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Intensifying tuberculosis case finding – opportunities, challenges and open questions

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Insufficient tuberculosis (TB) case finding constitutes a major barrier to effective TB control. Despite considerable progress in improving healthcare service availability and accessibility, many people worldwide who fall ill with TB have no access to quality care, particularly in countries with a high disease burden. For example, in 2016, a total of 6.3 million TB cases were reported to national TB control programmes (NTPs) worldwide, leaving a case detection gap of nearly 40% (an estimated 10.4 million people had TB that year) (1). Increasing efforts to close this enormous gap will be crucial in the forthcoming years to effectively reduce TB incidence and mortality worldwide. This article describes opportunities, current challenges and open questions towards intensifying TB case finding.

Failure to find TB – consequences to individuals and populations

Failure to timely identify and treat TB has serious implications for affected individuals, their families, and entire populations. Progressive undiagnosed disease is likely to result in severe, chronic or recurring illness, disability and loss in quality of life. Chronic or recurring disease also leads to inability to work and loss of income, causing poverty and catastrophic costs to individuals and their families (2). Ultimately, not finding and treating TB leads to loss of lives. Historical studies from the pre-chemotherapy (and pre-HIV) era show that 50% of individuals with untreated TB died within five years; of those who survived, more than one-third continued to suffer from infectious TB (3). Ten-year case fatality rates of untreated TB between 53 and 86% have been reported among smear-positive, HIV-uninfected people, with an average duration between disease onset and either natural recovery or death of approximately three years (4). A high mortality of untreated TB is expected among people living with HIV infection, with an estimated average survival time of less than six months (4) compared to an average duration to either self-cure or death of 3 years among HIV-uninfected people (4).

Delayed and insufficient TB case finding increases potential for onward transmission (5). Prevalence studies from several high burden communities in Southern African have documented large burdens of undetected TB (6-8). Individuals who fall ill with TB may live in a community for a long time before being detected and treated: for example, durations of infectiousness before diagnosis of up to 2 years have been estimated in Zimbabwe (9). This prolonged and undetected infectious TB increases population-wide transmission, undermining the impact of treatment programs on local disease epidemiology.

Opportunities for intensifying TB case finding

TB control programs worldwide traditionally rely on passive case finding (PCF), i.e. the self-presentation of symptomatic individuals ("presumptive cases") to health services to be diagnosed with TB. The World Health Organization (WHO) advocates the use of because actively searching for TB cases was deemed "prohibitively expensive" (10) while its impact on transmission was uncertain. An important limitation of PCF is that it relies on TB-specific symptoms (including cough for at least 2 weeks, fever, night sweats, weight loss) to be recognized (and reported) before individuals seek care and are evaluated for TB. Furthermore, low sensitivity and specificity of symptoms for active TB and under-recognition/under-reporting of symptoms poses a common barrier to timely diagnosis (11). Given the enormous case finding gap, there is consensus across the WHO and its partners that additional efforts are needed to promptly find, diagnose and treat TB to reduce morbidity, mortality and transmission.

Several promising opportunities exist that can help to intensify case finding in populations where PCF alone remains insufficient. The literature commonly distinguishes enhanced case finding (ECF), which aims at promoting self-presentation and diagnosis of presumptive TB cases, from active case finding (ACF), which describes efforts to actively reach out to seek and diagnose TB in the population. Often used synonymously with ACF is the term "systematic screening for TB" which the WHO defines as "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" (12).

The target group of intensified TB case finding activities can be meaningfully distinguished by whether individuals are already seeking healthcare for any complaints, including those who had been in contact with TB-specific services, and those who have not yet (or may never)

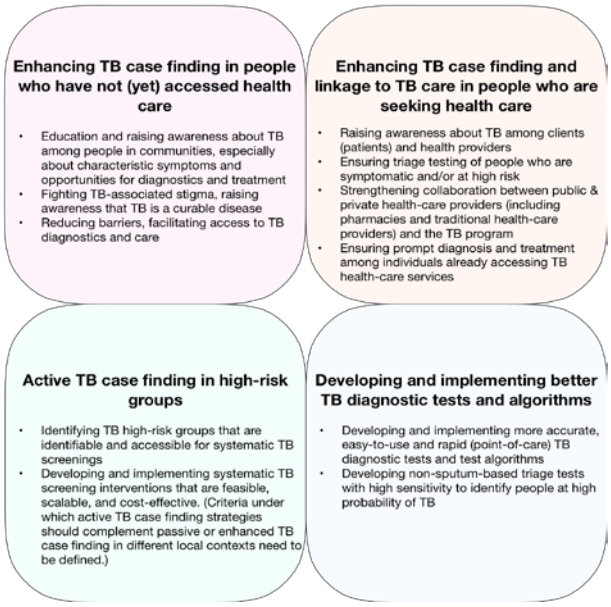

Figure 1. Overview of 4 principal categories of interventions to intensify TB case finding in populations

access healthcare services. We describe four principal categories (Figure 1) of interventions to intensify TB case finding in populations that address several shortcomings of PCF approaches.

Enhancing TB case finding in people who have not yet accessed (and may never access) healthcare. Improving access to TB care has always been a fundamental principle of the former and current global TB control strategies endorsed by the WHO. Besides making TB healthcare services more widely available, efforts are needed to promote healthcare seeking among presumptive TB cases who have not yet accessed healthcare.

Efforts to date have focussed on improving knowledge and awareness of TB and its characteristic symptoms (13) in populations and particularly in high-risk groups. However, an important challenge to these types of ECF activities is the fact that symptoms during TB may not always be specific or easily recognisable. Furthermore, several community-based case finding studies and TB prevalence surveys have documented considerable proportions of TB cases who did not report typical symptoms or no symptoms at all (12, 14), thus limiting the potential of raising symptom awareness to enhance case finding. This increases the need for diagnostics that can accurately rule-out TB in patients with few or minimal symptoms (see below). Closely related to improving knowledge and attitudes about TB, is the importance of reducing stigma through education and public health campaigns, which can also be used to offer individuals opportunities for diagnostic testing. Such campaigns aim at ensuring that case finding interventions gain community acceptance (15). Furthermore, to facilitate access to TB diagnosis and care, existing barriers for accessing TB services such as lengthy times (distances) and costs incurred by people need to be addressed (16). Combined interventions to raise awareness and facilitate access have been investigated. For example, a recent large community-randomised controlled trial in South Africa and Zambia combined community and school education and mobilization campaigns with enhancing access to sputum testing via mobile sputum collection points and open laboratory access to enhance TB case finding in high-burden communities, unfortunately without demonstrating an impact of ECF on local TB epidemiology (17).

Enhancing TB case finding and linkage to TB care in people who are seeking healthcare More recently, there is increasing recognition of the urgent need to find additional TB cases among people who are already seeking (or currently in) healthcare. Studies from high-incidence settings have documented high rates of (unsuspected) TB among individuals entering and exiting healthcare facilities (11) and poor adherence to screening algorithms by clinic staff (18). Interventions to enhance case finding include health education for people attending care and raising awareness among healthcare providers (practitioners) to encourage them to consider TB and refer presumptive cases to TB healthcare services. ECF strategies may focus on appropriate triages of symptomatic individuals in healthcare facilities to ensure timely diagnosis. Strengthening collaboration between (non-TB) public and private providers and the TB control program may help to shorten patients' diagnostic journeys (20) and ensure timely TB diagnosis. Strengthening collaboration between disease-specific services and programs, for example between HIV- , diabetes- and TB healthcare services, whilst minimizing the additional health seeking burden on patients could help enhance TB case finding. Of particular importance are efforts to ensure timely linkage to TB care among patients who were diagnosed outside TB healthcare services. Towards this aim, strengthening TB recording and reporting among providers outside the NTPs as well as unified data systems can be useful. Although efforts to ensure timely treatment initiation among already diagnosed TB cases do not directly count towards case finding efforts, they may help prevent initial loss to follow-up (and hence transmission) and are thus able to reduce the gap between incident TB cases and those who are reported to NTPs and initiate treatment. For example, a recent study from South Africa estimated that people already seeking TB

care contribute considerably to missing cases in the country due to loss to follow-up before treatment initiation, suggesting opportunities for interventions to reduce this initial loss (21).

Active TB case finding in high-risk groups (systematic screening for active TB)\ ACF is expected to shorten the time that people with TB remain undetected in communities and thereby pose a risk of infection to others (6). The development of effective and cost-effective ACF strategies is an important priority. The WHO promotes systematic screening for active TB and defines several risk groups that may be considered as target groups for screening (12), including groups in the community, in healthcare facilities, in residential institutions, immigration and refugee services, and workplaces (Table 1). Strong recommendations for systematic TB screening are currently limited to household contacts and close contacts of TB cases, people living with HIV (at each visit to a health facility), and current and former workers with silica dust exposure, whereas recommendations of screening in other risk groups remain conditional (12). The WHO advises that, before systematic screenings are considered, sufficient capacity for high-quality diagnosis, treatment and support must be available to match the anticipated increase in the number of cases detected. A rigorous assessment of the feasibility and acceptability of identifying, reaching and screening target group members must be made, as well as of the potential individual-level benefits, risks and costs associated with screenings. Furthermore, cost-effectiveness (cost benefits) at the population (health system) level must be considered (12).

Table 1. WHO-recommended risk groups to be considered for systematic TB screening (17)

Category	Risk group
Community	People living in geographical areas with a high prevalence and subpopulations with poor access (poor populations, urban slums, remote areas, refugees, homeless, etc)
Hospital outpatient and inpatient departments, and primary health-care centres	People previously treated for TB
	People with an untreated fibrotic lesion
	People living with HIV and people attending HIV testing
	People with diabetes mellitus
	People with chronic respiratory disease and smokers
	Undernourished people
	People with gastrectomy or jejunoileal bypass
	People with an alcohol- or drug-use disorder
	People with chronic renal failure
	People with immunocompromising treatments
	Elderly people
	People in mental health clinics or institutions
Residential institutions	Prisoners and prison staff
	People residing in shelters
	Other congregate settings (such as the military)
Immigration and refugee services	Immigrants from settings with a high prevalence of TB
	People in refugee camps
Workplaces	Health-care workers
	Miners or others who are exposed to silica
	Other workplaces with a high prevalence of TB

Better TB diagnostic tests and algorithms. Intensifying case finding requires efforts to improve current diagnostic tests and algorithms. Individuals with undiagnosed TB often perceive few characteristic symptoms. These individuals may be less likely to go to clinics to be diagnosed and treated, presumably because they do not yet feel sufficiently unwell; they may harbour low concentrations of bacilli and be unable to expectorate sputum (the main material used for current TB diagnostic tests) (22). Community-based interventions to find TB cases pro-actively may address some of these challenges, however, the technology to accomplish this is only starting to emerge and is yet to mature. Rapid tests like Xpert MTB/RIF Ultra, which may potentially approach sensitivity rates of culture (23) and which can be combined with the portable GeneXpert OMNI platform are promising, but need evidence of their utility to justify their expense. Importantly, tests like Ultra may have advantages over previous generation tests like Xpert MTB/RIF, which misses most cases of TB in patients with few symptoms. The only true point-of-care test (urine LAM) unfortunately has very low sensitivity in detecting TB among individuals who did not yet seek care. Thus, while these tools may be useful for enhanced case finding among symptomatic individuals, few rapid tools are currently available for ACF. Culture, coupled with mechanisms to ensure positive patients start and complete treatment, probably remains the most useful test for ACF. Thus, whether high risk community members have symptoms or not, could be used to decide if they get Xpert Ultra or culture as the delayed time to diagnosis resulting from use of culture is likely easier to tolerate in people without or with few symptoms.

Challenges and open questions

TB control programs worldwide need to address and tackle gaps in case finding to make considerable progress in TB control. We have emphasised four categories of interventions that national and local TB control programs may consider to intensify case finding. The choice of suitable interventions is thus dependent on the prevailing local context. There is also interdependency of the effect of interventions in each of the four categories. For example, the necessity for (and the effect of) ACF will depend on the extent to which ECF activities are successful to reduce case finding delay in a setting. Furthermore, the effect of both ECF and ACF is dependent on the availability of sensitive and rapid diagnostic tests.

For any intervention to intensify case finding, in particular for systematic screening, choosing the right

target group is challenging. For benefits to accrue from systematic screening, the target group must be at high risk of incident (and/or death from) TB. There should be at least suspicion that TB is underdiagnosed, or that there is considerable diagnostic delay. Target groups must be easily identifiable and reachable in populations, and screenings must be acceptable for target group members and their families. For benefits of systematic screening to extend to the population-level, the target group must be at high-risk but also contribute significantly to the overall prevalent TB burden and associated onward transmission. While the contribution of a specific high-risk group to overall TB can be estimated from TB prevalence surveys, knowledge about its contribution to transmission can be challenging to obtain.

The particular aim of a screening intervention should be considered. For example, a screening strategy may focus specifically on reducing mortality among severely ill (HIV co-infected) TB patients, whereas another screening strategy may aim at identifying as many TB cases as possible in order to impact transmission in a community.

The incremental benefits of intensifying TB case finding (relative to PCF alone) in settings may also change over time if the pool of undetected cases in a target group is eventually depleted, or if the rate of PCF changes over time. Temporary or periodic use of intensified case finding interventions might therefore be more reasonable than their indefinite use. Alternatively, dynamic case-finding policies may be considered, which allow decision makers to use easily observable indicators of TB surveillance, such as TB case notifications or screening yield over time, to determine when to make use of intensified case finding in addition to PCF in order to make more efficient use of existing resources (24). Mathematical modelling suggests that these dynamic case-finding policies dominate static policies that pre-specified the frequency and duration of case finding interventions irrespective of the current state and course of the TB epidemic (24).

Development and roll-out of better diagnostic tests is an important task for the international community to be able to intensify TB case finding worldwide. For screening, a rapid in-field test with high sensitivity for TB would be desirable to pre-select presumptive TB cases in the communities, so that the number of patients to be screened using more expensive tests (e.g., Xpert MTB/RIF Ultra) can be reduced. An advantage of such a triage test would be to identify patients with a high suspicion of TB at an earlier, asymptomatic stage and reduce our dependency of symptom-based diagnoses. Ideally, such a test should not depend on the use of sputa which is infectious and not always produced by patients, especially those with few symptoms, simple so that it does not require significant infrastructure or technical skills, potentially re-useable, and should ensure that people who test negative have a negligible probability of developing active disease. Promising candidates include blood-based host signatures (currently being refined into point-of-care tests) (25), breath volatile organic compound tests (26), and new approaches to detecting known biomarkers like LAM (27) but all. new tests need to satisfy the WHO's target product profile for triage tests (28). Importantly, as tests get more analytically sensitive, they could detect remnants of prior TB disease as patients with a history of TB make up large proportions of communities in some settings and confirmatory testing should therefore be mandatory (29). Unfortunately, nothing in the diagnostic pipeline suggests that we are close to a test that, on its own, meets all these criteria for ACF purposes and can simultaneously rule-in and rule-out disease with high confidence. Thus, when new tools become available, we need to carefully select the specific patient contexts in which they are used and design setting-specific algorithms. The diagnostic yield of any ACF strategy will be the primary determinant of its effectiveness.

Research priorities

Although various studies of TB case finding have been conducted, there is a lack of research to evaluate the individual and community-level benefits of suitable interventions in different contexts (30) as well as the feasibility and acceptability of different case finding interventions in different populations or target groups. A particular challenge is the assessment of population-level effects of intensified case finding, which requires complex and large investigations. Suitable study designs include cluster-randomised controlled trials, which measure outcomes of case finding interventions in intervention clusters compared to control clusters. Stepped-wedge cluster-randomised designs involve a random cross over of clusters from control to intervention until all clusters are in the intervention. Other possible designs include quasi-experimental studies that compare outcome measures in a population before and after the case-finding intervention is implemented, and non-randomized comparisons. The latter two designs are vulnerable to confounding, including possible baseline trends of passive case finding over time. Cost-effectiveness

(cost-benefit) analyses, in which epidemiological effects are related to costs are needed to identify most suitable case finding strategies. Transmission-dynamic mathematical models can help project population-level effects and cost-effectiveness of interventions to intensify case finding and thus guide their design and implementation in different populations (31, 32). Operational and qualitative research should accompany implemented interventions to enable lessons about their feasibility, acceptability, performance and scalability.

In conclusion, the need for intensifying TB case finding to strengthen the fight against TB has been widely recognized. Alternatives to the current passive case finding approach exist, including enhanced TB case finding strategies among people not (yet) seeking care and those already attending health services. Active TB case finding (systematic screening) should be considered for population subgroups that are identifiable, reachable, and at high risk of TB morbidity and mortality. In high-burden settings, TB case finding interventions in subgroups that contribute considerably to the overall (prevalent) TB burden and associated onward transmission are of particular interest. Innovation is needed to identify successful case-finding strategies in different local contexts and to develop novel diagnostic technologies for rapid triage in the field. Careful consideration of individual and community-level benefits (and harms) as well as costs and cost-benefits of different interventions is required to identify most feasible, (cost-) effective, and scalable strategies. More research, including trials of case-finding, cost-effectiveness analyses, mathematical models, operational and qualitative studies, and diagnostic research, will be required to inform intensified TB case finding in the future.

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