INT J TUBERC LUNG DIS 21(11):1101–1113

http://dx.doi.org/10.5588/ijtld.17.0271

STATE OF THE ART

Onions and prevalence surveys: how to analyze and quantify tuberculosis case-finding gaps

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SUMMARY

Finding the missing 4 million tuberculosis (TB) patients is one of the greatest challenges facing the TB community. The optimal approaches to this will vary by country, but there is no consistent process for analyzing the potential benefit of different strategies, or for deciding which approaches are most appropriate for a given setting. Here, I bring together the Onion Model—as a way to think through health system structures—and evidence from prevalence surveys. The result is a structured process for prioritizing different strategies for case finding. Outcomes vary widely by setting, pointing to the importance of each country undertaking such a prioritization process.

KEY WORDS: case finding; prevalence surveys; Onion Model; program design

IN 2015, THERE WERE AN ESTIMATED 10.4 million new (incident) tuberculosis (TB) cases worldwide, and case-finding efforts resulted in 6.1 million TB patients being notified, leaving a gap of 4.3 million between incident and notified cases.[1] Closing this gap is one of the primary challenges facing the TB community.

Most articles on TB case finding are limited to one or a few approaches, with a recent emphasis on active case finding (ACF). The few articles that consider the entire universe of case finding are often more of a list than a structured analysis,[2] or there is a limited division of strategies into patient-initiated vs. screening approaches.[3,4] In a more structured approach, the Onion Model was presented as a means to understand where TB patients are missed, with the 'layers' of the onion representing the different health-seeking steps and health system levels (Figure 1).[4–6] This framework plus a set of programmatic indicators was used for an assessment of case-finding strategies.[6]

However, with these indicators it was difficult to differentiate between correlation and causation (some indicators may have correlated with good program operations, rather than directly causing good program outcomes), and the framework has not been systematically pursued since. This leaves no standard approach for quantitative analysis and assessment of different case-finding approaches. Meanwhile, the increasing use of TB prevalence surveys[7] has provided a wealth of information on where these 4 million people are located, and clues on how to reach them.

Here, I bring together the Onion Model, these clues from prevalence surveys, and updated approaches used by TB programs. The result is a process for analyzing and quantifying the potential benefit of different case-finding approaches, thus structuring the process of deciding which of these strategies to pursue.

WHAT CASE FINDING CLUES CAN WE GATHER FROM TB PREVALENCE SURVEYS?

Modern TB prevalence surveys are not a perfect population-based TB screen—they are a one-off screen for adults only, limited to pulmonary TB, conducted within a limited geographic area, and with incomplete participation. Nevertheless, all participating adults in a particular geographic area undergo a chest X-ray (CXR) and are asked questions about a list of symptoms. Any indication of either a CXR finding or any single symptom leads to further diagnostic work-up. For the participating individuals, the survey thus tells us how much TB we are missing using the widest possible net to capture that TB.

This inclusive approach gives the best possible estimate for the total amount of TB, but it raises challenges for setting programmatic targets. If the program screened the entire population for TB using the prevalence survey algorithm, then in theory 100% of that country's TB could be found. But how much could be found if the country perfected only patient-initiated case finding,[8] or used only more conventional ACF approaches in which not every citizen had

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Article submitted 12 April 2017. Final version accepted 30 June 2017.

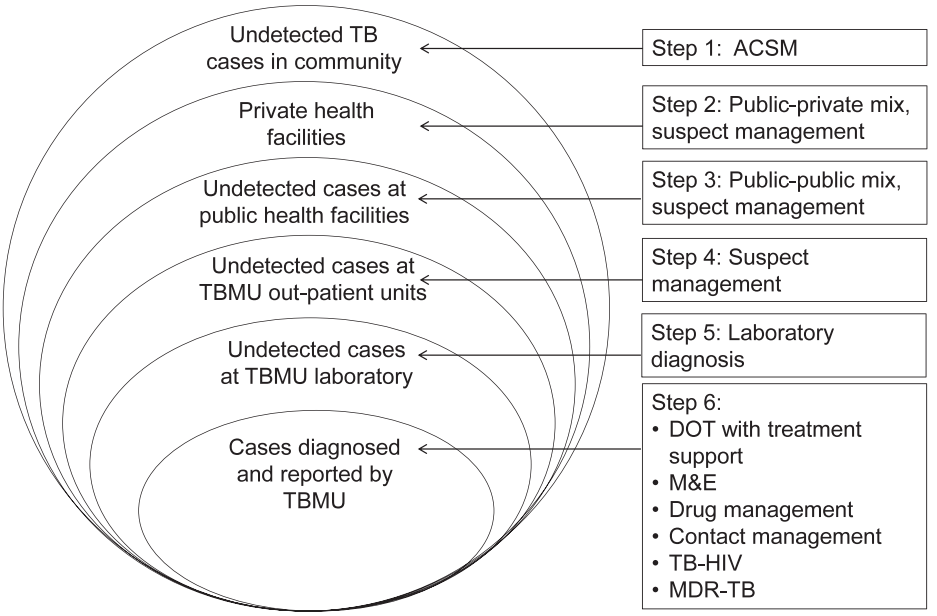

Figure 1 The Onion Model applied to TB case finding, as presented in Bassili et al.[6] TB = tuberculosis; ACSM = advocacy, communication and social mobilization; TBMU = TB management unit; DOT = directly observed treatment; M&E = monitoring and evaluation; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant TB.

a CXR? These are the questions explored further in this article.

Prevalent TB is the active TB disease that has been missed in the community and in the health system. However, prevalence surveys also tell us much more than just the amount of missed TB. An assessment team recently emphasized the importance of making full use of prevalence survey findings beyond the single prevalence number.[9] Most TB prevalence surveys identify the health-seeking behaviors of all bacteriologically confirmed TB cases, including previously missed patients. An analysis of 11 recent national TB prevalence surveys* indicates that eight of these 11 included questions on the health-seeking behavior of patients with symptoms, and nine included questions on the health-seeking behaviors of various subsets of the TB patients who were found in the survey.[2] I make use of these data in the analysis below.

THE TEN APPROACHES

This analysis starts with a simple but challenging question: How do we classify the various case-finding strategies, and how do we weigh up where the biggest gaps and opportunities lie? There is no single, correct classification scheme, but here I outline 10 ways of missing, and finding, TB cases (Table 1). The issues listed as numbers 2, 3, 5 and 6 fall comfortably in the previous analysis using the Onion Model (Figure 1), while the additional issues push the conversation further.

An updated Onion Model, outlined in Figure 2, provides the structure for the analysis. TB clinical care—the topic closest to National TB Control Programs (NTPs) and their comfort zones—is at the center of the onion. Successive outer layers address interventions that are increasingly broad and further out from the NTP (in the public system, private system, and finally the community). Two major topics related to algorithm choices are overarching.

Below, I discuss issues surrounding each of the 10 approaches in turn, summarize the possible case-finding yield from each, address the question of epidemiologic impact, and suggest a possible assessment to implement at country level.

Approach #1: Screening asymptomatics

Although TB is known for its slow clinical onset, it is striking in the prevalence surveys to see that 30–80% of prevalent TB is among asymptomatic cases.[7,10] These figures are generally available from prevalence surveys, although there are challenges with interpretation and comparison. First, the definition of 'asymptomatic' (or 'screen-negative') is highly variable between surveys. Second, symptom reporting depends on cultural and environmental determinants, with anywhere from 5% to 70% of the total population reporting any cough. Third, someone who is asymptomatic today (on the day of the prevalence survey) may become symptomatic tomor-

* The countries and years of the surveys analyzed were: Cambodia (2011), Indonesia (2013), Myanmar (2009), Pakistan (2011), Viet Nam (2007) in Asia; and Ethiopia (2011), Malawi (2013), Nigeria (2012), Tanzania (2012), Zambia (2014), and Zimbabwe (2014) in Africa.

Table 1 Ten ways to miss (and find) TB patients

#	Cases missed because:	Data source	Examples of possible responses
1	Person with TB has no symptoms (yet)	Prevalence survey	Unclear; could do CXR screening of high-risk, asymptomatic population, mass screening, or wait
2	Symptomatic patients are not seeking any treatment	Prevalence survey, health-seeking behavior survey, demographic and health survey, patient cost survey, percentage of people with TB symptoms who are diagnosed with smear-positive TB and 3+*	ACSM to encourage health seeking, ACF to reach people before health seeking, community TB to feed clients into the system, sputum collection points, transport, improve service availability
3	Facilities not covered by NTP	Prevalence survey, health-seeking behavior survey, service provision assessment/service availability and readiness assessment	PPM of public and/or private facilities
4	Non-TB parts of facilities not reached by NTP	Estimate of patient flows	ICF: HIV clinics; diabetes clinics; MCH clinics; FAST in OPDs, etc.
5	PHC and/or TB clinics not screening properly	Prevalence survey, estimate of patient flows	TB system strengthening: SOPs and/or SOC approach at PHC; strengthen recording and reporting, laboratories, etc.
6	Restrictive definition of 'symptomatic'	Prevalence survey may give clues	Define more people as 'symptomatic' (require shorter duration of cough, or 'any symptom').
7	Restrictive use of Xpert	Percentage smear-negative	Xpert for all; Xpert Ultra may strengthen
8	Poor access to CXR	LTFU study	Greater public sector CXR capacity
9	No contact investigation	Operational research on contact investigation	Increase resources and focus on contact investigation
10	LTFU during diagnosis	LTFU study	Strengthen and formalize linkages

* Higher numbers indicate insufficient numbers of clients being tested.
TB = tuberculosis; CXR = chest X-ray; ACSM = advocacy, communication, social mobilization; ACF = active case finding; NTP = National TB Program; PPM = public-private mix; ICF = intensified case finding; HIV = human immunodeficiency virus; MCH = maternal and child health; FAST = Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely, and Treat effectively based on rapid drug susceptibility testing; OPD = out-patient department; PHC = primary health care; SOP = standard operating procedure; SOC = standard of care; LTFU = loss to follow-up.

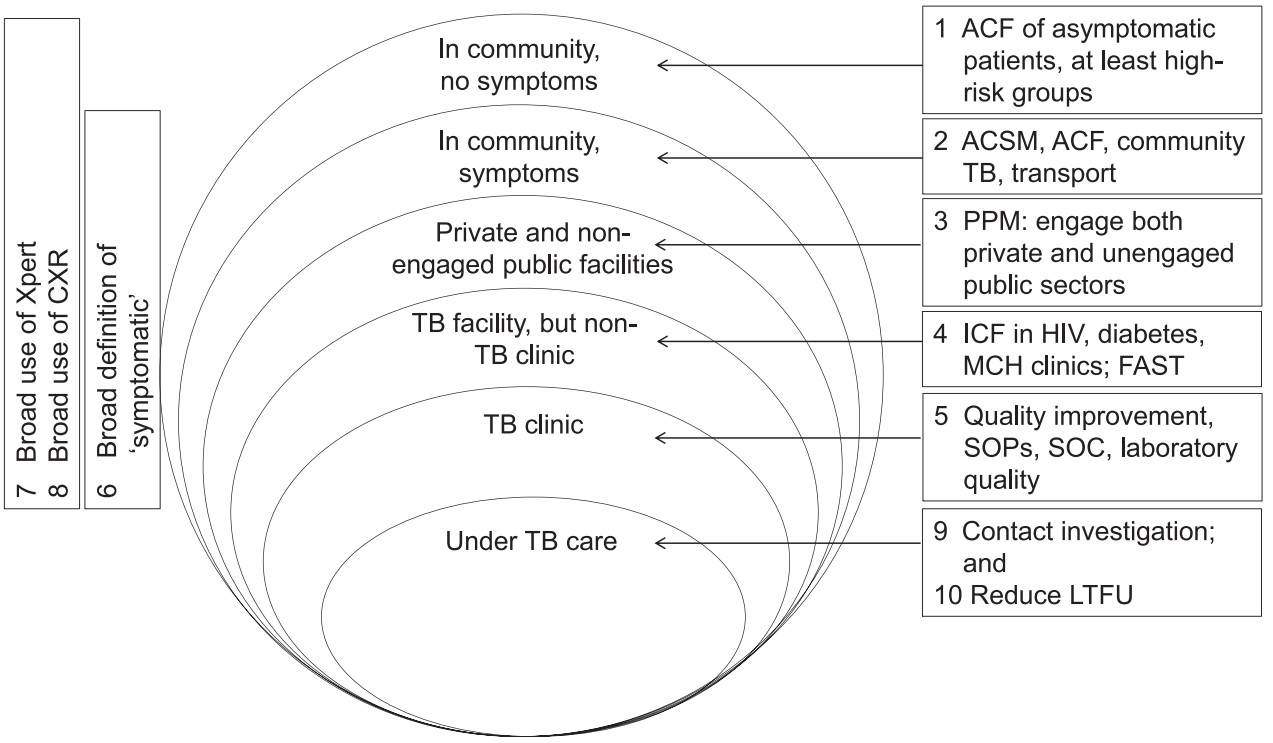

Figure 2 An updated Onion Model for TB case finding. The boxes on the right and left highlight interventions outlined in this article; these interventions can promote increased case finding at each stage, as patients move from the outside to the inside of the onion. ACF = active case finding; ACSM = advocacy, communication and social mobilization; TB = tuberculosis; PPM = public-private mix; ICF = intensified case finding; HIV = human immunodeficiency virus; MCH = maternal and child health; FAST = Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely, and Treat effectively based on rapid drug susceptibility testing; SOP = standard operating procedure; SOC = standard of care; CXR = chest X-ray; LTFU = loss to follow-up.

row, and thus move into a different diagnostic or programmatic category, but the timeline of this disease progression is unclear.

What actions could help to detect asymptomatic patients with TB? Mass CXR screening of asymptomatic patients is done in prevalence surveys, and used to be done for case finding.[11] Indeed, a large mass radiography campaign in 1950s Cape Town, South Africa, covering up to a population of 1 million, may have had epidemiologic impact, but these observational data are complicated by migration and political trends.[12]

We know from prevalence surveys that such screening—of a low-risk general population—yields a confusion of conflicting diagnostic information,[10] and sorting out these conflicting results in a programmatic setting would be challenging. Based on these concerns about false-positive results, the cost of the initial CXR, and the cost of following up those with a positive CXR, mass screening has not been recommended for decades unless restricted to high-risk populations. This approach could change with a completely new diagnostic (or combination of diagnostics) that combines exceptionally high sensitivity and specificity. Alternatively, as detailed in the next section, a more conservative approach is to screen symptomatic patients.

Approach #2: Reaching symptomatic patients who are not seeking treatment

Based on prevalence surveys, the percentage of individuals with TB symptoms who are not seeking treatment ranges from 10% to 65%* The larger this number, the greater the need for interventions described in this section. A good starting point is operational research to understand the cultural, physical, behavioral and financial barriers to treatment access. Based on those findings, strategies to overcome a lack of health seeking include advocacy to increase TB awareness and encourage health seeking, community TB efforts to feed clients into the health system via community cadres, increasing service availability and access (e.g., longer opening hours, more facilities, and transport subsidies), and ACF that reaches people before they seek care.

There is conflicting information on whether the first of these approaches, mass education campaigns for TB, can have a significant (probably time-limited) impact in a defined geographic area (e.g., a 52% increase in case finding in Cali, Colombia,[13] but no impact in Hong Kong SAR, China[14]). In Bangladesh, private sector TB drug sales halved over a period of 5 years, and pharmacists attributed this phenomenon to improved client knowledge about the existence of free TB treatment in the public sector.[15] As in human immunodeficiency virus (HIV) prevention work, combination interventions are more likely to be successful.[16] However, the cultural specificity of designing and implementing these campaigns, plus the inherent challenges in designing campaigns that are both strong in messaging and strong in impact measurement,[17] make it difficult to generalize about the typical yield from such campaigns. Finally, advocacy campaigns may have short-term impact and not address access-to-care issues (see below) that often drive health-seeking behavior.

For community TB interventions, the vast network of BRAC's *shasthya shebikas* (health volunteers) in Bangladesh gives an indication of what can be achieved.[18] These and some other community health workers identified 42% of all TB patients in the country in 2015.[19] Spectacular success with community TB (a three-fold increase in case finding) was demonstrated in Indonesia;[20] however, this was performed in a limited area for a limited duration. More widespread and sustained success requires a systematically supported community health worker cadre, with national reach, such as the *shasthya shebikas* in Bangladesh or the health extension workers in Ethiopia.[21,22]

ACF is a response to the idea that passive case finding in facilities is not sufficient to control TB.[23,24] The possible contribution of ACF is a complicated topic, as ACF is often used to describe interventions that include mass education campaigns, contact investigation, community TB, and even interventions at health facilities. However, if we take a narrow definition of ACF as conducting screening outside of health facilities, one review showed the possibility of a 25–75% increase in case finding from ACF in a population of 100–200 000.[25]

Some of the activities described in this article are clearly suitable for broad implementation. However, as ACF campaigns become broader, yield and impact increase, but efficiency and cost-effectiveness decrease.[26] Therefore, should ACF be a major push for the TB community? Some people say 'Give us the money to reach sufficient scale and we will make it happen'.[27] In response, others say that TB implementers are not just conservative, but rather there are non-trivial technical barriers,[28] including issues around sensitivity and specificity[24,29,30] (Table 2). Although many ACF efforts remain at limited scale,[30] there are large initiatives in both Russia[32] and India[33] that may yield clearer answers about impact.

Approach #3: Expanding coverage to non-NTP facilities

As clients move from the community to the health system, private providers are often their first stop. Since the late 1990s, guidance on public-private mix

* The exact numbers are 10% in Cambodia, 24% in Nigeria (plus another 28% self-medicating), 43% in Indonesia, 49% in Malawi, 56% in Viet Nam, 62% in Tanzania, and 65% in Zambia.

Table 2 Some of the arguments for[27] and against[28] a major push on ACF

	Counter-argument
Arguments against a major ACF impact	
ACF gets stuck in pilots. There is no national impact, and this is inherently not scalable[31]	To date, ACF has not been designed for national impact. No real effort has been made—this should be done
High-risk groups suitable for ACF are too small. Even at the national scale, ACF in these populations will not have a major impact[24]	We need broad-based screening campaigns
Broad screening is expensive	We need to find the money. Lack of money has never stopped the HIV community from pursuing expansion of effective interventions
Broad screening is predicted to yield a flood of false-positive results[24]	CXR use, followed by Xpert, is more specific
Even CXR plus Xpert is not specific enough without symptom screening[29]	As there is no 'gold standard', the specificity numbers for Xpert are questionable and may be higher[30]
Clinical follow-up of Xpert-negative results creates an even bigger specificity problem	Perhaps Xpert-negative results may be ignored with Xpert Ultra?
There may be reduced yield after the initial 'mop up'	Which means the job has been successfully done!
Mass screening was dismissed as an approach decades ago[11]	These approaches must be revisited now
Arguments in favor of a major ACF impact	
We are already doing population-based screening: that is what a prevalence survey is	Prevalence surveys are vast, expensive undertakings, using multiple tests per person, and even then the test results are conflicting
Technical assistance and guidance from partners has been overly pessimistic	This is the reality of disease dynamics and performance characteristics (sensitivity and specificity) of current diagnostic tests
Knowledge of TB status, and screening to obtain this information, is a human health right	Models for regular population screenings do not exist in low- or middle-income high-burden countries
There are political opportunities for big action on TB, especially in the BRICS countries	We do not have technically sound approaches to propose what would work at scale
It is already happening. Russian policy is to screen adults every 2 years and risk groups up to twice a year; in 2015, 68% of the population was screened and 60% of TB was detected by CXR screening;[32] India plans to find 6 million symptomatic patients by screening 120 million people in 18 states using house visits[33]	Could the Russian model be extrapolated to other settings? Will the India effort work?

ACF = active case finding; HIV = human immunodeficiency virus; CXR = chest X-ray; BRICS = Brazil, Russia, India, China, South Africa; TB = tuberculosis.

(PPM) has emphasized the need to link clients, wherever they are, to quality TB services.[34,35] A first step is to understand health-seeking behavior. In prevalence surveys, analyses of health-seeking behavior are variable (covering symptomatic patients, those on treatment, or both) and inexact (with inconsistent definitions of facility types, and ambiguity on whether answers represent the first action or the 'most recalled' action). Data on general health seeking can also be sourced from Demographic and Health Surveys and specialized studies, but TB prevalence surveys remain a rare and valuable chance to obtain a truly representative population sample specific to TB behaviors.

The first question to ask is where treatment is provided. The percentage of TB patients treated in the private sector varies from >40% to <5%,[10] and can be assessed by triangulating data from prevalence surveys,[10] inventory studies,[36] and drug-consumption studies.[15] A gap in the private sector between estimated and notified treatment volume—in Indonesia, for example, the private sector accounts for 42% of treatment[37] but only 9% of notifications[1]—suggests one source of under-reporting, and can be a major source of new notifications.[38]

However, even in countries with little or no private sector TB treatment, seeking health care from private providers can cause significant diagnostic delays that fuel ongoing transmission. PPM therefore aims to shorten the pathway to reach quality care. PPM action plans provide a framework for setting ambitious national targets for such facility coverage in both the public and private sectors.[39]

Patient pathway analyses offer a complementary approach.[40] Stakeholders use existing data sources to quantify gaps not only in current coverage of TB services, but also in the links between parts of the health system. This serves as a reminder that many patients initially encounter health facilities that are not equipped to diagnose and treat TB, and require referrals. Such analyses bridge across approaches 3, 4, 5 and 10 from this article, and provide a valuable opportunity to discuss how to make patient pathways more seamless.

Approach #4: Extending NTP reach further into health facilities

Once clients finally reach a public facility, TB services may exist but may not yet extend throughout the facility. This is an opportunity for intensified case finding (ICF). HIV clinics, diabetes clinics, maternal and child health (MCH) clinics, out-patient departments, and in-patient departments are obvious places to start.

ICF in HIV clinics is one of the 'three I's' for TB-HIV, which fall more on the HIV program.[41] There is strong justification for this approach, as the risk of developing TB is 20–37 times greater in people living with HIV.[42] Somewhat counterintuitively, it is the percentage of TB patients with HIV that defines the maximum TB case finding yield from this approach, as it is only those TB patients with HIV who will attend an HIV clinic and can therefore be found there. The maximum yield from this approach thus ranges from ~5% to 80% of all TB, depending on the country's coinfection rate.

Based on tracking cohorts, having diabetes triples a person's risk of developing TB.[43] About 15% of TB cases globally may be linked to diabetes,[44] although the highest TB risk is among those not in diabetes care, who are also the hardest to reach. There are limited data on the TB yield from screening diabetics.[45]

TB screening in MCH clinics can reach both mothers and children. The diagnosis of all estimated missing pediatric TB patients would increase total TB case detection by ~9%.[1] Screening mothers can result in relatively low yields if mothers are attending due to their child's need rather than their own symptoms, as this is more akin to general population screening,[46] although yields are higher among HIV-positive mothers.[47]

In hospitals, FAST (Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely, and Treat effectively based on rapid drug susceptibility testing) includes TB screening in out-patient and in-patient departments, which has positive outcomes for both infection control and case finding.[48] The total possible yield depends on the volume of health care seeking in hospitals vs. elsewhere in the health system. Screening criteria vary widely (see approach #6, below) and yields are not well analyzed. However, this can be a valuable investment, as the hospital allows many patients to be reached, and a DOTS corner typically centralizes the reporting function. TB treatment success in hospitals is typically $\leqslant$60%, so out-patient screening should be combined with an efficient mechanism to refer down the majority of cases.

Approach #5: Assessing the tuberculosis underperformance of primary health care and TB clinics

Health-seeking data from prevalence surveys were used above to highlight care seeking in private facilities not covered by the NTP. However, the same data can also be analyzed to look for the underperformance of public facilities. An example from Cambodia reveals the missed opportunities after people with TB sought care in both private and public sectors (Figure 3).[49]

Some prevalence surveys go one step further, and ask which diagnostic tests were performed after previous health seeking. For example, among symptomatic patients attending facilities with the appropriate diagnostics, only 37% (in Tanzanian facilities[50]), 11% (Zambian government community clinics) or 18% (Zambian government hospitals[51]) underwent smear microscopy.

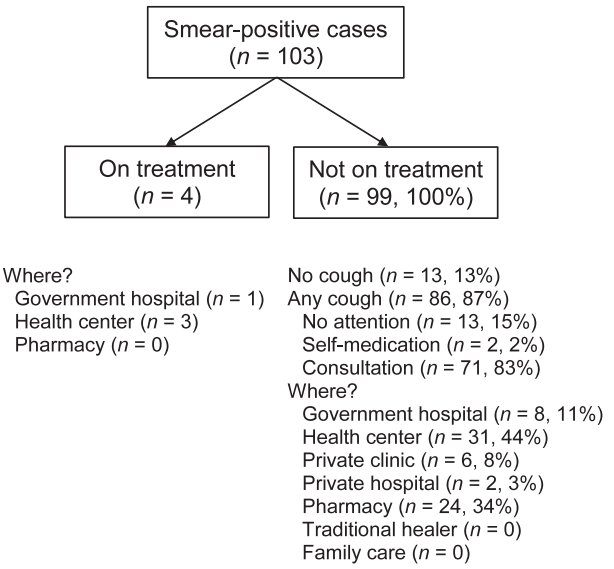

Figure 3 Health-seeking behavior of smear-positive cases found in the Cambodia prevalence survey.[49] Some previously undiagnosed individuals had no cough (13%), or did not seek attention (15%). Although 83% of symptomatic patients sought care, they were not diagnosed by the health system (instead being diagnosed for the first time by the prevalence survey team). These data reveal missed opportunities in all the facilities where those individuals sought care but were not diagnosed: in both private facilities (private clinics, hospitals and pharmacies) and the public sector (government hospitals and health centers).

Some of these individuals may have been bacteriologically undetectable at the earlier health-seeking event, but many others represent failures of the system. Determining the source of those failures requires more investigation, as it could lie with clinical workers, laboratory procedures, reporting, or other system issues. Possible responses include quality improvement cycles, such as use of standards of care (SOC) indicators to identify causes and possible interventions.[52] Another approach used training and dissemination of standard operating procedures in Nigeria to achieve a 41% increase in case finding in 11 states.[53] These efforts must be ongoing to maintain TB-specific awareness and knowledge among health workers. If not, people with the very non-specific symptoms of TB can easily go unrecognized in the system.

Approach #6: Using broader 'symptomatic' criteria

Which symptoms (or symptom combination) should be used to define a 'symptomatic' patient? This is sometimes a neglected part of TB programs, but is

Table 3 Increase in test volumes and case finding from broader screening criteria

Country	Restrictive definition	Broader definition	Number screening positive (and requiring diagnostic tests)	Increase in TB case finding
Myanmar[54]	>3 week cough	>2 week cough	40% increase	~20%
Myanmar		'Any symptom'	37% of entire population	~100% (39% of TB found by cough alone vs. 80% found by any symptom)
India[55]	>3 week cough	>2 week cough	58% increase	47%
Nigeria[56]	>2 week cough	'Any symptom'	36% of entire population	20%

TB = tuberculosis.

extremely important. This choice determines the pre-test probability that feeds into the rest of the diagnostic algorithm—and thus the performance possibilities for the tests, such as Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), that receive greater attention. The full case-finding potential of CXR and Xpert will not be realized if there is a restrictive symptom requirement up-front.

Again, prevalence surveys can provide clues if the appropriate data sets are analyzed (Table 3). Broader definitions increase not only case finding but also the number of patients requiring follow-up testing, and thus the burden on laboratory staff. There are no universal recommendations, as symptom reporting varies considerably according to country, but specifying duration clearly matters to keep the number of 'screen-positives' manageable. In the Zambia prevalence survey, for example, the percentage of patients screening positive was high when specifying 'any duration' for chest pain, cough, or fever, but decreased by respectively 4-, 5- and 7-fold by requiring a duration of >2 weeks for each symptom.

To determine optimal screening criteria for programmatic use, prevalence survey teams should analyze survey data to deduce the expected testing volume and yield when using all different combinations and durations of symptoms. Unfortunately, as surveys often present results only about individual symptoms (such as in Cambodia[49]), clear conclusions about optimal combinations are often not reached.

Approach #7: Broader use of Xpert

Studies before the roll-out of Xpert led to optimism that the new test, which is more sensitive than smear testing, could boost case finding. Modeling predicted a 30–37% increase,[57] and a study setting yielded a 35% increase,[58] as predicted based on sensitivity alone.[59]

However, findings in programmatic settings were more equivocal. In the TB NEAT trial, Xpert detected 68% of the patients with smear-negative TB,[60] whereas a subsequent analysis indicated that 93% of those patients would have been treated empirically anyway.[61] Similarly, in Brazil, Xpert yielded a 59% increase in bacteriological confirmation, but the overall notification rate did not change.[62] Greater success was seen in the context of community-based screening, where the availability of Xpert at point of contact (by using mobile vans) resulted in 53% more patients being initiated on treatment.[63]

It is clear that the extensive use of empirical treatment in routine settings modifies the gains expected from Xpert. Nevertheless, there are real advantages if Xpert converts empirical cases to bacteriologically confirmed cases. In one programmatic study, 45% of patients started treatment based on empirical decision making, but 60% of these were later found to be culture-negative, and thus likely to represent false-positive treatment decisions.[61,64] Relatively few Xpert studies have used culture as a 'gold standard' and assessed empirical treatment and false-positive results.

All of these numbers are likely to change with the introduction of Xpert Ultra.[65] However, as a general rule, Xpert will bring greater benefit in settings where current efforts struggle because empirical diagnosis is poor, i.e., when empirical diagnosis is slow, less common (thus missing a lot of TB), and less accurate (thus causing many false diagnoses).[61]

Approach #8: Maximizing the potential of chest X-ray

CXR can be used either in mass screening or in a clinical algorithm.[66] The discussion about the use of CXR in mass screening is similar to the earlier discussion on mass screening—broad use of CXR was historically encouraged, then discouraged, and is now being re-examined[11]—and requires similar trade-offs on cost, sensitivity, and specificity.[66] CXR is a good tool for key population screening, even in low-incidence countries.[67] Nevertheless, challenges include inter-observer variation and, in broader populations, the low specificity could potentially lead to overdiagnosis.

For CXR use with self-presenting patients, many symptomatic patients are at the primary health care level, but CXR availability is typically one level higher in the health system.[68] Referral of patients for CXR can result in delays, patient cost, and loss to follow-up. In earlier World Health Organization guidelines, therefore, CXR came far down in the algorithm, and was primarily suggested for assistance in diagnosing smear-negative TB and appeared after smear or Xpert and, for HIV-negative clients, after a trial use of broad-spectrum antibiotics.

More recently, however, prevalence surveys showed a much higher yield from CXR (detecting

83–97% of cases in eight prevalence surveys) than symptoms (detecting 25–70% of cases in 10 prevalence surveys). In response, new guidance outlines the options for putting CXR higher in the algorithm, both for patient-initiated health seeking (triage) and systematic screening.[66] These ideas are easier to implement thanks to mobile and digital radiography options; computer-aided detection (CAD) is also promising, although evaluation challenges remain.[69]

CXR can also be useful in reducing the number of clients needing Xpert (thus reducing cost), increasing algorithm specificity (by increasing the pre-test probability for Xpert, which is particularly important when using broad symptom criteria), and in achieving the global move from detecting only smear-positive TB to detecting all TB.

Approach #9: Increased contact investigation

Once an index TB patient has been identified, contact investigation is a core tenet and ethical imperative of TB control, but this is not without challenges. There are logistical challenges both with home visits (people are often not at home) and with requesting contacts to come to a health center (in Zambia, providers informed only 36% of eligible patients, of whom only half complied[70]). The definition of a 'contact' is unclear and setting-specific: too broad, and it becomes an inefficient mass screen; too narrow, and the yield suffers. In the Gambia, 28% of the child contacts with active TB were those who slept in the same bed as the index patient, but another 50% were also in the immediate household and the remaining 22% lived in the same compound.[71] Programs may also include smear-negative index cases (who are the source of 12–17% of transmission[72]) and non-household contacts (who are more important if diagnostic delays are significant), but both additions increase the programmatic burden.

How much TB can be found by contact investigation alone? Average TB prevalence in contacts in low- and middle-income settings is 3.1%.[73] If every index case yields three contacts and there is 100% investigation, the number of new cases found will increase national case finding by ~9%.[72] Many questions remain regarding the epidemiologic impact, cost-effectiveness, and optimal approaches for contact investigation.[72]

Approach #10: The care cascade: having found them, make sure you keep them

The last category that we examine is not a case-finding, but a case-holding approach. This is to emphasize that, having taken so much trouble to identify TB patients, we should make sure they are not lost in the system. One precedent for this discussion is the HIV care cascade, which highlighted that only 28% of people living with HIV in the United States in 2010 were virally suppressed, due to the multiple 'leaks' in the cascade from diagnosis to quality care.[74] A similar analysis for TB in India estimated that only 39% of TB patients actually complete the pathway to recurrence-free cure.[75] Pre-treatment losses in particular are significant (averaging 13–18%) and often ignored.[76]

SUMMARIZING THE CASE–FINDING POTENTIAL OF THE TEN APPROACHES

Table 4 outlines some estimates of the potential yield of the various strategies, and arguments for using each approach, based on the discussion above. Five points should be noted.

First, there are justifications to prioritize all of these approaches or a subset—the conclusion is not to focus only on one. Second, there are very wide ranges for the percentage of the TB burden that is missed due to each cause. This finding highlights the necessity of local analyses to determine the values for each country, rather than any attempt at global prioritization. Third, the numbers add up to far more than 100%, as the various causes and solutions overlap, either in a single process (e.g., CXR, Xpert and symptom choice are all part of designing diagnostic algorithms) or over time (a patient who is missed by community case finding can later be missed by a private provider and eventually found by an HIV clinic). Fourth, although ACF comes to mind first in many discussions on case finding, as it contains the words 'case finding', there is much more to case finding than just ACF. Fifth, prevalence surveys tell us a lot about which case-finding approaches to prioritize. As can be seen from the references and notes in Table 4, prevalence surveys can be used to quantify seven of the 10 causes of missed cases.

WILL CASE FINDING HAVE A SIGNIFICANT EPIDEMIOLOGIC IMPACT?

If the approaches mentioned above are implemented, improved case finding would seem to be the fastest way to epidemiologic impact, but there are reasons to doubt this conclusion. Modeling predicts that moderately high case detection rates may not be enough for a substantial impact on incidence.[77] ACF can yield higher case finding and less delay before treatment, but evidence of epidemiologic impact here is also lacking.[78] Meanwhile, reactivation keeps replenishing the TB pool;[79] stopping this reactivation requires very different types of interventions, such as preventive treatment,[80] vaccines, and addressing risk factors such as HIV, nutrition and living conditions—the latter changes being associated with the marked reductions in TB burden observed in many countries in the pre-antibiotic era.

Table 4 Ranking the responses

#	Missed cases because:	Proportion of TB burden being missed for this reason (or % increase possible by addressing it)	Prioritize a response to this source of missed cases?
1	Person with TB has no symptoms (yet)	30–80% missed[10]	Yes, in very high-risk populations (e.g., prisons); less clear elsewhere. A high percentage of asymptomatic individuals indicates that basic TB control is working, but makes the remaining job more challenging
2	Symptomatic patients are not seeking any treatment	~10–65% missed (based on seven prevalence surveys)	Yes. If this number is high, prioritize: • ACSM if surveys identify poor TB knowledge and beliefs that inhibit health seeking; • ACF if viable populations and algorithms can be designed; • community case finding and sputum collection points if community cadres exist; and • transport subsidies or improved access if access is a barrier
3	Facilities not covered by NTP	~5–40% missed due to private anti-tuberculosis treatment;[10] ⩾50% need referrals from private or are at non-engaged public facilities[34]	Yes. Ensure reporting from treatment sites (if any), and documented referral from first sites of health-seeking behavior
4	Non-TB parts of facilities not reached by NTP	HIV: average maximum yield 11%; range 5–80%[1] Diabetes: maximum yield <15%[44] MCH: ~9% maximum increase in total TB yield possible from children alone;[1] variable for mothers FAST: variable	Yes. Coinfection rate drives potential yield from ICF in HIV clinics; if only 5% of TB cases are coinfected, that is your maximum yield from HIV clinic ICF. Yield from mothers in MCH clinics and from FAST in OPDs depends on patient volumes
5	PHC and/or TB clinics not screening properly	100%-(#1 + #2 + #3 + #4). Can be up to 63%[50] or 89%[51] not tested despite seeking care	Yes, if prevalence survey shows major gaps in provider performance. Good topic for qualitative operational research to understand problems
6	Restrictive definition of 'symptomatic'	20%[54]–47%[55] increase possible	Yes, consider new definition based on full analysis of prevalence survey data
7	Restrictive use of Xpert	7%[59]–53%[63] increase possible	Yes, adopt Xpert for all symptomatic patients based on the principle of universal access to rapid diagnosis of drug-susceptible/drug-resistant TB. The case finding yield from this change will depend on what Xpert is replacing (i.e., the extent and competence of current empirical practices). Prevalence surveys can indicate what percentage of TB can be detected using Xpert
8	Poor access to CXR	30–80% if applied to asymptomatic patients (see #1); lower if applied to symptomatic patients, but still significant if definition of symptomatic is broad[66]	Yes, consider wider CXR use at the start of algorithms, as part of overall algorithm re-assessment for both triage and screening. Consider especially in combination with a broader definition of 'symptomatic' patients
9	No contact investigation	~9% increase possible[72]	Yes. Even more critical in low prevalence countries.
10	LTFU during diagnosis	Average 13–18% of cases lost; up to 38%[76]	Yes, via quality initiatives and monitoring and evaluation

TB = tuberculosis; ACSM = advocacy, communication and social mobilization; ACF = active case finding; NTP = National TB Control Program; HIV = human immunodeficiency virus; MCH = maternal and child health; ICF = intensified case finding; FAST = Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely, and Treat effectively based on rapid drug susceptibility testing; OPD = out-patient department; PHC = primary health care; CXR = chest X-ray; LTFU = loss to follow-up.

Indeed, substantial transmission may be occurring before symptoms appear and thus before case finding can remove patients from the transmission cycle.[81] Prevalence surveys indicate that significant numbers of smear-positive TB patients are either screen symptom-negative or have no cough of any duration (Table 5). This subset of asymptomatic smear-positive cases may be driving a large percentage of TB transmission; however, this is difficult to confirm without knowing more about the natural history of TB.[80]

For ACF and other case-finding approaches, the outcome metrics that are more useful (such as incidence reduction, rather than just case finding) are also harder to measure.[26] The Zambia/South Africa TB and AIDS Reduction (ZAMSTAR) Study was one of the largest attempts to assess such impacts, but it failed to demonstrate a statistically significant reduction in prevalence from implementing enhanced case finding and contact investigation[82] (although the interventions may not have been sufficiently intensive). The smaller DETECT TB Project did see a reduction in prevalence.[83]

However, ACF impacts may be underestimated in the short term,[84] intensive efforts in a defined

Table 5 Frequency of asymptomatic smear-positive TB

Country	Proportion of smear-positive survey cases who screen symptom-negative %	Proportion of survey cases who lack any cough %
Cambodia	56	SM+: 13; SM−: 28
Myanmar	61	SM+: 7; SM−: 39
Malawi	34	SM+: 21; SM−: 19
Zimbabwe	39	

SM+ = smear-positive; SM− = smear-negative.

geography may have greater impacts,[85] and the experience in Peru,[86] and data from a repeat prevalence survey in Cambodia,[49] show that programmatic efforts can lead to declines in burden. In addition, perhaps the focus of case finding should be less on epidemiologic impact and more on reducing mortality; this seems to be a clear success of the TB community's efforts, and it is a critical outcome.[87]

NEXT STEPS: SCREENING TOOLS, OPERATIONS RESEARCH, AND RISK ASSESSMENTS

What does this analysis suggest in terms of next steps? First, we need to look more carefully at all the details in prevalence survey data, and spend considerable time on further analysis beyond 'getting the number' for prevalence.[9] Prevalence surveys are a unique opportunity to obtain representative, population-based data on how TB patients 'fit' in the health system. In particular, prevalence surveys should be strengthened to 'look backwards' in a standardized way: take the confirmed cases and analyze how many could have been found via different screening criteria, different algorithms, and different improvements during the care-seeking cascade. All the results for this approach are available in the survey databases—it is a matter of prioritizing additional analyses.

These analyses are needed because there is no single answer to the question of what we should do on case finding.[88] The ranges of possible case-finding gains in each area vary enormously by country, and depend on the epidemiology, health system, and other opportunities. There is thus an ongoing need for operations research to assess and re-assess the relative yields and effectiveness of different approaches for each country, as epidemiology and programmatic context evolve.

Finally, the framework in this article (see Table 4 and the updated Onion Model in Figure 2) could be adapted as a simple assessment tool to guide in-country discussions. The objective would be to have reasonable estimations of the possible case-finding gains via each approach, leading to a menu of actions for each country. This should not be a choice of one or two interventions. This article outlines the wealth of different approaches available to find and treat TB patients, and programs should take advantage of as many approaches as possible to accelerate our shared aim of ending TB.

Acknowledgements

The author would like to thank C Vincent for suggesting case finding as a topic for investigation; C Sismanidis and I Law for providing prevalence survey reports; A Mohamed for assistance with extraction of prevalence survey data; C Colvin, J Creswell, D Dowdy, K Lönnroth, A Piatek, and S Sahu for productive conversations; and C Colvin and two anonymous reviewers for helpful comments on the manuscript.

WAW is employed by the US Agency for International Development (USAID), Washington DC, USA. The views and opinions expressed in this article are those of the author and not necessarily the views and opinions of USAID.

Conflicts of interest: none declared.

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RESUME

Trouver les 4 millions de patients de tuberculose (TB) manquants est l'un des plus grands défis auxquels est confrontée la communauté TB. Les approches optimales à ce défi vont varier selon les pays, mais il n'existe pas de processus uniforme pour analyser le bénéfice potentiel des différentes stratégies ou pour décider des approches les plus appropriées dans un contexte donné. Je rassemble ici le « modèle oignon » comme une façon d'examiner la structure du système de santé, et les preuves émanant des enquêtes de prévalence. Le résultat est un processus structuré visant à prioriser les différentes stratégies de recherche des cas. Les résultats varient considérablement en fonction du contexte, ce qui souligne l'importance que chaque pays entreprenne un processus de priorisation similaire.

RESUMEN

Encontrar los cuatro millones de pacientes con tuberculosis (TB) que se han pasado por alto representa una de las dificultades más grandes que afronta la comunidad que se ocupa de la TB. Los métodos óptimos de respuesta serán diferentes en cada país, pero no se cuenta con un mecanismo uniforme de análisis de los efectos favorables de las diversas estrategias ni con criterios para definir los métodos más apropiados en un contexto definido. En el presente artículo se reúnen el modelo de la cebolla como método de análisis detallado de la estructura del sistema de salud, y las pruebas obtenidas en las encuestas de prevalencia. Se obtuvo así un procedimiento estructurado de priorización de las diferentes estrategias de búsqueda de casos. Los resultados exhiben una amplia variabilidad en diferentes entornos, lo cual destaca la importancia de que cada país emprenda este proceso de priorización.