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Review

Scaling-up symptom-agnostic, community-wide screening toward global tuberculosis elimination: opportunities, challenges, and lessons from history

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ABSTRACT

There has been little change in global tuberculosis (TB) incidence in the 21st century. Although case notification has increased, millions of people with TB each year remain unreached. Recently there has been increased recognition that many people with undiagnosed, potentially infectious TB do not experience or report TB symptoms. Symptom-agnostic screening (e.g., by chest X-ray) can effectively identify such forms of TB. Although this activity is increasing globally and is beneficial to individuals screened, current levels fall far short of what is needed to impact transmission and population-level prevalence. A significant scale-up of symptom-agnostic screening across communities is required to improve treatment coverage and interrupt transmission. Although there are major political, financial, and health system challenges to undertaking such scale-up this is not without precedent. In the mid-20th century, in many countries that now experience a low TB burden, population-level chest X-ray screening was successfully undertaken and contributed to the decline in TB. In this article, we explore the challenges and opportunities that face countries wanting to scale-up symptom-agnostic screening and reflect on important lessons from the past.

Introduction

Globally in 2023, 8.2 million people with a new episode of tuberculosis (TB) were diagnosed and notified [1]. This is the highest number of TB notifications for a single year since the World Health Organization (WHO) started to compile country data on TB in the

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mid-1990s. However, this number still falls almost three million short of the 10.8 million (95% uncertainty interval 10.1-11.7 million) people estimated to have developed TB in 2023 [1].

WHO's End TB Strategy set a target of a 90% reduction in TB incidence and a 95% reduction in TB deaths by 2035 (compared with 2015 levels) [2]. These targets are fundamental to curbing the TB epidemic and removing the public health threat posed by TB in the world by 2035. However, progress has been insufficient and countries need to urgently reach individuals with undiagnosed TB to reduce population burden and transmission of TB [3].

TB screening to proactively identify unreached individuals with TB needs to be at the center of TB care and prevention strategies. Recently, awareness about the importance of asymptomatic TB (defined as a person with TB disease who did not report symptoms suggestive of TB during screening) has increased as findings from TB prevalence surveys have repeatedly highlighted that approximately half of all individuals with bacteriologically confirmed pulmonary TB detected in the community, experience or report no symptoms suggestive of TB [4,5]. This makes a strong case for the systematic shift toward "symptom-agnostic" approaches to TB screening (where testing for TB occurs regardless of the presence or absence of symptoms) and departing from the traditional "symptom-reliant" paradigm. In practical terms, this means one of two WHO-recommended approaches, either the whole population to be screened is offered sputum testing for the detection of *Mycobacterium tuberculosis* (*Mtb*) complex DNA by molecular WHO-recommended rapid diagnostic tests (mWRD) or alternatively chest radiography (CXR) is offered first, which can identify evidence of TB pathology prior to the onset of symptoms, followed by sputum testing with mWRD if the CXR exhibits parenchymal abnormalities suggestive of TB to reduce the number of sputum investigations performed and mitigate associated resource implications [6]. However, CXR has the additional advantage of detecting pulmonary TB, which may not be easily bacteriologically confirmed but yet may warrant treatment. The impact of the symptom-agnostic approach has recently been highlighted by the Active Case Finding for Tuberculosis (ACT-3) trial in Vietnam, which found a decline in prevalent TB from 389 to 126/100,000 in the space of 3 years through population-wide testing using a mWRD (Xpert MTB/RIF), in contrast to the virtual lack of impact on prevalence or transmission of trials which relied on symptoms for screening [7,8].

Following the TB screening guidelines issued by the WHO in 2013, which were updated in 2021, most high TB burden countries now recognize the need for screening and this activity is increasing globally; however, approaches typically focus on key vulnerable groups rather than the general population [6]. A survey conducted in 2024 found that almost all countries with high TB incidence have screening recommendations as part of their national TB program guidelines, including the use of new tools such as computer-aided detection (CAD) alongside digital CXR and mWRD, and policies for screening of key vulnerable groups including contacts of persons with TB and people living with HIV (report *in press*). In 2023, 114 countries reported the number of people newly diagnosed with TB who were identified through provider-initiated screening efforts in key vulnerable groups. In these 114 countries, a median of 12% (interquartile range 3-29%) of notified new and relapse cases originated from screening. Of 66 high-priority countries, 52 reported that in 2023 a median of 89% (interquartile range 25-100%) of administrative regions regularly undertook screening using CXR [1]. However, even in countries with well-established CXR screening programs, the total coverage of the population is insufficient to find all persons with TB. In Pakistan, for example, an ongoing (unpublished) analysis, 1,322,601 people between 2017 and 2022 underwent community-based screening for TB, representing 0.9% of the country's adolescent and adult population.

Any scale of screening will have the potential for individual benefit to those screened through earlier detection of disease and reduced morbidity and mortality [9]. To have population-level impact through reduced transmission, greater coverage of screening activity is needed which will require significant scale-up of symptom-agnostic screening. Historically, the feasibility of community-wide, symptom-agnostic screening has already been clearly demonstrated. In the mid-20th century across many parts of the world, large-scale screening was undertaken, typically with mass miniature radiography [10]. As TB incidence declined over time, these countries started to dismantle screening programs by the early 1980s [11]. After the WHO declared TB a global emergency in 1993, a global Directly Observed Treatment, Short-course (DOTS) strategy was recommended with a focus on the detection and treatment of symptomatic, smear-positive individuals self-presenting to health care facilities [12].

The impact of historic symptom-agnostic screening programs was largely forgotten but has been highlighted again by recent re-analyses of the data [13–15]. Although there have been technological advances, notably digitalization and portability of X-ray systems combined with CAD enabling automated interpretation of digital CXR without the need for radiologists and mWRD enabling rapid bacterial confirmation, in many ways, the approach to large-scale screening for TB in the 21st century is similar to the 20th century. In this article, we explore the opportunities and challenges of scaling-up and highlight what can and should be learned from historic experiences of community-wide screening for TB.

Scale of screening required for population-level impact

If countries that currently have a higher burden of TB are to scale-up symptom-agnostic screening, a number of key questions need to be addressed, in particular, the coverage and duration of screening required. The balance between coverage and duration of effort highlights an obvious trade-off. Lower coverage means the effort needs to be sustained for longer, whereas front-loading with high coverage means targets get reached sooner but require greater initial resourcing. Figure 1a shows these trade-offs in a scenario where community-wide, symptom-agnostic screening with mWRD is implemented for 1 to 5 years at different coverages of the adult and adolescent population. What this modeling highlights is that screening a limited proportion of this population is by itself unlikely to sufficiently reduce the incidence of infectious disease. Aside from the reduction in TB in the screened population, there is too much remaining transmission in the general population (which is the dominant source of infection in high-burden countries), which means the limited gains from each screening round are effectively overrun by transmission from the not-screened population [16,17]. Given the need for rapid TB decline and general up-front investment in setting up the screening campaign, coverage toward 50% of the population over 15 years of age should be targeted. The 20th-century experiences highlight that this scale could be achievable. Very high levels of coverage were achieved over short periods in cities and smaller European countries. For example, in Glasgow, 76% of the adult population was screened in 1957 and in Denmark, 65% were screened between 1950 and 1952 [15,18]. Over longer periods relatively high levels could still be achieved. Box 1 highlights screening activity in the Netherlands which achieved population coverage of a median of 19% over a 30-year period between 1950 and 1979. In the USA from the late 1940s X-ray screening was widely implemented screening approximately 16 million people per year (approximately 10% of the population) at its peak [19]. Countries that employed compulsory screening such as Norway and Australia managed to screen close to 100% of the eligible population (in Australia the average rate of

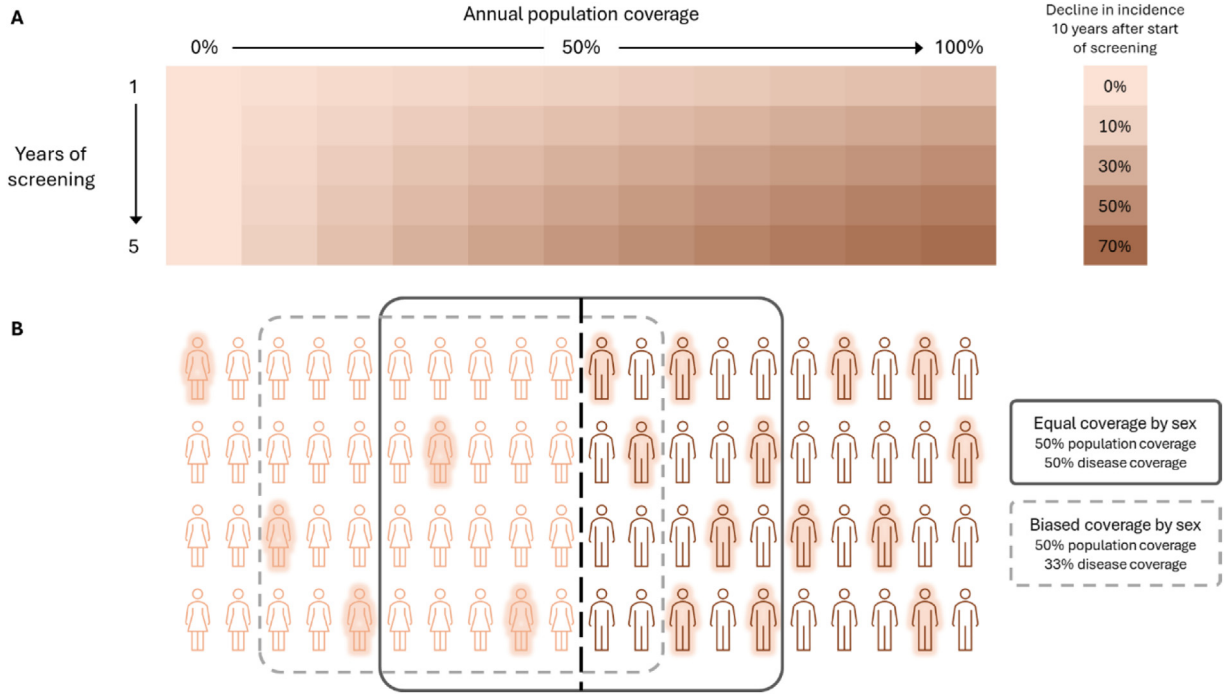

Figure 1. (a) Potential impact of community-wide screening using molecular World Health Organization-recommended rapid diagnostic tests on TB incidence 10 years after the start of screening for annual population coverage ranging from 0 to 100% with 1 to 5 years of screening. (b) Impact of biases in population coverage on disease coverage in community-wide screening. Population is divided into women (orange) and men (brown), with individuals with TB disease highlighted, in line with male-to-female ratios in TB prevalence. Solid black box shows the catchment of community-wide screening with equal coverage among men and women; dashed grey box shows the catchment of community-wide screening biased toward women.
TB = tuberculosis.

decrease in TB during the campaign period was over four times greater than before) [20,21].

Box 1. Experience of the Netherlands TB population screening programme

From 1950 to 1979, community-wide radiographic screening for tuberculosis (TB) was conducted in the Netherlands. This effort was spearheaded by employers (some of whom began as early as the 1930s). Since 1950, dedicated organizations have been established operating TB outreach population screening services. During these three decades, approximately 2.0 to 2.5 million individuals were screened annually (median 19% of the total population) (Supplementary Table 1) [22]. Of these, one-third were screened by employers, with an average screening interval of 1.5 years, whereas the remaining two-thirds were screened in outreach services operated by the screening organizations, with an average interval of 3 years.

Several important lessons emerged from this large-scale TB screening program in the Netherlands. First, the government played a critical role by providing a legal framework, culminating in the adoption of the Population Screening Act for TB in 1950. Second, the establishment of a national authority, mandated by law, ensured effective oversight. This authority was responsible for setting screening policies, granting permits to screening organizations, advising on the training curriculum for screening physicians (primarily pulmonologists), and collecting as well as reporting screening results. The third lesson highlights the significant role employers played in providing TB screening for their employees, which also contributed to reducing illness within the workforce.

Over time, the national authority made adjustments to the program, such as increasing the eligible screening age to 40 years and older persons. Screening yields declined sharply, from 117 cases per 100,000 people screened in 1950 to just 5 per 100,000 in 1979 [22]. In addition, public participation had waned, with compliance rates dropping from an initial 85-90% to below 50%. In 1979, the authority recommended discontinuing the population-wide screening program due to its diminishing effectiveness. During the 30-year screening period, TB notifications in the Netherlands decreased significantly, with an average annual reduction of 8%. The incidence rate fell from 159 cases per 100,000 people in 1950 to 12.6 per 100,000 by 1979 [23].

Targeted radiographic screening of high-risk populations, such as homeless individuals, prisoners, and migrants from countries with a high TB incidence, remains an effective intervention in countries that have achieved low TB incidence rates (fewer than 10 cases per 100,000 population). The success of these interventions depends on systematic data collection and regular evaluations to determine appropriate risk groups, refine screening algorithms, and decide when to continue or discontinue screening efforts [24]. In the Netherlands, a screening yield of more than 50 TB cases per 100,000 people screened is used as a criterion to justify the continuation of radiographic screening. Periodic evaluations have been instrumental in adjusting the eligibility criteria of high-risk populations for screening. Research and evaluations have also highlighted that a one-time radiographic screening upon arrival is insufficient to mitigate the risk of TB in certain migrant populations [25]. These groups benefit from additional TB infection testing, which is the next step in the pre-elimination phase of TB [26].

Another key question is the balance between focusing on populations with a high(er) risk of TB and simply achieving high coverage of the total adult population. Although the theoretically in-

creased yield and reduced screening cost per case detected from focusing on key vulnerable groups are appealing, there is no empiric evidence that such efforts alone have had a (sustained) impact on reducing the burden in the general population. Instead, community-wide symptom-agnostic screening campaigns should account for the demographic and socioeconomic characteristics of the population and the distribution of key vulnerable subpopulations therein to ensure that populations and geographies with high TB incidence are included, rather than missed. As TB is associated with social determinants of health such as poor nutrition, crowding, and poverty that tend to cluster spatially, having an awareness of where these geographic hotspots are is important [27]. People in certain marginalized and key subpopulations may have lower participation in screening campaigns, which will lead to a loss of impact. Figure 1b shows an example in the context of men. Although 70% of undiagnosed infectious TB is found among men in low- and middle-income income countries, men are typically underrepresented in community-screening efforts [28]. As a consequence, a campaign that has 50% population coverage but only 20% coverage of men may only pick up one-third of the total burden, blunting the potential impact of the screening effort. Rather than restricting screening to people with a higher risk for TB, community screening should instead be tailored to ensure equal/improved coverage of these individuals. History provides us with positive and negative examples. In a mass screening effort in Glasgow, some of the community engagement was tailored toward men (e.g., advertising at football matches), leading to high coverage of both sexes [15]. Whereas the Australian screening program purposefully excluded First Nations peoples from certain aspects, leading to persistently higher rates of TB decades on, compared with non-indigenous Australians [29]. We should heed these lessons as we look to achieve meaningful impact through community-wide symptom-agnostic TB screening.

A further consideration is what we should consider meaningful impact, and how we measure it. For measurement, we have a number of options, including trends in notification number needed to screen, immunoreactivity prevalence, or prevalence of bacteriologically confirmed disease. Disease prevalence provides the most direct metric, as both the target for screening and driver of other indicators such as notifications and transmission. However, cost and logistical challenges will likely force the identification of reasonable proxies, such as repeat immunoreactivity surveys to estimate trends in transmission [30]. A wider discussion is needed to decide on what counts as meaningful impact. One option is a 50% reduction in prevalence which would align with goals set in the first phase of the End TB strategy. Given the continued impact of TB and the high value for individuals, households, and society in reducing the burden, such a decline is urgently needed.

There are important differences in the challenges faced by countries today compared to the mid-20th century. Most notably, the movement of people both between countries and within countries is significantly greater today. A consequence of this is that over the time course of a screening intervention, the population composition in certain regions of a country may be very different and if net migration is from areas of higher TB burden the targeted reduction in prevalence might be more slowly met. Accounting for this in the modeling for and planning of screening will be important. In addition, developing platforms that allow for the sharing of data between regions where the movement of populations is common could help with follow-up and minimize duplication.

Making the investment case for scale-up of screening activity

Although there is strong and rapidly growing empiric evidence for symptom-agnostic, community-wide screening as a tool to meaningfully reduce the TB burden, the policy framework, infrastructure, and funding for those efforts at scale are currently inadequate. It is therefore key to engage with policymakers, product developers, and potential funders to enact change.

Crucially, the current WHO recommendations for community-wide screening only extend to populations where the prevalence of TB exceeds 0.5%, which would preclude nationwide screening programs in nearly all high-burden countries [6]. Although historic and contemporary efforts have shown epidemiologic impact in populations, most recently in Vietnam (decreasing TB prevalence from 0.4% to 0.1%), more such evidence is needed to enable this change, including an understanding of how to reduce the risk of overtreatment in communities with lower TB burden [7].

Aside from the policy framework, it is clear that community-wide, symptom-agnostic screening across high-burden countries will require unprecedented levels of investment [31]. This is likely to be orders of magnitude higher than current national TB program budgets and beyond the scope of traditional international donors such as Global Fund and the U.S. Agency for International Development (USAID) alone. Hence, they may require significant domestic funding and innovative financing that extends beyond TB and even health ecologies. To access the required funding, it is key to develop a strong investment case, which presents the economic case for action to a wide group of stakeholders, including local and global donors, product developers, and, crucially, national governments [32]. Such a project would maximize the value of the empiric evidence, present the projected costs and budgetary impact, market size, and highlight the return on investment in terms of improved equity and benefits for the community, longer-term savings to the health service as well as the potential economic benefits in terms of absolute gain in gross domestic product by curtailing the TB epidemic and averting death and disability.

Ultimately, individual countries will have to determine if the scale-up of TB screening makes sense nationally. This will depend on the trajectory of the TB epidemic locally, competing for public health and policy issues, and the state of the TB and health service more broadly, in particular, its suitability to complement and cope with scale-up of screening (see below). In addition, the wider socioeconomic progress will be relevant. Historically, 20th-century screening activity occurred with success in countries mainly with a smaller population than most of today's high-burden countries and a trajectory of economic development that sparked improvements in housing and nutrition, which likely had a synergistic effect alongside the impact of screening and helped to catalyze and sustain the effect. However, many higher-burden countries today are experiencing similar socioeconomic advances and potentially have favorable conditions to implement and benefit from similar scale-up of screening.

Importantly, scaling-up screening to achieve a 50% reduction in prevalence should only be needed for a finite amount of time which also helps with the investment case (Figure 1). Progress should be monitored and may need adjustment in terms of scale and duration to tailor to the local epidemiologic situation and targets. When transmission falls screening will become less generalized and more concentrated within certain high-risk groups, such as household contacts. Arguably, in some European countries, community-wide screening continued for too long with community-wide screening still occurring with prevalence <50/100,000 (Box 1).

In most low-burden countries that had historic reductions in TB incidence between the 1950s and 1980s as described, that steep trajectory has not been sustained and no country is close to eliminating TB. In some countries such as the UK, incidence has been increasing in recent years. Migration patterns continue to have an impact, transmission occurs in populations underserved by the health system such as the homeless, unfamiliarity with TB leads to diagnostic delays and onward transmission, and increasing use

of an expanding range of immunosuppressive therapies puts more people at risk of TB reactivation. Addressing these ongoing challenges which do require ongoing focused screening for both disease and infection, investments in diagnostics, technology and further training of health care staff is needed but costly. Making the case for significant investment in TB elimination in low-burden countries when there are many competing priorities and increasingly limited funds is not easy. Understanding the priorities of health systems to ensure the case for investment in TB is contextualized more broadly rather than narrowly disease-focused may help with this.

Community engagement for community-wide screening

Scaling-up community-wide TB screening has considerable complexities, with success dependent on participation. Although historically there are examples of countries implementing compulsory TB screening with the threat of fines or imprisonment, most screening activities are voluntary, and hence success requires broad community support [20]. Screening identifies both persons with symptomatic TB who are unable to access health care due to a combination of psychological, social, or economic pressures and health system-related access barriers, and persons with asymptomatic TB, who are currently unserved. Individuals in the latter group are indistinguishable from healthy persons and thus have no intrinsic motivation to present at a health facility for care. Proven strategies to increase participation have entailed community sensitization, demand generation to promote health-seeking, and minimizing the financial and logistical barriers to participation in screening [33,34].

However, if screening is to attract much of the population to participate, a well-organized media and communication strategy is vital. Mass advocacy using pamphlets, posters, films, radio, and newspaper advertisements, loudspeaker announcements, and incentives all featured in 20th-century screening campaigns and likely aided mobilization and participation [29,35]. In Glasgow those screened received a badge, which became highly sought after, and randomly selected people wearing badges received gifts [15,36]. Messaging on posters often emphasized the benefits of knowing one's TB status (similar to HIV screening), doing battle against TB (relevant to the post-war context), and patriotism but also addressed common concerns emphasizing speed, confidentiality, and modesty [35]. In the modern context, such campaigns will also need to include social media and strategies to mitigate consequent misinformation. Messaging and imagery must be locally appropriate and have community involvement from inception to implementation.

Health systems considerations for scaling-up screening

Population-wide, symptom-agnostic screening would represent a paradigm shift in the approach to TB case detection for most countries, bringing fresh focus to a long-recognized tension between vertical TB programming and health systems integration. A strategic approach to this integration is needed that recognizes the importance of sustained engagement with all six of the WHO building blocks of health systems: governance, information, financing, service delivery, human resources, medicines, and technologies (Figure 2) [37]. Such an approach takes action a substantial step further than vertically organized mass screening campaigns. To date, most of the work has been focused on medicines and technology; developing CXR and AI technology to be ever more portable and deployable in a decentralized manner to peripheral parts of the health system. This development clearly opens up these opportunities, but to realize the full potential of screening, challenges must be addressed, particularly in governance, service delivery, and human resources. A few examples of such challenges and potential solutions are outlined here for illustrative purposes, with a focus on digital CXR and CAD-based screening.

Large numbers of increasingly portable digital X-ray machines and CAD technologies have been procured by the national TB program, largely through Global Fund grants in recent years. Although there are national examples of the development of governance mechanisms and policies for oversight, coordination, and regulation, they have struggled to keep pace with rapid deployment in more peripheral parts of the health system. With a shift toward population-wide symptom-agnostic screening, even more X-ray machines will be needed for coverage and robust governance processes become even more important. In addition, this approach to CXR screening will detect non-TB related abnormalities and wide-scale deployment of digital XR platforms could be used beyond chest imaging, engaging beyond the TB program will be increasingly required. This may increase the cost-effectiveness of implementation by expanding the return on digital X-ray investment by detecting conditions beyond TB through both chest and other anatomical imaging. However, this will require additional capacity, particularly in the integration of cardiovascular and respiratory services into primary care, and effective coordination to ensure a smooth participant journey through the health system [38]. Other areas of governance will also need attention, especially with respect to the increasing portability and deployment of X-rays in the community, including regulation on radiation safety, and waste management and disposal. In the main, current policies and procedures are designed for X-ray deployment at the secondary care level and above, but need upgrading to make them fit for purpose in primary care, with much larger numbers of machines. Large-scale waste management and disposal will also require engagement beyond the health sector to include, for example, environmental authorities.

In service delivery, a key consideration is the importance of avoiding a situation in which a push toward more X-ray imaging in more peripheral health care facilities undermines existing X-ray imaging capability in secondary and more specialized care facilities. An obvious challenge relates to human resources (see below), but capacities for procurement, maintenance, and supply of accessories such as radiation protection devices, power generation, provision of spare parts, and break-down medical engineering need to be expanded in parallel with deployment at primary care, so as not to compromise their sustained provision in secondary care and other levels of the health system. In addition, ramping up of availability of supplies of diagnostics for microbiologic confirmation and drugs for treatment will be required to keep pace with screening.

Although AI (such as widely implemented CAD reading software for TB screening) may reduce the need for the time radiologists report CXR images, radiology expertise will be needed in human resource oversight and training. Furthermore, developing and sustaining sufficient capacity for high-quality chest image acquisition will be essential. Existing radiographer and radiography assistant numbers will need to increase and these cadres will need to focus more on the training of lower-skilled staff available, oversight, and quality assurance than on direct image acquisition. Ideally, consideration should also be given to capability of taking other kinds of X-rays (e.g., for fractures) to make the most of the technology investment. In addition, decentralizing this technology will necessitate investment in integrating digital databases with health system reporting infrastructure.

A further health systems consideration is the role of the private providers in screening. This is critical since several of the highest TB burden countries, including India, Indonesia, the Philippines, Pakistan, Bangladesh, and Nigeria have large private health care sectors [39]. Private providers may be required to support CXR-

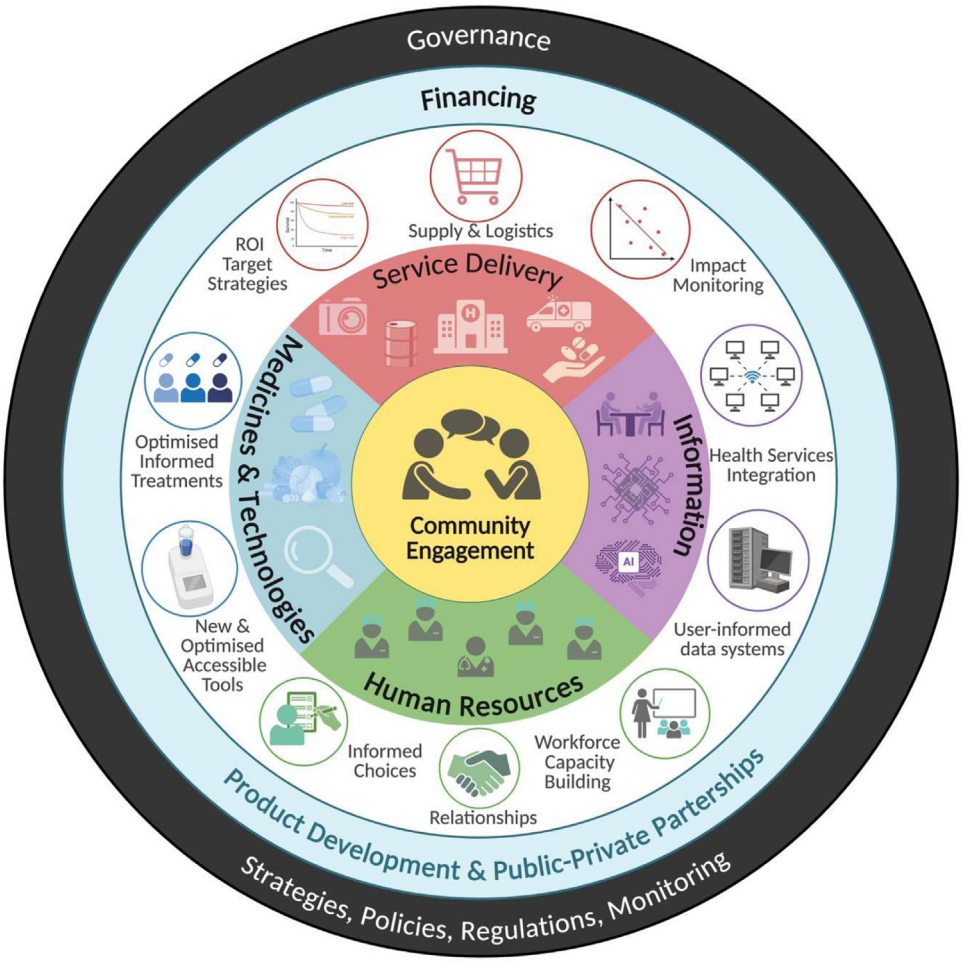

Figure 2. Requirements and considerations for national scale-up of symptom agnostic screening. Central to the effort is community engagement. Health systems strengthening will be required with consideration given to service delivery, information systems, human resources, and medicines and technologies. Critical to all these efforts will be the financing and governance framework.

based community-screening events by providing linkage to treatment, notification, and follow-up care for those diagnosed with TB, thereby preventing additional burdens on constrained public health care facilities. Although private providers will likely require financial incentives for participation in screening interventions, this has been demonstrated to be more cost-effective than non-monetary approaches [40]. Financing for private-sector engagement will require additional resources from TB programs; however, cost-sharing through other sources such as social-business models or health insurance schemes should be considered [41]. Corporate financing for occupational screening in high-risk industries can also potentially identify a high number of cases with limited budgetary implications for TB programs.

Improvement and replacement of tools for symptom-agnostic screening

Although scaling-up symptom-agnostic TB screening must initially leverage existing tools, improvements to their performance could be made. The diagnostic performance of CXR-CAD while impressive could be further improved by the inclusion of CXR of more people with asymptomatic TB, who typically have less advanced disease, into training sets. Currently, CAD software is recommended by the WHO for use in those over 15 years hence further development and validation work is needed in children. There is also scope to further maximize the utility of CAD to detect extrapulmonary TB within the imaging field of CXR (i.e., lymph node, pericardial, and spinal TB) and to continue to improve algorithms for the detection of non-TB pathology.

CXR is a highly sensitive tool for identifying TB pathology, but bacterial confirmation is dependent on the sampling and microbiologic approach. Diagnostic yield following CXR screening could be improved through modifications to existing sampling procedures. This may involve collecting additional sputum samples or performing sputum induction [42]. In addition, the CAD thresholds used for sampling often favor specificity over sensitivity to minimize the number of mWRD performed. Pooling of sputum samples could be considered in those with subthreshold scores to improve yield if established as cost-effective [43]. Furthermore, it is also important to improve existing screening algorithms with regard to rescreening those with CXR abnormalities but initial negative microbiology who remain at increased risk of disease progression [44]. Implementation studies should also explore including demographic and clinical variables, particularly, age, gender, sex, HIV status, and TB history, with the CAD scores to improve case detection [45]. In parallel, rigorous evaluation of alternative non-sputum samples like tongue swabs, bioaerosols, blood, and urine is warranted, especially among sputum non-productive individuals—crucially, these evaluations must purposefully include people with asymptomatic TB identified in the community [22,46]. Even if some of these non-sputum sampling approaches are less sensitive, given the significantly increased likelihood of obtaining a sample for testing, especially in asymptomatic populations diagnostic yield may be increased [23]. In addition, diagnostic developments should improve

on our current definitions of what constitutes a bacteriologic confirmation. Currently, a single sputum culture is often used as a gold standard dividing line between true and false positive diagnosis, but we know this underestimates the number of people who may benefit from treatment and thereby overestimates the challenge of overtreatment [42].

Ultimately, however, substantially increasing bacteriologic confirmation in those with radiographic abnormalities may require a pivot toward entirely new diagnostic approaches. A priority is developing biomarkers that can confirm TB when bacteria are absent from sputa. Potential biospecimens include blood, saliva, urine, stool, and aerosols, with targets ranging from live bacilli to bacterial RNA, metabolites, DNA, lipids, proteins, and markers of host cells responding to actively replicating *Mtb*. Promising examples include HLA-DR+ *Mtb*-specific T cells, CD34+ cells from blood harboring intracellular *Mtb* DNA representing the infection reservoir, cell-free circulating *Mtb* DNA amenable to rapid Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) detection, and phage-based assays that enhance mycobacterial cell lysis to improve DNA detection. Although exhibiting proof-of-concept, these have yet to demonstrate superiority over current microbiologic tests for detecting asymptomatic TB, and crucially even then development of an assay format to enable implementation at large scale could be a significant challenge for many of these biomarkers [24]. Importantly tests for viable bacilli if developed would also be highly relevant to screening and diagnosis of those with *Mtb* infection in the absence of disease providing a replacement for current suboptimal tests detecting only immunoreactivity.

Looking ahead, the development of point-of-care diagnostic biomarkers with sensitivity and specificity for detecting the underlying inflammatory processes of immunopathology detected radiographically as TB could potentially replace CXR altogether. Beyond just diagnosis, such biomarkers would need to demonstrate utility for monitoring treatment response, as a surrogate for drug sensitivity testing, when microbiology is negative. Eliminating CXR dependency through accurate cost-effective biomarker-based diagnosis could catalyze massive cost reductions and facilitate truly comprehensive community screening, provided the biomarkers perform robustly in community screening and across different population groups, including children and persons with extrapulmonary TB.

Conclusion

There has undoubtedly been significant progress made in the 21st century in the diagnosis and management of TB along with economic advancement in many high TB burden countries and significant advances in the management of HIV as a major risk factor for TB. However, despite this, the incidence of TB has stubbornly remained high, and progress toward the End TB targets for this metric are way off track. At the same time over the last 25 years, national prevalence surveys have reminded us that a large proportion of people with undiagnosed, potentially infectious TB in communities do not report symptoms. We can no longer afford to ignore this fact if we are serious about curtailing the TB epidemic. This will require a shift in mindset and approach, as well as a commitment to invest. Although the task of scaling-up, symptom-agnostic screening may appear daunting it is not unfamiliar and certainly achievable. Hundreds of millions of people were successfully screened in this way 50-80 years ago using inferior technology to what we have today, so while our tools may still be imperfect this cannot be an excuse for inaction.

Declarations of competing interest

DF and CM are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions, or policies of the World Health Organization.

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Ethical approval statement

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Author contributions

All authors were particpants at the WHO consultation on asymptomatic TB. HE, AKC, RMGJH, DF and CM conceived the article. All author contributed to writing sections of the article. KCM and AKC led on the design of figures. HE organised the final manuscript which was reviewed and approved by all authors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107875.

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