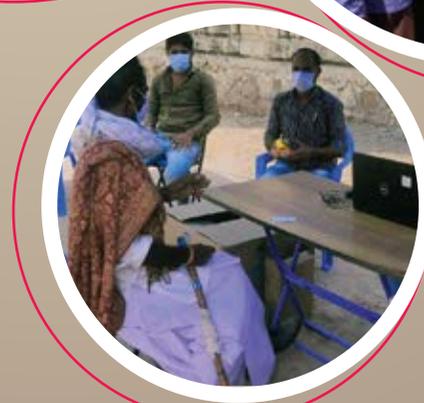World Health Organization
REGIONAL OFFICE FOR South-East Asia

Optimizing active case-finding for tuberculosis

Implementation lessons from South-East Asia

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REGIONAL OFFICE FOR **South-East Asia**

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Foreword

More than 4.3 million people in the WHO South-East Asia Region are estimated to have contracted TB in 2019, of which around 78% have been provided quality TB care. The Region has in recent years made substantial progress in increasing access to quality TB services, with the goal of ensuring at least 90% of TB patients complete TB treatment. Despite Regionwide efforts to maintain TB services throughout the COVID-19 response, the Region has recorded a 20–40% drop in TB notification in 2020.

All countries in the Region are committed to ending TB by or before 2030, which is one of the Region's eight Flagship Priorities. To catch up and reclaim the advantage against TB, countries must detect more cases and detect them early. Prevalence surveys in the Region and beyond show that a substantial proportion of TB patients may not visit a health facility because of no or mild symptoms. Without outreach efforts, vulnerable populations and marginalized groups may never be reached.

Active case-finding (ACF) will help minimize avoidable delays in diagnosis and initiation of treatment and will reduce the risk of unfavourable treatment outcomes, health sequelae, and adverse social and economic consequences. Active screening reduces TB transmission in a household, workplace, school or other community setting by removing people with prevalent disease and shortening the duration of infectiousness. When active screening is combined with appropriate diagnostic testing, policy-makers can enhance the uptake of TB preventive treatment (TPT) for people without TB disease, but who are at risk of progression.

Implementing ACF is expensive. However, if carefully planned and implemented, it will be cost effective and will support last mile efforts to reduce TB incidence. When used in conjunction with the 2021 WHO guidelines on systematic screening for tuberculosis disease, this publication – which is based on a review of publications on ACF from across the Region, in addition to several countries with similar settings – will help Member States plan and monitor ACF activities. I urge all stakeholders to appropriately leverage and apply the information contained herein, as together we continue to drive rapid and sustained progress towards the TB-free Region and world to which we are committed.

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Acknowledgements

Abbreviations and acronyms

ACF	active case-finding
ASHA	Accredited Social Health Activist
CAD4TB	computer-aided detection for tuberculosis
CHW	community health worker
CI	confidence interval
CN	case notification
CNR	case notification rate
CV	community volunteer
CXR	chest X-ray
DALY	disability-adjusted life years
DST	drug sensitivity testing
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GIS	geographical information system
HIV	human immunodeficiency virus
IGRA	interferon gamma release assay
INR	Indian rupees
LED	light-emitting diode
LED-FM	light-emitting diode fluorescence microscope
LTBI	latent TB infection
M&E	monitoring and evaluation
MDR-TB	multidrug-resistant tuberculosis
NCD	noncommunicable disease
NGO	nongovernmental organization
NIRT	National Institute for Research in Tuberculosis
NNS	number needed to screen
NNT	number needed to test
NTP	National Tuberculosis Programme
OD	operational district
PCF	passive case-finding
PLHIV	persons living with HIV

PPM	public–private mix
PPP	public–private partnership
PPV	positive predictive value
RNTCP	Revised National TB Control Programme (now called National TB Elimination Programme)
RR-TB	rifampicin-resistant tuberculosis
SEA	South-East Asia
TB	tuberculosis
TB REACH	multilateral funding mechanism of Stop TB Partnership
TPT	tuberculosis preventive treatment
TST	tuberculin skin test
US	United States
WHO	World Health Organization
Xpert	GeneXpert MTB/RIF

Glossary of terms

Active tuberculosis case-finding (ACF) is synonymous with systematic screening for active TB in at-risk populations, although it normally implies screening that is implemented outside of health facilities. *However, for the purpose of this evidence synthesis, the interventions generally conducted outside of health facilities were considered, such as screening of populations in community or specific settings.*

Close contact is a person who is not in the household but shares an enclosed space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode *(2)*.

Diagnostic procedure comprises any (combination of) method(s) used to determine the presence of TB infection (e.g. tuberculin skin test [TST]) or to confirm active TB (e.g. sputum examination or a rapid molecular test) in an individual.

Enhanced TB case-finding uses health information or education to provide information about what type of health-seeking behaviour is appropriate when people experience symptoms of TB; this type of case-finding may be combined with improving access to diagnostic services. Enhanced case-finding may or may not be combined with screening.

Household contact is a person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode.

Initial screening is the first screening test, examination or other procedure applied in the population eligible for screening.

Number needed to screen (NNS) is the number of persons who need to undergo screening in order to diagnose one person with active TB. It is the number of persons screened divided by the number of persons diagnosed with TB (roughly the inverse of the prevalence).

Passive TB case-finding is a person-initiated pathway to TB diagnosis involving the following steps: (1) a person experiencing symptoms that he or she recognizes as serious; (2) the person having access to and seeking care, and presenting at an appropriate health facility; (3) a health worker correctly assessing whether the person fulfils the criteria for presumptive TB, and (4) the successful use of a diagnostic algorithm with sufficient sensitivity and specificity. Passive case-finding may involve an element of systematic

screening if the identification of people at risk for TB is done systematically for all people seeking care in a health facility or clinic.

Repeat screening: rescreening in the same population at a given interval.

Risk groups: any group of people in which the prevalence or incidence of TB is significantly higher or presumed to be higher than in the general population. This classification may be based on surveys conducted within the country or another country with similar settings.

Screening test, examination or procedure for active TB: a test, examination or other procedure for active TB that distinguishes people with a high likelihood of having active TB from people who are highly unlikely to have active TB. A screening test is not intended to be diagnostic. People with positive results on a screening test should undergo diagnostic evaluation.

Second screening: a second screening test, examination or other procedure applied to persons whose results were positive during the initial screening.

Systematic screening for active TB is defined as the systematic identification of people with presumptive tuberculosis (TB) in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly. It is provider-initiated *(1)*.

Executive summary

The WHO South-East Asia (SEA) Region bears 44% of the global incidence of tuberculosis (TB). The average decline in annual incidence of 2.3% is much below the estimated annual decline of 10% needed to achieve the End-TB targets. TB case notification has improved over the years, but there is no significant impact on the incidence rate since a large proportion of cases are undiagnosed or in whom diagnosis is delayed. Such cases continue to feed the transmission process. Prevalence surveys conducted in countries such as Bangladesh, Indonesia and the Philippines report that nearly half of the TB patients did not seek any care because they had mild or no symptoms. A recent national prevalence survey in Nepal (2018–2019) showed that more than 70% of TB cases had no reported symptoms but had an abnormal chest X-ray (CXR). Therefore, passive, facility-based case-finding alone is inadequate for assisting national programmes to reach the End-TB targets. Until new breakthroughs in disease prevention occur, significant improvements in case detection and treatment will be essential to reduce the global TB burden.

Active case-finding (ACF) is defined by WHO as systematic screening for active TB, normally outside of health facilities but could also be undertaken at health facilities in a targeted population considered at higher risk of developing TB. The objectives of ACF are (i) targeted case-finding and (ii) prompt initiation of treatment to rapidly cure and render the disease non-infectious.

Considering the challenges faced by countries in implementing ACF activities, a rapid evidence synthesis of the published literature on ACF implementation (referred to as "review" from now on) in the SEA Region and other Asian countries (where the HIV incidence is low or is a concentrated epidemic) in the past 5 years was instituted with the objective of learning lessons that can be applied to countries in the Region.

Why ACF

Benefits to the community

ACF in household contacts has been shown to reduce disease in adults and infections in children. This review also shows notification of additional TB cases with ACF in other populations from several studies in India and Myanmar. ACF not only identifies TB patients but also those who are eligible for TB preventive therapy (TPT).

Benefits to patients

Benefits to the patients are manifold. ACF overcomes barriers to access in vulnerable populations, reduces the total costs of diagnosis and treatment, reduces the prevalence of catastrophic costs and overcomes the cost barrier for seeking TB care. ACF is seen as an instrument for reducing the broader socioeconomic consequences of TB.

ACF is cost effective when done right

Modelling shows that ACF interventions are highly cost effective, even if the costs of the interventions per case detected appear high. This is because the population-level benefits of ACF accumulate with time as additional cases are prevented. Based on studies that have assessed cost–effectiveness, the evidence review confirms this. It also confirms that the costs of implementing ACF are potentially affordable for national programmes. Further research on cost–effectiveness will need to include the impact of scaled-up preventive therapy, as ACF can identify those are eligible for TPT.

Key considerations for the implementation of ACF

Despite the clear benefits, the reported impact of ACF has been variable. A review in 2014 of the first wave of a TB REACH project showed large increases in overall case notifications across 28 projects. Although the majority of the individual projects showed an increase in case notification in the project area, the impact was variable in terms of overall increase in national notification. Some of the projects were not considered to be successful in terms of increase in case notifications. The possible reasons were that the ACF intervention was either not of adequate duration, used less sensitive screening algorithms or because the scale of the intervention was too small to make a significant contribution. There is a felt need for guidance on how to operationalize ACF for efficiency and impact. Member States of the Region have expressed the need for guidance on the operational aspects of ACF to make such activities effective in their local contexts.

This review presents some of the options for optimizing ACF activities to improve case notification based on a review of the evidence in Asia and other middle-income settings in other parts of the Region. The evidence synthesis here is based mostly on ACF activities undertaken in communities outside of health facilities.

A. Selection of population groups

According to WHO guidance, groups with a high TB prevalence should be prioritized for ACF. Some groups known to have a high prevalence are household contacts, people living with HIV (PLHIV) and prisoners. The selection of other high-prevalence populations

requires quality baseline prevalence and incidence rates, and a mapping of transmission "hotspots". Choosing the right populations in the right location is critical for successful ACF, and good data are fundamental to making the right choices in terms of population selection. In the absence of prevalence survey data, the available programmatic data can be modelled to identify such population groups.

B. Choice of algorithms

Inclusion of CXR and WHO-approved rapid molecular diagnostics (including Xpert MTB/RIF) into the diagnostic algorithm as per WHO screening guidelines increases the yield of TB cases. However, this may also be expensive, forming a major cost centre for ACF activities. Based on a review of expert opinion and feasibility of implementation, the important considerations in choosing an appropriate diagnostic algorithm are as follows:

1. the estimated prevalence of TB in the target population group;

2. the estimated accuracy of the algorithm;

3. the availability of resources – both human and financial.

Therefore, programmes may use symptom screening and sputum microscopy in a large population where the prevalence is high (some studies have considered a prevalence of more than 1.5% to be high) and resources are limited. Even in populations with a high prevalence, it would be important to remember that many cases will be missed, which will continue to spread the disease in the community.

An important limitation towards robust recommendations in this area is the small amount of community-based data globally, and in the SEA Region. Availability and recent introduction of new diagnostics also makes comparability of outcomes from earlier studies challenging. Further research is needed to determine the most feasible and cost-effective ACF approaches in different settings.

C. Challenges to ACF implementation in the field

While it is important to select the algorithms and population groups carefully, there are certain potential pitfalls during implementation. The yield of ACF can be compromised in the following situations:

1. decreased participation of targeted beneficiaries;

2. inappropriate/incomplete assessment of symptoms due to the lack of a standard questionnaire and/or inadequately trained staff;

3. drop-outs during referral for testing and loss to follow up between treatment initiation and completion;

4. inadequate capacity for obtaining a good sample and its appropriate transportation, resulting in a lower yield;

5. inadequate laboratory techniques, including preparation and reading of the sputum smear or sample handling, may also lead to a lower yield. Quality assurance of laboratory procedures is therefore important;

6. decrease in the overall impact of ACF due to diversion of staff from passive case-finding to ACF;

7. delay in treatment initiation leading to poor treatment outcomes of patients found by ACF, which may decrease the cost–effectiveness of ACF.

Recommendations for implementing ACF

1. Increase the efficiency of the process.

   (a) Prefer on-site availability of diagnostic and treatment initiation services during ACF activities over referral to a health centre to minimize loss to follow up during referral. In case this cannot be arranged, there is a need to ensure that the referral is supported financially and/or there is someone to accompany the person to guide and ensure quick attention at the health facility.

   (b) Monitor ACF activities using digital and virtual platforms such as a digital registration system to initiate and follow up those initiated on treatment. Digital platforms can also be used to monitor ACF activities for yield and drop-outs and improve future activities.

2. Select the appropriate population groups.

   (a) Prioritize groups with the highest prevalence such as household contacts and those in congregate settings such as prisons, PLHIV, workers exposed to silica and organic textile dust, and the homeless.

   (b) Analyse programme data and, where available, use prevalence survey data to identify population groups with a high estimated prevalence of, or risk factors for, TB. Modelling transmission dynamics can help with estimating the direct impact of spatial targeting on those screened as well as the indirect impact on transmission.

   (c) Review previous such activities in the country, which may also help to identify appropriate population groups.

   (d) Begin with easily identifiable high-risk target groups and then widen the scope of activities as resources and data permit.

3. Address affordability.

Costing should be part of the planning process and include major costs such as screening tests costed according to the tests as per the chosen algorithm, human resources and venue costs, depending on the number of days for which the activity needs to be conducted, costs of logistics and transportation, and patient support costs. Some of the costs, particularly those related to information dissemination and community mobilization among target groups, may be incurred prior to the activity itself but need to be planned for a comprehensive intervention. While deciding on costs, it must also be mentioned here that algorithms that use CXR and GeneXpert, although expensive, have been found to be cost effective in studies that did this analysis.

Some general considerations for addressing affordability are as follows:

(a) Use algorithms based on CXR as the first screening tool, though these may be costly as compared to algorithms with only symptom screening and sputum microscopy, but are more sensitive and useful in small populations like prisoners.

(b) Use algorithms with rapid molecular diagnostics in household contacts, as this is a highly sensitive test able to diagnose drug resistance early and would be cost effective.

(c) When resources are limited, use symptom screening and sputum microscopy in a large population with a high TB prevalence. Clinical screening and diagnosis should be an important component of the screening process. However, if resources permit, CXR may be used as screening tool and GeneXpert as a diagnostic tool.

(d) Integrate ACF with other health activities in the community, for example, screening for other communicable and noncommunicable diseases as well as for providing TPT in eligible populations.

(e) Under operational research conditions, consider the use of methods like pooling of sputum samples specifically for patients in whom CXR is normal. While considering pooling of specimens, it should be remembered that the procedure may reduce the number of cartridges but may increase human resource costs and will require accurate documentation and labelling.

(f) Utilize community resources for information dissemination, mobilization and outreach support.

(g) Plan for a mid-term review of activities for the yield, analysis of success and failures and course correction, if needed, to maximize output.

1
Background

The South-East Asia (SEA) Region is home to 44% of the global tuberculosis (TB) incidence. The average decline in annual incidence is 2.3% *(3)*, much below the 10% annual decline needed to achieve the End-TB target. Notification has improved over the years, but because of a large proportion of undiagnosed cases and delayed diagnoses that continue to feed the transmission process, the impact on the incidence rate is insignificant. Prevalence surveys in Bangladesh, Indonesia and Philippines showed that 41–48% of patients with symptoms did not seek any care *(4)*. In the national prevalence survey in Nepal (2018–2019), more than 70% of TB cases had no reported symptoms but had abnormal chest X-rays (CXRs) *(5)*. Until new breakthroughs in disease prevention occur, significant improvements in case detection will be essential to reduce the global TB burden.

WHO guidance states that systematic screening for active TB may be considered for geographically defined subpopulations with a high level of undetected TB (0.5% prevalence or higher), other subpopulations that have poor access to health care, and vulnerable or marginalized groups *(1)*. Active case-finding (ACF) is defined as systematic screening for active TB, normally outside of health facilities. The objectives of ACF are (i) targeted case-finding and (ii) prompt initiation of treatment to rapidly render the patient non-infectious.

The Stop TB Partnership and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) have supported ACF interventions in several countries. A review in 2014 of the first wave of a TB REACH project showed large increases in overall case notification across 28 projects. Although the majority of individual projects showed an increase in case notification in the project area, there was a variable impact in terms of overall increase in national notification. Some of the projects were not considered to be successful in terms of increase in case notifications. The possible reasons were that the ACF intervention was either not of adequate duration, or the scale of the intervention was too small to make a significant contribution *(6)*.

Countries acknowledge the challenge in choosing an ACF intervention that can make a significant contribution to national case notification with the limited funding available. This document does a rapid evidence synthesis of the published literature on ACF implementation in the SEA Region and other Asian countries (where the HIV incidence is low or is a concentrated epidemic) in the past 5 years with the objective of learning lessons that can be applied to countries in SEA. It also presents possible options to national programme managers and senior officials.

Objectives

At the outset, some of the questions considered were: (i) is ACF worth the resources and, if yes, what is a good method (selection criteria for vulnerable groups, operationalization of ACF, choice of testing algorithms, timing of ACF in relation to programme achievements, etc.), and (ii) are experiences in various countries enough to compile them as implementation guidance?

Therefore, the objectives of the evidence synthesis of ACF studies published in the past 5 years from SEA and other Asian countries were to review the following:

1. population groups for which ACF was implemented in countries of the SEA Region;

2. diagnostic algorithms used for ACF; consider their costs and feasibility;

3. the implementation arrangement: cost; operational feasibility (in terms of staff, time involved and complexity); treatment initiation of identified patients;

4. the effectiveness of ACF in reducing the delay in diagnosis, increase in notification, and the benefits to patients and the community;

5. based on the above, consider recommendations for selection of population groups for ACF, algorithm for screening and diagnosis, and optimization of the implementation methodology. Provide recommended options for ACF in the SEA Region.

2
Methodology

Title, abstract and full article screening were performed. The quality of studies was not assessed. However, community-based trials, where available, were prioritized when making conclusions and recommendations.

A few review papers that gave expert opinions, even when published prior to five years, were read for the full text to increase the understanding on ACF *(6–10)*. Other studies were read for abstracts. This helped in having a broad understanding of ACF globally and in refining the evidence synthesis.

The **research questions** considered were: what is the experience in the SEA Region, and how does it compare with other Asian countries for selection of population groups, algorithms and optimization of implementation?

Process followed

1. Review studies published from SEA and similar settings in the past 5 years on "general ACF" (not among contacts and outpatients) (i) to assess effectiveness in terms of reducing delay in diagnosis, increase in notification, population selection, operationalization; (ii) to get some indication of the resources used where possible; (iii) to assess the programme conditions under which ACF contributes significantly and in which population groups.

2. Compare the studies on "general ACF" with studies on ACF among contacts, in health facilities and other identified risk groups (to be considered after findings from the review of general ACF).

3. Analyse the ACF methodology used in the Region and results from the Global Fund grant data.

4. Have this document peer-reviewed to get further inputs.

Since HIV infection among people is an established risk factor and those infected are an accepted population group for active screening for TB, this population group was excluded from the search to keep the analysis focused on other groups.

Search strategy

A comprehensive literature search of publications over the past five years was performed in May 2020 in the following electronic databases: PubMed, Embase, Cochrane Database of Systematic Reviews and World Health Organization (WHO) Library. Some more studies were obtained after consulting with WHO experts. Primary studies as well as review studies were included. Search terms used were "active case-finding" and "tuberculosis".

- The title search in PubMed gave 53 articles. Some of these were comments, notice for errata and one was a duplicate (online version ahead of print).

- The title and abstract search in PubMed gave 203 studies, which included the 53 studies mentioned earlier. Two additional studies were found.

- The Embase search gave another six studies.

- One old seminal study was reviewed at the suggestion of a WHO expert.

The studies from the SEA Region and other Asian countries were read in full and data were extracted for different population groups to compare the algorithms, yield of cases and operationalization in terms of costs, personnel used, time and unique elements.

After removal of duplicate and irrelevant studies, data for SEA and Asian countries were extracted from **72** studies. Additionally, **14** studies were read for better understanding – background and review studies (ref Table 1 in Annexures).

3
Results

A. Population groups, algorithms used and implementation of ACF

This section describes the ACF studies in various population groups along with the algorithms used and implementation experiences. The emphasis is on countries in the SEA Region.

The results of all reviewed studies are in the tables for easy reference. Some exemplary studies are described in detail. To understand the implementation arrangements, the reader is advised to refer to the boxes in each section.

Additional cases from the ACF studies are given as either yield of ACF implementation or as the change in notification over past trends or in comparison to other areas.

1. Household contacts

Ten studies available over the past five years were reviewed in detail (refer Table 2 in Annexure for details). Of these, five were from India, one from Indonesia, two from Viet Nam, and one each from Cambodia and the Republic of Korea *(11–20)*. Of these, one study each from India and Viet Nam were on households of patients with multidrug-resistant TB (MDR-TB).

Three of these 10 studies were community-based trials. These are described in some detail. The first was the ACT2 (Active Case-finding for Tuberculosis) study in Viet Nam, a large, cluster randomized trial at clinics in rural and urban areas of 70 districts of Viet Nam. This was implemented by staff of the National Tuberculosis Programme (NTP). Household contacts were defined as those living with TB patients during the 2 months before the diagnosis. Those who had cough for two weeks, sputum for two weeks, any haemoptysis and CXR suggestive of TB were screened. Sputum microscopy was used for diagnosis. In the control districts, only self-referred patients underwent two sputum examinations and culture. In the intervention districts, household contacts of smear-positive adult TB patients (15 years or older) were invited to the clinics for clinical assessment and chest radiography at baseline and at 6, 12 and 24 months. In the 70 districts, 25 707 household contacts of 10 964 adult TB patients were recruited. In the 36 intervention districts, the rate of registration of TB patients among contacts was much higher as compared to the control districts (180 of the 10 069 contacts were registered as having TB; 1788 cases per 100 000 population) as compared with the control group (110 of 15 638 contacts were registered as having TB; 703 per 100 000).

In Cambodia, a low-income, high-burden country (case notification [CN] of >125/100 000), which had instituted rounds of ACF, a two-year quasi-experimental study was done to compare ACF efforts in 30 operational districts (ODs) with control ODs. Unique elements of this study were (i) selection of all household contacts and symptomatic neighbourhood

contacts of patients *within the past 2 years* because of the belief that some contacts have delayed presentation of TB; and (ii) use of *CXR and symptoms* for screening and *Xpert* for confirmation. The CN increased in the intervention districts (19% for all forms and 10% for bacteriologically confirmed [B+] cases) over the trend-adjusted expected cases and decreased by 2% in the control districts. This *increased CN gradually returned to pre-ACF levels over five to six quarters.* Even though CXR and Xpert were used for diagnosis, which normally increase the cost, the study was found to be *cost effective.*

In the Republic of Korea, household contacts were followed up for more than 2 years and the incidence was 1.1% in contacts, much higher than that in the general population (883 per 100 000 vs 70 per 100 000). The cumulative incidence was 0.5% at 3 months, 0.7% at 6 months, 0.9% at 1 year and 1.1% at 2 years. Since the household contacts diagnosed to have TB within 3 months of the index case were not counted as incident cases, the actual incidence would have been much higher.

In the Republic of Korea, the risk factors associated with TB among contacts were (i) age more than 65 years, and (ii) latent TB infection (LTBI) without treatment. The yield among children was low. Among people with LTBI and without TB preventive therapy (TPT), 4.6% progressed to TB, which is consistent with previous studies estimating that untreated LTBI turns into TB in 5–10% of cases.

Algorithms used. CXR was used as a screening tool in the Republic of Korea, India (Chennai and Chhattisgarh), Viet Nam and Cambodia. Xpert was used for diagnosis in Cambodia but culture and drug sensitivity testing (DST) was used in Chennai. The study from Chennai by the National Institute for Research in Tuberculosis (NIRT) showed that CXR as a screening tool for household contacts of pulmonary TB patients had a high sensitivity of 96% (95% confidence interval [CI]: 79.7–99.9) and high specificity of 90.9% (95% CI: 88.1–93.3).

Were additional cases found? Contact investigation contributes to an increase in case notification of all forms of TB. In the ten studies reviewed in this paper, additional cases, all forms, were in the range of 19% (Cambodia) and 63% (Chhattisgarh, India) compared to passive case detection alone. In Viet Nam, the prevalence was 1788/100 000 in household contacts compared to 703/100 000 in the control districts. In the studies from the SEA Region, prevalence among contacts ranged from 1% to 5% (*see* Table 2). However, under programme conditions where symptomatic contacts are asked to visit the clinic, 15% of the contacts, or worse, 25% of the symptomatic contacts could be lost (Chhattisgarh, India).

Implementation of ACF in the household

Community-based trials show that ACF in households leads to an increase in case-finding. In programme conditions, those identified with symptoms may fail to provide samples for diagnosis and the yield might be very low. The Indian studies from Chennai, Chhattisgarh and Kashmir were under programme conditions. In Chhattisgarh, 26% of symptomatic contacts did not come to clinic, implying that household contacts need support for sputum collection and for visiting health facilities.

The Indonesia study engaged community health workers (CHWs) for investigation of household contacts, after providing them with training and incentives. Incentives were also given to household members. The cost per screened household member was US$ 2 and US$ 6 for Intervention 1 and Intervention 2, respectively, while for those with TB symptoms, the cost was US$ 221 and US$ 808, respectively. The main cost was payment of personnel (Indonesia *(14)*). No person with TB was identified, implying that training and supervision of staff are crucial.

ACF in household contacts of MDR-TB patients. Two studies were available from the 5-year period *(18,19)*. In the India study, 17% of household members had at least one symptom of TB, 34 contacts of 1602 patients were diagnosed to have TB by Xpert, of whom 15 had rifampicin resistance. In Viet Nam, no new case was detected among households, but this study had poor participation and a short duration of follow up.

2. Prisons

Nine studies available from the 5-year period were reviewed (refer Table 3 in Annexure for more details) *(21–29)*. These included studies from all the regions except Europe. Three were from the SEA Region (Bangladesh, India and Thailand), two from Pakistan, one each from Brazil, Ethiopia, Iran and Malaysia (Eastern Mediterranean, Western Pacific regions and Region of the Americas). The prevalence of TB in prisons among these nine studies ranged from 0.13% to 8.5% and in SEA countries, the prevalence ranged from 0.2% in Bangladesh to 2% in Thailand. The genotyping study in Bangladesh estimated the rate of recent transmission during the study period (October 2005–February 2010) as 9.6%. However, when screening on entry and for current inmates was conducted from January 2009 to February 2010, the number of pulmonary TB cases declined significantly.

Algorithms used. In the nine studies, screening was done by cough and CXR in Brazil and Thailand, software-aided digital X-ray in both studies from Pakistan, any four symptoms in Malaysia, and chronic cough (2–3 weeks) in Bangladesh, Ethiopia, India and Iran. Xpert was used for diagnosis in Ethiopia, Malaysia and Thailand.

ACF among prisoners

A study in the Philippines (*please see* under vulnerable and marginalized populations) that used the same algorithm in multiple high-risk groups (urban poor, rural poor, etc.) concluded that prison inmates had a significant association with screening by "any symptom" and a large proportion of abnormal CXR results. A meta-analysis further recommended the use of CXR for screening in prison *(30)*.

In Malaysia, where the prevalence was 8.5%, screening by chronic cough would have identified only 25% of the prisoners but any one symptom identified more than twice (59%) the number of prisoners. Here, diagnosis was done by liquid culture and Xpert. In Ethiopia, while microscopy identified only eight patients, Xpert identified an additional 31. Similarly, in Bangladesh, 23% of the patients were smear negative and were identified by sputum culture.

Implementation of ACF in prisons. In India, while most prisons had doctors (82%), less than a fifth (18%) had diagnostic services. TB treatment was available in about half (54%) of the prisons. Sixty-five per cent of the prisons had one or more TB patients who were already on treatment before the ACF. Fifty per cent of prisons did screening for TB on entry and 59% of the prisons did regular screening at entry and of the inmates. Prisons with more than 500 prisoners and those doing regular screening were more likely to diagnose TB cases. On the other hand, the smaller subdistrict prisons lacked doctors and were more likely to not do screening.

Several challenges to ACF implementation were documented in the prisons. There may be poor-quality specimens, time-constrained access to the prison and excessive laboratory workload (Thailand). Prisoners could be released before testing (Thailand), or before completing their treatment (Malaysia).

Prisoners may have other infections – 7.5% of the inmates were HIV positive and 11.5% had TB/HIV coinfection (Thailand); 2% of the inmates had MDR-TB (Bangladesh).

3. Persons with diabetes

Three studies available from the 5-year period were reviewed (refer Table 4 in Annexure for further details) *(31–33)*. Two studies were from Pakistan and one from Nepal. In the two studies from Pakistan, one was a pilot study preceding the other. Bidirectional screening was done in a private setting with a large number of patients. The CAD4TB software (computer-aided detection for tuberculosis) increased the ease of use of X-ray, which was used for screening as well as clinical diagnosis. Nearly one fourth of those with diabetes did not undertake Xpert MTB/RIF testing. (The uptake of Xpert MTB/RIF testing among individuals with random blood sugar [RBS] >200 mg/dL and known diabetes mellitus was 76% and 77%, respectively). In Nepal, among 1019 patients with diabetes

from diabetic clinics, 21% had symptoms but only two patients were smear positive and none were found by Xpert.

Were additional cases found? The prevalence of TB was 10% among those with diabetes in Pakistan but only 0.2% in Nepal. The odds of developing TB were nearly 4.5 times higher in Pakistan in persons with previously diagnosed diabetes mellitus compared to those who were newly diagnosed. The possible reason for this difference in yield is the use of a more sensitive algorithm in Pakistan that included CXR.

4. Homeless persons

Only one pilot study from India was available in the five-year period (refer Table 5 in Annexure for further details) *(34)*. This was done by the NIRT, India. The algorithm was screening by any one of the four symptoms and mass miniature radiography (MMR); diagnosis by smear microscopy and culture. Chest symptoms were present in 8% and 2% had a past history of TB. The prevalence of TB in this group was found to be 1661/100 000, which is much higher than in the general population. The prevalence of smoking and alcohol consumption was 11% and 17%, respectively. Treatment completion rates were poor (1 in 5). The authors opined that incentives like food should be considered for improving participation in treatment.

5. Migrants

Three studies available from past five years were reviewed (refer Table 5 in Annexure) *(35–37)*. Two were from India and one from Nepal. The brick kiln workers were considered as internal migrants in all three studies. Two of the three studies gave the prevalence of symptoms only. The study from NIRT, India, included 4002 brick kiln workers and migrants from other districts. Brick kilns expose them to dust and smoke. The prevalence of symptoms was high. It was 9% in India and 14% in Nepal. However, no conclusion can be drawn on diagnosed TB cases as the only study that confirmed diagnosis had a high drop-out rate.

Algorithms used. Screening by symptoms was done by all three studies and a high prevalence of chest symptoms was seen in all three studies. Only one study conducted diagnostic tests, which was by sputum microscopy/Xpert.

Implementation of ACF in migrants

A district can have multiple kilns. In the Indian study, workers of one kiln were interviewed by the same field worker, which helped to establish a rapport. The workers had to spare about 30–35 min for the interview. The kilns are located 2–8 km away from the nearest village. This could be the reason for the high drop-out rate for diagnosis: only 39% of those with chest symptoms gave sputum for microscopy/Xpert.

6. Other congregate settings

Four studies available in the five-year period were reviewed (refer Table 6 in Annexure for further details) *(33,38–40)*. Of these, one each was from the Republic of Korea and Nepal, and two from India.

The study from the Republic of Korea had a prospective design and followed up more than 100 000 contacts of 2609 bacteriologically positive persons for an average of nearly three years. These contacts were from schools, workplaces, health facilities and various social welfare settings. Of the contacts, 499 developed TB of which *81.0% were diagnosed within 2 years*. Of the 163 contacts with LTBI who eventually developed active TB, 85% were diagnosed within 2 years. The incidence of TB in contacts was 146 per 10 000 person-years. The risk increased with age and was the highest in individuals aged ≥65 years.

In Tibetan refugee children who lived in boarding conditions in India, 26% of schoolchildren had exposure to a TB case in school and 3% had exposure to a TB case at home. Nearly one third (26%) of students reported exposure to someone with active TB in the previous 2 years at school.

Algorithms used. The studies from India and the Republic of Korea used a history of contact over 2 years. In the study from the Republic of Korea, CXR and screening for LTBI were prioritized for close contacts. In one Indian study, a majority of TB cases (n = 42/47 [90%]) were detected after CXR examination following TST positivity. In the second Indian study covering three states, 96 TB cases were found, 31 by smear microscopy but 34 (35%) were smear negative and Xpert positive. In Nepal, 2 weeks of cough and smear microscopy were included in the algorithm and Xpert was done only if the sputum smear was negative.

Were additional cases found? The prevalence of TB in schoolchildren at the seven boarding schools was 916 (range 371–3205) per 100 000. In the second Indian study covering three states, the overall prevalence was 346/100 000 (higher than the prevalence in the general population) but varied across states, and MDR-TB was found in 5%.

Implementation of ACF in Nepal

The study population included urban slum dwellers, factory workers, prisoners, refugees, monks/nuns, people living with HIV (PLHIV), household contacts of TB patients and patients with diabetes *(33)*. LED microscopes fitted in mobile vans and outreach workers carried out the ACF. However, only about half of the smear-negative persons went for Xpert testing. The number needed to screen (NNS) was reported for factory workers and refugees alone, which was 334 and 309, respectively.

7.   Children

Three studies (one each from India, Nepal and Pakistan) available in the 5-year period were reviewed (refer Table 7 in Annexure for further details) *(41–43)*. All studies used diverse strategies to find additional cases. Two of these were facility-based studies but the one from Nepal used multiple strategies to identify childhood TB cases.

Algorithms used. The algorithm used in Nepal was screening by a symptom-based questionnaire and TST, and diagnosis by CXR and sputum microscopy. In India, TST, CXR and microscopy were used.

Implementation of ACF for children

The Pakistan study carried out ACF in the paediatric outpatient department of tertiary hospitals *(43)*. An awareness campaign was done to attract patients. Out of more than 100 000 children, 5880 were identified by screening and 1417 were diagnosed with TB. An additional 390 children were identified by contact-tracing. For contact-tracing, household contacts of 774 index patients were investigated. Almost half (49%) of the contacts screened were children (3014 child contacts). This resulted in the diagnosis of an additional 390 children and 29 adults with TB. The TB prevalence was 12 940/100 000 or 13% among childhood contacts of new TB patients. Over a 17-month period, a threefold increase was observed in the notification of childhood cases.

In Bihar, India, ACF was done for children with severe acute malnutrition in nutrition rehabilitation centres *(41)*. Despite all children with severe acute malnutrition qualifying for TB screening due to their history of unexplained weight loss or no weight gain in the past 3 months, only 68% (n = 301) were screened by TST, 14% (n = 61) by CXR and less than 1% (n = 3) by microscopy. Among 39 diagnosed cases, 34 (87%) initiated TB treatment and 18 (53%) were registered with the Revised National Tuberculosis Control Programme (RNTCP). In the nutrition rehabilitation centres, NNS was low at 11.

In Nepal, several ACF strategies, such as household contact screening, public–private mix (PPM) services, mobile camps, door-to-door screening, school-based screening and screening at safe motherhood clinics, were used in the intervention districts (poor people and high population density) and compared with control districts *(42)*.

The number needed to identify one TB case was 41 in the two-day mobile health camp strategy in hard-to-reach areas, 44 in PPM services (i.e. diagnosis in the private sector and treatment at government centres), 108 in household screening, and 200 for community home-based care visits. Childhood TB case registration increased from 18.2 to 24.2/100 000 in the intervention districts and this was a significantly greater increase than seen in the control districts. The increase was significantly higher in children aged 0–4 years and in those with smear-negative pulmonary TB and extrapulmonart TB (EPTB). This was one of the few studies where children were included in mobile health clinics. The cost of covering 10 districts was US$ 225 000 and a nongovernmental organization (NGO) was engaged.

8. Other vulnerable and marginalized populations (those in urban slums and hard-to-reach areas, and tribals)

Thirteen studies that were available during the 5-year period were reviewed (refer Table 8 in Annexure for further details) *(33,44–55)*. One study each was from the Philippines and Papua New Guinea and 10 were from countries in the SEA Region (one from Nepal, two from Myanmar and seven from India). Diverse population groups were included as being vulnerable or marginalized. A lack of optimal access to TB services was the common feature in these populations.

Urban slums as a population group has been combined here with other vulnerable groups because several publications presented the results as a combined group. However, it is to be noted that, in urban settings, resources and facilities are better, such as CXR and highly sensitive tools, along with easier access to services. Hence, the planning approach to ACF among urban slums may differ from that for tribal and other hard-to-reach populations. It is also known that vulnerability in slums is high because of poor ventilation and crowded living conditions.

One study from Multan, Pakistan covered 100 HCWs (doctors and other staff). No other study from this period was available for screening among health-care workers (HCWs). Unfortunately, this study lacked sufficient details.

Algorithms used. The remaining 12 of the 13 studies reviewed for this population group used symptoms for screening (2 weeks cough or any one of four symptoms). Two studies also used CXR for screening (in Philippines for primary screening and in Myanmar for secondary screening). For diagnosis, six of 12 studies used Xpert and two studies also used CXR for diagnosis in addition to other diagnostics.

Were additional cases found? In countries of the SEA Region, the prevalence ranged from 0.2% to 1.5%. Only the tribal population from India *(53)* had a high prevalence of 1.5% (contrast with the NNS of 34 in the Indigenous population of Philippines). The large Axshya study demonstrated that the use of the same algorithm can give huge variation in yields across states *(33,44)*.

These studies showed marked heterogeneity in prevalence/NNS. Although studies of vulnerable populations from Myanmar *(51,52)* and India *(44,49,54)* concluded that there was an increase in case-finding with the ACF activities compared to the usual passive case-finding (PCF), NNS was high at more than 4000 in 2.4 million people examined in townships of Myanmar*(51)*, 2183 in urban slums *(49)* with Xpert and more than 3000 with sputum microscopy (SM), and approximately 1384 in combined urban and non-urban populations of Axshya. In another study from Myanmar, the NNS was 166 for ACF in the community *(52)*. In the Philippines, the NNS was 34, 45 and 48 in Indigenous populations, rural poor and urban poor, respectively. Similarly, in Nepal, the NNS showed marked variation in different population groups (refer Table 8 in Annexure).

**Implementation of ACF for vulnerable and
marginalized populations**

Vulnerable and marginalized population groups were identified based on the findings of a prevalence survey in Myanmar. The large multi-state ACF study in India, Axshya *(44)* identified populations based on the less expensive and less intense method of stakeholder consultations. Spatial mapping is mentioned in a few studies.

In Papua New Guinea, a simple methodology was adopted for reaching populations that were remote and far removed from the usual modes of transportation *(55)*. A message was sent to the villages in advance and staff from the nearby hospital visited the villages and screened those who self-identified first by symptoms and then by detailed symptoms and clinical examination. Sputum smear was done for the presumptive TB cases. For every TB patient on prior treatment, 6.6 more TB cases were identified. Overall, a prevalence of 0.9% smear-positive TB cases was considered conservative. This method gives a simple and cost-effective approach to finding TB cases in remote areas.

In the Philippines, the mobile team utilized a service bus to travel from one project site to another *(45)*. The mobile unit was equipped with all diagnostic equipment, including a digital CXR machine, light-emitting diode fluorescence microscope (LED-FM) and an Xpert machine for molecular diagnosis. The mobile unit also had a slide warmer, biosafety cabinet and refrigerator to temporarily store sputum specimens. The mobile unit had the capacity to screen over 250 individuals per day at a maximum while it screened around 50±100 individuals per day on average.

9. General population

Eleven studies were available for review during the five-year period (refer Table 9 in Annexure for further details) *(56–66)*. Of these, two studies were on pregnant women – one from India *(66)* and one from Pakistan*(58)*, both of which were health facility-based. Of the remaining nine, three were from China, one each from Cambodia and Pakistan, and four were from countries in the SEA Region. The SEA Region studies were from Thailand (one) and India (three). The three Indian studies were related and written at different stages of the project.

Some of the nine studies could have been considered with those in the vulnerable population group – for instance, the elderly or the rural poor. However, the two studies on the elderly gave very different results and no conclusion could be drawn. One was done in the general population and the other was combined with annual check-ups for the elderly. The studies on the rural poor did not have enough data to show that they were indeed from a vulnerable group. Hence, these were included among those in the general population.

Algorithms used. Screening by 2 weeks of cough shows huge differences across countries. The yield of TB cases was 4.5% and 12% in rural China *(57,59)* and 34% in the rural elderly in Cambodia *(60)*.

- ■ Screening by CXR (primary or secondary)

  - ● In China, screening by CXR was done after the screening by symptoms (secondary screening).

  - ● In Cambodia, for the rural elderly, CXR was combined with symptoms followed by Xpert and culture. *Among those with CXR abnormalities, 40% were asymptomatic*. The study concluded that CXR was the most effective component of the screening algorithm for identifying Xpert-positive cases.

- ■ Diagnosis by Xpert. In the Cambodia study *(60)*, it was noted that *only 32% of Xpert-positive patients had cough for 2 weeks or more*. Thus, the use of Xpert for diagnosis was important for increasing the yield. This is consistent with findings from Philippines *(45)* and another study from Cambodia *(67)*.

Were additional cases found? Although studies *(61,63–65)* concluded that there was an increase in case-finding with the ACF activities over the usual passive case-finding (PCF), but the NNS was high – 260 in rural Pakistan *(61)*, 87 in Cambodia (rural elderly) *(60)*. The prevalence of TB among pregnant women was very low (0.05% and 0.02%, or 50 and 20 per 100 000) in Pakistan and India, respectively.

Implementation of ACF in the general population

India (63). Sixteen districts of Haryana state in India were covered by the corporate sector in partnership with the government to make the state TB-free. A mobile van with CXR, microscope and Xpert was provided by the corporate partners and staff was provided by the corporate hospital. In order to increase participation, frontline informal workers (Accredited Social Health Activists [ASHAs]) helped with dissemination of information about the camps. To decrease the number of drop-outs, CXR and sputum examination were done in the same visit, unlike earlier, when CXR was done only for smear-negative patients. The initiative resulted in a 12% increase in case notification mainly due to an increase in clinically diagnosed cases. The proportion of new smear-negative cases changed from 17.5% to 18.2% after a year.

China (57). In this *retrospective cohort study*, 10 communities in a county were screened by symptoms and risk factors, following which sputum microscopy and CXR were done for diagnosis between 2013 and 2015. The NNS was calculated separately for those with HIV, past history of TB, and those with symptoms of TB (34, 29 and 39, respectively), which was much higher than the NNS in the general population (1478). There was no significant difference in the cumulative TB incidence or prevalence between the ACF and PCF areas during the screening time frame. The decrease in the number of cases detected in 2015 could be explained by earlier detection of most TB cases in 2013 and 2014 caused by the massive screening effort.

ACF in the elderly – two countries, two results

In Cambodia *(60)*, initial screening by symptoms and secondary screening by CXR were done and diagnosis was by Xpert. One third of the participants screened positive. Among these, 55% were positive by symptoms alone, 29% were positive by CXR alone and 17% were positive by both symptom and CXR criteria. *Among the Xpert-positive patients, only 32% reported a cough of 2 weeks or more, while 40% were asymptomatic and were identified because of an abnormal CXR.* Bacteriologically confirmed pulmonary TB was 1.3% in those more than 55 years old and increased with age: from 0.9% in the 55–64 years age group to 2.2% among those aged more than 74 years. According to the authors, *CXR was clearly the most effective component of the screening algorithm for identifying Xpert-positive cases.*

In China *(56)*, a pilot study conducted from March to June 2017 in a township of about 17 000 people showed different results from the study in Cambodia. Earlier, ACF case notification was lower than the national average and very few TB cases had been notified among seniors. The algorithm for the elderly was screening by symptoms and risk factors during routine annual check-ups followed by CXR (secondary screening). Those with a positive CXR or symptoms underwent sputum smear examination and culture. Three were diagnosed to have active TB, giving an *estimated detection rate of 146 per 100 000, which was much lower than the expected rate of 502/10 000 in the elderly in China.*

B.   Advantages of ACF

Benefits to the community

ACF leads to an increase in notification rates for TB. This has been seen in studies reviewed from India *(44,50,63)*, Myanmar *(51)*, Cambodia *(12)* and China *(68)*. A study from China *(57)* showed a significant decline in case notification in five years after three rounds of ACF in comparison to the PCF districts.

Benefits to the patients

Benefits to the patients are manifold.

1. A qualitative study concluded that nearly half the patients did not consider the symptoms serious enough to visit a health facility and about 10% did not know where to go or did not have the money or social support *(69)*.

2. ACF decreased the patient delay significantly *(57,70)*. When targeted at household members, ACF is beneficial for families because of earlier detection compared to PCF *(71)*.

3. ACF among marginalized and vulnerable populations reduces the total costs and prevalence of catastrophic costs due to TB diagnosis and overcomes the cost barrier to seeking TB care *(72–75)*. ACF is seen to be an instrument for reducing the broader socioeconomic consequences of TB *(73)*.

4. Patients identified by ACF tend to be older and living away from the health facilities *(44,51)*. ACF thus is seen to overcome the barriers to access for vulnerable populations *(44,53)*.

ACF is cost effective

A number of studies have found ACF to be cost effective. This has been seen with the community trial AIDS Clinical Trials (ACT)2. The estimated incremental cost–effectiveness ratio was US$ 544 (95% CI: 330–1375) per disability-adjusted life-years (DALYs) averted and the investigators conducted several sensitivity analyses around model inputs *(76)*. In Cambodia *(12)*, the use of CXR and Xpert was found to be *cost effective*. Similarly, in Pakistan, where patients were paid for the visits and health workers were given incentives in the ACF group, and media activities were done, ACF was found to be cost effective *(77)*. ACF leads to an increase in overall case notification, as seen in some of the studies published from Cambodia *(12)*, the People's Republic of China *(68)*, India *(44,50,63)* and Myanmar *(51)*. Another study from the People's Republic of China *(57)* showed a significant decline in case notification in five years after three rounds of ACF in comparison with the PCF districts. Modelling studies have also been conducted to demonstrate cost-effectiveness as detailed in Chapter 4, Section D

C.   Treatment outcomes of patients identified by ACF

The treatment outcomes of patients found by ACF in comparison to the general programme deserve a mention. Since the patients identified by ACF could be asymptomatic or minimally symptomatic, there has been concern in some quarters that these patients will either not start treatment or will interrupt it. Eight studies published in the past five years were reviewed for treatment outcomes; four from South-East Asia *(51,78–80)*, three from other Asian countries *(45,60,80)* and one from Peru *(71)*. Each study was from a diverse setting, involving different population groups. However, the main points are as follows:

Initial loss to follow up: in the studies where this was given, it ranged from 3% in a large Indian study of 5 million households *(44,78)* to 25% in a district with large proportion of migrants *(81)*. It was 4% in Myanmar *(51)*, 3% in Cambodia *(60)* and 17% in Philippines *(45)*. It was nil in the study of contacts of TB cases in Peru *(71)*.

Treatment outcomes of those started on treatment: the treatment success rate in patients diagnosed by ACF ranged from 67% in Haridwar district, India *(81)* to 95% in Cambodia *(80)*. Peru had a treatment success rate of 73% in both ACF and PCF patients *(71)*. All the

other studies had a treatment success rate of 85% or higher in ACF or at least the same as in PCF groups. In Haridwar district, the proportion of unsuccessful treatment outcomes was 33% (n = 18) among ACF patients compared to 14% (n = 25) among PCF patients (adjusted relative risk: 2.6, 95% CI: 1.7–4.0). The patients detected by ACF were older, had a lower proportion of retreatment and EPTB. In the large Axshya study also, patients found by ACF were older but the analysis was done after adjusting for age, sex and distance of residence from the microscopy centre, and it was seen that ACF-diagnosed people had a 17% lower chance of unfavourable outcomes at the end of treatment compared to those diagnosed by PCF. Although this was not statistically significant, it was a big difference *(78)*. In one of the two studies from Myanmar, 5% of the patients did not have a report on treatment outcome *(79)*. The treatment success rate was high in the two Cambodian studies of patients aged 55 years or more *(60)(80)*. In one study, the *health facility was given US$ 2 per patient* as support for treatment initiation and follow up *(80)*.

The Philippine study *(45)* had a very high proportion of bacteriologically positive cases (97%) and was considered as one of the factors for patients to have had high adherence to treatment. However, there was a high rate of initial loss to follow up of 17%. In this study, although the treatment success rate for all populations was high – 89.5% in rifampicin-susceptible patients and 83.3% in rifampicin-resistant patients – a relatively higher loss to follow-up rate was observed in the Indigenous population (7.5%) and the rural poor (6.4%).

Based on the few studies available for understanding treatment outcomes in patients diagnosed by ACF, it is seen that treatment outcomes are not compromised by ACF. This is consistent with findings of a review study *(78)*.

D. Implementation lessons

Some implementation lessons and challenges common to all population groups in the ACF studies of this review are given below.

1. *Process for identification of vulnerable populations.* The vulnerability of some groups to TB is universal knowledge, for example, prisoners, PLHIV and household contacts. Others need to be identified. Some examples are given below.

   (a) In the Axshya study spanning several states and districts in India, the populations living far from public health facilities were operationally defined as "marginalized and vulnerable", and were identified by a population-mapping exercise with the help of multiple stakeholders such as programme managers, community representatives and NGOs *(44)*.

   (b) In Myanmar, a similar criterion of limited access to health-care services was used but, in addition, the findings of a nationwide TB prevalence survey (2009 and 2010) were also included. Prevalence was known to be more in urban than rural areas, in states than regions, in certain ethnic minority groups than the general population *(51)*.

(c) Similarly, a prevalence survey in Cambodia helped identify those above the age of 55 years as a vulnerable group (prevalence of 2400 cases per 100 000) *(80)*.

(d) Vulnerable populations can also be identified from Census data as in a study from south India where two districts were chosen for ACF because of a higher proportion of people from disadvantaged castes and tribes *(50)*.

(e) Prior studies can help in the identification of groups with a high TB prevalence. This was used as guidance for implementing ACF in Tibetans *(38)* and tribals *(53)*.

(f) Characteristics of patients – India's large ACF study also identified the characteristics of patients found by ACF as distinct from patients found by PCF. These were: likely to be more than 65 years age, no formal education, lower monthly income, living in rural areas and more than 15 km from health facilities. Advanced age, rural area and distance are the criteria used in other countries *(51,56,80)*.

(g) Spatial targeting – this concentrates screening within geographical "hotspots" of TB incidence that arise as a result of several different mechanisms. It uses Geographic Information System (GIS) and mobile communications technology in combination with certain factors such as size of the area (concentric circles around the index case), incubation time after notification to propose a neighbourhood contact-screening strategy. Thus, it helps in targeting the population to be screened around the index case such that there is a reasonable yield of cases *(82)*. Modelling of transmission dynamics can help with estimation of the direct impact of spatial targeting on those screened as well as the indirect impact on transmission *(49)*. There are instances in which a few hotspots have been identified, which contribute to most of the transmission in the city, and focus case-finding in those areas. Though advantageous, spatial targeting can be effective only if there is a high-quality TB surveillance system or periodic surveys to identify true spatial clusters of TB. The MATCH (Mapping and Analysis for Tailored Disease Control and Health System Strengthening) approach can be used to target interventions using existing data, and to use mapping and spatial analysis techniques to inform decision-making *(83)*.

2. *Example of community-level screening* (symptoms and referral for sputum microscopy) by NTP staff in a district with vulnerable populations in India *(46)*

The NTP staff was supported by community volunteers (CVs). Based on screening for one of four symptoms, 1.1% of the population was diagnosed as presumptive TB cases. Of these, only 85% went for sputum examination to the health facility. Of the 29 found to be sputum-positive, 20 (69%) started treatment.

**Insights on ACF from focus group discussions with patients
and health-care workers**

One study *(46)* included focus group discussions with patients and health workers, which provided insights for implementation from the patients' and the health workers' perspectives. For patients, stigma, lack of support from family members, fear of loss of livelihood, transportation costs, preference for private health care and overcrowded public hospitals were important. For health workers, a target-oriented approach, insufficient incentive, inappropriate timing of ACF, perceived disrespect, poor counselling, lack of cooperation between the TB and general health staff, shortage of staff and long turnaround time of Xpert were important.

Some suggestions to improve ACF activities from the health workers' and patients' perspectives were as follows:

1. having a mobile van with CXR and Xpert;

2. providing financial support to patients for transportation for CXR, sputum microscopy and Xpert;

3. issuing identity cards to workers involved with ACF so that their activities are considered authentic by the people they visit;

4. providing monetary incentives and face masks for workers visiting the houses;

5. training workers in counselling on sputum production and in sputum collection;

6. involving local community leaders.

3. *Example of ACF implemented by community volunteers and NGOs for community-level screening*

This is a common model found in this review.

(a) In Kolkata, India, part-time paid and trained CVs were used from the local community for ACF in urban slums for house-to-house screening. This was not welcomed by the community because of stigma and lack of understanding of the purpose of the activity. A third of the presumptive TB cases asked to go to the health facility for testing did not do so *(49)*.

(b) CVs and NGOs implemented the ACF intervention in the large Axshya project of 5 million households in India *(44)*. The CVs visited 1000 households in a month, line-listed those identified by screening and referred them for sputum microscopy. For those unable to go, the CVs did sputum collection

and transportation. They were supervised by the NGOs, by district and state supervisor. Almost 40% of the patients needed sputum collection and transportation. Yet, altogether only 54% of the presumptive TB cases underwent sputum examination. This compromised the potential yield of TB cases. Almost all those diagnosed were started on treatment. The lessons from this large study were that support for sputum collection and transportation is an important component of implementation of ACF *(44)*.

(c) In Myanmar *(84)*, as in Axshya project, NGOs engaged local CVs after training. Presumptive TB patients were identified and referred to the local TB centres. However, in the 84 townships where ACF activities were carried out over 4 years, the proportion of presumptive TB and total cases contributed by ACF was seen to decline from 6% to 4%. Possible reasons for the decline in case-finding were lack of payment to the volunteers, high turnover of volunteers, lack of compensation to the volunteers for sputum transportation and to presumptive TB cases to go for sputum examination. A need for closer supervision was felt. Also, the number of presumptive TB cases was not entered in the reporting system, which might have resulted in errors. Thus, monitoring of ACF activities is important.

(d) CVs implemented ACF in Indonesia *(14)*. Although all those identified as presumptive TB cases went for sputum examination, no TB cases were identified and only 1%, less than expected, of those screened were found to have chronic cough. One of the reasons considered was lack of a good sputum sample despite training *(14)*. Supervision was considered important for ACF activities.

(e) In a rural tribal population in India *(85)*, CVs did house-to-house visits and ACF activities were low cost and highly cost effective. An important lesson was that this arrangement still resulted in higher laboratory workload and resource commitment from the NTP.

4. *Examples of ACF implemented with mobile vans as a one-stop shop by NTP staff*

(a) In rural Cambodia *(60)*, for screening the elderly, a mobile van with CXR and a nurse and doctor were stationed at a selected site. The nurse conducted an interview and did a CXR. The physician read the CXR and made the decision to treat. Xpert testing was done on-site initially but later shifted to a provincial laboratory. Free transportation to this screening site was provided to the participants. A week before this planned mobile site, awareness sessions were organized in the villages for the public and community leaders, and house-to-house information provided. Patients were referred for treatment. On average, 100 persons could be screened daily this way and the patient spent less than 45 min *(60)*. This is, however, a feasible yet **resource-intensive** method: up to 19 persons as well as equipment (CXR, Xpert) are required.

Free transportation for participants, training of staff, external quality control of processes, daily sample transportation and extended laboratory operating hours to receive specimens have to be arranged.

(b) The Philippines study also used mobile vans except that Xpert testing was on-site *(45)*. In an Indian study, this arrangement helped in overcoming the challenges of referrals for sputum microscopy or CXR *(63)*.

(c) In Myanmar, mobile vans with a portable digital X-ray and sputum microscopy were used regularly *(51)*. With eight staff, including a nurse, laboratory technician and X-ray technicians (no doctor), the mobile van went to different settings where community awareness had been conducted 2–4 weeks earlier and the local staff had identified presumptive TB patients. The difference in this model was that the local TB coordinator was present at the site and started TB treatment on site with referral to the local TB unit for follow up. For Xpert testing, patients were referred to the local TB unit. Although almost all (97%) the presumptive TB cases came to the mobile van for CXR, of those with abnormality, only about half (51%) went for testing by sputum microscopy, which was done in the health facility. *Referrals for diagnosis gave a high drop-out rate.* However, on an average, ACF contributed 25% of additional cases in the respective townships. The treatment success rate for new smear-positive cases was 93%.

5. *Example of ACF by private–public partnership (with a mobile van).* A corporate hospital pooled resources from other industries and provided ACF services in coordination with the state and district TB programmes/government. This initiative provided staff and a mobile van fitted with an X-ray machine, microscope and Xpert. The initiative was scaled up to cover 16 districts and contributed 12% of additional cases *(63)*.

6. *Monitoring and evaluation (M&E) and use of technology.* ACF requires multiple repetitive processes such as enumeration of houses, line-listing of people screened and referred for testing, linking their test reports to those of the contact, coordination for initiation of treatment, and M&E of ongoing ACF activities. Coordination is needed between patients and services as well as among various agencies involved in these processes. This can be facilitated by the use of hand-held data recording devices that have a decision-support system, m-health services for coordination with beneficiaries, and electronic systems (for example, mobile-based EpiCollect) *(43,85)*. Many ACF studies reviewed for this paper used retrospective programme data for monitoring or reporting results. For ongoing monitoring and operational research for ACF activities, it is important to use current data supported by electronic systems. Qualitative studies should also be part of the operational research.

7. *ACF activities can be implemented in coordination with other health programmes*

   (a) In China, screening for TB among the elderly has been coordinated with the programme for an annual physical check-up for the elderly *(56)*.

   (b) HIV testing centres have been used to conduct ACF for TB in Haiti *(87)*.

   (c) India's national noncommunicable disease (NCD) programme has house-to-house visits for hypertension and diabetes screening, which can be combined with symptom screening for TB, thereby saving costs and staff time.

8. *Media activities prior to ACF*

   (a) Community mobilization and community-based screening could be key to increasing the uptake of ACF *(62)*. Awareness generation about a week before implementing the ACF intervention was found to be effective *(7,25,38,42,43,46,51,54,64,88)*. Mostly, these consisted of information to the community about the activities but specific information about TB was also given in some instances, which helped in overcoming stigma and increased participation. The type of media campaign did not have much influence *(61)*. Importantly, despite media activities, ACF continued to be cost effective *(77)*.

   (b) In a large study that covered over 400 000 households of vulnerable populations in 15 districts in the Indian state of Jharkhand, media activities were conducted in the form of public announcements and wall paintings, and stalls in the markets on fixed days. Additionally, house-to-house visits for identifying presumptive cases also included TB information. These communication activities combined with sputum collection and transportation by CVs who were paid and supervised, resulted in an increase in case notification in the intervention areas in comparison to the baseline as well as to the non-intervention areas in the short term, similar to what was also seen in the Cochrane review of 2017 *(54)*.

   (c) A Cochrane review from several countries, including one from Pakistan, compared the effect of health promotion activities with no intervention on increased attendance for TB screening. The data suggested a temporal association between the intervention period and an increase in the number of smears and people tested. However, the corresponding increase in the number of TB case notifications was not convincing *(89)*.

Summary of challenges to ACF implementation

From the review of studies, it is understood that ACF implementation poses multiple challenges:

(a) Participation of the people was unsatisfactory because of an indifferent attitude of the community due to stigma and lack of awareness about TB.

(b) Assessment of symptoms is compromised due to the lack of a standard questionnaire or inadequately trained staff.

(c) Coordination for transfer of samples and receiving test results is a challenge.

(d) Drop-outs during referrals for testing was seen in many studies (Axshya, urban slums of Kolkata and Agra, and tribal populations of India *(53)*, including in populations that had challenges with access to health services to begin with). In Agra, India, only 40% of the patients reached the health facility on their own for investigations, while 60% had to be supported by CVs *(48)*. In the multistate large Indian study, Axshya, only 22% of the referred presumptive TB cases reached the microscopy centre *(44)*.

(e) In the algorithm based on sputum microscopy, the yield could be lower if the technique and skills in getting a good sample are compromised, as well as preparation and reading of the smear. Quality assurance is therefore important.

(f) The site for the mobile van/ACF camp should be well selected and prepared.

(g) The community should be prepared.

(h) Training and regular supervisory support should be provided to health-care workers/volunteers.

(i) Diversion of workers from PCF to ACF will decrease the overall impact of ACF.

(j) Counselling should be done for those found to have TB and for initiation on treatment.

(k) If the treatment outcome of patients found by ACF is poorer, it decreases the cost–effectiveness of ACF.

Good practices from the review for optimizing implementation of ACF

(a) Some methods used to increase community participation are use of the media a week before the ACF intervention. This has been tried in many studies *(61,63)*, a innovations such as seed and recruit method in Cambodia (90,91), house-to-house screening by volunteers instead of invitation to the people, and in-kind incentives in Indonesia *(14)*.

(b) Adequate training of volunteers to ask for symptoms, asking of symptoms from each household member instead of the head of the household, incentives to the volunteers all play a role in the quality of screening *(48)*.

(c) Drop-outs to testing can be prevented with sputum collection and transportation instead of referral to the laboratory *(44,53)*, if testing is available on-site (X-ray camps by the public–private partnership (PPP) model for ACF in the general population) *(63,64)*, if CVs accompany the patients (slums) *(48)*, if patients are compensated for their travel costs, as in Pakistan *(43)*.

(d) Drop-outs to treatment can be prevented if CVs have the added responsibility of initiating patients on treatment *(53)*, or by the use of mobile health technology to coordinate between ACF and PCF and smoothly transition the patients from ACF to programme care *(92,93)*.

(e) Diagnosis by SM requires quality assurance. For processing a high volume of X-rays, software of different kinds has been used in the field *(24)*.

(f) Use of volunteers *(44,48)*, engagement of NGOs (53) and the private sector through PPM *(63–65)* can prevent diversion of workers from the regular programme. Though it overburdens laboratories, it still needs to be considered in some cases.

(g) A digital system should be used for recording patient data and for coordination between screening, diagnosis and treatment initiation.

(h) Activities can be optimized by combining house-to-house or clinic activities with other health programmes.

E.   Costs of ACF

Most of the studies have considered costing incremental to the national programme. For TB REACH projects, a standardized tool is being developed to compare ACF interventions across different countries *(94,95)*. A review of studies from different population groups showed the following:

1. X-ray and Xpert are expensive *(56,92,96,97)*. If analysis is done along four sets of activities – pre-implementation, screening, diagnosis and treatment – then in countries that employed X-ray and/or Xpert for diagnosis, the diagnostic activities cost 50% of the total costs.

   (a) Costs were 59% in Tajikistan where CXR and Xpert were done for all, and 45% in Cambodia where Xpert was done only if the CXR showed an abnormality. In China, where CXR was used for screening of the elderly, 62% of the project costs were due to X-ray. Similarly, in the Viet Nam ACF2, major costs were due to diagnostics.

   (b) Xpert can result in about a third of the costs *(92)*; in the Tajikistan programme, the recurrent cost was mainly the Xpert cartridge, priced at about US$ 10 (34%). It was the most significant cost driver.

2. Pooling of sputum – one of the strategies for reducing costs is pooling of sputum for ultra assay after CXR. As per the results of a publication referenced here, this resulted in a decrease in costs and time by at least 26% and could potentially be 35% *(92)*. The recommendation is to pool the samples of those with a normal CXR while individually testing those with an abnormal CXR. However, the challenges would include storing of sputum, ensuring correct recording and avoiding contamination. There is also a potential for increased cost of human resources because of repeat procedures for sputum testing.

3. Mobile vans and portable X-rays *(43,51,64)*. Three studies that used mobile vans with portable X-rays successfully provided costs. Costs are from the India study from 2016 (US$ 1 was INR 64), the one-time cost of a van including fabrication was approximately US$ 36 000 and for the equipment (portable X-ray machine and a digital reader and printing of the X-ray) approximately US$ 10 000. The usual operating costs in such vans are expected to be annual maintenance of the equipment, insurance of the van (about US$ 390 per year) and fuel. In Nepal, the cost of covering 10 districts with mobile clinics was US$ 225 000 and an NGO was engaged *(42)*.

4. Payment to personnel and travel costs are big components *(14,92,94,95)*

   (a) In ACF interventions that use screening by symptoms and diagnosis by sputum microscopy in a government laboratory, stipends to staff and their travel costs comprise the majority of the expenditure *(14,92,94)*.

   (b) In ACF interventions that use Xpert and CXR, payments to personnel are the second-highest costs.

   (c) Some studies paid a regular stipend combined with an "incentive" or by the number of tasks completed and travel costs *(14,94)*. The costs of supervisors and training were additional. Regular salaries were also given *(64)*.

5. A time motion study in India was helpful in understanding costs *(94)*.

   (a) One staff spent 50% of time in travelling to communities with an average of 22 TB patients (95% CI: 19.14–24.94) seen per day per person. The other major time-consuming activities were administrative work (12%) and laboratory-based work (9%).

   (b) The cost of travel of HCWs was about half a dollar a visit. This means US$ 0.50/person screened and US$ 20.82/person completing TB treatment. Based on the average cost to the programme, this means US$ 35 to support a patient with 45 visits to complete treatment.

   (c) On an average, one staff can do 22 (19–25) patient visits per day *(94)*. A well-trained team of six, as in surveys, can screen 250 individuals a day *(8)*. The time motion study noted the time taken as 5 minutes for initial and follow-up visits for screening *(94)*.

6. Indirect implications on the staffing of the national TB programme. With specimen transportation from the field to the programme laboratories for sputum examination, ACF resulted in an increased workload on the laboratories – an average of a 20% increase with some experiencing up to 40% increase. This has largely been not welcomed by programme staff.

4
Discussion

To begin with, expert opinions on the choice of algorithms are discussed followed by results from population groups and implementation of ACF.

A.   Choice of algorithms

An important parameter for comparing algorithms is the yield of an algorithm, which is the total number of TB cases detected. The yield of a prevalence survey is considered as a gold standard. In a prevalence survey, screening is usually by symptoms and CXR, and diagnosis by sputum culture. A positive predictive value (PPV) of 90% for an algorithm implies that false positives are no more than 10%. This level is considered as an acceptable level of accuracy *(8,9)*. PPV varies with the prevalence of TB in the group in which ACF is being implemented.

General guidance of experts (8,9) for screening by symptoms and diagnosis by smear microscopy

1.   If the TB prevalence is at least 1.5% (in population groups such as prisoners, miners, etc.), a PPV of 90% can be achieved by screening those with cough for 2 weeks or more and diagnosis by sputum microscopy. The yield will be 26% of that seen in a prevalence survey.

2.   For the same population group as above, if instead of cough for 2 weeks, screening is done by any one of four symptoms (cough for 2 weeks, fever for 2 weeks, haemoptysis in the past 6 months, chest pain in the past 1 month), then the yield increases to 30.5%.

   WHO has recommended universal DST and Xpert for diagnosis. Indeed, recent prevalence surveys have used Xpert in place of culture. In line with this, a third recommendation on algorithms is as follows *(98)*:

3.   *An algorithm that has CXR screening (which has high sensitivity) followed by confirmatory testing with Xpert (to increase the specificity) can achieve the lowest NNS and highest PPV, and the validity is least amendable to setting-specific variation.* However, resource requirements for tests and equipment may be prohibitive in some settings and a reason to opt for symptom screening and sputum microscopy.

B.   Population groups

1. Household contacts

WHO endorses systematic screening of household contacts as they are at an increased risk of infection. A meta-analysis from 2013 showed that 3.1% of contacts in resource-

limited settings had co-prevalent TB *(99)*. The incidence is known to be the greatest in the first year after exposure. Other studies have shown that 63–95% of contacts develop TB within 2–5 years of contact, especially if they have untreated LTBI *(40,100)*.

Lessons on CXR- and Xpert-based algorithms from the Philippines study of multiple population groups

In the Philippines study *(45)*, screening was done by symptoms and CXR, and diagnosis by Xpert.

- Among those screened, only 22% had cough for 2 weeks whereas 70% had one or more of the four symptoms. Thus, use of any symptom gives a higher yield of presumptive cases than cough for 2 weeks alone. However, cough for more than 2 weeks showed a significant association with TB diagnosis in all target populations after adjustment (any symptom showed a significant association only in prison).

- The largest proportion of people with presumptive TB was found in prisoners (39.0%), followed by the urban poor (22.5%), the rural poor (16.1%), Indigenous population (15.1%) and those in high school (3.1%). Indigenous populations had a large proportion of symptoms (both cough for 2 weeks and any one of four symptoms) while prisoners had a large proportion (39%) of CXR abnormalities.

- For diagnosis, smear positivity was the highest in the urban poor while Xpert positivity was the highest in Indigenous populations.

- Diagnosis by Xpert: among the four populations, the proportion of smear-negative (Xpert-positive) patients was small in the urban poor (4.0%) but constituted a substantial proportion in the rural poor (61.8%), prison (40.1%) and Indigenous populations (67.9%).

- The Philippines study concluded that the combined use of CXR and Xpert contributed the most to increased case detection. It increased the yield by 39% in Indigenous populations and 23% in the rural poor as they were smear negative and did not have cough for 2 weeks or more. This might be because of fewer symptoms or a milder form of the disease.

Lessons from Cambodia

In Cambodia *(60)*, screening was done with symptoms and CXR, and diagnosis by Xpert. Fifty-five per cent were positive by symptoms alone, 29% by CXR alone and 17% had both symptoms and CXR criteria. Among the Xpert-positive patients, only 32% had cough for 2 weeks or more *while 40% were asymptomatic and identified because of an abnormal CXR.* Thus, use of Xpert for diagnosis was considered important for increasing the yield.

Household intervention is considered important to break the chain of onward transmission by identifying contacts with LTBI and giving preventive treatment, and by identifying TB disease and giving appropriate treatment. In 2018, only 27% of the eligible household contacts received TPT *(3)*. With country commitments made at the UN High-Level Meeting on TB (UNHLM-TB) in September 2018 to cover 4 million children under the age of 5 years and 20 million other household contacts of TB patients, this group is of high importance.

In this review, the community trials in the Republic of Korea, Viet Nam and Cambodia, and Indian studies have shown an increase in additional cases in the district programme with household contact screening. The issue is whether ACF should be considered for household contacts over and above household intervention in the routine programme. ACT2, implemented by national TB programme staff, shows that ACF districts had a higher notification rate than control districts. Thus, it seems prudent to consider household contact screening as one of the ACF strategies, in addition to the routine screening envisaged in the programme.

Since all three community trials considered contacts over two years, it would be appropriate to consider ACF among households of all patients registered in the past two years, i.e. every alternate year. This would enable national programmes to target other high-risk groups in the intervening years, if required.

Algorithm for ACF in household contacts. Based on the NIRT study in Chennai *(16)*, which showed that CXR for screening had high sensitivity (96%) and specificity (91%), it can be recommended as the screening tool for household contacts. For diagnosis, Cambodia used Xpert, which has a better yield than sputum microscopy. Nepal used cough for 2 weeks followed by sputum microscopy and, if negative, Xpert (refer Table 8 in Annexure). Thus, depending on the available resources, the options are to use symptoms alone or symptoms and CXR for screening. If CXR is not an option, then for higher sensitivity, any of the four symptoms can be used instead of cough for 2 weeks. That would increase the number of samples for Xpert but can compensate to some extent for the lack of CXR.

In programme conditions, implementation arrangements for household contact-tracing have been seen to have challenges of drop-outs and linkage to treatment. These would need to be addressed during the planning stage.

Further research evidence is needed on inclusion of children in ACF among household contacts, as the current evidence is insufficient and contradictory. The prospective study from the Republic of Korea found age more than 65 years to be a risk factor and had a low yield among children. This was also seen in the Indian study by NIRT *(16)* whereas in Nepal *(42)*, household contact-tracing for children was found to be useful. Community-based trials (Cambodia *(12)* and Viet Nam *(11)*) did not include children.

2. Prisoners

WHO estimates the TB prevalence in prisons to be 10–100-fold higher than that in the general population *(101)*. A systematic review from 2013 estimated a median prevalence of active TB of 2712/100 000 (1763–4563/100 000) in low- and middle-income countries *(30)*. The median estimated fraction of TB in the general population attributable to exposure to TB in prisons is 8.5% *(102)*. Second, prisoners are a captive population that can be covered with minimal resources. Services for prisoners address the issues of equity and access. Third, as the Bangladesh study estimated, the rate of recent transmission in prisons was 9.6%, which declined significantly with regular screening *(28)*. Fourth, in SEA Region countries as in Bangladesh, prisons could have a higher prevalence of MDR-TB.

The prevalence of TB varies widely in prisons in the three SEA countries – Bangladesh, India and Thailand. However, as the Indian study shows, the results vary within the country too and are associated with the size of the prison and the available health services in the prison.

The studies in this review noted several challenges with ACF in prisons. However, there are many other similar challenges with getting permissions that are not covered here *(103)*. Prisoners should have regular screening for TB during their stay as well as at entry and exit. Screening at entry can be with CXR. Ideally, prison staff should also be included in the regular screening. A partnership with prison authorities should be part of the multisectoral accountability framework. The NTP should coordinate with prison authorities to ensure continuity of services for the prisoner-patients at the time of exit from prison. ACF for TB can be combined with that for HIV, where appropriate, to increase the cost–effectiveness as well as efficiency of implementation.

Algorithm for screening. Although a meta-analysis of prison studies recommends CXR for screening, the Philippines study concluded that prison inmates had a significant association with screening by "any symptom" and a large proportion of abnormal CXR results *(45)*. Thus, in resource-constrained settings, screening by one of the four symptoms can be a second option. Xpert can be considered as a first option for diagnosis as additional cases were diagnosed with Xpert in Ethiopia, Nepal (refer Table 8 in annexure) and Bangladesh, as it identifies rifampicin-resistant TB (RR-TB).

3.   People with diabetes

In 2015, an estimated 1 million people globally had TB–diabetes mellitus comorbidity, comparable to nearly 1.2 million patients with TB–HIV coinfection. Available evidence from China, Bangladesh, the Republic of Korea, Nepal and Pakistan shows a TB prevalence that is 1.8–9.5 times higher in those with diabetes than in the general population *(104)*. Diabetes mellitus is also associated with delayed sputum conversion, treatment failure, relapse and death, and is considered a risk factor for MDR-TB *(105)*.

In this review, there is wide variation in prevalence in the studies from Nepal and Pakistan (0.2% and 10%, respectively) *(31,33)*. The extent of regular screening in both the population groups is not known. Older studies from India showed that patients with diabetes had a large proportion of known TB cases and the yield of additional cases (screening by symptoms at each visit followed by testing) was very poor (NNS=812) *(106,107)*.

The 2018 guidelines from the Union recommend symptom screening be done at the initial visit for newly diagnosed diabetes patients and diagnosis by Xpert to detect RR-TB. X-ray-aided diagnosis played a part in the algorithm for screening patients with diabetes in Pakistan *(31)*. Hence, screening by CXR could be recommended. Diagnosis should be done by Xpert and CXR used for clinical diagnosis. Appropriate investigations should be considered for EPTB.

4. Homeless persons

Rationale for considering homeless persons. Most countries in SEA are experiencing urbanization. Large cities have a high proportion of homeless populations. For instance, according to India's 2011 Census, five metros – Mumbai, Kolkata, Bangalore, Delhi and Chennai – contribute to 26% of the country's homeless population. By some estimates, there are approximately 1.8 million homeless persons in India and approximately 3 million in Indonesia *(108)*. Normally, these are "hard-to-reach" populations for the programme. In many industrialized countries, TB rates among the homeless were up to 20 times higher than the general population *(109)*.

In one study included in this review, the proportion of TB patients was found to be 1661/100 000, which is much higher than in the general population *(34)*. This is in line with the observations in developed countries. However, as seen elsewhere, treatment completion rates are poor in this group, further challenging ACF efforts. This group can be considered for ACF but appropriate planning and resource analysis are needed, given the size of this group and the fact that treatment follow up may be difficult. Considering the mobility of the group, screening and diagnosis should be done at one time. CXR with Xpert in a mobile van would thus be appropriate, as was done in the study. Participation by NGOs and food incentives would be important to help with completion of treatment.

5. Migrants

Rationale for considering migrants. With urbanization, many countries have a significant proportion of their population as internal migrants. For instance, in India, this population is estimated to be about 30%. This mobile population is considered as "hard-to-reach" by local programmes.

Brick kiln workers are "seasonal migrants", working for 3–8 months every year. Smoke, heat and dust from brick kilns are one of the major causes of respiratory illness and symptoms.

Though all workers are exposed to dust and smoke, moulders are more likely to be directly exposed to dust while bakers have more proximal exposure to smoke.

Occupational risks should be considered among migrants and they should be considered for ACF. If the prevalence of symptoms is high, as in the case of brick kiln workers, screening can be done by any one of the four symptoms. Diagnosis can be done by Xpert or sputum microscopy. Participation by NGOs becomes important as the kilns are located far from the nearest village and health facilities. NGOs could also help in linking migrants with treatment facilities at the closest destination.

International migrants and refugees face similar challenges. They are underreported due to gaps in surveillance, treatment and resources *(110,111)*. NTPs will not only have to give them attention but also engage in cross-border collaboration.

6.   Congregate settings

Rationale for considering congregate settings. Some populations that are in congregate settings other than prisons are likely to be infected with TB and have the predisposition to develop active disease. This has been seen in the Republic of Korea as well as Tibetan children in India *(38–40)*. Congregate settings are small groups but because of the high transmission in these conditions, screening can be highly effective. However, the choice of population should be guided by evidence. For instance, all schoolchildren should not be considered as being in a congregate setting and targeted for ACF as prevalence can be very low – 0.2% (NNS=495). Religion-affiliated boarding schools, orphanages, different welfare homes that have occupants from the low-income group can have the situation seen in the studies and should be carefully selected for screening. Selection can be guided by small studies before adoption of these populations for regular ACF activities.

Screening can be done by symptoms and CXR at entry. Regular screening can be done by symptoms. In case of children, TST/interferon gamma release assay (IGRA) can be used. Diagnosis can be done by Xpert as in the Tibetan study or smear microscopy as in the Korean study. Xpert helps in finding additional cases and RR-TB cases. ACF activity should not just be only for all boarders, but also include workers and caretakers. Multisectoral partnerships with advocacy will be important for including ACF activities on a regular basis.

7.   Children

Rationale for considering children. Globally, less than 10% of notified cases are children. Three studies *(41–43)* show a big gap in the identification of children in health facilities and describe different approaches to case-finding. ACF interventions in children can increase case notification and, conversely, investigating for TB in children can lead to the detection of infectious adult patients, called source case investigation.

Further evidence is needed for ACF among children in households, as discussed above. Multiple strategies, including health facility settings as well as community settings, should be considered. Involvement of NGOs and use of mobile vans can be considered, as in Nepal *(42)*. Importantly, participation of trained medical staff or paediatricians will be required for this group for diagnosis as well as treatment.

Algorithms in children. National guidelines should be followed and, ideally, diagnosis should be done with CXR and Xpert. Studies such as the one of Tibetan schoolchildren in the congregate setting demonstrated the usefulness of TST and CXR *(38)*. However, as seen in Nepal, screening by symptoms and TST, and diagnosis by CXR and sputum microscopy can also increase the yield.

8. Vulnerable and marginalized populations (those in urban slums and hard-to-reach areas, and tribals)

Rationale for considering vulnerable populations. Various prevalence surveys have shown that urban slums have a higher prevalence of TB than rural areas. Findings of a meta-analysis indicate that the odds of developing TB are almost five times higher in urban slums *(112)*. Tribal or Indigenous populations are also included in this group as they live in hard-to-reach areas with challenges of access to health services.

The comparison across studies in this group is hard because of the heterogeneity of the group, with urban slum populations, tribals, the rural poor all considered together. The biggest study is Axshya, India, which covered 20 million people in 4.9 million households of urban slums, prisoners, tribal and other vulnerable populations *(44)*. Three other studies covered multiple populations though none of them were as big as Axshya *(33,45,46)*.

Axshya and other studies led to an increase in case notification. However, *the NNS was high (i.e. many people needed to be screened in order to diagnose one TB case), except when the population had a high HIV prevalence or in select population groups.*

The total contribution of cases and its impact on national case notification will depend on the size of these population groups and extent of their coverage with ACF. For high population coverage, it is important that ACF strategies are cost effective. In a high-prevalence group, screening can be done by 2 weeks of cough and, if costs permit, digital mobile CXR with or without the software can be added (Philippines) *(45)*. Diagnosis should preferably be done by Xpert but if resources do not permit, consider sputum microscopy. Two weeks of cough and sputum microscopys seem to be a reasonable strategy for urban slums (Philippines) as well as for rural remote populations (Papua New Guinea) *(55)*. Screening with symptoms and CXR, and diagnosis by Xpert gives the best results.

Sputum collection and transportation is a better option than referring patients to the health facility for testing but covering large sections of the population will need careful planning and management. Training of personnel, preparation of communities and other

arrangements for optimum community participation and to contain drop-outs from the study can be a massive operation.

9.   General population

Rationale for considering the general population. WHO gives a conditional recommendation for communitywide screening for active TB only in geographically defined subpopulations with high levels of undetected TB (prevalence of 1% or more). Thus, select groups of the general population tend to overlap with vulnerable populations (limited access). Heterogeneous population groups have been included in this review. Cambodia and China targeted the elderly population but had different results *(56,60)*. In India, ACF was done in the rural population in one state and it was evident that a significant contribution was made to smear-negative case notification because access to X-ray was poor *(63)*. This study is also one of the two examples of an ACF intervention by the private sector, the other being from Pakistan *(77)*.

As for vulnerable populations, a high NNS was seen in the studies considered in the general population. Not all ACF will identify large numbers of people with TB and there was considerable heterogeneity in the results, which underlines the importance of selecting the population to be screened and choice of screening algorithms. ACF in the general population requires careful consideration of costs and efforts against the expected yield. Certain groups such as pregnant women should not be included, as was clear from the two studies in this review *(58,66)*. However, this can be contextualized as per expert opinion and country needs. The factors to consider for ACF in the general population are the same as those mentioned for vulnerable populations.

C.   Factors that influence the guidance for planning or implementation of ACF

Factors that influence the guidance for ACF are (i) rigour of the study, (ii) selection of population groups, (iii) accuracy and yield of the algorithm, (iv) duration of ACF efforts, (v) implementation arrangements, and (vi) costs.

(i)   **Rigour of the study**. Community-based randomized controlled trials offer robust evidence and few such studies have been done in the world and none in the SEA Region. This review included studies from Viet Nam *(11)* and Cambodia *(12)* on household contacts and from Philippines *(45)* and China *(57)* on multiple population groups. This review also included large multiprovincial studies from the Axshya project *(44)* and multidistrict studies from India *(54,63)*. Studies from other SEA countries (Bangladesh, Indonesia, Myanmar, Nepal and Thailand) over the past five years have also been included. There is a predominance of Indian studies and many SEA countries such as Bhutan, Democratic People's Republic of Korea, Sri Lanka and Timor-Leste have no published studies in the past five years.

(ii) **Population groups**. ACF in household contacts seems to be the most promising in terms of proven increase in case-finding and consistent methodology through community trials. NTPs can consider screening those who have been household contacts of patients for the past two years in alternate years, with the added benefit of introducing TPT. The challenge of screening children during household ACF will remain.

While selection of other population groups such as children is important, multiple approaches to identification and targeting of groups will be required, which are specific to the country context. These are given in the Recommendations section.

The advice is to first begin with easily identifiable high-risk target groups, and then widen the scope as resources allow *(113)*. it is important to understand that the *size of the population group will also play an important role in determining if the ACF activities will impact the national case notification rate.* The groups with the highest risk for TB, if small in size, would yield a smaller number of absolute TB cases than ACF in a bigger-sized group with only a moderately elevated risk. The success of ACF activities also depends on the proportion of undiagnosed cases in the risk groups and the algorithm used for screening.

(iii) **Algorithms**. More experience is required under field conditions but based on the rigorously carried out studies in the Philippines *(45)*, Cambodia *(60)* and by NIRT, India *(16)*, screening by symptoms and CXR and diagnosis by Xpert can be considered as a first option. In high-prevalence and low-resource settings, screening by symptoms and diagnosis by sputum microscopy can still be considered as the yield of ACF is expected to be *additional* to that of the programme *(8)*.

(iv) **Duration of ACF efforts**. It is clear from the studies in Cambodia and China that ACF efforts have to be continued beyond two years *(12,57)*. There is some evidence from an old study in a European country that ACF efforts, when continued for four years alongside a well-functioning PCF programme, resulted in a huge decrease in prevalence (from 150 cases in 1960 to 91 in 1964) but the incidence of smear-positive TB stayed at 25 cases in the study population *(10)*.

(v) **Implementation arrangements for ACF**. *Implementation of ACF is as important as the choice of screening and diagnostic algorithm or perhaps even more.* A highly sensitive and specific algorithm will be compromised if there is a drop-out between the stages of screening and diagnosis (could be as high as 50% *(35,44))*; or between diagnosis and treatment *(63)*; or between treatment initiation and treatment completion. *An algorithm with 90% accuracy resulting in only 50% of patients initiated on treatment will be as good as an algorithm with half the yield but with all the patients started on treatment.*

(vi) **Costing of ACF**. Cost comparison across countries is difficult. For TB REACH projects, a standardized tool is being developed to compare ACF interventions across different countries. Some general principles can be learnt from this review.

Almost half the costs are due to diagnostics (CXR and Xpert). Costs associated with CXR can be decreased by using a digital reader and thus avoiding printing of films. A digital reader along with a portable X-ray machine and mobile van lead to high capital costs. Recurring costs are those of cartridges (about US$ 10 per cartridge), personnel and travel costs (travel stipend to the staff, fuel costs). The Cambodia study showed that even with the use of CXR and Xpert, ACF remains cost effective *(12)*. None of the studies in the review included the costs of added workload in the NTP laboratories, which would need to be offset with additional staff for a sustained programme.

D. Advantages of ACF and its cost–effectiveness

Community randomized trials from Brazil *(114)*, Zambia and South Africa *(115)* have shown that 3–5 years of ACF in household contacts helps to reduce disease in adults and infections in children. Targeted case-finding for TB and prompt initiation of treatment is recommended in low-incidence, high-resource settings but there is an argument for using the same epidemiological approach in high-incidence, low-resource settings *(7)*. This is because TB medications almost immediately render the patient non-infectious, thereby breaking the chain of transmission.

ACF leads to an increase in overall case notification, as seen in some of the studies reviewed in this paper from India *(44,50,63)*, Myanmar *(51)*, Cambodia *(12)* and China *(68)*. Based on modelling, it is predicted that an increase in case detection by 25% will lead to a reduction in incidence by 22–27% in 10 years; and even if the interventions cost US$ 2500 per case detected in India, and US$ 5000 per case detected in China and South Africa, they are still expected to be cost effective because the population-level benefits of ACF accumulate with time as additional cases are prevented *(116)*. By another model, if the level of case detection due to the intervention is sustained for 5 years, 24% of cases would be averted, and if the case detection is not sustained, then too, 13% of the cases would be averted. The reduction in mortality will be almost twofold *(117)*. A study from China *(57)* showed a significant decline in case notification in five years after three rounds of ACF in comparison to the PCF districts.

Modelling thus far has not considered preventive therapy in children and in adults. While the inclusion of preventive treatment will add to the cost but, with further decrease in transmission due to decreased progress from LTBI to active disease, the cost–effectiveness will improve.

E. Treatment outcomes

There have been concerns that motivation for and adherence to treatment could be low, as patients found by ACF have mild or no symptoms. In the studies included in the review, treatment outcomes have generally not been compromised. A review stated that

the effect of ACF on treatment outcomes needs to be further evaluated with a sufficiently powered study *(89)*. The district-level study from Haridwar, India showed low treatment outcomes *(81)*. The district also showed high initial loss to follow up, as did the study from the Philippines *(45)*. Important factors that determined low treatment success rate were elderly and Indigenous populations, the rural poor and patients with RR-TB (Haridwar and Philippines). Haridwar, a holy town, also had a large proportion of migrants. A decrease in successful treatment outcomes can compromise the effectiveness of ACF activities. It is, therefore, important for an ACF intervention to work with a high-quality surveillance system and monitor outcomes on an ongoing basis. Additionally, ACF should be viewed as a comprehensive package for the targeted group, with treatment support as an important component. Closer monitoring and supervision should be an integral part of the ACF package. Ongoing operational research on treatment outcome for ACF in different population groups and settings will be helpful. The high initial loss to follow up in Haridwar, India and Philippines was not explained but is likely due to migration in the former.

F.   Considerations for ACF

Although ACF is a recommended intervention, it is important that the following suggestions by different authors are considered *(8,9)*:

(i)   ACF should be implemented while achieving implementation efficiency of TB programmes, including optimal availability of CXR and Xpert in health facilities. In hard-to-reach populations such as slums, NTPs should ensure an outpost/CV or a local private provider for provision of regular services for sputum collection and transportation, and coordination for treatment with the local TB unit. Providing free diagnostic services in the private sector and ensuring widespread availability of Xpert will also help in increasing case-finding *(9)*.

(ii)   ACF should not be conducted at the expense of the TB programme. Staff and diagnostic resources for ACF should be additional to those already in place for PCF. In other words, patients found by ACF should be additional to those found by PCF. Diversion of resources or loss of implementation efficiency of TB programmes in health facilities implies a potential loss of that additional case-finding *(9)*.

(iii)   ACF should be conducted in the context of a good TB control programme to ensure that patients found with the intervention are linked to effective treatment.

(iv)   Coordination of ACF and prevention activities should be considered.

(v)   ACF should not result in harm to the patients (for example, by a false diagnosis of TB and unnecessary treatment) *(8,9)*.

5
Monitoring of ACF activities

This section is based on a review of studies included in this paper and a review article by Ho et al. *(113).*

Monitoring ongoing ACF activities

1. Monitor the NNS for each group of the population where ACF is carried out.

2. Compare the NNS with the costs of covering the population group.

3. Monitor the effectiveness of ACF – drop-outs between screening and diagnosis, drop-outs between diagnosis and treatment (initial loss to follow up or treatment initiation rates), loss to follow up from treatment.

4. Monitor whether there was an additional increase in notification of bacteriologically positive or all forms of cases when ACF activities were carried out compared to the previous year (or in comparison to a control district). (This is different from measuring the direct yield of ACF.)

Medium-term measures (1–2 years or over 1–2 rounds)

5. Treatment outcomes in ACF cases versus PCF cases

6. Reduced time to initiation of treatment in ACF cases versus PCF cases (operational research)

7. Notification trend over the next 3–5 years. The initial measure will be an increase in case-finding/notification as compared to the trend in the past in the intervention area and in comparison to a control district. This will mostly be seen as a result of finding more prevalent cases. As this goes down after 1–2 rounds of ACF in the group, notification will be expected to decrease *(10).* This is also considered as a long-term indicator as it is dependent on the local epidemiology and ACF efforts.

Long-term measures (over 3–5 years)

8. Reduced morbidity and mortality as the disease is identified earlier

9. Reduced transmission in the community as evidenced by a decreased prevalence of TB infection in children

10. Reduced prevalence of TB disease in the community. Should also incorporate population-level effects and cost–effectiveness estimates using a long-term time frame.

11. The number of operational research or small pilot studies carried out in the country should be based on earlier ACF experience. As transmission decreases in the community, the NNS will increase and a modification in strategy might be needed to decrease costs and remain cost effective. At the very least, one needs to review the ACF data (yield, treatment outcomes, etc.) and costs to focus on the End-TB target.

6
Recommendations for implementing ACF

It is important to note that the ***impact of ACF interventions will depend on the scale, frequency and choice of population groups***. ACF interventions have to be implemented repeatedly and thus should:

1. include a reasonably accurate algorithm,

2. select appropriate population groups, and

3. be cost effective to remain sustainable over repeated rounds.

Cost will be the defining consideration but ACF is a cost-effective strategy *(97)*.

1. Increase the efficiency of the process

    (a) Prefer on-site availability of diagnostic and treatment initiation services during ACF activities over referral to a health centre to minimize loss to follow up during referral. In case this cannot be arranged, there is a need to ensure that the referral is supported financially and/or someone accompanies the person to guide and ensure quick attention at the health facility.

    (b) Monitor ACF activities using digital and virtual platforms such as a digital registration system to initiate and follow up those initiated on treatment. Digital platforms can also be used to monitor ACF activities for yield, tracking of patients from identification to screening to diagnosis to completion of treatment, and to finding contacts and drop-outs, and to improve future activities.

    (c) Compare the yield of different algorithms and ensure the ability to initiate all diagnosed patients on treatment. If implementation capacity and funding is limited, focus on groups with a high prevalence where a smaller number of persons are required to be screened to get a high yield. A high yield but no follow up on initiation of treatment (or preventive therapy) for those who are eligible must be avoided.

    (d) Invest in operational research and innovation for ACF – pooling of sputum samples for rapid molecular diagnostics, use of rapid molecular diagnostics as a first test, and ACF for TB and diabetes. If feasible, consider mathematical modelling for predicting the population-level impact, cost–effectiveness and optimal duration and frequency of specific ACF interventions.

2. Select the right population groups

    (a) TB control programmes should begin with easily identifiable high-risk target groups and then widen their scope of activities as resources allow *(113)*.

    (b) Analyse programme data and, where available, prevalence survey data to identify the population groups with a high estimated prevalence of or risk factors for TB *(110)*. Modelling transmission dynamics can help with estimation

of the direct impact of spatial targeting on those screened as well as indirect impact on transmission.

(c) Review previous such activities in the country to help identify appropriate population groups.

(d) Prioritize groups with the highest prevalence such as household contacts and those in congregate settings such as prisons, workers exposed to silica and organic textile dust and the homeless.

(e) Choose the appropriate population size. A small group with a high prevalence will contribute fewer cases than a large group with a moderate prevalence.

Some of the priority population groups such as health-care workers have not been included in this evidence synthesis because of lack of quality publications on ACF among this group from the SEA Region in the past five years. However, the basic principle remains the same of using a sensitive algorithm such as CXR with GeneXpert when resources permit.

3. Select algorithms with an eye on affordability and repetitive rounds of ACF (Table 2)

From the review, it seems that an algorithm composed of CXR screening followed by confirmatory testing with Xpert is the first choice. A review of the costs of ACF implementation in the past five years show that rapid molecular diagnostics and CXR can account for as much as 50% of the total costs. However, studies have also shown this algorithm to be cost effective. In the ACF interventions based on symptom screening and sputum microscopy, personnel are the most expensive cost heads. Therefore, the choices for selection of algorithms must be strategic and may vary according to populations and resources. Some general considerations for addressing affordability are as follows:

(a) Use algorithms based on CXR as the first screening tool. These may be costly but are more sensitive in small populations such as prisoners.

(b) Use algorithms with rapid molecular diagnostics in household contacts, as these are highly sensitive tests and able to diagnose resistance early.

(c) When resources are limited, use symptom screening and sputum microscopy in a large population with a high prevalence. Clinical screening and diagnosis should be an important component of the screening process. Even in these populations, it should be important to remember that many cases will be missed and they will continue to spread the disease in the community. (This algorithm has been used in remote tribal populations in this review.) Additionally, one needs to be aware of the recent developments in diagnostics, which can make the algorithms feasible and affordable universally. However, if resources permit, CXR as screening tool and GeneXpert as a diagnostic tool may be used.

(d) Integrate ACF with other health activities in the community, for example, screening for NCDs as well as for providing preventive treatment in eligible populations.

4. Monitor ACF activities for yield and drop-outs, as well as their intermediate and long-term effects on additional case notification, treatment outcomes and mortality. Regular monitoring will help with modification of algorithms, achieving cost–effectiveness and efficiency in operations.

7
Limitations

1. One of the major limitations of this study was that the scope of work changed mid-way. This was partly because of the pandemic, which prevented discussions with the countries on their experiences.

2. Studies from Africa were not included, primarily because the HIV prevalence is high and therefore the situation is different. Only a few studies from Latin American countries are included.

3. PLHIV could not be studied because only two studies were available from the initial search from SEA and Asia. With a subsequent fresh attempt, it was felt that a separate comprehensive search was needed on multiple parameters to do justice to the topic. Finally, because regular screening for TB is recommended in PLHIV for which guidance is available, this group was dropped from this paper.

4. The limitations in the studies reviewed were as follows:

   (a) The method of calculating NNS could be different across studies (e.g. *(51)* considered NNS among presumptive cases), and many studies did not give NNS.

   (b) Multiple publications for the same study, e.g. Axshya study had publications for the overall study and state-wise study. This might bias the understanding and recommendations. Similarly, some studies on ACF implementation had separate publications on different aspects, which were not always connected/referred to or they were published more than 5 years ago. This led to suboptimal understanding.

   (c) Few studies looked at the population-level impact on notifications and none on the incidence of TB.

5. Substantial heterogeneity among the studies reviewed made it difficult to come to a conclusion about ACF on the whole. Most population groups had very few studies, which were mostly observational.

6. ACF studies for the past five years in all the population groups are a heterogeneous mix. This mix does not give a large enough number of studies to analyse and draw conclusions for certain groups such as children, migrants, the homeless and those in congregate settings as there are very few studies.

7. Some countries had not published any ACF studies in the past five years (Bhutan, DPR Korea, Maldives, Sri Lanka and Timor-Leste) and some had very few (Bangladesh and Indonesia). ACF has likely been implemented in all the countries but since these are not published, their experiences are not reviewed, resulting in a bias.

8. There is a substantial risk of bias because of the observational design of most studies. In each subgroup, except for household studies, mostly observational studies have been included.

Because of these limitations, the recommendations of this report/review need to be interpreted with caution. Policy recommendations must consider evidence of the cost–effectiveness and the overall impact on case-finding. At the regional and global levels, there is a need for investment in well-designed, robust randomized studies in specific population groups. Operational research is also needed for improving implementation in the field.

Annexures

Table 1: Studies reviewed for population groups with algorithms and operationalization, and costs (n=number of studies)

S. no.	Study focus	Studies reviewed from SEA (n)	Studies reviewed from other Asian countries (n)	Studies from rest of the world
1.	**Household contacts (Urban/ Rural)**	Indonesia (1) India (4)	Viet Nam (2) Cambodia (1) Republic of Korea (1) Malaysia (1)	
2.	**Prisons**	India (1) Thailand (1) Bangladesh (1)	Malaysia (1) Pakistan (2)	Ethiopia (1) Iran (Islamic Republic of) (1) Brazil (1)
3	**Diabetes**	Nepal (1)	Pakistan (2)	
4.	**Homeless & migrants**	India (3) Nepal (1)		
5.	**Children**	India (1) Nepal (1)	Pakistan (1)	
6.	**Congregate settings**	India (2) Nepal, one study among multiple population groups	Republic of Korea (1)	
7.	**Vulnerable populations**	Urban slums, tribals, rural poor in India (7) Myanmar (2) Nepal (one study among multiple population groups)	Papua New Guinea (1) Philippines (1); Health-care workers in Pakistan (1)	
8.	**General population**	India (4) Thailand (1)	China (3) Cambodia (1) Pakistan (2)	
9.	**Treatment outcome**	India (3) Myanmar (2)	Peru (1) Cambodia (2) Philippines (1)	
10.	**Costing**	India (1)	Cambodia & Tajikistan (1) Zimbabwe (1) Viet Nam (1)	

S. no.	Study focus	Studies reviewed from SEA (n)	Studies reviewed from other Asian countries (n)	Studies from rest of the world
11.	**Catastrophic costs**	India (2) Nepal (1)	Cambodia (1)	
12.	**Review & background reading**	14		

Table 1 gives the following information:

- 10 studies were on ACF in household contacts of index cases (five from the SEA Region, five from other countries in Asia).

- Nine studies were on ACF in prisons (three from the SEA Region, three from other countries in Asia and three from other countries outside Asia).

- 25 studies were on ACF in populations with difficulty in access, those that were hard to reach or vulnerable (tribals, migrants, persons with diabetes, children, the homeless) (18 from the SEA Region and seven from other countries in Asia).

- 11 studies were on ACF in the general population, including the elderly, and pregnant women (four from SEA and six from other countries in Asia).

- Costing was informed by a total of 12 studies.

- Catastrophic costs were mentioned by three studies.

- 14 studies were for review or background reading. These included studies from Africa and low-incidence countries, and opinion pieces by experts.

Table 2: Active case-finding in household contacts

S. no. and country	Screening by	Diagnosis confirmed by	Proportion of TB observed in the population group
1. Viet Nam 70 districts *(11)* Urban and rural	Screening was done in those with 2 weeks of cough, 2 weeks of sputum, any haemoptysis and chest X-ray suggestive of TB	Diagnosis was by sputum microscopy	1788/100 000
2. Cambodia *(12)*	First screening by any four symptoms at home by community volunteer Second screening by any symptom by clinicians at health facility and chest X-ray on same day	Xpert on same day for those with abnormal chest X-ray	Not known but 19% additional cases (all forms) and 10% additional cases bacteriologically positive in the intervention districts
3. Republic of Korea *(13)* Urban	Screening chest X-ray or sputum test for TB and a tuberculin skin or QuantiFERON-TB Gold In-tube test for latent tuberculosis infection in contacts	Sputum microscopy	2-year incidence was 1.1% (at 1 year, 883 per 100 000 compared to 70 in general population)
4. Indonesia *(14)* Bandung city (includes 139 villages)	Cough for more than 2 weeks. Two interventions were carried out: (i) house-to-house ACF, and (ii) household contacts and neighbourhood were screened	Sputum microscopy	In (i) 5100 screened, 48 identified but 38 gave samples and 0 diagnosed; In (ii) 88 household contacts and 423 neighbours screened, 4 had symptoms and 0 had TB.
5. India, Kashmir *(15)*	Symptoms	Sputum microscopy	4.50%

S. no. and country	Screening by	Diagnosis confirmed by	Proportion of TB observed in the population group
6. India, Chennai *(16)*	All contacts who were willing to participate had CXR and were evaluated for any symptoms	Sputum microscopy & culture/drug susceptibility testing	5.3% (29/544) **(Note:** number needed to screen [NNS] is 19) (In this study, 71 had abnormal CXRs, of whom 50 had symptoms and 21 were asymptomatic. Of those asymptomatic, 3 had extrapulmonary TB (EPTB); of those symptomatic, more than 50%, i.e. 23 had sputum microscopy+ and 3 culture and drug sensitivity testing).
7. India, Chhattisgarh *(20)* Rural	Symptom (cough for 2 weeks, fever, weight loss)	Sputum microscopy & CXR (for those negative by sputum microscopy)	1.01%
8. Malaysia *(17)* Urban	First screening by tuberculin skin test Second screening by CXR	Sputum microscopy	1.50%
9. Viet Nam *(18)* (for multidrug-resistant TB [MDR-TB])	First screening by clinical assessment (any symptom suggestive of TB); if negative then CXR Second screening by CXR	Xpert if symptom or CXR positive	99 index cases (with R resistance) Their 417 contacts were investigated (of these, 292 were household contacts) At enrolment, 48 were presumed cases Of these, 1 of 417 had drug-sensitive [DS]-TB) At 6 months, 27 of 160 had presumptive TB Of these, 0 were diagnosed to have TB
10. India *(19)* Urban (for MDR-TB)	Symptoms	Xpert	34 of 4771 contacts were diagnosed to have TB; of these, 15 had rifampicin-resistant (RR) TB

Note. *Please see Table 8 for Nepal data on household contacts.*

Table 3: Active case-finding among prisoners

S. no. and country/ setting	Screening by	Diagnosis confirmed by	Proportion of TB observed in the population groups in the studies
1. Thailand (Suratthani Central Prison) Jul–Dec 2015 *(27)*	Questionnaire (4 symptoms, past history, etc.) & chest X-ray	Sputum microscopy & Xpert	The prevalence of TB disease in the prison was 2.1% or 2096/100 000; prevalence of bacteriologically positive TB was 1.5% (prevalence was 10 times higher than in the general population)
2. Bangladesh (Dhaka Central Jail), October 2005 to February 2010 *(28)*	Cough for more than 3 weeks	Sputum microscopy, culture & drug susceptibility testing as well as genotyping	Not given by authors. Difficult to calculate because of different time periods. Authors published elsewhere the results from 2005 to 2008, which gave the prevalence as 222/100 000 – 21 times higher than in the general population
3. India *(25)*	Symptom screening (2 weeks cough)	Sputum microscopy	80 additional patients were found (study does not give the number of existing TB patients, which could be more than 102)
			Number of prisoners: 5093
			Number identified by screening: 1149 (19%)
			Number identified by diagnosis: (only 84% of presumptive TB patients had sputum microscopy) – 80 diagnosed to have TB
4. Pakistan, Karachi *(29)*	Chest X-ray with computer-aided detection for TB	Xpert	Tuberculosis yield was 1.8% of screened patients (& 25% of presumptive cases)
5. Pakistan, Baluchistan *(24)*	Digital X-ray with computer-aided detection for TB	Xpert	1% (5 of 567)
6. Malaysia *(21)*	Any symptom	Sputum microscopy, Xpert and liquid culture	8.5% (48 of 559) overall (but 7.7% if only newly diagnosed considered)
7. Ethiopia *(22)*	Symptom screening (2 weeks cough)	Sputum microscopy, Xpert	1789 per 100 000 (including 5 existing patients with pulmonary TB) (derived as 1.8%)

S. no. and country/ setting	Screening by	Diagnosis confirmed by	Proportion of TB observed in the population groups in the studies
8. Brazil (23)	Cough any duration and chest X-ray	Sputum microscopy, culture & drug susceptibility testing	1898 per 100 000 (derived as 1.8%)
9. Tehran (26)	Symptoms	Sputum microscopy	0.13%

Note. *Please see Table 8 for data on prisoners from Nepal and Philippines.*

Note. In Baluchistan, 82 (14%) jail staff and 129 (23%) staff's family members were among those screened (63% were prisoners). None of the studies had done secondary screening.

Table 4: Active case-finding in patients with diabetes

S. no. and country/ setting	Screening by	Diagnosis confirmed by	Proportion of TB observed in the population groups in the studies
1. Pakistan (32) Patients with diabetes	Verbal screening	Chest X-ray, Xpert MTB/ RIF test	Prevalence not known. Uptake of testing by presumptive TB cases among those with diabetes attending the clinic was 5.9%. (This study was a pilot for the study at S. no. 2).
2. Pakistan (31) Patients with diabetes	Digital chest X-ray with computer-aided detection for TB	Xpert (even X-ray could be considered)	10% (375 of 3824) (54/1428=3.7% among newly diagnosed TB); 13.3% among known patients with diabetes
3. Nepal (33) Patients with diabetes	Symptoms	Sputum microscopy If negative, then Xpert MTB/RIF	**Note:** NNS is 510 (2 of 1019 were positive by smear microscopy)

Note. None of the studies did secondary screening.

Table 5: Active case-finding in homeless persons and migrants

S. no. and country/ setting	Screening by	Diagnosis confirmed by	Proportion of TB observed in the population group
1. India, Chennai *(34)* Homeless	Any 1 of 4 symptoms + MMR	Sputum microscopy and culture	1661/100 000
2. India, Tamil Nadu *(35)* Migrant brick kiln workers	Any one of the 4 symptoms	Not done	
3. India *(36)* Migrant brick kiln workers	Any one of the four symptoms	Chest X-ray, sputum microscopy & Xpert	0.2%
4. Nepal *(37)* Migrant brick kiln workers	Chronic cough	Not done	NA

Note. None of the studies had done secondary screening;

Table 6: Active case-finding in congregate settings

S.no. and country/ setting	Screening by	Diagnosis confirmed by	Proportion of TB observed in the population groups in the studies
1. Republic of Korea *(40)* Congregate settings (schools, health facility, workplace, social welfare settings, etc.)	Chest X-ray & latent TB infection (LTBI) screening for contacts; LTBI screening, tuberculin skin test or interferon gamma release assay (IGRA) (TST +ve if induration of ≥10 mm (≥5 mm in newborns with no BCG). IGRA was QuantiFERON-TB Gold In-tube test, +ve if 0.35 IU or more	Sputum microscopy	146/100 000 person-years
2. India, Himachal Pradesh *(38)* Tibetan refugee children	First screening by symptoms and clinical exam (tuberculin skin test for TB infection) Second screening by chest X-ray	Xpert, culture and chest X-ray (for clinically diagnosed)	853/100 000 among Tibetan school students

S.no. and country/ setting	Screening by	Diagnosis confirmed by	Proportion of TB observed in the population groups in the studies
3. India (Himachal, Karnataka & Uttarakhand) *(39)* Tibetan refugee schoolchildren, monks and nuns who live in congregate settings	First screening by symptoms Second screening by chest X-ray	Sputum microscopy if no history of contact or past history of TB (Xpert for those with past history of TB and contacts)	346 cases/ 100 000persons

Table 7: Active case-finding in children

S. no. and country/ setting	Screening by	Dx confirmed by	NNS	Proportion of TB observed in the population group
1. Pakistan, health facility, children *(43)* Children (intervention was in a rural setting and engaged four public sector hospitals)	Any 1 of 4 symptoms, contact with person with TB for previous 2 years, lymph node enlargement	Chest X-ray, sputum Xpert; complete blood count & erythrocyte sedimentation rate, ultrasound		Prevalence of all forms of childhood TB was 1332 per 100 000 (1.3%) at the participating health facilities. Prevalence of childhood TB in contacts was (12 940/100 000) (*see* box below)
2. India, Bihar *(41)* Children with severe acute malnutrition	Tuberculin skin test, chest X-ray, sputum		11	The equivalent of 89 TB cases per 1000 children screened

S. no. and country/ setting	Screening by	Dx confirmed by	NNS	Proportion of TB observed in the population group
3. Nepal (7 intervention districts) *(42)* Children	Symptoms, chest X-ray, sputum		Number needed to identify 1 TB case was 41 in two days. Mobile health camp strategy in hard-to-reach areas, 44 in public–private mix (PPM) services (diagnosis by private practitioners and treated at government centres), 108 in household screening, and 200 during community home-based care visits	

Table 8: ACF in vulnerable and marginalized populations

S. no. and country/ setting	Screening by	Diagnosis confirmed by	NNS	Prevalence of TB in the studies
1. Philippines, Palawan *(45)* Rural poor, rural, urban areas, prisons, Indigenous population, high school	Symptoms & chest X-ray	2 spot samples – sputum microscopy x 2 samples with LED-fluorescent microscopy (LED-FM) and Xpert test with one sample	Overall 33 (45 for rural poor, 48 for urban poor; 16 for prisons, 34 for Indigenous population and 495 for high school)	

S. no. and country/ setting	Screening by	Diagnosis confirmed by	NNS	Prevalence of TB in the studies
2. Nepal (29 municipalities in 22 districts) *(33)* Urban slum dwellers, factory workers, prisoners, refugees, monks/nuns, people living with HIV (voluntary counselling and testing centres [VCTCs]), household contacts and patients with diabetes (clinics)	2 weeks cough (only for people living with HIV any symptom)	Sputum microscopy (Xpert if sputum microscopy negative)	NNS for people living with HIV –17 Household contacts – 29 Slums – 197 Prisoners – 261 Factory workers – 334 Refugees – 309 Diabetes – 510	
3. India, Karnataka *(46)* Urban slums, mobile population & tribes, people living at construction sites	Any 1 of 4 symptoms	Sputum microscopy (also did chest X-ray & Xpert where required)		29 TB patients diagnosed of 152 342 (19/100 000)
4. India *(44)* Urban slum, rural and tribal population	2 weeks of cough	Sputum microscopy (one morning, one spot) at the health facility		Prevalence was 8% among those who underwent sputum examination (14 447 smear-positive cases in 4.9 million households)
5. India, Agra *(48)* Urban slums	2 weeks of cough	Sputum microscopy		7 TB patients of 21 870 (32/100 000)

S. no. and country/ setting	Screening by	Diagnosis confirmed by	NNS	Prevalence of TB in the studies
6. India, Kolkata *(49)* Urban slums	Any 1 of 4 symptoms	Sputum microscopy, chest X-ray and Xpert (as per national guidelines)	2183 (177 out of 386 242)	
7. India, Karnataka *(50)* Vulnerable populations (based on caste, tribal population, slums)	Cough for 2 weeks	Sputum microscopy		Number of smear-positive TB cases increased by 8.8% compared to pre-intervention period (658 cases in a population of 34 million)
8. Myanmar *(51)* Hard-to-reach areas (rural, hilly)	First screening by any 1 of 4 symptoms Second screening by chest X-ray	Sputum microscopy (2 samples) and Xpert	Approximately 4700 (504 out of 2 400 000)	
9. Myanmar *(52)* Hard-to-reach areas (townships) household and neighbourhood intervention (household) and community intervention	Any 1 of 4 symptoms	Chest X-ray (if sputum microscopy negative), sputum microscopy, GeneXpert (in 2 sites)	766 (house-holds and neighbour-hoods) & 166 (community)	
10. India (2 tuberculosis units [TUs] of a district for intervention, 2 TUs for control) *(53)* Tribal population (Saharia community)	Any 1 of 4 symptoms	Sputum microscopy (2 samples)		1.5%

S. no. and country/ setting	Screening by	Diagnosis confirmed by	NNS	Prevalence of TB in the studies
11. India, Jharkhand 15 districts (36 TUs) *(54)* Marginalized and vulnerable populations	Symptoms	Sputum microscopy		At baseline, the case notification rate (CNR) was lower in districts selected for ACF than the non-ACF districts. After ACF, CNR increased in both ACF and non-ACF districts, more in former. After ACF was over, CNR in ACF districts went back to being lower than in non-ACF districts.
12. Papua New Guinea *(55)* 26 villages with poor access	First screening by symptoms Second screening by symptoms & clinical examination	Sputum microscopy		Prevalence of smear-positive TB was 0.9%
13. Pakistan, Multan *(47)* Doctors and other hospital staff	Tuberculin skin test	Sputum microscopy, Xpert, chest X-ray		10%

Table 9: Active case-finding in the general population

S. no. and country/ setting	Screening by	Diagnosis confirmed by	NNS	Proportion of TB observed in the population groups
1. China *(56)* Elderly >65 years (rural)	First screening by symptoms (2 weeks cough) at home visit & risk assessment Second screening: referred for chest-X ray if symptoms or risk factor present	Sputum microscopy & culture (one spot sample & referral for two more)		146 tuberculosis cases per 100 000 seniors (lower than the expected 502 in this group)
2. China *(57)* Retrospective cohort of 10 communities between 2013 and 2015	First screening by symptoms (2 weeks cough) at home visit & risk assessment Second screening by chest X-ray	Three samples for sputum microscopy	Cumulative NNS were 34, 39 and 29 in HIV/AIDS-infected individuals, people with symptoms suggestive of TB and history of previous TB, respectively, compared to 1478 in the general population	
3. China *(59)* Rural (2 sites)	First screening by any one of four symptoms Second screening by chest X-ray	Three samples for sputum microscopy, Lowenstein–Jensen culture, Xpert		475 and 196 per 100 000 population of the 2 sites
4. Cambodia *(60)* Elderly (>55 years) rural	Symptoms & chest-X ray	Xpert and culture	87 to one diagnosed Xpert-positive case	

S. no. and country/ setting	Screening by	Diagnosis confirmed by	NNS	Proportion of TB observed in the population groups
5. Pakistan *(61)* Rural areas of four districts	Symptoms	Sputum microscopy	260 in simple chest camp (SCC) and 258 in infotainment chest camp (ICC)	
6. Thailand *(62)* Hua Hin district	Any 1 of 4 symptoms, risk assessment and chest X-ray	Sputum microscopy & CXR	Calculated as 123	
7. India, Haryana, (public–private partnership [PPP]) *(63)* Rural	2 weeks cough	Strategy 1 – sputum microscopy and CXR only if sputum microscopy negative; Strategy 2 – CXR & sputum microscopy for all persons with chest symptoms		Strategy 1 – 11% of 1609 presumptive TB patients Strategy 2 – 8% of 1731
8. India, Haryana, (PPP) *(64)* Rural	2 weeks cough	Strategy 1 – sputum microscopy and CXR only if sputum microscopy is negative Strategy 2 – CXR & sputum microscopy for all persons with chest symptoms		Strategy 1 – 121 were presumptive or CXR suggestive, of whom 39 diagnosed as TB but 24 started on treatment Strategy 2 – 596 were presumptive or CXR suggestive. Of these, 67 (including 11 bacteriologically positive) were diagnosed to have TB

S. no. and country/ setting	Screening by	Diagnosis confirmed by	NNS	Proportion of TB observed in the population groups
9. India, Haryana, (PPP) *(65)* Rural	Cough for more than 2 weeks	CXR & sputum microscopy (Xpert if sputum microscopy negative and CXR positive)		284 TB patients diagnosed of 2973 presumptive TB cases (161 bacteriologically positive, 106 clinically diagnosed and 17 extrapulmonary TB [EPTB]) 2973 presumptive TB patients underwent CXR and sputum microscopy; 471 (15.8%) had abnormal CXR findings suggestive of TB, 129 (4.3%) were smear-positive and 17 were EPTB 325 had abnormal CXR but were smear-negative. Of these, 147 (45.2%) had Xpert testing, yielding 32 positives (21.8%). For 178, Xpert test was not done but 106 (60.0%) of them had CXR suggestive of TB (clinically diagnosed TB) Thus, a total of 284 cases of TB (161 microbiologically confirmed, 106 clinically diagnosed, 17 EPTB) were identified, giving a potential diagnostic yield of 19.6%

S. no. and country/ setting	Screening by	Diagnosis confirmed by	NNS	Proportion of TB observed in the population groups
10. India *(66)* Pregnant women	First screening by symptoms Second screening by CXR	Sputum microscopy		0.02% (20 per 100 000)
11. Pakistan, Karachi *(58)* Pregnant women in urban area	Verbal symptomatic screening followed by sputum samples	GeneXpert test (sputum culture and shielded CXRs in two other sites)		Calculated as 0.05% (50 per 100 000)

Table 10: Results of evidence synthesis of ACF based on studies from South-East Asia (SEA) and the rest of Asia, published in the past five years (2015–May 2020): findings on prevalence and population groups with suggestions for algorithms

S. no	Population group	Algorithm for consideration	Remarks
1.	Households	Screening by cough of any duration and CXR + diagnosis by rapid molecular diagnostics	Household contact-tracing is done under programme conditions. To supplement this with ACF, household contacts from 2 years ago can be included. ACF in households contributes additional cases to districts (community-based trials in Viet Nam, Cambodia). Consider repeating every alternate year. Can add neighbourhood contacts with symptoms.
2.	Prisons	Screening by symptoms and CXR + diagnosis by rapid molecular diagnostics	Prevalence in prisons can vary depending on overcrowding and practice of screening at entry; rapid molecular diagnostics help in identifying RR-TB.
3.	Diabetes patients	Screening by CXR or 1 of 4 symptoms + diagnosis by rapid molecular diagnostics	If CXR is not used for primary screening, then it should be used to complement rapid molecular diagnostics for diagnosis. A narrative review showed that TB prevalence is 1.8–9.5 times higher in people with diabetes as compared to the general population but in an Indian study, most patients in the diabetes clinics were already diagnosed. Further research is needed on this.
4.	Homeless persons	Screening by symptoms and CXR + diagnosis by rapid molecular diagnostics	Advisable to use one-stop opportunity for diagnosis and treatment. Difficult to link them to treatment. Hence, NGO involvement is crucial.

S. no	Population group	Algorithm for consideration	Remarks
5.	Migrants with occupational risks	Screening by symptoms + diagnosis by sputum microscopy and rapid molecular diagnostics	Studies from SEA show a high prevalence of symptoms (9–14%) in brick kiln workers who are internal migrants. (No other migrant groups are considered in the ACF studies.) Therefore, symptomatic screening alone might be sufficient in this group.
6.	Congregate settings	Screening by symptoms and CXR at entry (only symptoms for regular screening) + diagnosis by rapid molecular diagnostics	Prevalence in the SEA Region is based on Indian studies in Tibetan boarding schools. Prevalence will vary from one setting to the other. (Algorithm used is the same as in prison. Indian studies used CXR for secondary screening.)
7.	Children	Screening by symptoms, IGRA/TST + diagnosis by rapid molecular diagnostics and CXR	Children less than 15 years of age form a diverse group. Older children will be able to produce sputum. Under-5 children with severe malnutrition will have the lowest NNS. Unlike in adults, clinical assessment by a physician will be a critical component of the diagnosis of TB in children.
8.	Vulnerable populations	Screening by symptoms + diagnosis by SM (ideal is screening by CXR and diagnosis by Xpert)	Screening by any 1 of 4 symptoms and diagnosis by sputum microscopy was used in tribal populations, which gave a yield of 1.5%. Indigenous populations in Philippines also had a high prevalence of symptoms. In large sections of the population, CXR can be used, as in Cambodia and Philippines. Two weeks of cough and sputum microscopy seems to be a reasonable strategy for ederly in urban slums (Philippines) as well as for rural remote populations (Papua New Guinea).
9.	Elderly population	Symptoms and CXR + diagnosis by rapid molecular diagnostics	In the elderly, where prevalence was expected to be high (based on survey findings), CXR was used for initial screening in Cambodia. The Philippines study concluded that the combined use of CXR and rapid molecular diagnostics largely contributed to increased case detection. Both studies used *mobile vans*. Many studies used CXR for secondary screening, but this is known to not add substantially to the yield.

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The WHO South-East Region in 2019 accounted for nearly a million missing TB patients from the estimated incidence. Active case-finding (ACF) or systematic screening for tuberculosis is an important tool to reach out to missing TB patients. When appropriately implemented, the activity is cost effective, helps to reduce diagnosis and treatment delays, and prevents the spread of the disease. This document presents an analysis of published ACF studies from the Region. It can be used by Member States for effective planning, implementation and monitoring of these activities.

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