

# Getting to Zero

A Guide to the  
**Search, Treat, Prevent**  
Comprehensive Approach

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# Introduction

Tuberculosis (TB) is an airborne disease that is both curable and preventable, yet more than 1.5 million people around the world died from the disease in 2014. An estimated 9.6 million people became sick with TB in the same year; a total that includes 1 million children as well as 480,000 people with multidrug-resistant TB (MDR-TB) requiring treatment with second-line anti-TB drugs. Although almost everyone who becomes sick with TB can be treated effectively, the number of new TB cases has declined at an unacceptably slow pace of just 1.5% per year since 2000.<sup>1</sup>

Making real progress against the global TB epidemic will require a paradigm shift as called for by the Global Plan to End TB 2016 – 2020. It will require new strategies to search for and diagnose everyone who is sick with TB, to treat them promptly and effectively, and to prevent future TB cases by stopping the transmission of TB infection.

A comprehensive approach integrates three simultaneous strands of activities: SEARCH - TREAT - PREVENT. The aim of this document is to summarize this approach and provide evidence-based arguments for implementing it urgently in the fight against TB.

# Key Messages

## Search Actively - Test Properly

- + Delays in diagnosis contribute to the spread of TB
- + Targeted active case-finding finds more people with TB earlier
- + Active case-finding requires proper testing and diagnostic tools
- + Active case-finding reduces TB transmission in communities
- + Active case-finding can reduce the global burden of TB

## Treat Effectively - Support Through Treatment

- + Effective TB treatment rapidly reduces infectiousness
- + Widespread testing for drug resistance can ensure effective treatment
- + Strengthening health systems can reduce treatment delays
- + Patients need to be supported throughout treatment

## Prevent Exposure - Treat Exposure

- + Protecting people from exposure prevents future TB cases
- + Preventive therapy for high-risk groups reduces new TB cases
- + Shorter preventive therapy regimens can reduce the treatment burden
- + Preventive therapy can also reduce new MDR-TB cases
- + Mass preventive therapy can have a population-level impact

# I Search

## Search Actively - Test Properly

A person who is infected with TB bacteria can become sick with active TB disease. This can happen as quickly as within a few weeks after infection or as long as decades later. People with TB infection who become sick can transmit the infection to other people in their families, communities and places of work. Therefore, one of the fundamental tenets of good epidemic control for tuberculosis is to actively search for people who are sick with TB or who have TB infection and treat them.

Of the 9.6 million people who became sick with TB in 2014, only 6 million were recorded and reported by countries to the World Health Organization (WHO). This is consistently the situation for the last 8 years – yearly, more than 3.6 million people sick with TB and MDR-TB (3.6 million cases) were “missed” by health systems.<sup>2</sup> Missed cases are people sick with TB who are never diagnosed or treated or were treated in the private sector and were not recorded to national or international registers. Those that are not diagnosed or treated continue to transmit the infection in their families, communities and places of work. The large proportion of missed people with TB is a major cause of the slow progress in stopping the global TB epidemic.

## Delays in diagnosis contribute to the spread of TB

In most of the world, people with TB are diagnosed with the disease only after they seek care for their symptoms at a health

care facility. A person can have TB for a long period without noticeable symptoms or with symptoms that are not severe enough for them to seek care. By the time people are sick enough to seek care, they may have been infectious for a long time.

Diagnosing people only after they seek care directly contributes to the spread of TB. A study of TB patients and their contacts in the United States found that patients with undiagnosed TB were more likely to pass on the TB infection to their contacts; the longer the delay in diagnosis, the more likely they were to have transmitted the infection. More than half of patients in the study had a delay of at least 90 days between having their first symptoms and starting TB treatment, and 40% of the contacts of those patients had been infected with TB.<sup>3</sup>

## Targeted active case-finding finds more TB cases earlier

Targeted active case-finding involves actively seeking out and screening people who are at higher risk of becoming sick with TB.<sup>4</sup> The strategy reduces transmission rates because it finds more people with TB and diagnoses them earlier, so that people who are infectious can be removed from their communities for treatment before they transmit TB to more people. Currently, targeted active case-finding activities for TB focus primarily on just few of the the key populations and groups with high exposure: contacts of people who have TB, including children; people living with HIV; and people who seek care at health facilities in areas where TB is prevalent.

Targeted active case-finding is effective in finding new TB cases among people key populations and groups with high exposure who are screened, and works better than mass screening of the entire population. Across many studies in low- and middle-income countries, the rates at which people sick with TB transmitted it to

their contacts, finding that an average of more than 3% of contacts had active TB disease and more than 50% of contacts had TB infection.<sup>5</sup> The risk was highest during the first year of exposure, for children under 5 years of age, and for people living with HIV.<sup>6</sup> An analysis of many studies that used targeted active case-finding to screen people living with HIV for TB symptoms found that on average, the strategy identified one additional case of TB for every 100 people who were screened.<sup>7</sup> Many studies carried out in a range of settings have examined the impact of screening people who visit general healthcare facilities for TB, which finds new TB cases in an average of 5%-10% of the people screened.<sup>8,9,10,11</sup> To optimize effectiveness, active case-finding efforts should be informed by local epidemiologic data.<sup>12</sup>

The following table summarizes the estimates of the percentage of new TB cases that will be found among people screened using different active case-finding activities:

Type of active case-finding activity	Expected % of new TB cases
Screening household contacts of TB patients in low-/middle-income countries	1% - 5%
Screening people at general healthcare facilities in high TB-burden areas	5% - 10%
Screening people treated for HIV in low-/middle-income countries with HIV prevalence >5%	1% - 25%

## Active case-finding requires proper testing and diagnostic tools

Active case-finding activities are only as effective as the tests and diagnostic tools that are used. Countries with the highest TB burdens still rely heavily on an older diagnostic test called sputum smear microscopy, in which a patient's sputum sample is examined under a microscope for the presence of TB mycobacteria.

Compared with newer and more sensitive diagnostic methods, sputum smear microscopy is very unreliable: it has an overall failure rate of around 50%, meaning that half of people tested are “smear negative” despite having TB; in children, it fails to detect TB around 90% of the time.<sup>13</sup> In people living with HIV, it fails to detect TB more than 70% of the time.<sup>14</sup> Sputum smear microscopy cannot detect TB that develops outside of the lungs (extrapulmonary TB), nor can it determine if the person has drug-resistant TB.<sup>15</sup>

Although they are generally less infectious than smear-positive patients, smear-negative patients can transmit the disease to others. A study in the United States of more than 1,500 TB patients found that at least 17% had contracted TB from a smear-negative patient and around 27% had contracted it via a chain of transmission that began with a smear-negative patient. Smear-negative patients were estimated to be at least 22% as likely to transmit TB as smear-positive patients.<sup>16</sup>

Relying only on smear microscopy for diagnosis causes many people who are sick with TB to remain undiagnosed and untreated while they continue to be infectious. More sensitive diagnostic tests are available that can detect a higher proportion of TB cases. These include combinations of the following diagnostic tools: radiography (chest X-ray); mycobacteriological culture; molecular diagnostic tests (such as the Xpert MTB/RIF test); and clinical algorithms.<sup>17</sup> Bacteriological culture of a patient's sputum sample is a very accurate diagnostic method (some types can also test for drug

resistance) but the results can take 2-6 weeks, while new types of molecular diagnostic tests take only hours or days to identify people with drug-resistant TB.

Clinical algorithms for diagnosing TB can help to identify and promptly treat patients with TB that is not confirmed by other tests. Chest X-ray is often part of that clinical algorithm because it is much more sensitive than sputum smear microscopy in detecting TB in the lungs. X-ray can also detect the most common forms of extrapulmonary TB. Children have trouble producing the sputum needed for TB diagnostic tests, including tests for drug resistance, so they should be treated for TB based upon clinical diagnosis.<sup>18</sup> Clinical algorithms are an essential tool in diagnosing TB in children and people living with HIV, most of whom have smear-negative pulmonary TB or extrapulmonary TB not easily detectable using currently available diagnostic tools.<sup>19</sup>

## Active case-finding reduces TB transmission in communities

Studies have shown that using targeted active case-finding reduces the rates at which TB disease and TB infection are transmitted in communities. A study in Brazil examined the effect of screening household contacts of people with TB. After 5 years, the communities where active case-finding was carried out had 10% fewer reported TB cases, which was 15% lower than the number of cases reported in communities where household contacts were not screened.<sup>20</sup> Studies in Zambia and South Africa reported similar results after 4 years: communities where household contacts of TB patients were screened had 18% lower rates of TB among adults and 55% lower rates of TB infection among children compared with communities where active case-finding was not used.<sup>21</sup>

# Active case-finding can reduce the global burden of TB

The benefits of active case-finding accumulate over time, because finding and treating people with infectious TB prevents them from transmitting the disease to others. Projecting forward, mathematical models based on data from the current TB epidemics in China, India, and South Africa predict that targeted active case-finding can have a substantial impact on the TB mortality, incidence, and prevalence<sup>22</sup>:

## If 25% more TB cases are diagnosed and treated, then after 10 years:

- ↓ 40% - 44% fewer people will die from TB-related causes (mortality)
- ↓ 22% - 27% fewer people will be get TB each year (incidence)
- ↓ 30% - 33% fewer people will be sick with TB (prevalence)

This goal of a 25% increase in the number of detected cases is feasible with active case-finding activities. One study analyzed 19 year-long active case-finding activities, which were associated with a 35% increase in reported TB cases.<sup>23</sup> Active case-finding activities are also highly cost-effective interventions—even if finding a single new case costs as much as \$2500 USD in India and \$5000 USD in South Africa or China—because they help stop transmission. Of course, these projections are dependent on active case-finding being linked directly to the delivery of prompt, effective treatment.



# Treat

## Treat effectively - Support through treatment

Until they are treated effectively, people sick with TB disease remain infectious. Stopping the global TB epidemic will require treating people with the correct medications as quickly as possible after diagnosis.

For people with TB disease that is not drug resistant, treatment generally involves taking four different first-line drugs for a period of 6 months. That regimen will not have an effect on drug-resistant TB disease, which requires treatment with a combination of 5 or more effective second-line drugs for as long as two years. The treatments for both types of TB disease are lengthy and the medicines used can cause side effects, so a key component of TB care delivery is to support each patient in completing the entire treatment regimen.

## Effective TB treatment rapidly reduces infectiousness

Diagnosis must be followed by prompt effective treatment, because people who are diagnosed with TB but are not treated immediately are more likely to transmit TB to others. Long delays between diagnosis and treatment further increase the risk of transmission. A study in China found that people who went 30 days after diagnosis before treatment had a significantly higher chance of transmitting TB and after 90 days without treatment, they were 2.3 times as likely to transmit it.<sup>24</sup>

Evidence gathered over the past 60 years has shown that effective TB treatment very quickly reduces the chance that a patient will infect others, even while the patient is still culture-positive or smear-positive. A pivotal study in India during the 1950s found that TB patients being treated effectively in their homes were no more likely to transmit TB to their family members than TB patients who being treated in sanatoria and isolated from their families.<sup>25</sup>

Studies that expose guinea pigs to patients with TB have shown that effective treatment makes a TB patient non-infectious very rapidly, often within 24 hours. In an early study, TB patients who had started treatment were 98% less likely to transmit TB to the guinea pigs than patients who had not yet started treatment; more recent studies have reported that patients receiving no or inadequate treatment for drug-resistant TB were the source of virtually all transmission to guinea pigs. Patients being treated for drug-resistant TB were not infectious, even those who had started treatment within the past 2 weeks.<sup>26</sup>

## **Widespread testing for drug resistance can ensure effective treatment**

Some people develop MDR-TB because they became sick with drug-susceptible TB in the past, but did not receive a complete and effective treatment regimen. However, people who are sick with MDR-TB can also pass the MDR-TB infection to other people, and are doing so at increasing rates. In fact, globally, most patients with MDR-TB have never previously been diagnosed with TB. For example, in 2013, within the WHO European region, 14% of patients who had never been previously treated for TB had MDR-TB.<sup>27</sup> Although the proportion of MDR-TB among patients who have previously been treated for TB is higher—in the WHO European region it is almost 50%—there are fewer patients in the retreatment group.

Some TB control policies do not test a patient with TB for drug resistance until a standard first-line drug regimen (taking 6 months) has been unsuccessful. Once a sample is collected for conventional testing of drug resistance, the results can take further weeks or months. Thus, patients may have infectious, untreated, drug-resistant disease for many months before being started on effective treatment. Treatment with inappropriate first-line drugs can cause patients with drug-resistant TB to develop more resistance to additional types of TB drugs (known as amplification of resistance); these patients also tend to have worse treatment outcomes and are more likely to relapse with TB after undergoing months of treatment.<sup>28</sup>

As with drug-susceptible TB, patients with drug-resistant TB quickly stop spreading the infection once they are treated with the correct regimen.<sup>29</sup> Widespread testing for drug-resistant TB using new rapid molecular testing can shorten the delay in treating patients with the correct regimen, substantially reducing the time they are infectious. Such programs have been implemented in countries with high rates of drug-resistant TB and have proven to be feasible. A TB hospital in Russia tested all patients with symptoms suggestive of TB for drug resistance using Xpert within 2 days of admission. Within 10 months, more than 150 patients with MDR-TB were identified and started appropriate treatment within five days of diagnosis.<sup>30</sup> The microscopic observation drug susceptibility (MODS) assay is a rapid test that can diagnose TB and test for drug resistance. In certain districts of Peru, the MODS assay was used to screen every patient who started treatment for TB. The result was a significant decrease in the time it took to diagnose patients with drug-susceptible TB (from 118 days to 33 days) and patients with MDR-TB (from 158 to 52 days).<sup>31</sup>

Standardized risk criteria can be used to guide decisions about treatment for drug-resistant TB in cases where tests for drug resistance are unavailable, or the test results are pending. For example, if a child is clinically diagnosed with TB and lives in the

same household as an adult with drug-resistant TB, then the child would be treated for drug-resistant TB. A study examined the households of people with drug-resistant TB (source cases), and found that when another person in a household also became sick with TB (secondary cases), the secondary case had the same pattern of drug resistance as the source case more than 50% of the time.<sup>32</sup>

## **Strengthening health systems can reduce treatment delays**

Reducing the delay between diagnosis and treatment is critical for stopping transmission and ensuring that patients have the best chance for a good treatment outcome. Delays in initiating treatment for TB have been widely reported. For example, a study in South Africa reported that only 20% of patients with drug-resistant TB had started treatment within the 2 weeks after their diagnosis. MDR-TB patients faced an average delay of 17 days between diagnosis and treatment, despite having rapid nucleic acid tests (Xpert MTB/RIF) results available within hours.<sup>33</sup> Gaps in the health delivery systems can exacerbate treatment delay at multiple points in the process, but protocols can be put in place to initiate effective treatment promptly. Such practices include collecting accurate contact information for patients at the first diagnostic visit and optimizing the processes of receiving, accessing, and communicating results to patients.

## **Patients need to be supported throughout treatment**

Patients can also contribute to treatment delays and uncompleted treatments. Not only must they be able to access treatment after diagnosis, but they must be willing and able to start and maintain

the lengthy treatment regimen. Patients may choose to decline or stop treatment for various reasons: they may not feel very sick from the disease; treatment may interfere with their ability to work; or the nearest health facility may entail travelling long distances. Having TB remains socially stigmatizing in many communities, causing some patients to become isolated or depressed. Additionally, TB is driven by poverty and is itself a driver of poverty, so every attempt has to be made to make treatment easier for people suffering from the disease.

## Examples of strategies for supporting patients through TB treatment:

- ✓ Following up actively with people who do not start treatment
- ✓ Providing incentives and enablers for patients to start treatment
- ✓ Monitoring patients during treatment
- ✓ Providing transportation assistance and/or food assistance as needed
- ✓ Providing social support through treatment supporters and patient support networks
- ✓ Providing cash transfers to patients and/or their families

Integrated care can reduce the burden of time and effort that TB treatment can impose upon patients, making them more likely to complete treatment. Depending on the specific setting, TB care might be integrated into other public healthcare services such as HIV care or maternal-child health programs.<sup>34</sup> Partnerships with community advocates and other public sectors can bolster TB detection and treatment efforts, as can partnering with private hospitals and providers in areas where many patients seek care in the private sector.<sup>35</sup> Approaches that address economic and social barriers to treatment adherence and completion are also important for a comprehensive TB program to be successful; this is equally true for other components of the SEARCH-TREAT-PREVENT framework.<sup>36</sup>



# Prevent

## Prevent Exposure - Treat Exposure

An estimated one-third of the global population is infected with TB (1.86 billion people), but most of those people will not become sick with active TB disease.<sup>37</sup> People who are infected with TB but are not sick make up a reservoir of potential future cases of TB, and it is estimated that roughly 10% of them will eventually have active disease, 5% within the first two years after infection. Even if health systems were able to find and instantly treat every new case of TB, or if there were an effective new vaccine for preventing TB, the epidemic would still not be stopped. People who are already infected will continue to become future TB cases and spread the disease further. Shrinking that reservoir of people who are infected with TB is the only way to stop the epidemic.<sup>38</sup> This will require protecting people from exposure to TB bacteria, and treating people who have been exposed to TB with preventive therapy.

## Protecting people from exposure prevents future TB cases

TB is an airborne disease that can be spread anywhere by any untreated patient, but transmission of TB is more likely in crowded, poorly ventilated settings and inside homes or healthcare facilities where people are sick with TB. In healthcare facilities, patients and staff can be protected from exposure by implementing simple practices such as isolating and providing paper masks for people with symptoms suggestive of TB<sup>39</sup> and improving ventilation by opening windows and doors.<sup>40</sup> Another strategy is screening

people who live or work in settings with a higher exposure risk — such as mines, prisons, and factories—so that they can be treated and protect others from infection.

## **Preventive therapy for high-risk groups reduces new TB cases**

People who are infected with TB bacteria have a 10% risk of becoming sick with the disease at some point in their lives. Testing a person for TB infection can be done using the tuberculin skin test (TST) or the interferon gamma-release assay (IGRA) blood test. If a person tests positive for TB infection, then treatment with appropriate preventive therapy can significantly reduce the person's chance of developing active TB disease. Treatment with a drug called isoniazid given daily for at least 6 months is the most common regimen for preventive therapy, but there are also other therapies that are shorter, easier to deliver, and shown to be as effective (e.g. isoniazid and rifapentine given once weekly for 3 months). Decades of clinical studies have shown that preventive therapy can keep people with TB infection from becoming sick. In adults with TB infection who do not have HIV and have otherwise healthy immune systems, isoniazid preventive therapy can reduce the risk of developing active disease by 60%, and one person will be saved from TB if 35 infected people take isoniazid for 6 months.<sup>41</sup>

Although the average person infected with TB has a 10% lifetime risk of becoming sick with the disease at some point in their lives, certain groups of people have an even higher risk of becoming sick with TB if they are infected with the TB bacteria, including: children younger than 5 years of age; people living with HIV; and people who have other types of chronic illnesses.<sup>42</sup> However, preventive therapy can significantly reduce the chance that people in these

high-risk groups will become sick with TB if they are infected.

Among children with TB infection under the age of 16 years, preventive treatment with isoniazid reduces the risk of becoming sick with TB by almost 60%. Adults living with HIV who are also infected with TB have a 30% chance of developing active disease if they do not receive preventive therapy; treatment with 3-12 months of isoniazid therapy reduces that risk by between 32% and 62%.<sup>43</sup> People infected with both HIV and TB who are being treated for HIV with antiretroviral therapy have a 60% lower chance of developing active TB, so combining TB preventive therapy with antiretroviral therapy has an even more powerful effect.<sup>44</sup>

## Shorter preventive therapy regimens can reduce the treatment burden

The length of treatment and the potential side effects can make it difficult for patients to complete preventive therapy regimens, and health systems can have difficulty administering and monitoring patients' treatments. However, preventive therapy regimens are available that are shorter but highly effective, and can ease the burden on both patients and health systems. These regimens include: 3-4 months of treatment with rifampin once daily; 3-4 months of treatment with rifampin plus isoniazid once daily; or 3 months of treatment with rifapentine plus isoniazid once weekly.<sup>45</sup>

## Preventive therapy can also reduce new MDR-TB cases

Clinical studies are still underway, but evidence is mounting that appropriate preventive therapy can also protect people exposed to drug-resistant TB from developing active disease. A recent policy brief on preventive therapy for MDR-TB reviewed a set of

observational studies that included more than 600 people who were treated with preventive therapy for MDR-TB.<sup>46</sup> Across the following four settings, only two patients became sick with MDR-TB after treatment with preventive therapy:

Setting	Contacts who become sick with MDR-TB after preventive therapy
South Africa	2/41 (5%)
USA	0/50 (0%)
USA	0/30 (0%)
Micronesia	0/119 (0%)

## Mass preventive therapy can have a population-level impact

In the 1950s, a study in the United States investigated using isoniazid preventive therapy to treat household contacts of people with TB. In households where contacts were treated, the number of new TB cases was 60% lower than in households where contacts were not treated; this reduced risk of developing TB was sustained for twenty years.<sup>47</sup> More recent studies in Brazil looked at the effect of active case-finding combined with preventive therapy for household contacts of TB patients. After five years, the number of new TB cases was 10% lower in those communities, compared with a 5% increase of new TB cases in communities where

household contacts were not screened.<sup>48</sup> Another study screened patients enrolled in HIV clinics in Brazil and treated those who had TB infection with preventive therapy, which reduced the number of new TB cases among the clinics' patient population by between 25% and 30%.<sup>49</sup>

Mathematical models predict that using preventive therapy in low- and high-income countries would be cost effective and have a large population-level impact. In India, for example, models predict that scaling up mass preventive therapy from 2025 onward would reduce the incidence of TB to one case per million people by 2050 (the incidence in India is currently estimated at 1710 per million). By 2035, the number of deaths due to TB in India could drop from 190 people per million to fewer than 10 per million of the population.<sup>50</sup>

# Search, Treat, Prevent

## Key Sources

### Search

search actively · test properly

Topic	First Author	Year
Delays in diagnosis contribute to the spread of TB	Golub	2006
Targeted active case finding (ACF) is effective for higher risk groups (new cases)	Yuen	2015
1-5% of household contacts of TB patients have TB themselves	Fox	2013
Screening HIV patients for TB is crucial	Kranzer	2010
Case notification through sustainable private sector innovations	Khan	2012
Active case-finding efforts should be informed by local epidemiologic data	Theron	2015
Sputum smear microscopy is a poor TB test compared to other options	Murray	1990
Sputum smear microscopy is a poor TB test for people with HIV compared to other options	Lawn	2011
ACF and preventive therapy reduces TB incidence in communities (Brazil)	Cavalcante	2010
ACF reduces rates of transmission in communities (southern Africa)	Ayles	2013

# Search, Treat, Prevent

## Key Sources

### Treat

treat effectively · support through treatment

Topic	First Author	Year
Once a patient is receiving effective treatment, he or she has a low risk of transmitting TB to others (India)	Kamat	1966
Effective treatment quickly makes MDR-TB patients non-infectious	Dharmadhikari	2014
Outcomes are worse when treatment with correct drugs is delayed	Lew	2008
F-A-S-T strategy for transmission control	Barrera	2015
Using the rapid Xpert MTB/RIF test can reduce the time it take for a patient to start MDR-TB treatment	Naidoo	2014
A comprehensive approach to stopping tuberculosis would address poverty alleviation and sustainable development	Ortblad	2011

# Search, Treat, Prevent

## Key Sources

### Prevent

prevent exposure · treat exposure

Topic	First Author	Year
Treatment of TB infection as a core component of comprehensive strategy	Rangaka	2015
Giving people who may have TB paper face masks to wear can reduce the risk of TB transmission	Dharmadhikari	2012
ACF and preventive therapy reduces TB incidence in communities (Brazil)	Cavalcante	2010
Improving natural ventilation can decrease TB transmission risk	Lygizos	2013
Preventive therapy for high-risk groups reduces new TB cases (INH specific)	Smieja Akolo	2000 2010
Shorter regimens are available that are as effective as isoniazid for preventing TB disease	Villarino	2015
Preventive Therapy can also reduce MDR-TB cases	Seddon	2015

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