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How to eliminate tuberculosis 2

Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment

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This is the second in a [Series](#) of four papers about how to eliminate tuberculosis

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To halt the global tuberculosis epidemic, transmission must be stopped to prevent new infections and new cases. Identification of individuals with tuberculosis and prompt initiation of effective treatment to rapidly render them non-infectious is crucial to this task. However, in settings of high tuberculosis burden, active case-finding is often not implemented, resulting in long delays in diagnosis and treatment. A range of strategies to find cases and ensure prompt and correct treatment have been shown to be effective in high tuberculosis-burden settings. The population-level effect of targeted active case-finding on reducing tuberculosis incidence has been shown by studies and projected by mathematical modelling. The inclusion of targeted active case-finding in a comprehensive epidemic-control strategy for tuberculosis should contribute substantially to a decrease in tuberculosis incidence.

Present situation and rationale for change

Tuberculosis is a global epidemic with an estimated 9 million new cases and 1.5 million deaths in 2013.¹ Although tuberculosis has been curable for almost 70 years—and despite the fact that millions of individuals are treated every year—the annual rate of decline of tuberculosis incidence globally has averaged only 1.5% for more than a decade.^{1,2} Part of the reason for this sluggish progress is that a substantial proportion of people who fall sick with tuberculosis are never diagnosed and treated. WHO estimates that 3 million people with tuberculosis are “missed” each year by health systems, leading to the persistence of infectious cases and the airborne disease’s transmission within families and communities.¹

Key messages

- Stopping transmission is an essential component of halting the global tuberculosis epidemic; this requires finding individuals with tuberculosis and promptly initiating the correct treatment
- Actively searching for tuberculosis cases in high-risk groups is an efficient and effective way to improve tuberculosis case detection
- Initiation of effective treatment rapidly renders patients non-infectious
- The efficacy of strategies to actively find cases and ensure prompt effective treatment has been shown in high tuberculosis-burden settings
- The ability of targeted active case-finding and prompt treatment to reduce tuberculosis incidence in the population has been suggested by both empirical evaluations and mathematical modelling
- By applying existing knowledge comprehensively and exhaustively to stop the production of new infections and new cases, we can make a substantial impact on the tuberculosis epidemic

Transmission of tuberculosis leads to new infections and new cases of disease. If the global tuberculosis epidemic is to be stopped, not only must existing cases be treated, but the transmission that is constantly producing new infections and cases must also be halted. Trying to eliminate tuberculosis without stopping transmission would be like trying to empty a basin full of water without first turning off the tap that fills it.

Crucial steps to stopping transmission are finding people who have the disease and ensuring that they are immediately put on effective treatment so that they can be rapidly rendered non-infectious. In low-incidence, high-resource settings such as the USA, Canada, and the European Union, policies of targeted active case-finding are in place to limit transmission of tuberculosis in households, communities, and congregate settings.^{3–5} Targeted active case-finding means actively seeking out and screening individuals at increased risk of having the disease so that they can be diagnosed early, and, through correct treatment, rendered non-infectious. Targeted active case-finding is a fundamental strategy for disease control that has been used to stop epidemics ranging from smallpox to severe acute respiratory syndrome to Ebola virus disease, and has been recognised as a crucial component of the epidemic-control response to tuberculosis since the 1930s.^{6–8}

By contrast, most tuberculosis programmes in low-income and middle-income countries with high burdens of tuberculosis have adopted policies that rely on passive case-finding—waiting for the sick to seek care if they are able. Driven in large part by concerns over cost, this strategy prioritises treatment success among passively detected cases and considers case detection to be of secondary importance.^{9–11} However, by the time sick individuals seek treatment for their symptoms, they have been infectious for some time, and transmission in the family and community has already occurred.^{12,13}

The reliance on passive case-finding for tuberculosis has contributed to the present failure to prevent transmission at the level required to turn the tide of the tuberculosis epidemic.¹²

Improvement of case detection by actively searching for sick individuals is only the first step in stopping transmission. The second step is to ensure that individuals with tuberculosis are rapidly diagnosed and put on an effective treatment regimen. Delays in diagnosis and treatment contribute to persisting transmission of tuberculosis.^{12,13} Diagnostic and treatment policies in high tuberculosis-burden countries have largely relied on conventional sputum smear microscopy as the main diagnostic technique and on a standard empirical treatment regimen of four first-line anti-tuberculosis drugs.¹⁴ However, sputum smear microscopy has severe limitations: it fails to detect about half of all tuberculosis cases;¹⁵ its sensitivity in children sick with tuberculosis is about 10%;¹⁵ its sensitivity in people living with HIV who are sick with tuberculosis is less than 30%;^{16,17} it cannot diagnose patients with extrapulmonary tuberculosis, who represented 15% of notified cases in 2013;¹ and it cannot detect drug resistance. Furthermore, although cases that are detectable by sputum smear microscopy are generally more infectious than those that are not, the non-detectable cases have been shown to cause 13–17% of transmission in low-incidence settings.^{18,19} Reliance on smear microscopy rather than more sensitive procedures for diagnosis thus allows infectious cases to remain undetected in the community for longer. In addition, policies that rely on both sputum smear microscopy and empirical treatment with a standard first-line anti-tuberculosis regimen can result in long periods of ineffective treatment for patients with drug-resistant tuberculosis.

The tuberculosis epidemic cannot be successfully and rapidly curbed without use of recognised control measures for communicable diseases, including targeted active case-finding and prompt initiation of the correct treatment. These activities are both feasible and effective in high tuberculosis-burden settings at present, despite the challenges facing health systems in many of these countries. Thus, with adequate resource investment and political will, substantial decreases in tuberculosis incidence are possible.

Data and successes

Since the 1930s, a range of approaches to targeted active case-finding, tailored to local epidemiology, have been shown to improve tuberculosis case detection.^{6,20,21} By focusing on populations at high risk for tuberculosis, targeted active case-finding strategies detect substantially more cases per number of people assessed than would be detected by screening in the general population. The expected yields of a few common approaches are described in table 1.

Once a tuberculosis case is identified, further transmission from that individual can be stopped almost immediately by initiation of effective treatment. A seminal prospective, randomised, controlled study³² done at the Tuberculosis Chemotherapy Center, Madras (now Chennai), India, in the 1950s reported that household members of patients with tuberculosis who were treated at home had no greater risk of tuberculosis disease or infection after 5 years than household members of patients who were treated in sanatoria and thus restricted from contact with their families. Furthermore, since the 1950s, independent studies have measured the infectiousness of patients with tuberculosis who were being treated in hospital using an experimental model in which highly susceptible guineapigs were exposed to the air from a ward of patients with tuberculosis, and then tested for tuberculosis infection. These experiments repeatedly showed a rapid reduction in the patients' infectiousness after initiation of effective therapy, even while they might remain sputum smear positive.^{33–35} In the earliest experiments, patients began treatment on the day of admission to the hospital; guineapigs exposed to patients who started effective treatment for drug-susceptible tuberculosis were only 2% as likely to be infected as guineapigs exposed to untreated patients, suggesting that the patients were rendered non-infectious almost immediately after initiation of multidrug therapy.³³ In later studies using a similar experimental set-up, rapid attenuation of infectiousness was reported for patients with drug-resistant tuberculosis who were treated effectively with regimens that contained sufficient drugs to which the infecting strains were susceptible.³⁴ By contrast, these guineapig exposure studies have repeatedly reported most infections to be associated with patients who have undiagnosed or ineffectively treated drug-resistant tuberculosis, underscoring the importance of rapid initiation of the correct regimen and the danger of protracted infectiousness in these patients.^{33–36} Epidemiologically, the continuing transmission of drug-resistant strains that results from diagnostic failure or an absence of effective treatment is suggested by the prevalence of drug resistance in patients who have never

	Expected prevalence of newly diagnosed tuberculosis in people assessed
Household contact investigation in low-income and middle-income countries ^{22–24}	1–5%
Screening of outpatients in general health-care facilities in high tuberculosis-burden settings for tuberculosis symptoms and assessment of symptomatic individuals ^{25–30}	5–10%
Screening of people receiving HIV-associated health care in low-income and middle-income countries with HIV prevalence of more than 5% ³¹	1–25%
Untargeted screening in general population in 22 high tuberculosis-burden countries ¹	0.1–0.7%

Table 1: Expected yields for different active case-finding strategies

Strategies	
Targeted active case-finding	<p>Perform contact investigations of patients with tuberculosis</p> <p>Screen clients attending health facilities</p> <p>Use programme data to identify groups of people that account for a disproportionate share of the tuberculosis burden; groups can be defined by individual risk factors or geography</p> <p>Consider, pilot, and assess different targeted active case-finding strategies to find out what works best in a given setting</p> <p>Increase uptake of screening through awareness campaigns, community engagement, initiatives to mitigate stigma, and incentives</p>
Prevention of transmission in health facilities	<p>Provide paper masks to individuals suspected of having tuberculosis until they are receiving effective treatment</p> <p>Reduce contact between individuals suspected of having tuberculosis and other people seeking care, particularly susceptible individuals such as young children and people with HIV; contact can be reduced by having patients wait in different areas on the basis of risk and symptoms, or by scheduling clinics for different types of patients at different times</p> <p>Expedite diagnosis for individuals suspected of having tuberculosis</p> <p>Open windows in waiting areas or use outdoor waiting areas where feasible</p>
Prompt initiation of effective therapy	<p>Develop protocols and strengthen health systems to ensure that results of diagnostic procedures are received and acted on promptly</p> <p>Use chest radiography and clinical algorithms in addition to bacteriological testing for diagnosis, especially for young children and people with HIV</p> <p>Use rapid molecular tests that can detect both tuberculosis and drug resistance</p> <p>Initiate presumptive treatment for drug-resistant tuberculosis when a contact of a patient with drug-resistant tuberculosis is diagnosed with tuberculosis</p>
Formation of partnerships	<p>Integrate tuberculosis care with other health-care services such as HIV care and maternal-child health programmes</p> <p>Engage community members who advocate for best practices, encourage health-care-seeking behaviours, and support patients through treatment</p> <p>Partner with private sector providers to ensure that patients with tuberculosis receive timely diagnoses and appropriate treatment, and that they are reported to the national tuberculosis programme even if they receive care in the private sector</p>

Table 2: Key activities and strategies to be considered for prevention of tuberculosis transmission

been treated for tuberculosis; across the WHO European Region in 2013, 14% of patients without previous treatment had multidrug-resistant tuberculosis.¹

The combination of active case-finding and prompt initiation of effective treatment reduces transmission by removing infectious cases from the population before additional transmission occurs. Although the effect of these activities at a population level is difficult to measure over a short timeframe, evidence suggests that they have a role in reducing tuberculosis incidence. In a community-randomised trial in Brazil, eight communities matched according to socioeconomic indicators were assigned to either an intervention or control condition. In the intervention communities, outreach workers actively sought out household contacts of tuberculosis cases for prompt screening, and treatment was given for both tuberculosis disease and infection.³⁷ The control communities received the local standard of care, which relied on contacts to present to health facilities for assessment, and did not routinely provide preventive therapy. At baseline, the two sets of communities had nearly identical annual tuberculosis case notification rates (340 cases per 100 000 individuals in communities receiving the intervention and 339 per 100 000 in the controls). After 5 years, the intervention communities had a statistically significant 15% lower annual tuberculosis case notification rate than the control communities ($p=0.04$). A community-randomised trial in Zambia and South Africa allocated 24 communities to four intervention conditions involving different combinations of case-finding interventions such that each group was similar with respect to baseline prevalence of tuberculosis and HIV infection, and demographic characteristics.³⁸ After

3 years, communities in which household contacts of patients with tuberculosis were systematically assessed had an 18% lower prevalence of tuberculosis in adults ($p=0.095$) and a 55% lower rate of tuberculosis infection in children ($p=0.063$) than communities in which household contacts were not assessed.

Translation of knowledge into strategy and action

Key strategies to consider

Targeted active case-finding and prompt initiation of effective treatment are crucial components of epidemic control for infectious diseases. Although optimum methods for both can vary across settings, general strategies that have proven effective in a range of settings can provide a starting point for implementation. Table 2 presents key activities and strategies to be considered for stopping tuberculosis transmission in the context of a comprehensive approach to stopping the tuberculosis epidemic.

Active case-finding in high-risk groups

In view of the inability of passive case-finding alone to halt tuberculosis transmission, targeted active case-finding is important in all settings. However, different characteristics are associated with increased tuberculosis risk in different places, and the efficacy of any single approach to active case-finding can vary widely across settings.²⁰ Thus, each tuberculosis programme has to identify what combination of targeted active case-finding activities is the most effective in the local context.

One high-risk group that is present in all settings is contacts of patients with tuberculosis. Contact

investigation refers to the process of systematically identifying and screening contacts of patients with tuberculosis.³⁹ Since the risk of transmission increases with the intensity and duration of contact, contact investigation in the household and other places where patients with tuberculosis live (eg, workers' dormitories, prisons) is a logical case-finding strategy to consider in all countries. Common components of contact investigations include patient interviews in the clinic, asking patients to bring household members and other close contacts (particularly children) to the clinic for assessment, and home visits by a health-care worker to identify and screen household members. Although programmes generally prioritise the most infectious cases for contact investigation, investigations of children, who generally have non-infectious forms of tuberculosis, can lead to detection of infectious adult cases; this is sometimes called a source case investigation since transmission is assumed to have occurred from the adult to the child. At a children's hospital in Texas, USA, 17–24% of children diagnosed with tuberculosis were accompanied to the hospital by an adult with previously undiagnosed pulmonary tuberculosis.^{40,41}

Another generally applicable strategy for targeted active case-finding is regular screening of social or demographic risk groups that contribute a disproportionate number of cases to the local tuberculosis burden (panel). This strategy is important in both low-burden settings and high-burden settings. Analysis of routinely collected programme data can help identify high-risk groups in a particular location. Furthermore, in some high-burden settings, analysis of programme data can identify geographical hotspots where community-level interventions such as door-to-door screening and deployment of mobile diagnostic units could be a high-yield activity (see Theron and colleagues,⁴⁶ paper 1 in this Series). In countries where genotyping is practised, such as China, the combination of genotype and geographical data might allow even more specific identification of transmission hotspots.

One practical consideration for the implementation of targeted active case-finding activities is how to convince individuals to undergo screening for a stigmatised disease, especially if screening requires time and effort on the part of the individual. Strategies that have proven successful at encouraging uptake of services for other stigmatised health issues (eg, HIV, leprosy) have included coupling services for a stigmatised health issue with services for a non-stigmatised one, and community-based awareness campaigns to reduce stigma.⁴⁷ Several successful active case-finding initiatives for tuberculosis have incorporated advocacy and community mobilisation activities into their strategies.²⁰ Material incentives can also be useful in encouraging people to undergo screening; two randomised controlled trials in the USA reported that small monetary incentives doubled the proportion of homeless people who returned to the clinic to have their tuberculin skin tests read.⁴⁸

Another practical consideration is what screening and diagnostic algorithm to use. Strategies for targeted active case-finding typically use screening algorithms that progressively reduce the number of individuals at each step of assessment to ensure that time-intensive and resource-intensive procedures such as sputum culture and full clinical assessment by a physician are done for individuals who are likely to have tuberculosis. A common first step is to ask individuals about symptoms and risk factors, and move only those who are symptomatic or high risk to the next step of assessment. However, the choice of symptoms included in the initial interview can greatly affect the performance of the symptom screen, with trade-offs between sensitivity and specificity. In a prevalence survey in western Kenya,⁴⁹ where the prevalence of bacteriologically confirmed pulmonary tuberculosis was 0·6%, the presence of cough for 2 weeks or longer had 52% sensitivity and 89% specificity in predicting tuberculosis, whereas the presence of any tuberculosis symptom (cough, haemoptysis, weight loss, fever, or night sweats) had 90% sensitivity and 32% specificity. Furthermore, for children, additional symptoms such as reduced playfulness and failure to reach an age-appropriate weight are important components of a symptom screen. Finally, the comparatively high sensitivity (94%) and specificity (73%) of an abnormal chest radiograph for predicting tuberculosis in the western Kenya survey⁴⁹ (with similar results reported from other prevalence surveys) strongly supports inclusion of chest radiography into screening algorithms.

The decision to implement targeted active case-finding activities has practical implications for the tuberculosis

Panel: Examples of targeted active case-finding policies in risk groups that contribute disproportionately to local tuberculosis burden

Across the WHO African Region in 2013, the prevalence of HIV in adults aged 15–49 years was 4·5%,⁴² but an estimated 34% of tuberculosis cases were associated with HIV.¹ Screening people with HIV for tuberculosis is therefore a crucial strategy for tuberculosis case detection.

In Russia, about 0·5% of the population is incarcerated. However, prisoners accounted for 27% of tuberculosis cases in 1995.⁴³ Since then, Russia has focused on addressing tuberculosis in prisons, enforcing both mandatory screening and directly observed treatment.⁴³ These policies have been credited with reducing the proportion of tuberculosis cases that were detected in prisons to 12% in 2004.

In the USA, tuberculosis incidence among homeless people is roughly 10 times the incidence in the general population.⁴⁴ National guidelines recommend that staff in homeless shelters monitor clients for persistent cough and ensure prompt assessment either at the shelter or by providing transportation to a health-care facility.⁴⁵

	Example of implementation
Requesting that patients with tuberculosis wear surgical masks	When admitted to hospital, patients receiving multidrug-resistant tuberculosis treatment at the Airborne Infections Research Facility in Emalahleni, South Africa, were asked to wear surgical masks during the day, excluding mealtimes; infectiousness of air from the ward was reduced after the intervention ⁵³
Manipulation of clinic schedules to reduce risk of transmission to susceptible individuals in waiting rooms	At the Indus Hospital in Karachi, Pakistan, before the establishment of a separate tuberculosis clinic, clinic schedules were arranged so that no paediatric clinics were run on days during which patients with tuberculosis were seen (personal experience of FA).
Opening windows or doors, or both	In various hospital spaces in Lima, Peru, the amount of ventilation was nearly 20 times higher when windows and doors were opened than when they were closed. With open windows and doors, these spaces were better ventilated than spaces with mechanical ventilation systems (eg, fan-based systems) ⁵⁴

Table 3: Administrative and environmental strategies for airborne infection control

programme and the health system as a whole. Active case-finding activities require staff and diagnostic resources in addition to those already in place to support passive case-finding. Additionally, if active case-finding activities are successful, the number of patients requiring treatment will increase in the short term, even though subsequent reduction in transmission should reduce the number of cases in the long term. Therefore, anticipation of increased diagnostic and treatment capacity should be part of the planning process for any active case-finding activity. Furthermore, monitoring and assessment should be planned to ensure that the people screened by an active case-finding initiative are those at the highest risk rather than those who are easiest to reach, and that increases in diagnoses represent true case detection and not overdiagnosis. Finally, while active case-finding activities have as their main goal the prompt diagnosis and treatment of tuberculosis disease, they can also provide a platform for the diagnosis and treatment of tuberculosis infection and exposure to prevent development of future cases (see Rangaka and colleagues,⁵⁰ paper 3 in this Series). Therefore, the coordination of case-finding and prevention efforts should be considered.

Prevention of transmission in health-care facilities

Health facilities are a unique setting in which targeted active case-finding can be combined with administrative and environmental infection control measures to prevent nosocomial tuberculosis transmission. Facilities where individuals who are sick spend hours waiting for health care in crowded and poorly ventilated waiting areas can promote transmission within the facility. Detection of these cases as soon as possible is thus crucial to prevent transmission. One strategy to identify cases and prevent nosocomial transmission is to screen individuals in waiting areas for tuberculosis symptoms and quickly separate symptomatic individuals from the general population. This type of rapid triage was instrumental in halting nosocomial transmission during the 2003 outbreak of severe acute respiratory syndrome in Asia.⁷

For tuberculosis, the strategy “Finding TB cases Actively, Separating safely, and Treating effectively” (FAST) has helped facilities introduce procedures that reduce the risk and duration of exposure to tuberculosis for both patients and health-care workers.⁵¹ The FAST

strategy includes cough monitoring in waiting rooms and admission wards to identify individuals who might have tuberculosis, rapid diagnosis for those with tuberculosis symptoms, prompt separation of patients with suspected drug-resistant tuberculosis, and rapid initiation of effective treatment for all forms of tuberculosis. Although designed for health-care facilities, the FAST strategy could be adapted to other congregate settings as well.⁵² Additionally, a range of administrative and environmental interventions can further augment efforts to prevent transmission within facilities, without substantial additional resource investment (table 3).

Implementation of the FAST strategy in hospitals has reduced both unsuspected tuberculosis and delays in the initiation of effective treatment. After implementing FAST, the National Institute of Diseases of the Chest Hospital in Dhaka, Bangladesh, reported that 9% of patients admitted as so-called non-tuberculosis patients in fact had tuberculosis.⁵¹ In a tuberculosis hospital in Voronezh, Russia, implementation of FAST using a molecular diagnostic test reduced the time from admission to initiation of multidrug-resistant tuberculosis treatment to less than 5 days, compared with the weeks that patients would wait to receive results from mycobacterial culture and conventional drug susceptibility testing.⁵¹

Diagnosis and prompt initiation of effective treatment

The FAST strategy provides an integrated and streamlined approach that combines active case-finding, diagnosis, and treatment into a single facility-based protocol. When active case-finding is focused outside a health-care facility, strategies are needed to ensure that individuals identified as being at risk for tuberculosis are linked to appropriate diagnosis and treatment, since searching for cases will not have any effect unless these cases are promptly diagnosed and effectively treated.

In view of the limitations of sputum smear microscopy, the goal to diagnose all tuberculosis cases can only be accomplished through the use of other modalities such as radiography, molecular diagnostic tests, bacteriological culture, and clinical algorithms.²¹ Because children and people with HIV are less likely than others to have bacteriological confirmation of tuberculosis, use of clinical algorithms for these two groups is essential.⁵⁵⁻⁵⁷

In the future, rapid biomarker-based tests that do not rely on detection of bacteria in sputum could improve the speed and accuracy of diagnosis, particularly in children and people with HIV. Technologies under development at present include antigen detection tests and tests to analyse volatile organic compounds in breath or urine.⁵⁸

Failure to suspect or identify drug resistance at the time of tuberculosis diagnosis can result in patients receiving inadequate treatment regimens, which prolongs both illness and infectiousness and potentially causes amplification of drug resistance.^{59,60} Patients can deteriorate and remain infectious for months in places where policies allow treatment for drug-resistant tuberculosis to be considered only after a patient has been unsuccessfully treated with a first-line regimen. Therefore, use of new molecular diagnostic tests to rapidly diagnose drug resistance and presumptive treatment for drug-resistant tuberculosis are both integral to stopping transmission of drug-resistant strains. Molecular diagnostic tests can detect drug resistance in hours or days rather than the weeks needed for conventional culture-based drug susceptibility testing. In settings with high prevalence of drug resistance, such as Russia, Peru, and various southern African settings, universal drug susceptibility testing using molecular tests has been shown to be feasible, reducing the time to diagnosis of drug resistance and initiation of second-line treatment.^{51,61,62} In settings with low rates of drug resistance in the general tuberculosis patient population, rapid molecular testing of people suspected of having tuberculosis or patients meeting certain criteria for being at an increased risk of drug resistance (eg, contacts of an individual with drug-resistant tuberculosis, individuals with a history of tuberculosis treatment, patients not responding to treatment, and refugees) has proven to be a feasible intermediate step toward universal drug susceptibility testing.

Standardised risk criteria can also be used to identify individuals who should receive treatment for drug-resistant disease, even in the absence of a drug susceptibility test result. For example, high concordance of drug susceptibility test pattern has generally been reported between the index case and secondary cases within households of patients with drug-resistant tuberculosis.⁶³ Therefore, presumptive treatment for drug-resistant disease is warranted for household members of patients with drug-resistant tuberculosis who are themselves diagnosed with tuberculosis, especially young children who are most likely to not have bacteriological confirmation and be infected with the same strain as the index patient.

Even a perfect diagnostic technology or algorithm cannot have an effect on transmission if patients are not rapidly started on treatment. Thus, not only is the method of diagnosis important to consider, but also the timeliness and ease with which patients receive diagnostic results and are linked to care. High rates of

failure to initiate treatment after diagnosis have been reported in a range of settings.⁶⁴ Sometimes, gaps in the health-care delivery system can lead to a failure to communicate test results or an absence of action based on these results.^{65,66} In KwaZulu-Natal, South Africa, only 20% of patients with rifampicin-resistant tuberculosis had started tuberculosis treatment within 2 weeks of testing using the Xpert MTB/RIF assay, which yields results within hours.⁶⁷ In other situations, patients themselves might decline treatment despite receiving a diagnosis of tuberculosis, particularly if they have no or mild symptoms or if treatment interferes with their ability to work. Nearly a quarter of patients diagnosed with sputum smear-positive tuberculosis during a community survey in India did not initiate treatment, with the two most common reasons being lack of interest in treatment and having symptoms too mild to warrant treatment.⁶⁸ Therefore, strategies are needed to ensure that all individuals diagnosed with tuberculosis are informed of their diagnoses, counselled appropriately, and promptly treated. Strategies could include the collection of accurate contact information during the initial diagnostic encounter, optimisation of diagnostic procedures and communication systems to reduce time to diagnosis and treatment, active follow-up of people who do not initiate treatment, incentives for initiation of treatment, and oversight and support for individuals requiring it during treatment. In some countries, regulations exist that allow a tuberculosis programme to compel a patient to accept treatment despite his or her refusal; the decision about how to balance the rights of a patient with the public health system's mandate to protect the public is complex and warrants careful consideration.⁶⁹

Partnerships to extend case-finding and care

A health-care system that requires patients to seek or receive tuberculosis care within specific tuberculosis-focused settings or programmes might result in patients spending substantial time and effort accessing tuberculosis care, in addition to their other health-care needs. This burden can discourage patients from either seeking or remaining in care. Thus, a system that makes it easier for patients to access tuberculosis services in conjunction with other health-care services would probably improve both case detection and the probability of treatment initiation and completion.

Many logical points of integration between tuberculosis services and other health-care services exist. The FAST strategy offers one example of a way to integrate tuberculosis screening into primary care settings. Additionally, integration of tuberculosis and HIV services by use of a range of approaches is widely advocated, and is an obvious area for improvement in many countries with high burdens of both diseases. Maternal-child health programmes (including Integrated Management of Childhood Illness screening programmes and

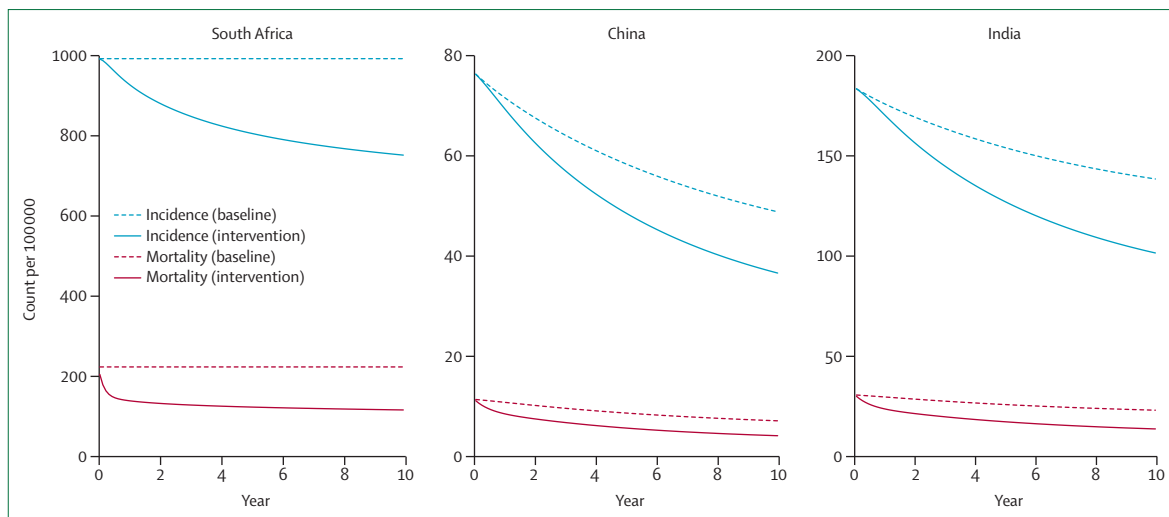


Figure: Projected impact of sustained active case-finding after 10 years in China, India, and South Africa⁶⁶

Impact represents reduction after 10 years compared with baseline, assuming an active case-finding programme that detects and treats 25% more cases than would otherwise be detected and treated in view of present epidemiological trends in each country. The additional cases detected are assumed to come from a homogeneous population, with detection occurring at a random point of disease progression. Figure courtesy of David Dowdy.

malnutrition clinics) provide a platform to offer tuberculosis treatment or preventive therapy to young children.⁷⁰ Other important points of contact include clinics treating patients with diabetes, chronic obstructive pulmonary disease, or lung disorders associated with smoking, all of which are associated with an increased risk of tuberculosis.^{71–74} Achievement of this sort of coordination of care will require tuberculosis programmes to partner with other stakeholders in the general health services rather than working in isolation.

Partnerships outside the public health-care sector can also improve the effectiveness of many of the strategies discussed thus far. For example, engagement of community members who advocate for best practices, encourage health-care-seeking behaviours, and support patients through treatment can help ensure that interventions initiated by the tuberculosis programme have wide-reaching and sustained effect. Additionally, partnerships with other government sectors, such as those in charge of prisons or social welfare programmes, can ease access to vulnerable or hard-to-reach populations. Finally, partnerships with the private sector are necessary in settings such as south Asia, where 80% of patients seek care from private providers.⁷⁵ In view of the large number and the heterogeneity of private providers, it is an immense undertaking for national tuberculosis programmes to effectively engage these providers to ensure that patients with tuberculosis receive timely diagnoses and appropriate treatment, and that all tuberculosis cases are reported to the national tuberculosis programme even if they are diagnosed and treated in the private sector. Although strategies will vary across settings, some approaches that have proven successful include use of large private hospitals with associated clinic networks as reporting centres for the national

tuberculosis programme; use of mobile phone-based platforms to help report screening or diagnostic results from private facilities; and mass media campaigns that give publicity to private facilities that have partnered with the national programme to offer testing and treatment.^{29,75}

Projection of impact

What impact would be expected from a commitment to identify and treat more people with tuberculosis than is achieved at present? Models consistent with the present tuberculosis epidemics in China, India, and South Africa predict that an increase in case detection by 25% can achieve a 40–44% reduction in tuberculosis-associated mortality, a 22–27% reduction in incidence, and a 30–33% reduction in prevalence in 10 years (figure).⁷⁶ Furthermore, these interventions were deemed to be highly cost effective, even if the costs of the interventions were as high as US\$2500 per case detected in India, and \$5000 per case detected in China and South Africa. Importantly, these projections show that the population-level benefits of active case-finding accumulate with time since removal of infectious cases from the population prevents the development of additional cases in both the near-term and long-term future; thus an assessment at the end of 1 year is unlikely to show a substantial effect, even though the 10 year projected benefit is substantial. These projections assume that detection is synonymous with prompt and effective treatment, so all case-finding has to be directly linked to the immediate delivery of care.

Achievement of a 25% increase in case detection is feasible in view of the strategies already discussed. Of 19 active case-finding initiatives, each lasting 1 year, undertaken in 11 countries, the median increase in notification rates of sputum smear-positive tuberculosis

cases was 35%, after controlling for historical trends in case notification rates and changes in case notification rates in control populations that did not receive the interventions.²⁰ In one of these initiatives, undertaken in Karachi, Pakistan, a combination of screening outpatients in clinics and a mass communication campaign encouraging people with prolonged cough to seek care more than doubled the case notification rate in the intervention area compared with the control area.²⁹ A model consistent with local tuberculosis epidemiological data projected that if the level of case detection achieved during the intervention year were maintained, 24% of the tuberculosis cases and 52% of the tuberculosis deaths that would have occurred in the absence of the intervention would be averted in 5 years; even if the level of case detection were to fall back to baseline immediately after the intervention year, 13% of cases and 25% of deaths would be averted.⁷

Conclusion

Stopping an epidemic requires stopping transmission. For an airborne disease without an effective vaccine, stopping transmission requires finding all cases promptly and rendering them non-infectious through treatment. The only way to accomplish this is to search actively for cases, use effective diagnostic methods and algorithms, initiate patients promptly on the correct therapy, and support them through to cure. The knowledge necessary to do these activities exists and successes have been documented across a range of settings.

While major changes to existing policies and care delivery systems will take time, action in the near future is possible. Some administrative and environmental interventions, such as providing individuals suspected of having tuberculosis with surgical masks until treatment begins and, where practical, opening windows in health facilities, can be implemented immediately without changes to existing systems or large investment of resources. Others, such as performing basic household contact investigations, implementation of the FAST strategy, and expansion of the use of molecular diagnostics, will require some additional human resources, training, and capacity building, but can be rapidly accomplished within the context of existing health-care delivery systems. Still others, such as integration of health-care services, have a slightly longer timeframe because they require the development of partnerships and the reorganisation of existing systems. The development and deployment of new point-of-care diagnostic technologies could accelerate these efforts by making diagnosis easier in the future.

By applying existing knowledge comprehensively and exhaustively, we can stop the production of new tuberculosis infections and cases and make a substantial impact on the epidemic. These efforts would certainly be aided and enhanced by the development of new diagnostic tests, vaccines, and treatments. However, with sufficient commitment of resources, engagement with

stakeholders outside national tuberculosis programmes, and careful planning to ensure that all the components of a new comprehensive strategy are coordinated, tuberculosis rates can be substantially reduced.

Contributors

CMY, SK, and MCB conceived the idea for this Series paper. CMY wrote the first draft, and all other authors revised it for important intellectual content. All authors approved the final version of the manuscript as submitted for publication.

Declaration of interests

We declare no competing interests.

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