ, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): A cluster-randomised trial. The Lancet. 2010;376(9748):1244-53.
11. Datiko DG, Yassin MA, Theobald SJ, Blok L, Suvanand S, Creswell J, et al. Health extension workers improve tuberculosis case finding and treatment outcome in Ethiopia: a large-scale implementation study. BMJ Glob Health. 2017;2(4):e000390.
12. Yassin MA, Datiko DG, Tulloch O, Markos P, Aschalew M, Shargie EB, et al. Innovative community-based approaches doubled tuberculosis case notification and improve treatment outcome in Southern Ethiopia. PLoS One. 2013;8(5):e63174.
13. Tulloch O, Theobald S, Morishita F, Datiko DG, Asnake G, Tesema T, et al. Patient and community experiences of tuberculosis diagnosis and care within a community-based intervention in Ethiopia: a qualitative study. BMC Public Health. 2015;15(1):187.
14. Datiko DG, Lindtjørn B. Health extension workers improve tuberculosis case detection and treatment success in southern Ethiopia: a community randomized trial. PLoS One. 2009;4(5):e5443.
15. Degner NR, Joshua A, Padilla R, Vo HH, Vilke GM. Comparison of Digital Chest Radiography to Purified Protein Derivative for Screening of Tuberculosis in Newly Admitted Inmates. J Correct Health Care. 2016;22(4):322-30.
16. Delva GJ, Francois I, Claassen CW, Dorestan D, Bastien B, Medina-Moreno S, et al. Active Tuberculosis Case Finding in Port-au-Prince, Haiti: Experiences, Results, and Implications for Tuberculosis Control Programs. Tuberc Res Treat. 2016;2016:8020745.
17. de Vries G, van Hest RA, Richardus JH. Impact of mobile radiographic screening on tuberculosis among drug users and homeless persons. Am J Respir Crit Care Med. 2007;176(2):201-7.
18. van Hest R, de Vries G. Active tuberculosis case-finding among drug users and homeless persons: after the outbreak. Eur Respir J. 2016;48(1):269-71.
19. Fatima R, Qadeer E, Enarson DA, Creswell J, Stevens R, Hinderaker SG, et al. Success of active tuberculosis case detection among high-risk groups in urban slums in Pakistan. International Journal of Tuberculosis and Lung Disease. 2014;18(9):1099-104.
20. Fatima R, Qadeer E, Yaqoob A, Haq MU, Majumdar SS, Shewade HD, et al. Extending 'Contact Tracing' into the Community within a 50-Metre Radius of an Index Tuberculosis Patient Using Xpert MTB/RIF in Urban, Pakistan: Did It Increase Case Detection? PLoS One. 2016;11(11):e0165813.

21. Ford D, Datta B, Prakash AK, Tripathy JP, Goyal P, Singh S, et al. Fifth year of a public-private partnership to improve the case detection of tuberculosis in India: A role model for future action? Indian J Tuberc. 2019;66(4):480-6.
22. John S, Gidado M, Dahiru T, Fanning A, Codlin AJ, Creswell J. Tuberculosis among nomads in Adamawa, Nigeria: outcomes from two years of active case finding. Int J Tuberc Lung Dis. 2015;19(4):463-8.
23. Kan XH, Zhang LX, Yang JA, Zhang J, Chiang CY. Mobilising elementary and secondary school students for tuberculosis case finding in Anhui, China. Public Health Action. 2012;2(4):152-6.
24. Karamagi E, Sensalire S, Muhire M, Kisamba H, Byabagambi J, Rahimzai M, et al. Improving TB case notification in northern Uganda: evidence of a quality improvement-guided active case finding intervention. BMC Health Serv Res. 2018;18(1):954.
25. Kolappan C, Subramani R, Radhakrishna S, Santha T, Wares F, Baskaran D, et al. Trends in the prevalence of pulmonary tuberculosis over a period of seven and half years in a rural community in south India with DOTS. Indian J Tuberc. 2013;60(3):168-76.
26. Liu K, Peng Y, Zhou Q, Cheng J, Yu H, Tang L, et al. Assessment of active tuberculosis findings in the eastern area of China: A 3-year sequential screening study. Int J Infect Dis. 2019;88:34-40.
27. Lorent N, Choun K, Thai S, Kim T, Huy S, Pe R, et al. Community-based active tuberculosis case finding in poor urban settlements of Phnom Penh, Cambodia: a feasible and effective strategy. PLoS One. 2014;9(3):e92754.
28. Lorent N, Choun K, Malhotra S, Koeut P, Thai S, Khun KE, et al. Challenges from Tuberculosis Diagnosis to Care in Community-Based Active Case Finding among the Urban Poor in Cambodia: A Mixed-Methods Study. PLOS ONE. 2015;10(7):e0130179.
29. Maggard KR, Hatwiinda S, Harris JB, Phiri W, Kruuner A, Kaunda K, et al. Screening for tuberculosis and testing for human immunodeficiency virus in Zambian prisons. Bull World Health Organ. 2015;93(2):93-101.
30. Mallick G, Shewade HD, Agrawal TK, Kumar AMV, Chadha SS. Enhanced tuberculosis case finding through advocacy and sensitisation meetings in prisons of Central India. Public health action. 2017;7(1):67-70.
31. Thapa B, Chadha SS, Das A, Mohanty S, Tonsing J. High and equitable tuberculosis awareness coverage in the community-driven Axshya TB control project in India. Public health action. 2015;5(1):70-3.
32. Thapa B, Prasad BM, Chadha SS, Tonsing J. Serial survey shows community intervention may contribute to increase in knowledge of Tuberculosis in 30 districts of India. BMC public health. 2016;16(1):1155-.
33. Marks GB, Nguyen NV, Nguyen PTB, Nguyen TA, Nguyen HB, Tran KH, et al. Community-wide Screening for Tuberculosis in a High-Prevalence Setting. N Engl J Med. 2019;381(14):1347-57.
34. Miller AC, Golub JE, Cavalcante SC, Durovni B, Moulton LH, Fonseca Z, et al. Controlled trial of active tuberculosis case finding in a Brazilian favela. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2010;14(6):720-6.
35. Parija D, Patra TK, Kumar AMV, Swain BK, Satyanarayana S, Sreenivas A, et al. Impact of awareness drives and community-based active tuberculosis case finding in Odisha, India. International Journal of Tuberculosis and Lung Disease. 2014;18(9):1105-7.
36. Rao VG, Bhat J, Yadav R, Sharma RK, Muniyandi M. Declining tuberculosis prevalence in Saharia, a particularly vulnerable tribal community in Central India: evidences for action. BMC Infect Dis. 2019;19(1):180.

37. Reddy KK, Ananthakrishnan R, Jacob AG, Das M, Isaakidis P, Kumar AM. Intensified tuberculosis case finding amongst vulnerable communities in southern India. Public Health Action. 2015;5(4):246-8.
38. Rendleman NJ. Mandated tuberculosis screening in a community of homeless people. Am J Prev Med. 1999;17(2):108-13.
39. Sanaie A, Mergenthaler C, Nasrat A, Seddiq MK, Mahmoodi SD, Stevens RH, et al. An Evaluation of Passive and Active Approaches to Improve Tuberculosis Notifications in Afghanistan. PLoS One. 2016;11(10):e0163813.
40. Sanchez A, Massari V, Gerhardt G, Espinola AB, Siriwardana M, Camacho LA, et al. X ray screening at entry and systematic screening for the control of tuberculosis in a highly endemic prison. BMC Public Health. 2013;13:983.
41. Shargie EB, Mørkve O, Lindtjørn B. Tuberculosis case-finding through a village outreach programme in a rural setting in southern Ethiopia: community randomized trial. Bull World Health Organ. 2006;84(2):112-9.
42. Shewade HD, Gupta V, Ghule VH, Nayak S, Satyanarayana S, Dayal R, et al. Impact of Advocacy, Communication, Social Mobilization and Active Case Finding on TB Notification in Jharkhand, India. J Epidemiol Glob Health. 2019;9(4):233-42.
43. Tsegaye Sahle E, Blumenthal J, Jain S, Sun S, Young J, Manyazewal T, et al. Bacteriologically-confirmed pulmonary tuberculosis in an Ethiopian prison: Prevalence from screening of entrant and resident prisoners. PLoS One. 2019;14(12):e0226160.
44. Vyas A, Creswell J, Codlin AJ, Stevens R, Rao VG, Kumar B, et al. Community-based active case-finding to reach the most vulnerable: tuberculosis in tribal areas of India. Int J Tuberc Lung Dis. 2019;23(6):750-5.

Appendix 5 Data extracted from and characteristics of included studies with routine case-notification outcomes

Study characteristics						Population size		Pre period					After (intervention) period				
Study	Country	Population	Distance to healthcare	Cost of healthcare	Access to healthcare	ACF population	Control population	Months	ACF pop cases	ACF pop BC cases	Control pop cases	Control pop BC cases	Months	ACF pop routine cases	ACF pop routine BC cases	Control pop cases	Control pop BC cases
Cluster-randomised trial																	
Miller 2010	Brazil	Urban slums	Ready access to local health services. Mean distance bus line to clinic 180 - 250m	TB diganosis and treatment provided free of charge	Standard	24,177	34,410	-	-	-	-	-	9.6	81	81	101	101
Controlled before-after studies																	
Aye 2018	Myanmar	Urban slums (& "neighbourhood contacts")	Not stated. Township health centres	Public-private mix. Treatment provided free of charge	Standard	1,696,972	1,700,000	36	7,229	-	12,189	-	36	6,443	-	9,962	-
Cegielski 2013	USA	General population - urban	Not stated. Urban USA so likely not far	Not stated. Most healthcare private in USA	Restricted	3153	155,000	120	15	-	113	-	120	0	-	75	-
Datiko 2017 / Yassin 2013	Ethiopia	Remote rural	Transport facilities limited and relatively expensive, making travel to health facilities challenging	Is of benefit if diagnosis and treatment at low cost to patient'	Restricted	3500000	1,200,000	12	3,968	2,534	2,497	949	54	15,058	5,765	5,483	2,551
Kan 2012	China	General population - rural	Not stated. Township health centres and village doctors	Free services at county dispensary for TB	Restricted	15,443,456	29,256,544	15	-	1,966	-	4,565	15	-	5,014	-	14,353
Parija 2014	India	General population - rural	Not stated. Each village has a CHW	Free TB treatment and diganosis	Restricted	6,090,000	6,060,000	3	-	967	-	364	3	-	831	-	367
Vyas 2019	India	Rural: Indigenous groups	Long distances and no public transport	Not stated. Healthcare often private in India	Restricted	1,000,000	1,000,000	12	1,440	907	1,524	839	12	1,694	711	1,787	793
Before-after studies																	
Corbett 2010	Zimbabwe	General population - urban	Lived within 2km of primary care clinic	Not stated. Basic healthcare usually free in Zimbabwe	Standard	110,432	-	6	-	154	-	-	35	-	670	-	-
Fatima 2016	Pakistan	Urban slums "neighbourhood contacts"	Not stated. Urban so unlikely far to BMU	Not stated. Screening and treatment free through NTP in Pakistan	Standard	18,000,000	-	24	100,384	28,159	-	-	24	104,785	26,978	-	-
Fatima 2014	Pakistan	Urban slums perceived high risk or hard to reach	Access to primary health clincs poor although many private clinics'	Screening and treatment free of charge through NTP, but this intervention using private GPs who charge	Hard to reac	6,045,105	-	18	10,374	8,933	-	-	18	11,023	8,275	-	-
Ford 2019	India	Remote rural	Limited access to CXR facilities (part of diagnostic algorthim)	Not stated. Intervention uses public-private mix and healthcare often private in India	Restricted	100,000	-	12	6,599	3,111	-	-	12	6,715	-	-	-
Lorent 2014	Cambodia	Urban slums - perceived high risk or hard to reach	High prevalence and/or restricted access to TB services. Treatment delay due to travel distance and inconveient opening times	Treatment delay due to perceived cost of treatment.	Hard to reac	1,156,466	-	15	4,073	1,610	-	-	15	3,778	1,338	-	-

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	**Identify the report as a systematic review, meta-analysis, or both.** Do community-based tuberculosis active case-finding interventions affect subsequent health-seeking behaviour? A systematic review	Yes (page 1)
ABSTRACT			
Structured summary	2	**Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.** Done – see paper abstract	p. 3-4
INTRODUCTION			
Rationale	3	**Describe the rationale for the review in the context of what is already known.** The effect of ACF on subsequent health-seeking behaviour has not previously been reviewed. We therefore aimed to systematically review the evidence of indirect effect of ACF on routine facility-based TB case notifications and proxy behavioural outcomes such as knowledge, attitudes and perceptions (KAP) that could inform the mechanisms of any effect on subsequent health-seeking behaviour.	6
Objectives	4	**Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).** Methods includes all this information (too long to usefully copy and paste excerpts).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. No formal protocol exists, although concept notes were shared with WHO in the lead up to the commissioning of review.	

PRISMA 2009 Checklist

Eligibility criteria	6	**Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.** See paragraph within methods entitled “Inclusion and exclusion criteria”	10
Information sources	7	**Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.** “The literature search included all studies identified in a previous review by Kranzer et al in 2013 (6), covering the period 1 Jan 1980 to Oct 13 2010, and an additional search of PubMed, EMBASE, Scopus and the Cochrane Library for papers published between 1 Nov 2010 and 4 Feb 2020 (subsequently updated to 13 April 2020) (search strategy in Appendix 1).” “Reference lists from eligible manuscripts were examined and expert opinion on other available papers was sought from members of the WHO TB Screening Guideline Development Group for this and the accompanying review on TB ACF effectiveness.”	10-11
Search	8	**Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.** In appendices 1 & 2	Appendices 1 & 2
Study selection	9	**State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).** “Studies identified through the updated search were title and abstract double screened for eligibility by FN, AES and LHC and then the full text of these and all studies from the Kranzer and colleagues review were reviewed by two of HRAF, RMB and MN. Inclusion decisions were resolved by consensus and discussion with ELC and PM.”	10
Data collection process	10	**Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.** “Data was extracted from studies independently by two of HRAF, RMB and MN and entered into a spreadsheet.”	10
Data items	11	**List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.**	8-9 & 11

		The outcomes were "routinely-diagnosed TB case notifications and proxy behavioural outcomes." "To establish routinely diagnosed case notification rates, person-years of follow-up and notified TB cases diagnosed only through routine screening activities were extracted or calculated from available data using simple arithmetic. None of the studies presented case notification ratios for routine diagnosis; we calculated these from the available overall and ACF-specific case notification data." "The proxy behavioural outcomes we examined were knowledge, attitudes and practices (KAP) within communities, ever-tested for TB, recent testing for TB, TB stigma and social norms." "We classified studies according to level of healthcare access within the target population based on distance to and cost of care on a scale of 'Adequate' (routine free healthcare available within catchment area), 'Restricted' (access restricted due to distance and/or cost) or 'Hard to reach' (populations specifically selected as hard to reach)."	
Risk of bias in individual studies	12	**Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.** "For randomised studies, the Cochrane Risk of Bias (ROB) tool was used to assess risk of bias. Non-randomised studies were assessed for risk of bias using ROBINS-I and qualitative studies were assessed through the Critical Appraisal Skills Programme (CASP) checklist."	12
Summary measures	13	**State the principal summary measures (e.g., risk ratio, difference in means).** "For randomised and before-after studies we calculated the CNR ratio (intervention vs control groups or baseline vs post intervention populations) and for controlled before-after studies with a non-randomised comparison group the outcome measure was a comparison of the before to after TB CNR ratio in the two comparison groups: the ratio of the CNR ratios."	11-12
Synthesis of results	14	**Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.** "Where data was available confidence intervals were calculated using Stata. For studies affected by clustering, three possible values (0.01, 0.05 and 0.1) of the intra-cluster correlation coefficient (ICC) were estimated and used to calculated three possible confidence intervals using the Cochrane recommended method… Confidence intervals for KAP scores are presented as reported by the authors."	12

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	**Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).** NA	N/A
Additional analyses	16	**Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.** We classified studies according to level of healthcare access within the target population based on distance to and cost of care on a scale of 'Adequate' (routine free healthcare available within catchment area), 'Restricted' (access restricted due to distance and/or cost) or 'Hard to reach' (populations specifically selected as hard to reach). Outcome measures did not appear to be associated with reported healthcare accessibility.	11
RESULTS			
Study selection	17	**Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.** PRISMA diagram is figure 2	Fig 2
Study characteristics	18	**For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.** Table 1	Table 1
Risk of bias within studies	19	**Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).** Figure 6	Fig 6
Results of individual studies	20	**For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.** Table 2 & Figures 4 & 5	Table 2 Figs 4 & 5
Synthesis of results	21	**Present results of each meta-analysis done, including confidence intervals and measures of consistency.** No meta-analysis done; "The small number of published studies that specifically address this important issue were at risk of bias introduced by the design or completeness of evaluation, and critical differences in study design precluded meta-analysis	NA – no meta-analysis

PRISMA 2009 Checklist

Risk of bias across studies	22	**Present results of any assessment of risk of bias across studies (see Item 15).** NA	NA
Additional analysis	23	**Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).** Table.1 specifies level of healthcare access for the population each study was conducted on.	Table 1
DISCUSSION			
Summary of evidence	24	**Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).** Our main finding was the need for more evidence: we found mixed weak evidence that TB ACF may be effective at indirectly increasing routine TB case notification rates for non-bacteriologically confirmed TB, and insufficient evidence to conclude whether or not ACF impacts subsequent health-seeking behaviour.	25
Limitations	25	**Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).** Limited number of studies reporting on relevant outcomes with wide range of study designs and interventions meant meta-analysis was not appropriate. A high proportion of studies were at serious or critical risk of bias and there was limited availability to adjust for confounders as this data was not consistently reported.	28
Conclusions	26	**Provide a general interpretation of the results in the context of other evidence, and implications for future research.** ACF has potential to impact subsequent health-seeking behaviour through an increase in TB knowledge, earlier care-seeking if TB symptoms are detected, or follow-up after a negative ACF test, but reporting of the impact on routinely diagnosed TB case-notifications is limited and only one trial addressed proxy behavioural outcomes. Evaluation of routine TB testing and other proxy behavioural outcomes in ACF and comparator communities should be included as standard in study designs.	29
FUNDING			
Funding	27	**Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.** This research was funded in part by WHO to inform their TB screening guideline development process. WHO facilitated discussions among authors at design stage, but had no role in conduct of review.	12

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

B Ethics Approval Certificate from Malawi College of Medicine Research Ethics Committee (COMREC) for SCALE study

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the Colleg e of Medicine Research and Ethics Committee (COMREC) has reviewed an d approved a study entitled:

P.12/18/2556 - Sustainable Community-wide Active Case Finding for Lung hEalth (SCALE) Version 4.0 dated 5 April 2019 by Prof. Liz Corbett

C

As you proceed with the implementation of your study, we would li guidelines, national guidelines and all requirements by COMREC s your study

Approved by
College of Medicine

06-May-2019

(COMREC)
Research and Ethics Committee

Dr. YB. Mlombe - Chairperson (COMREC)

C Ethics Approval Letter from London School of Hygiene and Tropical Medicine (LSHTM) for SCALE study

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
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Observational / Interventions Research Ethics Committee

Prof Liz Corbett
LSHTM

7 March 2019

Dear Liz

Study Title: Sustainable Community-wide Active case finding for Lung hEalth (SCALE)

LSHTM Ethics Ref: 16228

Thank you for responding to the Interventions Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant. **Approved**

documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Advertisements	TS01a General Flyer TB Prevalence Survey English_v1.0_HF	29/10/2018	1.0
Advertisements	Appendix 3.11.a PS01a General Flyer TB Prev Survey Eng_v1.0	29/10/2018	1.0
Advertisements	Appendix 3.12.a PS67a Flyer Tuberculin Skin Test Survey Eng v1.0	29/10/2018	1.0
Protocol / Proposal	TS06QE SCALE PRE PREVALENCE HOUSEHOLD QUESTIONNAIRE Eng V1.0	30/10/2018	1.0
Protocol / Proposal	TS07QE SCALE PRE PREVALENCE INDIVIDUAL QUESTIONNAIRE Eng V1.0	30/10/2018	1.0
Protocol / Proposal	PS06QE SCALE POST PREVALENCE HOUSEHOLD QUESTIONNAIRE Eng V1.0	30/10/2018	1.0
Protocol / Proposal	PS07QE SCALE POST PREVALENCE INDIVIDUAL QUESTIONNAIRE Eng V1.0	30/10/2018	1.0
Protocol / Proposal	PS15FM-Sputum Collection Form v1.0	30/10/2018	1.0
Protocol / Proposal	PS15FMb - TCulture Results v1	30/10/2018	1.0
Investigator CV	CV Liz_Corbett 2018. Current	30/10/2018	2018
Investigator CV	CV_KatherineFielding	30/10/2018	2018
Investigator CV	CV Maheswaran_CV	30/10/2018	2018
Investigator CV	CV Peter MacPherson	30/10/2018	2018
Investigator CV	CV Peter Dodd2018	30/10/2018	2018
Investigator CV	CV for Nicola Desmond	30/10/2018	2018
Investigator CV	Sinjani_George CV	30/10/2018	2018
Investigator CV	Lingstone S. Chiume - Full Epi CV_opt	30/10/2018	2018
Information	CF02a Sputum Collection Oral Consent v1.0 English	30/10/2018	1.0

Sheet			
Information Sheet	TS21a Sputum Collection Verbal Consent v1.0 English	30/10/2018	1.0
Information Sheet	TS05FMa Consent form for TB Prevalance Survey_English v1.0	30/10/2018	1.0
Information Sheet	TS09a Xray Consent Form English v1.0, 30 October 2018	30/10/2018	1.0
Information Sheet	TS17a HTS Consent Form English v1.0	30/10/2018	1.0
Information Sheet	PS69FMa Consent form for Tuberculin Skin Test Survey_ v1.0 30 October 2018	30/10/2018	1.0
Information Sheet	PS21a Sputum Collection Verbal Consent v1.0 English_30 October 2018	30/10/2018	1.0
Information Sheet	PS09a Xray Consent Form English v1.0 30 October 2018	30/10/2018	1.0
Information Sheet	PS05FMa Consent form for TB Post Prevalance Survey_30 October 2018_v1.0	30/10/2018	1.0
Advertisements	Appendix 2.4.a CF01FLa_Flyer for TB ithe_ACF_Eng_v1.0	30/10/2018	1.0
Protocol / Proposal	Topic Guide Exploring motivations for and experiences of testing among presumptive TB patients v1.0	05/11/2018	1.0
Protocol / Proposal	Topic Guide Exploring motivations for and experiences of testing for TB among outpatient HCW v1.0	05/11/2018	1.0
Information Sheet	Tu04FMa Consent form for Presumptive TB Patient Interviews v1.0	05/11/2018	1.0
Information Sheet	TU07FMa Oral Consent for Presumptive TB Survey v1.0	05/11/2018	1.0
Information Sheet	Tu06FMa Consent form for HCW Interviews v1.0	05/11/2018	1.0
Protocol / Proposal	CF09a Sputum Form1 v0.2	09/11/2018	1.0
Protocol / Proposal	Tu02Qa Presumptive TB patient testing survey v0.6	09/11/2018	1.0
Protocol / Proposal	SCALE Trial LSHTM protocol v1.0 29.11.2018	29/11/2018	1.0
Other	Liz Corbett GCP Certificate 2018	04/12/2018	2018
Sponsor Letter	SCALE Sponsor letter 2018-KEP-203_Corbett_sponsor_04122018	04/12/2018	2018
Investigator CV	CV_Helena_Feasey_Oct2018	30/12/2018	2018
Information Sheet	PS68a Participant Information Sheet for tuberculin skin test_v2.0_English_10Jan2018	10/01/2019	2
Information Sheet	PS02a Post-Intervention Prevalence Survey Participant Information Sheet_v2.0_English	10/01/2019	2
Information Sheet	TS02a Pre-Intervention Prevalence Survey Participant Information Sheet_v2.0_English	10/01/2019	2
Covering Letter	LSHTM Response letter SCALE 30.01.19	30/01/2019	1
Information Sheet	PS69FMa Consent form for Tuberculin Skin Test Survey_ v3.0	30/01/2019	3
Information Sheet	PS05FMa Consent form for TB Post Prevalance Survey v3.0	30/01/2019	3
Information Sheet	TS05FMa Consent form for TB Prevalance Survey_English v3.0	30/01/2019	3

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor John DH Porter Chair

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