CENTER FOR GLOBAL HEALTH DELIVERY
HARVARD MEDICAL SCHOOL

PROCEEDINGS

Global Consultation on Best Practices in MDR-TB Care (Part 1)

Comprehensive Approach to Search, Treat, and Prevent MDR-TB

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 The authors would like to thank Annie Smidt at Durable Creative (www.durablecreative.com) for design support in the production of this resource.

International Standard Book Number ISBN-13: 978-1-944302-25-2

Suggested citation: Global Consultation on Best Practices in MDR-TB Care (Part 1). Proceedings of the Harvard Medical School Center for Global Health Delivery. 2021, Dubai, United Arab Emirates.

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Comprehensive Approach to Search, Treat, and Prevent MDR-TB

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Harvard Medical School Center for Global Health Delivery

July 8th and 11th, 2019

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1 Introduction

The workshop Global Consultation on Best Practices in MDR-TB Care was held by the Harvard Medical School Center for Global Health Delivery-Dubai between July 8th and 11th, 2019 in Dubai, United Arab Emirates. More information about the Center for Global Health Delivery – Dubai is provided in Box 1-1. The workshop convened a large group of global experts in caring for people with drug-sensitive tuberculosis (TB), drug-resistant TB (DR-TB), and multidrug-resistant TB (MDR-TB) to explore best practices for MDR-TB care within the context of a comprehensive approach for TB elimination. The comprehensive approach involves actively searching for people with TB, treating TB with the best available new regimens, and preventing TB through post-exposure management of persons exposed to TB at home.

To underscore the urgent need for widespread adoption of a comprehensive approach to eliminating all forms of TB, a brief history of the evolution of the global TB control strategy over the past three decades was provided by Salmaan Keshavjee of Harvard Medical School, Brigham and Women's Hospital, Partners In Health, and Advance Access & Delivery. Directly observed treatment, short course (DOTS) was the recommended TB control approach at the international policy level between 1993 and 2005. DOTS emphasized political commitment, smear microscopy, standardized short-course treatment, quality drug supply, and standardized monitoring.

In 2006, the Stop TB Partnership[1] brought about improvements to these recommendations. Their efforts garnered much-needed attention to tackle the mounting burden of MDR-TB, which required reduced dependence on smear microscopy and increased laboratory capacity. The Stop TB strategy called for the expansion of DOTS in addition to addressing MDR-TB and HIV/TB coinfection. The Stop TB agenda also called for strengthening health systems, empowering people with TB, engaging all health providers, and promoting new research in TB control. The major drivers of these changes were five Green Light Committee projects focused on treating MDR-TB. They were providing data to the WHO and demonstrating that MDR-TB could be managed in high-burden settings.

Keshavjee explained that there are four key principles of epidemic control: (1) actively searching for disease in high-risk populations; (2) starting treatment quickly with the most effective treatment; (3) ensuring successful treatment; and (4) using preventive measures to prevent disease in people who are not sick. The DOTS program traditionally only delivers on the third key principle: ensuring successful treatment. The Stop TB strategy added a focus on the treatment of MDR-TB and HIV coinfection, along with other important factors, but the other three key principles were still not being applied.

In 2015, WHO developed the End TB strategy[2] as a general roadmap to TB elimination. It calls for early diagnosis with systematic screening of high-risk groups, treatment of DS-TB and DR-TB with patient support, and the use of preventive treatment. It also recommends collaborative management of comorbidities including HIV, putting in place bold policies and supportive systems, as well as fostering research and innovation.

The Zero TB Initiative,[3] established in 2014, was created to promote a comprehensive approach in the quest to eliminate TB, one community at a time. The initiative is working across the world to create islands of elimination with strong local partners in areas with high burdens of TB by utilizing a proven, comprehensive, community-based care platform. Its three core elements are search, treat, and prevent:

1 For more information about the Stop TB Partnership, see http://www.stoptb.org/ (accessed December 11, 2019)
2 For more information about WHO's End TB Strategy, see https://www.who.int/tb/post2015_strategy/en/ (accessed December 11, 2019).
3 For more information about the Zero TB Initiative, see https://www.zerotbinitiative.org/ (accessed December 11, 2019).

- Search: Targeted active case-finding with good diagnostics
- Treat: Effective treatment of DS and DR-TB with patient support
- Prevent: Improve infection control and expand preventive treatment

Keshavjee pointed out that the three core elements are compatible with WHO's End TB strategy. However, the Zero TB approach adds the strategic element of targeting municipalities as the unit of political intervention. He emphasized that country-level decision makers who wish to pursue a comprehensive approach should be confident and assured that the Zero TB approach is supported by a sound scientific evidence base and aligned with global policy recommendations, including WHO's End TB strategy.

Global, comprehensive TB control recommendations will not be made until locally focused coalitions take the initiative to run pilot projects and learn how to feasibly implement such programs, said Keshavjee. Global policy did not adequately address MDR-TB until there were data available; similarly, global policy will not integrate the comprehensive approach until there are more data from locations that have begun implementing the approach. Colleagues around the world are already in the process of expanding and strengthening the evidence base to support the comprehensive approach, which is attracting increasing attention among global TB policy makers and funders of TB programs.

Box 1- 1. Harvard Medical School Center for Global Health Delivery – Dubai

Salmaan Keshavjee, director of the Center and professor of global health and social medicine at Harvard Medical School, described the mission and activities of the Harvard Medical School Center for Global Health Delivery – Dubai. Harvard Medical School's mission is to nurture a diverse, inclusive community dedicated to alleviating suffering and improving health and well-being for all through excellence in teaching and learning, discovery and scholarship, and service and leadership. The Center contributes to this mission through its focus on the last phase of health care delivery. Research, medical education, and training activities at the Center are aimed at addressing some of the most pressing health challenges in the region and at improving health care delivery systems and patient outcomes for diseases prevalent in the United Arab Emirates, Middle East, North Africa, and neighboring regions in Africa, Asia, and Europe. The Center's areas of focus are diabetes and obesity, surgical care, infectious disease, and mental illness, with special consideration granted to projects that focus on the health of women and children. Cooperative and faculty research awards offered at the Center link Harvard researchers with local practitioners and scientists working to ask important questions and generate new knowledge around the myriad delivery gaps being faced. The Center has hosted workshops, symposia, and major courses for more than 2,500 attendees from more than 100 countries, with accompanying proceedings and policy briefs. Keshavjee noted that the practical goal of the Center's work is to affect meaningful changes through a two-pronged approach of accompaniment and praxis—that is, the process by which a theory, lesson, or skill is enacted, embodied, or realized.

1.1 WORKSHOP ORGANIZATION AND OBJECTIVES

The workshop Global Consultation on Best Practices in MDR-TB Care took place over four days:

- *Day 1: Principles of the Zero TB Initiative and novel MDR-TB treatment*

- *Day 2: Implementation of operational research conditions and an all-oral shorter regimen*
- *Day 3: Monitoring under operational research conditions and an all-oral shorter regimen*
- *Day 4: Post-exposure management of persons exposed at home to MDR-TB*

The workshop featured a combination of presentations, discussions, and small working group sessions. The workshop agenda and participant list are provided in Appendix 1.

These proceedings, Global Consultation on Best Practices in MDR-TB Care (Part 1), summarize the content of the first and fourth days of the workshop, which focused on how MDR-TB care fits within the comprehensive approach to search, treat, prevent, and ultimately eliminate TB. Companion proceedings, Global Consultation on Best Practices in MDR-TB Care (Part 2), summarize the second and third day of the workshop, which focused on implementing and monitoring operational research and an all-oral shorter regimen for MDR-TB.

The objectives of Day 1 were (a) to understand the components of a comprehensive program to drive down TB rates and (b) to understand how MDR-TB care fits into a comprehensive approach. Day 1 included presentations on the comprehensive approach used by the Zero TB Initiative, with a focus on the principles of active case-finding, treatment, and preventive therapy. Case examples illustrated the comprehensive approach and shared programs' experiences in applying the approach to the challenge of MDR-TB. Day 4 focused on post-exposure management of persons exposed to MDR-TB at home. Presenters and participants reviewed experiences in delivering preventive therapy for MDR-TB and brainstormed about approaches to delivering preventive therapy in households of patients receiving shorter regimens for MDR-TB disease.

1.2 ORGANIZATION OF THE PROCEEDINGS

These proceedings are organized into four chapters:

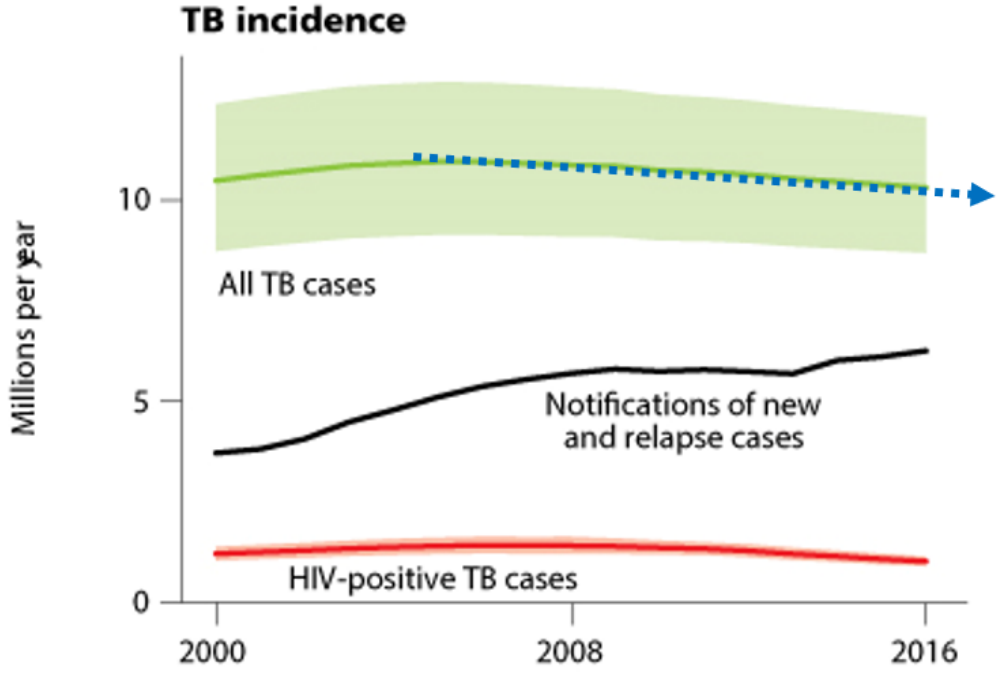
- *Chapter 1. Introduction*
- *Chapter 2. Zero TB Initiative: a comprehensive approach for TB elimination*
- *Chapter 3. The comprehensive approach applied in MDR-TB*
- *Chapter 4. Post-exposure management of persons exposed at Home to MDR-TB*

2 Zero TB Initiative: a comprehensive approach for TB elimination

2.1 ZERO TB INITIATIVE: FUNDAMENTAL PRINCIPLES AND CASE STUDIES

This chapter summarizes the opening presentation by Salmaan Keshavjee of Harvard Medical School, Brigham and Women's Hospital, Partners In Health, and Advance Access & Delivery. He laid out the scientific basis and components of a comprehensive program to drive down TB rates and explored how MDR-TB care fits into a comprehensive approach for TB elimination. He began with an overview of the current global burden of TB (see Figure 2-1). TB recently surpassed HIV to become again the biggest infectious killer of adults worldwide—causing around 2 million deaths each year—and TB remains that biggest killer of people living with HIV. The current TB situation is grim, he said. Prevalence surveys estimate that 10 million new cases of TB occur each year. However, only 60% of those cases are ever reported to health authorities. Global TB incidence is declining at a rate of just 1.5%-1.8% per year, which is insufficient to achieve TB elimination. The rate of decline has stagnated, despite well-established knowledge about how to lower TB rates faster.

Figure 2-1. Global TB incidence (2000-2016)



Source: Keshavjee presentation; data sources: Raviglione et al. 2012; World Health Organization 2017

2.1.1 What do we know about how to stop the TB epidemic?

Keshavjee traced the history of seminal discoveries and innovations that have evolved over the past 150 years in the effort to stop the global TB epidemic. He framed his discussion around a sequence of five pivotal observations that shape our current understanding of TB control.

Robert Koch identified Mycobacterium tuberculosis (MTB) in 1882 through a novel staining process. This discovery—now called smear microscopy—was momentous because it allowed for the detection of TB disease. Smear microscopy became the norm for identifying TB until the early 20th century, but its use was relatively short-lived because of its low sensitivity. Its effectiveness was first questioned as early as 1903.[4] Smear microscopy is only about 50% sensitive overall, with just 20% sensitivity in children and in people living with HIV. Wilhehm Conrad Röentgen invented the X-ray machine in Germany in 1895, which superseded smear microscopy and revolutionized TB diagnosis. This technique was a breakthrough for TB because X-ray is much more sensitive for diagnosing TB. A change in the lungs can be viewed with an X-ray image, with about 90% sensitivity for detecting TB. Chest X-ray diagnosis was used to implement early TB screening efforts. In 1897, Robert Phillip developed the first TB program, which began in Edinburgh, Scotland with hospital-based X-ray screening and was followed by the first community-based screening campaign.[5] The literature from the time emphasizes the importance of detecting TB as early as possible. By the time an individual's smear microscopy test is positive, he or she can already infect other people in the community.

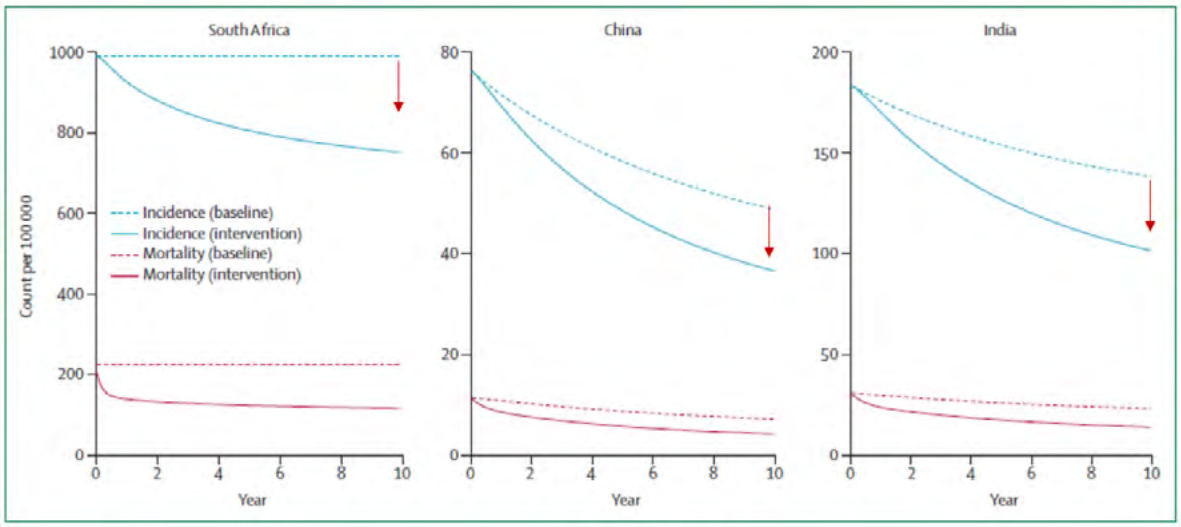
2.1.1.1 Active case-finding can detect TB cases and reduce transmission

The first breakthrough observation in TB control was that if a more sensitive test were used to screen for TB, then more people with TB can be found, said Keshavjee. Active case-finding using chest X-ray was a critical turning point in the development of TB care. Even though there was no cure for TB at the time, active case-finding helped to identify active cases, to reduce transmission, and to reduce TB mortality. Numerous studies from the early 20th century looked at the effectiveness of contact screening. In New York City in 1934, 25,170 close contacts were screened for TB and 824 cases were diagnosed, 90% of which were previously unknown (≥3000 cases per 100,000 people).[6] Similar results were found in a number of communities in the US and Europe in the 1940s and 1950s. Active case-finding contributed to finding new cases of TB at an earlier stage; it was identified as a critical step in reducing TB mortality through early case detection.[7] However, because there was no cure, people with TB were sent to sanitoriums; this also helped to reduce transmission.

Today, it is well established that active case-finding reduces TB in communities. Figure 2-2 illustrates the projected reductions in TB incidence and mortality compared to baseline over 10 years of active case-finding in South Africa, China, and India. Keshavjee noted that the rate of TB infection in children is a marker of transmission in a community, because children usually get TB from their parents or other infectious adults in the close social circle.

4 Williams 1903
5 Phillip 1937
6 Edwards 1940
7 Golub et al. 2005

Figure 2-2. Projected impact of sustained active case-finding after 10 years (South Africa, China, India)



Source: Yuen et al. 2015

2.1.1.2 Emergence of drug-resistant TB strains

The second pivotal observation in the history of TB control was that drug resistance emerged with each new drug used, while less drug resistance was observed when drugs were used in combination. A breakthrough in TB treatment occurred in 1943, when streptomycin was isolated in the laboratory of Selman Waxman; the first TB patient was treated and cured with the drug in 1944. Over the next two decades, other drugs for treating TB were developed: para-aminosalicyclic acid (PAS) (1948); thioacetazone (1948); isonicotinic hydrazide (INH) (1951); pyrazinamide (1952); cycloserine (1952); rifampin (1957); and ethambutol (1962). Some of these drugs are still used today as part of first- and second-line treatments for TB.

From the beginning, it was understood that improper treatment led to drug resistance. The first 100 patients treated with streptomycin had a high relapse rate, and many of their isolates were resistant to streptomycin. Although the first patient treated with streptomycin in 1944 was cured, a 1948 trial discovered that about 40% of patients relapsed and had developed streptomycin resistance. When streptomycin was given with PAS, however, the patient's relapse rates were lower and they developed resistance less frequently. People thought that isoniazid would be a cure-all when it was developed in 1951, but it soon became clear that it also led to drug resistance. Rapid selection of INH-resistant strains was observed when isoniazid was used alone, but less isoniazid resistance was observed when isoniazid was given with streptomycin. Rifampin resistance was also observed as soon as it was used.

This lesson was reinforced as it occurred with each new drug: resistance develops when drugs are not given in combination. This is attributable to various factors, including the nature of the bacteria (including the fact that TB bacteria divide slowly) and the penetration of the drug. The principle that multiple drugs must be used is the cornerstone of knowledge about antimicrobial resistance, which applies to TB treatment as well as to cancer treatments and antivirals. Multiple mechanisms must be hit at the same time for a sustained cure. "The best drugs must be used up front for the best chance of cure," he emphasized.

2.1.1.3 Drug-resistant strains of TB can be transmitted to others

The third critical observation was that drug-resistant strains from TB patients retain their ability to be transmitted to others. After the advent of drugs to treat TB, many people speculated that drug resistance would create non-transmitted bacteria, based on the presumption that chromosomal mutation would lead to less fit bacteria. This hypothesis was discredited as early as 1955. At the time, WHO had recommended that poor countries use isoniazid monotherapy to reduce the cost of TB treatment. The British Medical Research Council was alarmed by this recommendation, as it contradicted emerging evidence about drug resistance. They conducted the first national drug-resistance survey in Britain and confirmed that drug-resistant strains could be transmitted. Although streptomycin, PAS, and INH were relatively new to the market at the time, primary resistance to all three drugs was found in the surveyed community. This indicated that the drug-resistant bacteria had been transmitted, because resistance was found in patients who had already been treated with one of the three drugs. It is now understood that drug-resistant strains are as fit as drug-susceptible strains and can still be easily transmitted, so drug resistance cannot be ignored in TB treatment.[8]

2.1.1.4 Effective treatment for TB stops transmission rapidly

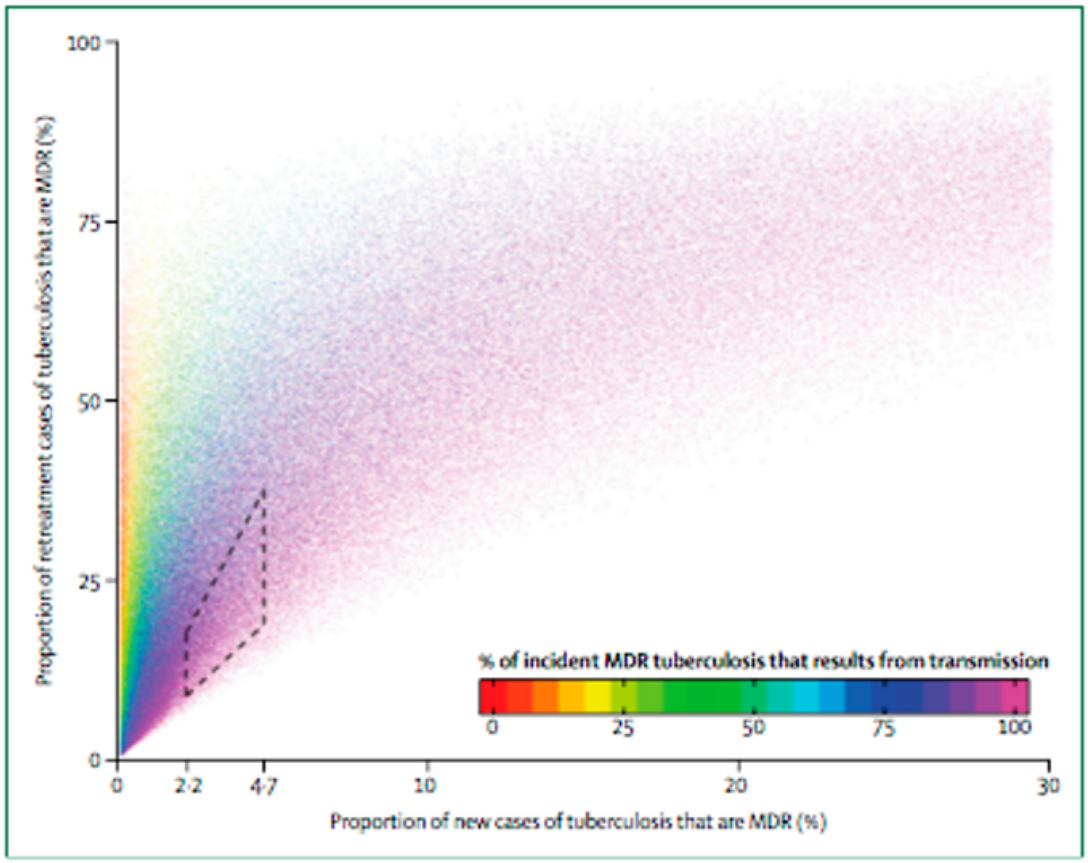
The fourth crucial observation was that effective TB treatment stops transmission rapidly. When patients are started on an effective TB treatment regimen, they are less infectious after as little as 24 hours of treatment. Modern medicine and research were largely focused on syphilis and TB in the 20th century, noted Keshavjee. In 1959, Richard Riley studied how long people with TB were infectious by using air transmission tests with guinea pigs.[9] Riley showed that smear-positive patients with untreated drug-susceptible TB transmitted the infection to 100% of the guinea pigs; smear-positive patients who were treated transmitted the infection to just one guinea pig. Riley also showed that if drug-resistant patients were treated with drug-sensitive TB regimens, the guinea pigs still became infected. In sum, TB transmission is greatly reduced just 24 to 48 hours after a patient begins treatment, even though patients are still coughing up bacteria.

2.1.1.4.1 The majority of DR-TB is due to transmission

Many clinicians still presume that MDR-TB is the result of poorly executed TB programs. While DR-TB can be acquired, the majority of MDR-TB is caused by person-to-person transmission. Figure 2-3 shows modeling data estimating the proportion of incident MDR-TB that is due to transmission, on the basis of WHO estimates. This highlights the critical importance of giving patients the best therapy immediately to stop the transmission of DR-TB or DS-TB.[10]

8 Becerra, Huang and Lecca et al 2019
9 Riley et al 1995
10 Kendall et al. 2015

Figure 2-3. Proportion of cases of MDR tuberculosis that arise by transmission



Source: Dheda et al. 2017; adapted from Kendall et al. 2015

2.1.1.4.2 Treating TB infection is essential to stopping transmission

The fifth critical observation was that treating TB infection—wherein individuals have been exposed to TB but have not yet progressed to active disease—is an essential part of stopping transmission. This was first observed in the 1950s when a community-based treatment model was implemented in Alaska based on good outcomes from similar models in India. The US Public Health Service built health facilities and began a campaign of active case-finding using chest X-ray. All forms of TB disease were treated, but when new cases emerged the following year, it became clear that there were cases of "latent" TB infection. To explore this discovery, George Comstock and colleagues conducted the first community-based trial of TB infection treatment using isoniazid prophylaxis. TB transmission declined rapidly as a result of this strategy of active case-finding, treatment of all forms of TB disease, and treatment of contacts with isoniazid prophylaxis. Between 1950 and the early 1960s, the annual risk of TB infection among children aged 1-3 years in Alaska dropped from 25% to virtually nil.[11] The experience in Alaska demonstrated that there is a successful path to rapidly reducing TB.

Keshavjee explained that global TB policy has almost completely ignored the billions of people with TB infection. Many people are infected with TB, but only 6%-10% of those with TB infection will develop TB disease within two years of being infected. The bulk of the risk is in the first two years after exposure and infection, so it is very important to detect and treat people during the

11 Kaplan et al. 1972

first 2 years after exposure. An estimated 10 million people develop TB each year. If each of those people has 2-3 contacts who also need treatment, then 20-30 million people need to be treated for TB infection per year. This is not an impossible task, he said.

Global TB control strategies have focused overwhelmingly on individuals with active TB disease. In 2012, there were approximately 3 million notified cases of smear-positive, pulmonary TB worldwide. However, with TB's limited case detection rate, not all patients with smear-positive pulmonary TB are being diagnosed and treated. The sensitivity of smear testing for detecting pulmonary disease is only 50%-60%, so a large population of people with smear-negative, pulmonary disease are either not being diagnosed or not being prioritized. Furthermore, only 60%-70% of TB is pulmonary, so there is a large population of people with extrapulmonary TB who are not being diagnosed. These undiagnosed or de-prioritized forms of TB are more common in vulnerable populations. Current TB policies disproportionately miss children and people living with HIV. He estimated that, as a result of TB control strategies skewed toward the 3 million people with smear-positive TB, there are about 6 million "missed" cases of TB each year.

Treating "latent" TB infection is a critical component of the strategy for TB elimination, said Keshavjee. An incorrect characterization of the distinction between latent infection and active disease was propagated in the years after Comstock's seminal work in Alaska. Latent infection was wrongly presumed to be asymptomatic and not contagious, while active disease was presumed to be symptomatic and mostly contagious. In recent years, research on the pathophysiology of TB has driven a shift toward rectifying this mischaracterization by modeling TB as a spectrum based on the balance between bacteria and the immune system. Patients may spread mycobacteria at intermediate points along this spectrum. In the past, patients with PPD-positive skin test results who did not have active disease were generally not treated; it is now understood that they may have intermittent disease and thus may be periodically transmitting. As the understanding of the spectrum model improves, it is becoming clear that treating TB infection is not merely an option—it is a core intervention that is necessary to stop the epidemic.

2.1.1.4.3 Effectiveness of preventive therapy

Preventive therapy protects the people with TB infection who have simmering, low-grade disease as well as people who will progress to full-blown, active TB. The early research in Alaska was just the beginning of the evidence for the protective effect of preventive therapy. About two dozen randomized controlled clinical trials of preventive therapy using various regimens and in different populations—including children, people with and without HIV, contacts of people with TB, and people who are TST-positive—demonstrate that the effectiveness of preventive therapy is incontrovertible. Meta-analyses of these trials show that on average, preventive therapy has a >=60% protective effect in high-risk groups. This means that TB disease was prevented in more than half of the people who would have otherwise developed it. Evidence supports the use of preventive therapy for those exposed to DR-TB as well. A meta-analysis of 25 studies found that 7.8% of household contacts of MDR-TB patients developed TB. Most of the contacts who developed TB did so within 3 years of exposure. 47.2% of these contacts had latent TB infection (LTBI).[12]

2.1.1.4.4 Preventive therapy saves lives

It may seem that preventive treatment is not worth the effort that it will take to deliver it to high-risk groups. When considering individual risk, the value of preventive therapy becomes very clear. Individuals who develop DS-TB have a 10% risk of dying from the disease if they are diagnosed and treated. Globally, the risk of dying from MDR-TB if a patient is diagnosed and treated is around 50%, but since only 20% of MDR-TB cases are diagnosed, the actual risk of

12 Shah et al 2014

death for a person with MDR-TB is roughly 75%. XDR-TB outcomes are even worse. Because so few XDR-TB cases are detected, the risk of death from XDR-TB is around 98%. Since 1 in 10 contacts gets TB, 1 in 10 contacts faces the same risk of death from TB. Roughly 1% of DS-TB contacts will die, while 7.5% of MDR-TB contacts and 10% of XDR-TB contacts will die. Preventive treatment addresses these risks among those exposed to TB.

2.1.1.4.5 TB cannot be stopped by focusing on index cases

TB programs tend to address patients with TB as individuals with disease, but patients with TB should be thought of as part of a community. Some members of a community will have TB, which is why active case-finding is important. Some members of a community will have been exposed to TB and may or may not subsequently develop TB disease. Preventive treatment addresses this part of the community. TB programs cannot stop TB by focusing only on the index case. In order for modern TB programs to succeed, the unit of intervention must change from individuals to communities. Historically, successful TB programs have been successful by identifying communities at risk and targeting interventions at the community level.

2.1.2 Why the global TB epidemic has not been stopped

Keshavjee highlighted the history of divergent TB recommendations for rich and poor countries, which has led to the implementation of bad biomedical practices. In 1964, WHO's Expert Committee on Tuberculosis discouraged the use of isoniazid preventive therapy on the basis of cost, logistical difficulties, and the likelihood of default. WHO's Expert Committee on Tuberculosis was presented with evidence from George Comstock's research showing the lasting benefits of preventive therapy; yet, they deemed the use of isoniazid preventive therapy "irrational."[13] In 1982, WHO and its partner, the International Union Against Tuberculosis and Lung Disease, argued that 'in practice [isoniazid preventive therapy] has virtually no role in developing countries."[14] This attitude was reaffirmed in 1993 when WHO declared that TB was a global emergency. This declaration was accompanied by the development of the directly observed treatment–short course (DOTS) approach, which has been the primary focus of TB control efforts for the past 25 years. DOTS emphasized political commitment, but it called for diagnosis with sputum-smear microscopy, despite the knowledge that X-ray technology had been known to be superior to smear microscopy for nearly a century. Standardized short-course chemotherapy under DOTS does not involve testing for drug sensitivity even though isoniazid mono-resistance is between 8%-28% in most settings. Thus, the four-drug regimen will result in of patients developing MDR-TB. Additional components of DOTS are a regular supply of high-quality drugs and standardized recording and reporting. While DOTS was simple, easy, and low-cost, it was scientifically unsound. The DOTS approach does not adhere to three of the four basic principles of epidemic control (shown in Box 2-1); it does not involve active case-finding, it does not call for correct regimens—which would require some kind of drug sensitivity testing—and it does not call for the treatment of contacts.

13 Comstock et al 1979
14 McMillen 2015

Box 2--1. Basic principles of epidemic control

- Search actively for newly-infected people among the contacts of current patients using X-ray or some other diagnostic tool.
- Start therapy quickly for people with disease; give the safest, most effective multidrug therapy in the shortest time.v
- Ensure adherence to therapy with supports.
- Treat all contacts that do not yet have disease with post-exposure prophylaxis.

2.1.3 Case studies of TB control

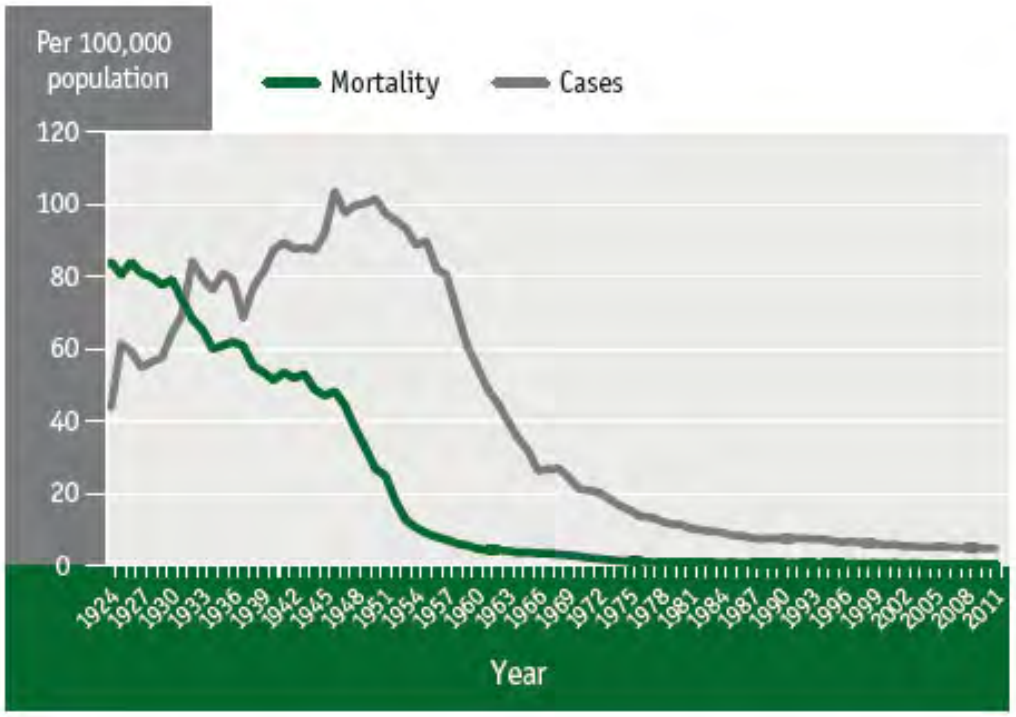
To demonstrate that TB control and elimination are achievable goals, Keshavjee presented case studies from the following locations:

- Canada (1924-1994)
- Alaska (1950s-1960s)
- New York City (1988)
- Russia (2000s)
- Singapore (1980-2010)
- Taiwan (2005-present)
- Chuuk, Federated States of Micronesia (2009-2012)

2.1.3.1 Canada (1924-1994)

Evidence from Canada, as well as other countries, suggested that, in some settings, X-ray screening alone can bring down TB mortality rates. This occurred prior to the availability of TB antibiotics (see Figure 2-4).

Figure 2-4. TB case rates and death rates in Canada (1924-1994)



Source: Keshavjee presentation

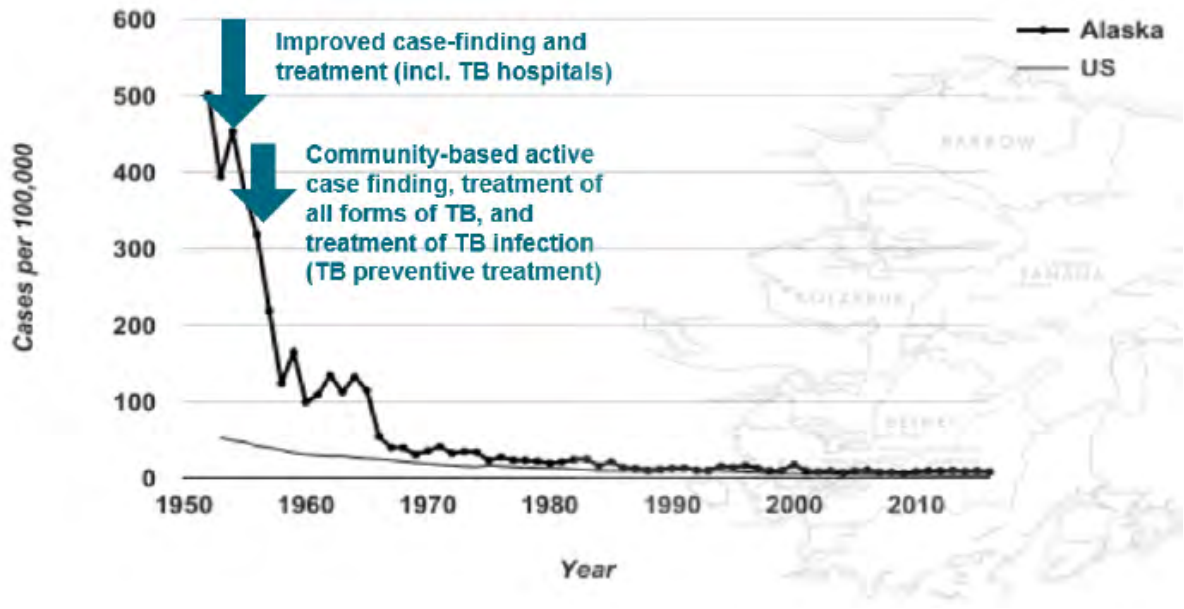
2.1.3.2 Alaska (1950s-1960s)

The experience in Alaska demonstrates that adding antibiotics to X-ray screening brings TB mortality down even more quickly.[15] Prior to Comstock's intervention, Alaska had some of the highest rates of TB in the US, with a prevalence of ~2,000 per 100,000 population; in some areas, 25% of infants became infected in the first year of life. People were living with malnutrition, inadequate housing, poverty, and alcoholism, all of which contribute to the development of TB disease. Between 1953 and 1956, the annual mortality from TB fell to 282 per 100,000 population. Initially, a hospital-based program was implemented, but as data emerged from India showing that community-based treatment was possible, the US Public Health Service started its own community-based program. They first initiated active case-finding through systematic screenings of families of TB patients and high-risk communities and then initiated community-based treatment. After the observation that TB seemed to reappear in families that had been screened and active cases were already treated, a randomized controlled trial of TB preventive treatment using isoniazid was initiated in 1957. After community-wide TB screening and treatment, people without TB disease were randomized to receive isoniazid or placebo. The findings were remarkable, said Keshavjee. Rates of TB in the intervention group were less than half of the rates in the control group who did not receive preventive treatment, and the risk of getting sick with TB was reduced by 70% compared to those who were not given preventive treatment. This treatment model was rapidly rolled out community-wide in larger groups. Figure 2-5 illustrates that with this combination of active case-finding, treatment of active disease, and provision of TB preventive treatment, rates of TB in Alaska dropped very rapidly. TB preventive treatment became the standard of care in the US by the early 1960s. Follow-up studies in Alaska also

15 Comstock et al 1979; Porter and Comstock 1962

demonstrated that people who received isoniazid prophylaxis had a reduced risk of TB that endured over the next 19 years.

Figure 2--5. TB incidence rates in Alaska and the US (1952-2016)



Source: Keshavjee presentation

2.1.3.3 New York City (1988)

In 1988, New York City had seen the number of cases of TB increase by nearly three-fold in just 15 years. In central Harlem, the case rate of about 200 per 100,000 people exceeded that of many lower-income countries. Nearly 20% of patients with TB in the city had MDR-TB, with the proportion of MDR-TB patients more than doubling in 7 years. In 1991, New York City had 3% of the country's population but it accounted for 61% of all MDR-TB cases in the entire country. They implemented a program of active case-finding, treatment of all forms of TB, treatment of TB infection, and patient support; teams of nurses were assembled to find patients and deliver their medicines.[16] As a result, the case rate dropped from a peak of 51.3 per 100,000 population in 1992 to just 6.9 per 100,000 in 2016.

2.1.3.4 Russian Federation (2000s)

After its economic collapse in the 1990s, Russia faced an emerging MDR-TB epidemic that continues today. The country had very high rates of incarceration, detention, alcoholism, and unemployment that contributed to the spread of disease, coupled with a surging HIV epidemic. They had discontinued some effective components of Soviet-era community-based TB control. In Tomsk Oblast, they revived a comprehensive strategy for TB control that rapidly reduced TB incidence. By treating all patients in a TB program (supported by the Global Fund), TB rates dropped rapidly by 55% and TB mortality dropped by 80% (see Appendix 2). Insights from Tomsk were combined with solid transmission control approaches elsewhere in Russia. In Voronezh, the model of active case-finding, treatment of all forms of TB, treatment of latent

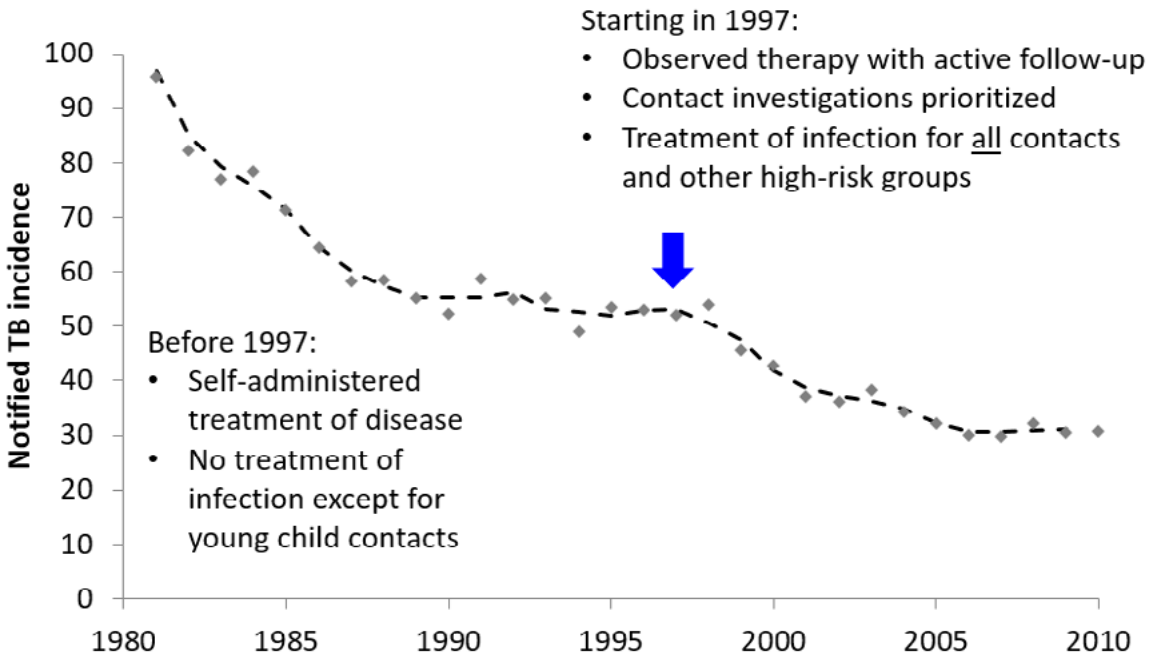
16 Shalo 2010a; Shalo 2010b

TB, and patient support dropped TB rates from 69 per 100,000 to 10 per 100,000 (Appendix 3).

2.1.3.5 Singapore (1980-2010)

In Singapore, TB incidence stagnated during the 1990s. During that time, treatment of disease was self-administered, with no reporting of outcomes; there was no treatment of TB infection except for in young children who were household contacts of TB patients. This led to a drop in the TB incidence rate that was followed by a plateau (see Figure 2-6). To combat the stagnating TB incidence, they instituted a new program with key components of directly observed therapy with active follow-up of patients struggling with adherence, prioritization of contact investigations, and treatment of infection for all contacts as well as high-risk groups, such as people in prisons, nursing homes, and mental institutions. Following implementation, TB incidence began to drop again and continued to decline through the 2000s.

Figure 2-6. Notified TB incidence rate per 100,000 population in Singapore (1980-2010)



Source: Chee and James 2003

2.1.3.6 Taiwan (2005-2016)

Taiwan had a similar experience to Singapore in the 2000s. Using scientific literature from NYC,[17] they implemented a program of active case-finding, treatment of all forms of TB, treatment of TB infection, and patient support. Within a decade, their TB incidence rate had dropped from 73 cases to 44 cases per 100,000 population (see Appendix 4).

2.1.3.7 Chuuk, Federated States of Micronesia (2009-2012)

A global reduction in incidence of only 1.5% per year is not enough when New York, Alaska, Russia, and myriad other sites have observed much greater annual reductions in incidence. New York is not the only example of successful reductions in incidence in settings that had a high burden of MDR-TB. In 2007, Chuuk expe-

17 Keshavjee noted that Taiwan is not a member of WHO, so it does not receive program advice from WHO consultants.

rienced an MDR-TB outbreak and received support from the US Public Health Service. They screened contacts, treated active cases, and offered contacts prophylactic treatment for MDR-TB exposure with fluoroquinolone plus another drug. Among the 119 infected contacts, 15 refused and 104 began treatment for MDR-TB infection. Of the 104 who initiated treatment, 93 (89%) completed treatment, while four contacts discontinued due to adverse effects. None of the 104 contacts who received MDR-TB infection treatment of any duration developed MDR-TB disease; however, 3 of 15 contacts who refused treatment and 15 unidentified contacts developed MDR-TB disease.[18] These interventions eradicated the MDR-TB epidemic, although a few MDR-TB cases were later found among people who did not accept treatment and others who entered the island with TB (see Appendix 5). The experience in Chuuk shows that successful TB control is possible, even in communities with MDR-TB.

2.1.3.8 Comprehensive programs are needed to eliminate TB

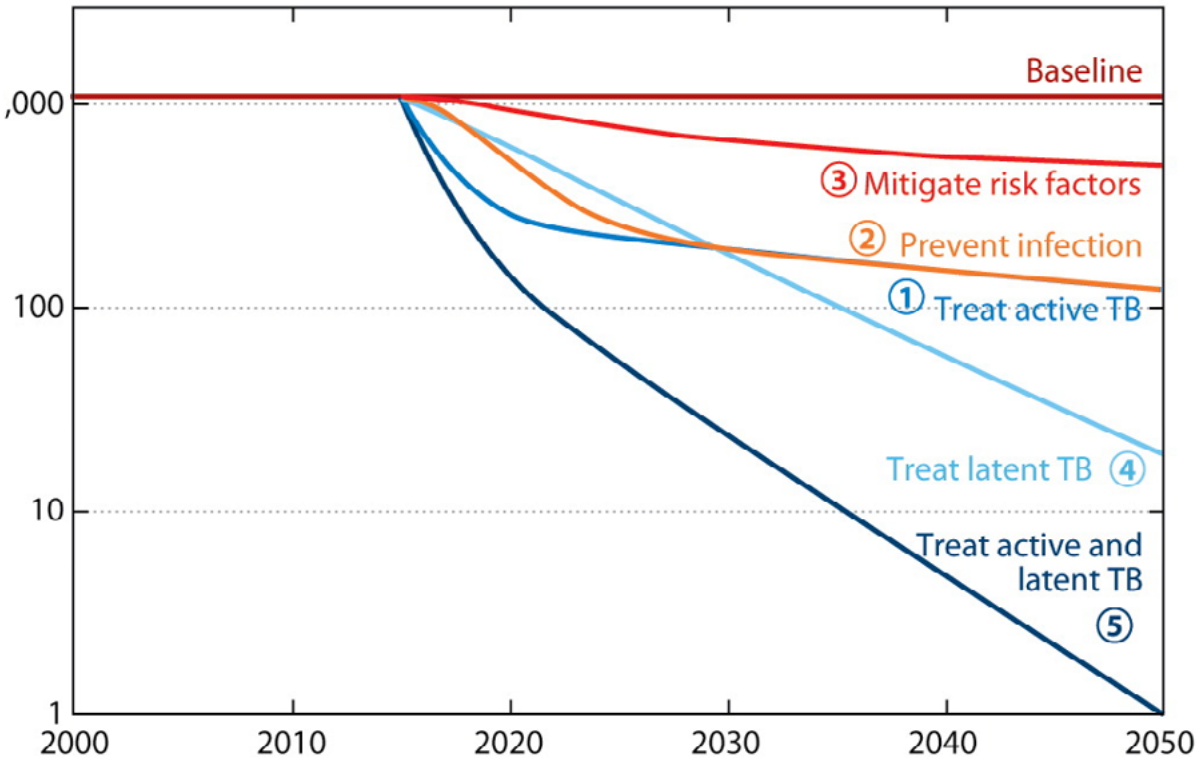
The common feature of these successful case examples is that they implemented comprehensive programs, said Keshavjee. A comprehensive program has three core elements:

- **Search** actively and test properly
- **Treat** effectively and support through treatment
- **Prevent** exposure and treat exposure

All three components must be carried out simultaneously, because the different parts rely on each other to be effective. For years, the mistake in TB control has been to focus on treating only certain forms of TB. Programs that are good but not comprehensive often have initial positive impact on TB incidence, but the rate will eventually plateau unless all components of the Search-Treat-Prevent approach are put in place (see Figure 2-7).

18 Bamrah et al 2014

Figure 2-7. Projected impact of strategies to eliminate TB by 2050



Source: Dye et al. 2013

At the UN High Level Meeting on Ending TB, all member countries agreed to treat a total of 30 million people for TB infection by 2022. The global community has known and acknowledged that a comprehensive approach is necessary for TB elimination, yet many good TB programs are not using a comprehensive approach. In Peru, for example, the good but non-comprehensive TB program catalyzed an initial decrease in TB incidence in the 1990s, which has plateaued since the early 2000s. Similarly, in Thailand, TB incidence dropped quickly for several years before reaching a plateau at 160-180 cases per 100,000 population, where it has remained since around 2012. Mexico is dealing with a similar stagnation of TB incidence after an initial drop.

2.1.4 Zero TB Initiative: a social strategy for TB elimination

Keshavjee introduced the Zero TB Initiative, a civil society initiative that is an alliance between Harvard Medical School, the Stop TB Partnership, IRD, Advance Access and Delivery, and Partners In Health. The purpose of this alliance is to demonstrate the strategy for TB elimination through a comprehensive approach to driving down TB based on the Search-Treat-Prevent chakra. The Zero TB Initiative (ZTBI) and Zero TB Cities Projects are working to create islands of elimination by supporting local coalitions against TB. Partner sites commit to using a comprehensive approach for epidemic control by utilizing all components of the Search-Treat-Prevent strategy. Figure 2-8 provides more detail on the initiative's guiding principles.

Keshavjee explained that this initiative is about more than just TB—it is a delivery program that can be used to strengthen health systems. It is broadly realized that an effective TB program is a wedge to build and strengthen programs against other public health challenges. Community-based, patient-centric programs are the only viable approach against infectious diseases such as TB, hepatitis C, and HIV, but also against diabetes, heart disease, and other health challenges. A platform for community-based care delivery for TB and DR-TB links the clinic with

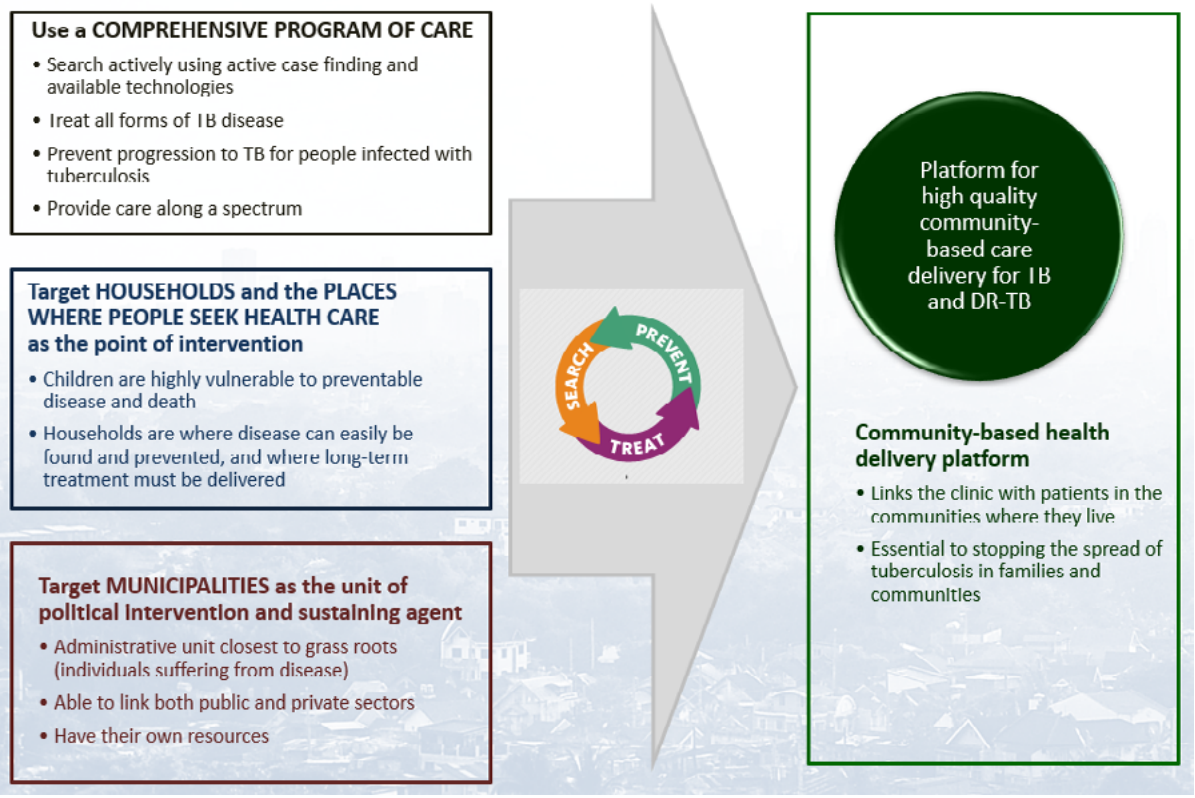
patients in the communities where they live, work, and seek treatment. This is essential to stopping the spread of TB in families and communities. Extending the reach of the clinic is actually about creating a platform for health delivery that is exactly the same platform needed to deal with chronic diseases—such as diabetes, heart disease, COPD, and mental health issues—in the 21st century. TB can be seen as an entry point into developing this new platform for health care delivery. Keshavjee noted that some implementers raise concerns about the cost of a comprehensive model since the upfront costs are higher than a non-comprehensive approach. Initially, active case-finding and expanded treatment increase the overall cost of TB control. As an example, colleagues from New York City have reported that when New York began fighting TB in 1988, they spent US$300-400 million per year on patient care; however, now they spend US$13 million per year. Keshavjee suggests that instead of spending the same amount every year on a non-comprehensive approach, programs should invest now in comprehensive care with confidence that the cost of TB care will decrease as they move toward elimination.

The Search-Treat-Prevent model is actually more complex than the simple name might suggest. Colleagues in Pakistan have developed the model and implemented a comprehensive TB control program. In areas where they implemented a comprehensive approach, they saw a surge in notifications, followed by a reduction in notifications.[19] A similarly-comprehensive program has been implemented in northern Lima, Peru. They began community-based screening in a community where planners expected TB rates of 70 per 100,000, but the yield of testing has been over 700 per 100,000 in some zones. Among army recruits, the rate is over 1,000 per 100,000.

Many cities have joined the Zero TB global coalition. Coalitions in Thailand, China, Germany, Russia, South Africa and other countries are pushing this model forward, along with other partners. Box 2-2 lists the current, new, and potential Zero TB Cities and districts.

19 Keshavjee noted that the brief increase from 2014-2016 represents a lapse in funding which led to a brief increase in TB notifications.

Figure 2-8. Zero TB Initiative



Source: Keshavjee presentation

Box 2-2. Current, new, and potential Zero TB cities and districts

Almaty, Kazakhstan**
Balti, Moldova
Bangkok, Thailand
Batumi, Georgia
Chennai, India
Dhaka, Bangladesh*
Durban, South Africa**
Giessen, Germany
Hai Phong, Vietnam
Hanoi, Vietnam
Ho Chi Minh City, Vietnam
Indore, India**
Karachi, Pakistan
Kathmandu, Nepal**
Lima (Carabayllo), Peru
Manila, Philippines**
Mexicali, Mexico**
Mtata, South Africa
Mumbai, India**
Muscat, Oman**
Nakhon Si Thammarat, Thailand
Odessa, UkraineShenzhen, China*
Sofia, Bulgaria**
Tbilisi, Georgia**
Ulaanbaatar, Mongolia**
Vladimir, Moscow

* First of multiple cities planned

** Discussions of alignment underway

2.2 TARGETED ACTIVE CASE-FINDING

Courtney Yuen, Harvard Medical School, USA, discussed the conceptual framework of active case-finding and the issues programs should consider when implementing such strategies. Each year, around 40% of people who get TB are missed by health systems, with the percentage of missed cases remaining consistent in recent years.[20] This large share of missed cases underscores the need for targeted active case-finding to find and treat more people with TB.

2.2.1 The need for active case-finding

Yuen explained that missed diagnoses and delays in treatment[21] lead to more transmission of TB.[22] She provided an overview of the data that support the impact of active case-finding in reducing treatment delays and consequently reducing TB transmission. Table 2--1 illustrates the relationship between delayed treatment of TB patients and occurrence of TB infection among the patients' household contacts, among one cohort in China and one in the US. In the two cohorts, the length of treatment delay ranges from less than 1 month to more than 3 months. As the treatment delay increases for the index patient, the percentage of household contacts with TB infection also increases. Conversely, transmission of TB decreases when index patients are treated promptly.

Table 2- 1: Delayed TB treatment increases transmission

TB index patient treatment delay	*Household contacts with TB infection*	
	China	USA
<30 days	8%	24%
30-60 days	20%	
60-90 days	26%	
>90 days	27%	40%

Sources: Lin et al. 2008; Golub et al. 2006

2.2.2 Active case-finding reduces TB in communities

Yuen defined targeted, active case-finding as seeking out and screening individuals with a high risk of having TB. Targeted active case-finding is an effective strategy to (1) find more individuals with TB and (2) promote early diagnosis. Two cluster-randomized trials have investigated the effects of active case-finding interventions on TB prevalence in communities, providing evidence that active case-finding can indeed reduce TB incidence. One study in Rio de Janeiro, Brazil, found that after 5 years, communities with active case-finding had 15% fewer reported cases than control communities.[23] A study that observed the effects of active case-finding interventions in Zambia and South Africa found that after 3 years, communities with active case-finding had 18% lower TB prevalence and 55% lower rates of TB infection in children.[24] Both studies used relatively short time frames—measuring TB after 3 or 5 years—and both studies observed decreases in TB in communities after a few years of active case-finding implementation.

20 World Health Organization 2017
21 Treatment delay is the amount of time between the onset of a patient's TB symptoms and the patient's diagnosis and treatment.
22 Yuen et al 2015
23 Cavalcante et al 2010
24 Ayles et al 2013

The projected impact of active case-finding interventions has been modeled based on epidemic data from China, India, and South Africa. Researchers modeled a 10-year sustained active case-finding program that would increase case detection by 25% compared to current detection rates. This model projects that if 25% more TB cases are diagnosed and treated, then after ten years[25]:

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

She noted that this model only projects the impacts of active case-finding and putting those with TB on treatment; it does not account for the impacts of preventive therapy.

2.2.3 Who should be screened?

It is important to critically evaluate which groups to screen when designing an active case-finding program, Yuen remarked. TB is not evenly distributed among populations; in each community, there are high-risk and low-risk groups. The highest risk group is a small cohort, thus requiring fewer resources to screen them. However, if TB programs only target high-risk groups for screening, people with TB in lower-risk groups will not be detected. Screening greater numbers of people reduces TB in populations, but it also increases the resources required for screening. TB programs must seek to balance feasibility with impact in designing their active case-finding strategies. For example, contacts of people with TB are an example of a group with high individual risk that, when actively screened for TB, yields low population impact. The Stop TB Partnership—which has funded many grants for TB programs—has found that some contact investigation programs do find TB cases (among contacts), but because TB contacts represent such a small proportion of the population, these contact investigation programs have low impact at the population level.

Ultimately, decisions about which groups to screen should be based on local epidemiology. See Box 2-3 for an example from the US. Reducing TB in a given setting requires careful consideration of (1) which population groups have the bulk of TB cases, (2) how many people are in that group, (3) how many cases can be found in that group, and (4) what resources would be required to screen that group. Yuen emphasized that screening very high-risk populations may yield only a small number of cases, so targeting only the highest risk groups will not lower TB rates in most communities. Additionally, populations that are easier to screen (e.g., school children) may be at lower risk of having TB. Decision makers should consider whether screening easy-to-screen groups is an effective use of resources.

Yield is not the only consideration. Many program designers focus on the percentages of people who are likely to have TB in groups that are screened. This is an important consideration, but vulnerability and the consequences of missed cases should not be overlooked. For example, although child contacts of TB patients comprise a small proportion of the TB burden, a child with a missed case of TB is vulnerable to developing potentially fatal meningitis. The impact of finding missed cases is also critical. It is a success if active case-finding detects TB in a person 3 months before they would have come for treatment on their own. However, it is an even greater success to detect TB in a person who would not have gone to a health facility at any point, because this kind of detection prevents transmission which would otherwise occur. "Additionality" is another key consideration: the goal is to find more cases, as well as to speed detection of cases that may have been found anyway.

25 Azman et al 2014

Box 2-3. Using local epidemiology to inform screening decisions: example from the US

The burden of TB in the US is relatively low, but it is not decreasing. It has been speculated that TB is not declining in the US because it is not being detected in the larger but lower-risk groups that account for many cases of TB each year. The highest risk of TB in the US is found among TB contacts (TB rate of around 600 per 100,000). However, because the US has so few TB patients overall, there are only around 100,000 TB contacts in the country. Contact investigation in the US targets contacts from the household, workplace, and other settings—on average, there are ten contacts per TB case. Still, contacts of TB account for less than 500 cases of TB in the US each year. Homeless people and people living with HIV comprise a risk group that is about 17 times larger than the TB contact group. Although the TB rate in this group (30-80 cases per 100,000) is lower than the rate among TB contacts, more TB cases are found among homeless people and people living with HIV (around 800 cases per year) than contacts because the group is much larger. The US has strong screening guidelines for contacts, people who are homeless, and people living with HIV. However, the bulk of TB in the US actually occurs in a group comprising immigrants and people with diabetes (about 6,800 cases of TB per year). The rest of the US population has a TB risk of only around 1 per 100,000, which is very low. Even though the group of immigrants and people with diabetes has a substantially lower TB rate (about 5-15 per 100,000) than the other two high-risk groups, the size of this group is much larger—about 73 million people. Some have argued that making progress in reducing the burden of TB in the US will require active case-finding and treatment of infection. Screening everyone in this group would be an enormous undertaking that would require major investments in testing and treatment programs.

2.2.4 Screening and evaluation methods

It is also important to balance resources and impact when choosing screening and evaluation methods, said Yuen. "Screening" refers to how people who require diagnostic testing for TB are identified. "Evaluation" refers to the procedures used to diagnose TB. Figure 2-9 shows different screening and evaluation methods. Those on the left side require the fewest resources, but also are the least sensitive; those on the right require more resources but will find more cases. For both screening and evaluation, the easiest tests are the least sensitive and the hardest tests are the most sensitive. Inevitably, programs must accept some tradeoffs between the resources that are required and the sensitivity of the screening and diagnostic tools. No single solution is best for every setting and population. Currently, most programs skew toward the easier, less sensitive end of the continuum. However, in order to maximize impact, these programs need to move toward more sensitive methods.

An example of a simple but low-sensitivity method of identifying people for evaluation is to ask if they are coughing. This is a very common method, especially in health facilities,[26] because a person with minimal training can ask people if they have been coughing for more than 2 weeks and refer them to submit a sputum sample for smear microscopy. Individuals who do not report a cough persisting 2 weeks or more are not evaluated. Although this method requires few resources, it is not very sensitive;

26 Cough screening in health facilities can increase notifications. Merely coughing in a health facility would not otherwise indicate that an individual should be screened for TB. Optimizing health facilities for TB detection and taking advantage of the patients passing through health centers is a worthwhile approach for increasing TB detection, but additional methods are required to find TB cases in those who are not visiting health centers.

prevalence surveys consistently show that over half of people with bacteriologically confirmed TB do not report prolonged cough. Rudimentary cough screening can be augmented with a symptom and risk questionnaire. Asking about the presence of any TB symptom (e.g., cough, fever, weight loss, night sweats) and risk factors (e.g., previous TB or TB in the family) takes more time and somewhat more training, but it captures more people with TB. However, it also requires more resources, such as requiring the lab to run more tests. Chest radiography is even more sensitive than symptom screening, but it requires specific infrastructure to be available.

The spectrum of evaluation processes is similar to that of screening processes, ranging from smear microscopy to mycobacterial culture and radiography, and it requires a similar tradeoff between resources and sensitivity. Smear microscopy is the most common diagnostic test across the world, but it only detects 65% of culture-confirmed pulmonary TB cases. GeneXpert is better, with around 90% sensitivity for culture-confirmed TB, but it requires more resources in terms of the equipment, cartridges, and lab capacity. It would be even more sensitive to perform mycobacterial culture or ensure that everyone has a chest radiograph, but both require even more infrastructure and human resource capacity. Yuen noted that X-ray machines are expensive, but so are GeneXpert cartridges. When considering cost, it is important to consider that investment in infrastructure adds value over time as well as system capacity.

Yuen concluded with a summary of three key takeaways from her presentation (see Box 2-4).

Figure 2-9. TB screening and evaluation methods

	Easiest (fewest resources required) → Hardest (most resources required)		
	Least sensitive for case detection → **Most sensitive for case detection**		
Screening method	Ask if person is coughing	Symptom and risk questionnaire	Chest radiography
TB evaluation method	Smear microscopy	GeneXpert or other molecular test	Mycobacterial culture, radiography

Source: Yuen presentation

Box 2-4. Targeted active case-finding: key takeaways

- Active case-finding is important for stopping TB transmission
- When choosing groups to screen, population size and TB risk must be balanced
- When choosing screening and evaluation methods, it is necessary to balance available resources with sensitivity of methods

2.2.5 Discussion

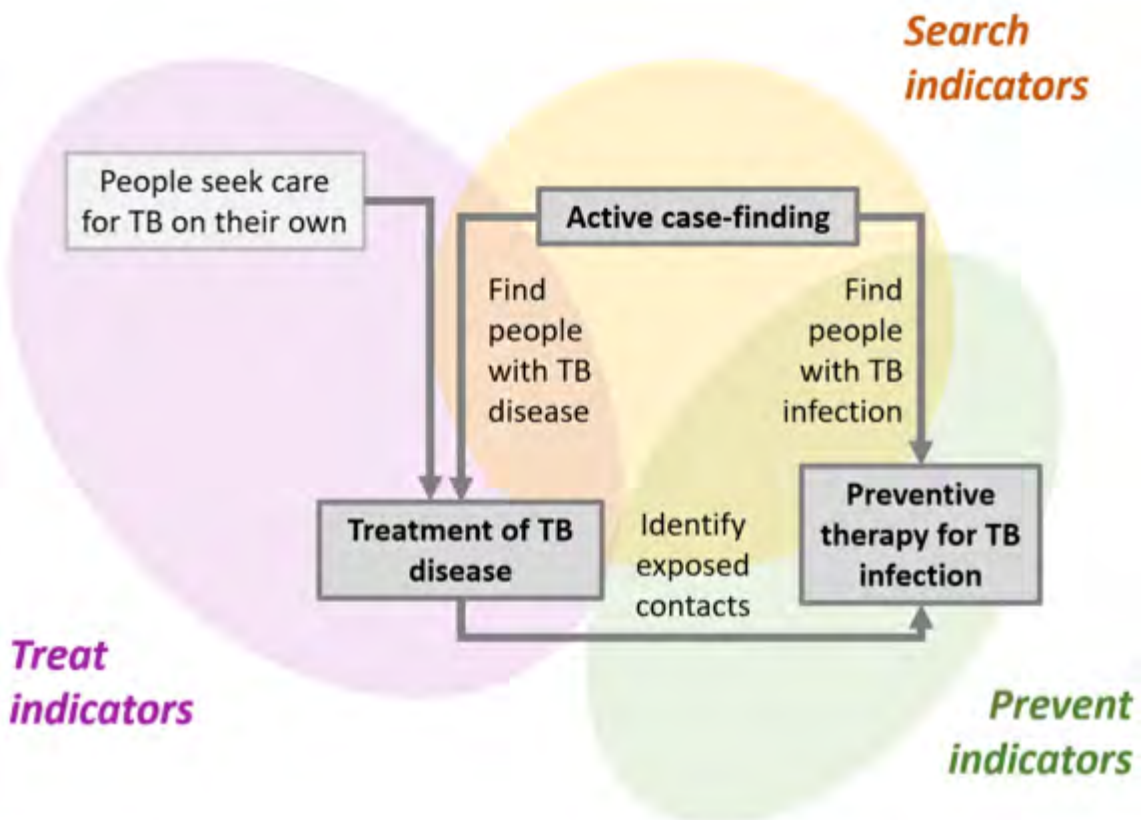
When asked about the reliability of X-ray screening, Yuen explained that prevalence surveys screen all participants with both X-ray and symptom screening methods, then collect and analyze sputum samples from everyone with abnormal X-rays or with reported symptoms. Based on this process, X-ray has been found to have a sensitivity of around 90%.

Charles Sandy, Ministry of Health and Child Welfare, Zimbabwe, asked which methodology should be used to identify and prioritize risk groups. Yuen specified two questions related to this issue: (1) whether programs know what the risk groups are and (2) how programs decide how to prioritize risk groups once they have identified them. In many settings, researchers may need to analyze health system records in order to identify risk groups. Once risk groups are identified, certain groups can then be prioritized for screening. No formula exists for making these determinations and they usually need to be made based on practical considerations of available resources, feasibility, and expected impact of screening.

Patrick Migambi, Rwanda Ministry of Health, remarked that data collection is not sufficient to identify high-risk groups in many countries. He asked what minimum data should be collected in order to be able to identify high-risk groups. Yuen replied that programs will not know what works until they begin active case-finding. Active case-finding should be approached with an experimental attitude, aiming to expand approaches that work and discontinue approaches that do not work.

Migambi also noted that a chest X-ray is very sensitive, but it is expensive and difficult to implement. These issues are especially challenging in rural settings, where access to healthcare facilities is limited. Advocacy is needed to eliminate the barriers to chest X-ray screening. Chest X-ray is expensive, agreed Yuen, but so are GeneXpert cartridges. When considering costs, planners often overlook costs that are subsidized by governments or the Global Fund. For instance, 1000 GeneXpert tests cost around US$10,000, regardless of who is paying for them. X-ray machines cost about US$50,000, but X-ray screening reduces the number of GeneXpert tests needed. If planners think about these costs holistically, there is a compelling argument for investing in X-ray. Additional human resources are required to implement X-ray screening, but some of this burden can be offset by the use of automated X-ray interpretation. Yuen's work in Peru utilized the computer-aided detection for tuberculosis system (CAD4TB), which has been validated for individuals aged 4 years and older. A radiology technician is still required to operate the X-ray machine, but the diagnostic interpretation is made by CAD4TB.

Figure 2-10: The links between the search, treat, and prevent cascades of care



Source: Yuen presentation

2.3 MONITORING AND EVALUATION FOR A COMPREHENSIVE APPROACH TO TB

2.3.1 Cascade of care model

In a cascade of care model, each activity is presented as a series of steps ('cascade'), with indicators to measure progress throughout the cascade. Measurement captures the numbers of people who progress through each step and the numbers of people who are lost from the health system between each step. The indicators of these cascades are the percentages of people who successfully progress from each step to the next step in the cascade. In a perfect cascade of care, 100% of the individuals who enter the cascade complete the last step of the cascade.

The framework is intended to be general and each program must choose which data to collect. These decisions will be informed by the data available in different settings. Data should be consistent within a program over time and should disaggregate between meaningful groups. Programs may disaggregate those with MDR-TB from those with DR-TB, those with HIV from those without HIV, or any other setting-specific groups. At minimum, children should be disaggregated from adults. TB programs should create systems that collect these data routinely. In many settings, electronic medical record systems are not in place. Many settings do not have standardized patient care data collection in their health systems. In the meantime, data can be collected through operational research. Programs must help determine how to best collect data and what kind of information is best to collect.

Active case-finding cascade

Yuen began by describing the active case-finding cascade, which has five steps: (1) person sick

with TB, (2) possible TB identified, (3) TB evaluation, (4) TB diagnosis, and (5) treatment initiation. Figure 2-11 depicts each of those steps and their associated gaps and opportunities to close those gaps. In order for a person with TB to be detected, that person must be identified as a candidate for screening. If that person does not connect with the healthcare system or the healthcare system does not reach that person, he or she will be lost to follow-up. Once identified as a candidate for screening, the person must be evaluated. Many individuals enter healthcare facilities with respiratory symptoms, but they are never evaluated for TB. Once evaluated, a person must be diagnosed. Individuals can be lost at this step due to incomplete evaluation or inadequate methods of evaluation. For example, an individual with smear-negative disease could not be diagnosed through smear microscopy. Many national algorithms address this specific issue by directing smear-negative patients to further evaluations; still, many individuals are lost to follow-up at this step in the cascade. Once diagnosed, individuals can still be lost to follow-up. Sometimes this is because the importance of treatment is not communicated effectively to the patient. This particular issue is more common in active case-finding than passive case-finding, she noted. In passive case-finding, people diagnosed with disease have sought out care; those diagnosed through active case-finding have been sought out by the health system and may not be prepared to receive a diagnosis.

Figure 2-11: Active case-finding cascade: gaps and opportunities

CASCADE STEP	GAPS CAUSING PEOPLE TO BE LOST	OPPORTUNITIES TO CLOSE GAPS
Person sick with TB		
↓	• Person does not reach healthcare system • Healthcare system does not reach person	• Active searching for people at risk of TB
Possible TB identified		
↓	• No one considers that the person may have TB	• Effective screening programs • Increase awareness of TB signs and symptoms
TB evaluation		
↓	• Evaluation not completed • Sputum-smear-negative disease not diagnosed	• Train doctors in clinical TB diagnosis • Improve access to radiography
TB diagnosis		
↓	• Results not communicated • Importance of treatment not communicated	• Communicate effectively • Programs for follow up
Treatment initiation		

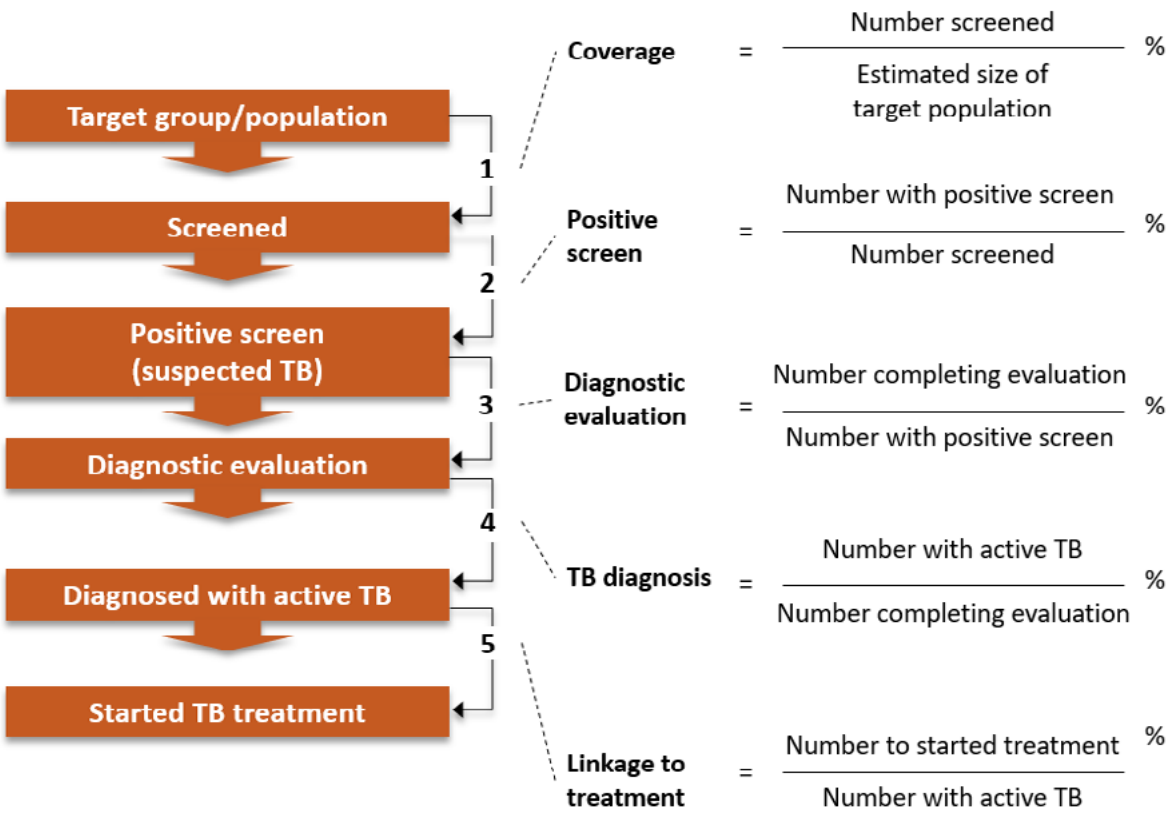
Source: Yuen presentation

2.3.1.1 Closing the gaps in active case-finding cascades

The first gap in the active case-finding cascade is closed through active case-finding itself. Actively searching for individuals with TB is how health care systems can identify those with possible TB. An effective screening program is necessary to close the next gap and increase the total number of individuals who are evaluated. Screening programs need to be monitored to ensure that those who are identified as potentially having TB are brought through to the next step in the cascade: TB evaluation. For example, an individual identified as potentially having TB needs to receive guidance on proper sputum sample collection. Otherwise, if the person gives a poor sputum sample and has TB, they may be lost to follow-up because of inadequate evaluation. Ensuring that all healthcare providers are aware of signs and symptoms of TB can also help to ensure that those who are identified as potentially having TB are asked to participate in a TB evaluation. Once a person enters the evaluation process, they must be successfully diagnosed to stay in the cascade. The gap from evaluation to diagnosis can be closed through training in clinical TB diagnosis and capacity building, such as expanded access to radiology. The pre-treatment loss-to-follow-up gap can be closed through effective communication protocols as well as programs for follow-up. In South Asian countries, call centers have been implemented to follow up with TB-positive patients to monitor whether they have begun treatment. Community health workers (CHW), if available,

can play a similar role for individuals who have been diagnosed with TB. Figure 2-12 provides guidance for calculating the indicators between each step of the cascade.

Figure 2-12. Calculating indicators of progression through the active case-finding cascade



Source: Yuen presentation

2.3.1.2 Example of using the active case-finding cascade

Yuen presented an example case in which program implementers were able to use the indicators from the active case-finding cascade to identify what was working in the program and what needed to be fixed. In this case, the TB program used two strategies, both of which utilized community symptom screening. In the first strategy, people found to have symptoms in the community were referred to a health center for evaluation. In the second strategy, people found to have symptoms in the community were asked to give a sputum sample at the time of screening; a healthcare worker then transported the sample to a health center. In this strategy, people with symptoms did not need to go to a health facility unless they were diagnosed with TB. Figure 2-13 compares the results of the two strategies. With the first strategy, none of the people referred to the health center actually completed a diagnostic evaluation, due to multiple barriers to access in the community, and thus no one was diagnosed with TB or linked to treatment. With the second strategy, 56% of people identified with symptoms were able to provide a sputum sample for evaluation, 20% were diagnosed with TB, and 99% of those who received a diagnosis were linked to treatment. Based on these findings, the first strategy was abandoned and the program began to implement sputum collection for all individuals with potential TB symptoms. The program also retrained staff to collect sputum more effectively, thus increasing the sputum collection rate to more than 85%.

Figure 2-13: Comparison of two search strategies

Cascade step	Number of people		Indicator	Value of indicator	
	Strategy 1	Strategy 2		Strategy 1	Strategy 2
Positive symptom screen	524	1,836			
Completed diagnostic evaluation	0	1,030	Proportion completing evaluation	0%	56%
Diagnosed with TB	0	206	Proportion diagnosed with TB	N/A	20%
Started treatment	0	204	Linkage to treatment	N/A	99%

Source: Yuen presentation

2.3.2 Treatment of TB disease cascade

The cascade of care for TB disease treatment begins where the active case-finding cascade ends, Yuen noted. Evaluation and diagnosis of TB link the case-finding and treatment cascades (see Figure 2-14). Once individuals initiate treatment for TB disease, they are faced with a series of barriers to completion of treatment, including: long, toxic treatment regimens; depression; stigma; and difficulty accessing health facilities for DOT when DOT is required. WHO and others have considered treatment completion to be the end of the treatment cascade; however, the actual goal of treatment is TB-free survival. In clinical trials of TB therapy, TB-free survival is the outcome used to measure success. It is possible for an individual to complete an ineffective regimen, have their case status declared 'treatment completed' and still be susceptible to relapse. This is especially possible in settings without the capacity to monitor patients by culture analysis. Therefore, the treatment cascade should go beyond treatment completion and include TB-free survival.

2.3.2.1 Closing the gaps in TB disease treatment cascades

To bring patients from diagnosis to treatment completion, programs must offer (1) comprehensive treatment support, (2) alternatives to facility-based DOT, and (3) new drug regimens for MDR-TB. To ensure TB-free survival among those who complete treatment, programs must (at least) monitor cultures and create a system for patient follow-up one year after treatment completion. Long-term follow-up can be difficult to implement, but it should be the goal of TB programs. India's newest TB program guidelines include two years of post-treatment-completion monitoring; the reason is that losses in the treatment cascade can accumulate.[27] Of the roughly 1.6 million people diagnosed with TB in 2013, 87% of patients started treatment, 86% of that group had a successful treatment outcome, and 86% of that group was TB free after one year. However, due to the accumulated losses at each step, only 64% of those diagnosed with TB had TB-free survival after one year. It is important to consider not only the indicators between steps in the cascade, but also the percentage of patients

27 Subbaraman et al 2016

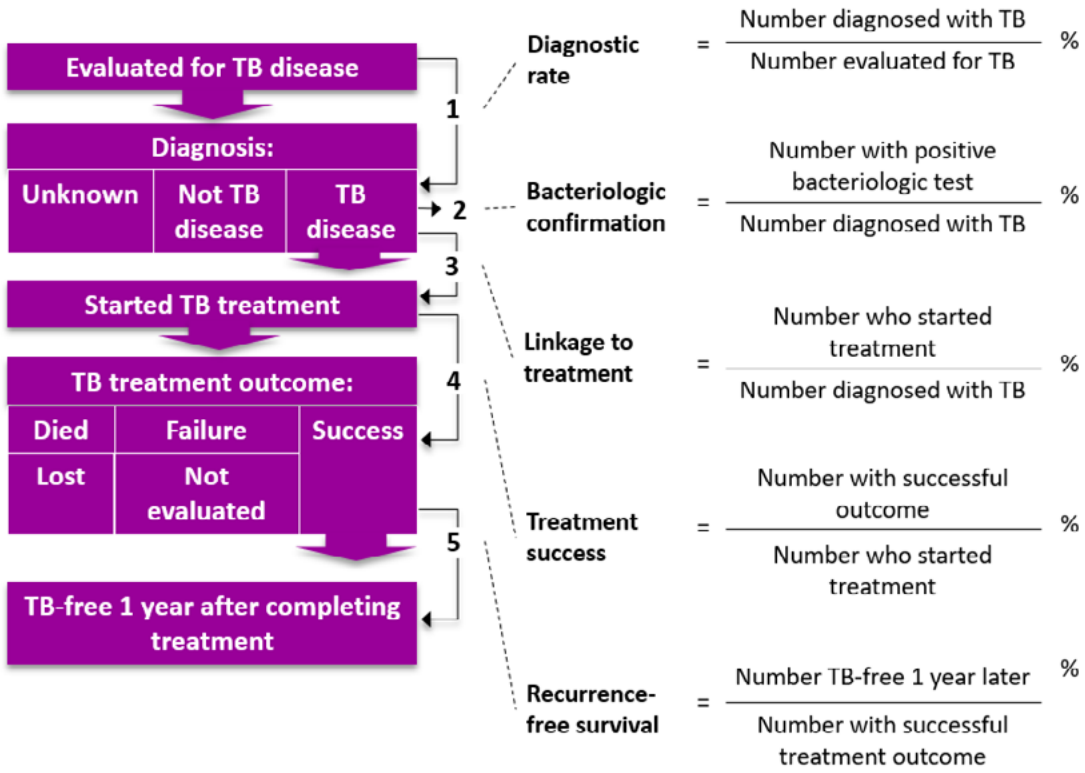
who successfully complete the entire process. Figure 2-15 provides guidance on calculating the indicators of progression through the treatment of TB disease cascade.

Figure 2-14: Treatment of TB disease cascade: gaps and opportunities

CASCADE STEP	GAPS CAUSING PEOPLE TO BE LOST	OPPORTUNITIES TO CLOSE GAPS
TB evaluation		
	• Evaluation not completed • Sputum-smear-negative disease not diagnosed	• Train doctors in clinical TB diagnosis • Improve access to radiography
TB diagnosis		
	• Results not communicated • Importance of treatment not communicated	• Communicate effectively • Programs for follow up
Treatment initiation		
	• Long, toxic regimens • Depression and stigma • Difficulty getting to health facility for DOT	• Comprehensive treatment support • Alternatives to facility-based DOT • New drugs for MDR-TB
Treatment completion		
	• Ineffective regimens • Lack of monitoring cultures	• Monitoring cultures • Follow up for 1 year after treatment
TB-free survival		

Source: Yuen Presentation

Figure 2-15. Calculating indicators of progression through the treatment of TB disease cascade



Source: Zero TB Initiative -A best-practice framework of program indicators

2.3.3 TB prevention cascade

Yuen explained that the TB prevention cascade begins when a person is exposed to TB (Figure 2-16). Once people have been exposed to TB, they must be identified and evaluated by the health system. Often, these individuals are never identified and, in many settings, they are not tested for TB infection. Additionally, providers are often unaware of preventive therapy. Many individuals who have been exposed to TB never enter the prevention cascade. Evaluation in this case refers to ruling out active TB disease. Once TB disease is ruled out, preventive therapy can be prescribed. Evaluation is often not completed due to lack of accessibility to X-rays, lack of provider awareness, or lack of provider experience in ruling out TB. In many cases, providers perceive the consequences of inaction as being minimal, whereas they perceive the consequences of being wrong about a patient's TB status as being severe. Patients may refuse to initiate treatment due to long regimens, fear of adverse events, lack of understanding, and the fact that they do not feel sick. The way providers recommend preventive treatment to patients has a significant impact on whether patients initiate treatment. If doctors show conviction about the importance of preventive therapy, patients are more likely to initiate this treatment. If providers waver or equivocate about whether patients should initiate treatment, then patients are less likely to initiate treatment. It is difficult for patients who do not feel sick to take medication for three months, which is the length of the shortest preventative regimens.

Figure 2-16: Prevention cascade: gaps and opportunities reventive regimens.

CASCADE STEP	GAPS CAUSING PEOPLE TO BE LOST	OPPORTUNITIES TO CLOSE GAPS
Person exposed to TB		
↓	• Many people exposed to TB are never identified • Lack of testing for TB infection	• Targeted testing for TB infection in high-risk groups
Evaluation		
↓	• Evaluation not completed • Providers lack awareness about preventive therapy • Providers lack experience in ruling out TB	• Train doctors in how to rule out TB and in the management of preventive therapy
Prescription of preventive therapy		
↓	• Lack of awareness • Fear of adverse events	• Communicate effectively the importance of preventive therapy
Initiation of preventive therapy		
↓	• Long regimens • Patients do not feel sick	• Use shorter regimens • Accompaniment and support
Completion of preventive therapy		

Source: Yuen presentation

2.3.3.1 Closing the gaps in preventive therapy cascades

Targeted testing for TB infection must be expanded to close the gaps in preventive therapy cascades, Yuen remarked. Alternatively, programs in settings where infection rates are exceedingly high—to the extent that testing is not necessary—should expand the capacity for TB evaluation. Providers need to be trained in (1) ruling out TB, (2) managing preventive therapy, and (3) appropriately communicating the importance of preventive therapy and the risk of developing TB if individuals choose not to initiate treatment. TB programs must also implement new, shorter regimens to improve treatment completion rates. Accompaniment and support should be provided throughout the TB prevention cascade, just as they are provided in the TB disease treatment cascade.

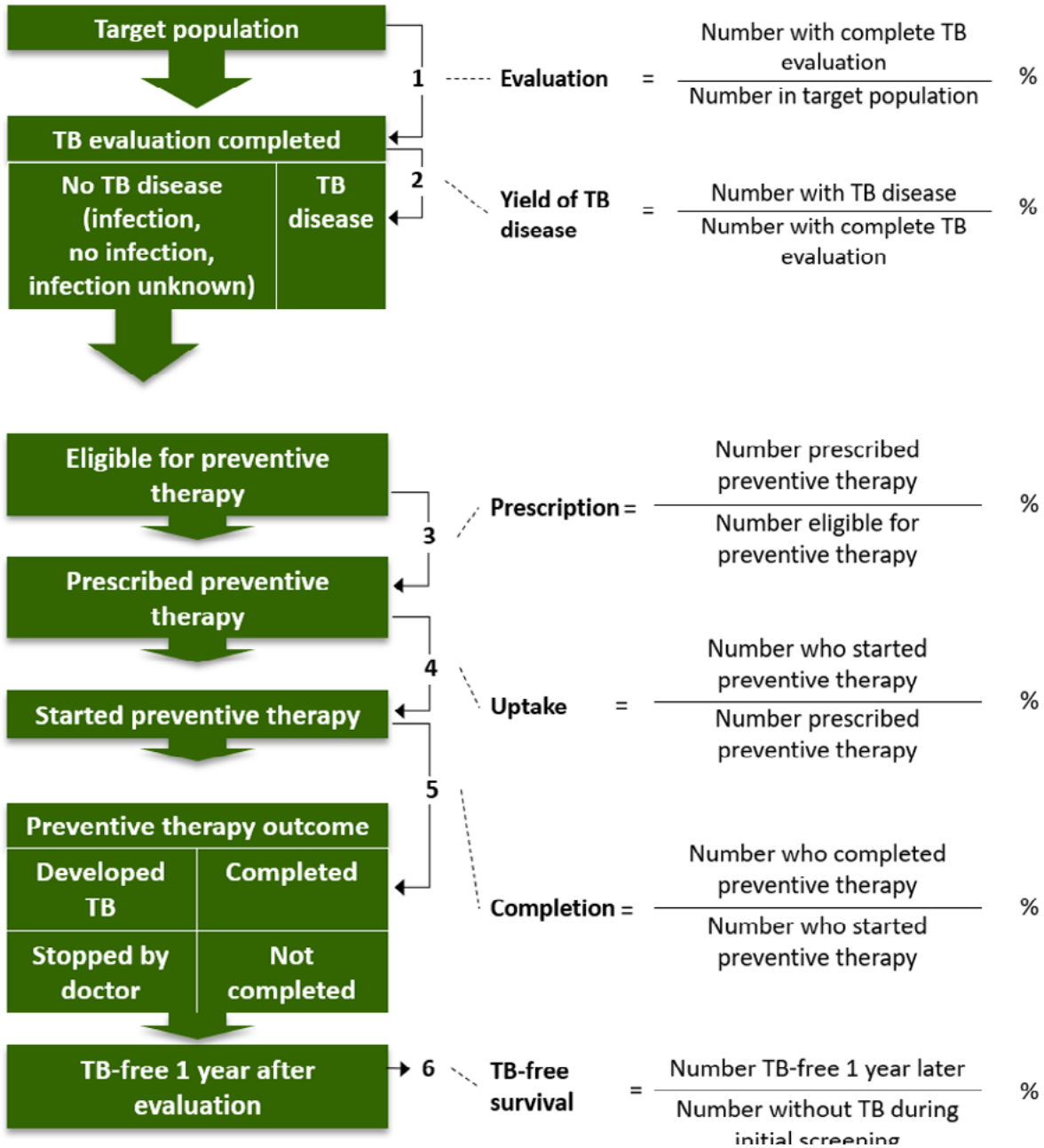
2.3.3.2 Example from Peru

In Peru, researchers studied the impact of household accompaniment on contact management. Household visits were conducted after a patient was diagnosed with TB disease to counsel families on the importance of TB evaluation for contacts. Transport vouchers and preventive isoniazid DOT were also offered to the families.

DOT provides treatment delivered to the home, while self-administered treatment requires parents to pick up medications from the health center. The preventive therapy cascade indicators for child contacts were used to evaluate the impact of these interventions. The combination of counseling families, household visits, and transportation vouchers was a very effective combination in closing the gap between identification and evaluation (from 70% to 95% completion [p=0.004]).[28] They found that the largest gap in the preventive therapy cascade was caused by doctors not prescribing preventive therapy to family members after evaluation. This intervention was community-facing, so researchers had not included a plan for how to address this issue through the intervention. Preventive therapy and initiation were relatively small gaps at baseline, but they improved slightly during the intervention. Overall, the gap between evaluation and preventive therapy prescription minimized the impact of the intervention. In this case, despite improvements in the indicators for each step in the cascade, the total proportion of children who were identified and completed preventive treatment was only 40%. Although this proportion had doubled from 20% to 40% as a result of the interventions, the proportion is still too small. Once again, this demonstrates how losses between each step in the cascade can accumulate.

28 Yuen et al 2019

Figure 2-17. Calculating indicators of progression through the preventive therapy cascade



Source: Zero TB Initiative -A best-practice framework of program indicators

2.3.4 Key takeaways

Active case-finding, treatment, and prevention can all be assessed as cascades of care, Yuen reiterated. Researchers must evaluate the cascade as a whole to identify and improve gaps in care. The data and information presented by Yuen, as well as additional tools and recommendations, have been compiled into a guide published by the Zero TB Initiative.[29]

29 For more information, see "A best-practice framework of program indicators for monitoring a comprehensive approach to the tuberculosis epidemic," (Accessed Sept 1, 2019)

2.3.5 Discussion

2.3.5.1 Considerations related to healthcare providers

Lynda Foray, from the Sierra Leone Ministry of Health, remarked that the TB program in Sierra Leone encountered resistance from doctors. Doctors were invited to receive training, but they sent assistants or nurses. Doctors had little knowledge about TB or the TB program in Sierra Leone. Yuen agreed that promoting provider buy-in needs to be part of the planning process. Sivakumaran Murugasampillay, World Health Organization, Zimbabwe, noted that as attention moves from disease management to infection control, work in the field is being done primarily by nurses and CHWs. The operational policies need to be simplified and tailored so that healthcare providers can execute them in their settings. Furthermore, the focus needs to shift from individuals with disease to keeping households and villages free of transmission.

2.3.5.2 Methods of follow up

Saleem Kazmi from Pakistan asked about the recommended method of post-treatment-completion follow-up and whether GeneXpert tests should be used. Yuen noted that WHO has made no applicable recommendation because its own cascade ends at treatment completion. Jennifer Furin, Harvard Medical School, USA, pointed out the distinction between follow-up for MDR-TB contacts who have not initiated treatment and follow-up for TB disease patients after treatment completion. She noted that routine GeneXpert is not recommended after TB treatment completion, because GeneXpert can detect very small quantities of mycobacterial DNA. The only reason to conduct GeneXpert testing once a person has already been diagnosed with or treated for TB disease is to test for newly-developed rifampicin resistance. Routine sputum culture testing may be an option for post-treatment-completion follow-up. Karl Le Roux, Zithulele Hospital, South Africa, concurred and added that there are available recommendations for monitoring treatment response that do not include GeneXpert, due to the likelihood of false positives when monitoring treatment response.

2.3.5.3 Determining numbers needed to screen and evaluating case-finding strategies

Rosa Herrera, Health Services of Mexicali, Mexico, asked about a general, incidence-based number-needed-to-screen threshold that countries can use to develop their budgets and plan their TB programs. She also asked how programs should determine when to abandon active case-finding strategies that seem not to be working. Yuen remarked that there should not be a universal approach to developing screening targets. For example, Mexico has a relatively low incidence compared to South Africa, so the number needed to screen may be lower in South Africa, because there are so many more cases to find. In settings with lower TB incidence, countries must screen more people to find cases. Similarly, there is no universal threshold for determining whether a case-finding strategy is successful. Strategies should be evaluated in comparison with a given location. For example, a program may evaluate the "number needed to treat" for two different strategies and discontinue the strategy with the higher number needed to treat. In northern Lima, Peru, Yuen and her colleagues expected to find a yield of around double the case notification rates, given the finding from prevalence surveys that around half of TB cases are missed. In fact, they found five times more TB cases than the case notification rates in that community. This demonstrates why the measure of success cannot be fully defined until active case-finding begins.

2.3.5.4 Baseline data collection

Le Roux asked how projects have been collecting baseline data, given that prevalence surveys are an expensive way to collect that data. Palwasha Khan, Interactive Research & Development, Pakistan, explained that a prevalence survey is being conducted in Karachi, Pakistan. The survey is being conducted in adults using CAD4TB and Ultra. The project included an IGRA survey for children aged 2-4 years and, although it has been logistically complicated to use IGRA at scale, they have completed around 1,800 IGRA tests in children.

2.3.5.5 Yield of active case-finding

Murugasampillay remarked that the thresholds for TB control need to be updated. After 10 years of Global Fund investment, incidence rates should be below 300 per 100,000 population. In high transmission zones, there is a strong case for active case-finding to reduce transmission; the low yield associated with active case-finding must be accepted and accounted for in the planning process. Yuen added that the most effective way to achieve a very low number needed to screen is to screen only the highest risk groups. Consequently, prioritizing the number needed to screen as a program indicator discourages screening in other groups with lower risk. Screening lower-risk groups will ultimately yield more cases, requiring programs to screen more people in order to increase the yield.

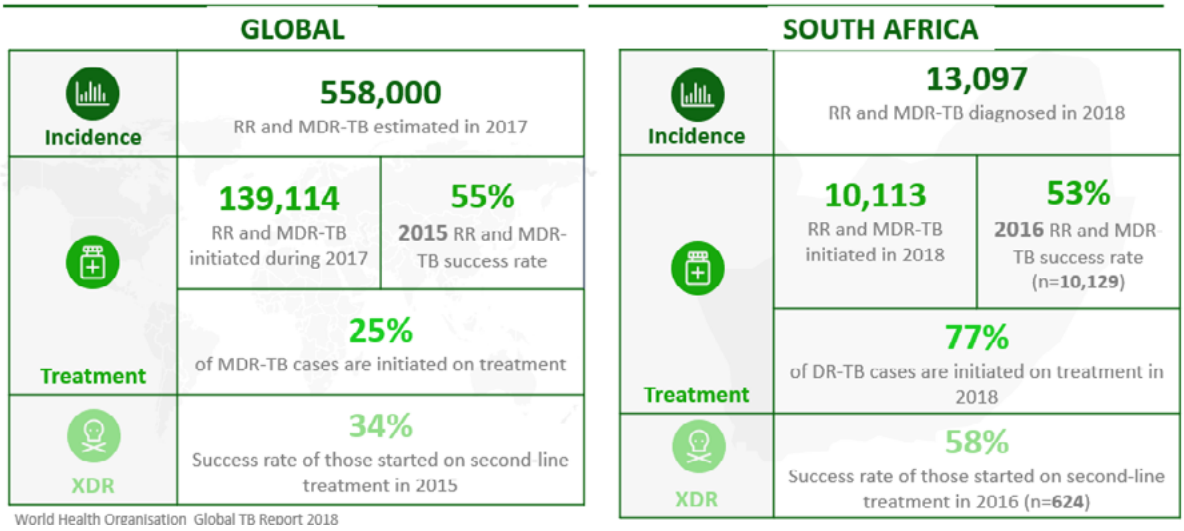
3 The comprehensive approach applied in MDR-TB

3.1 SEARCH, TREAT, AND PREVENT FOR MDR-TB: EXPERIENCE IN SOUTH AFRICA

Norbert Ndjeka, National Department of Health, South Africa, discussed the MDR-TB program in South Africa in the context of huge efforts to fight TB in the country, which have been made possible through partnerships between academic institutions, NGOs, and the government. South Africa's experiences have revealed lessons both about what should be done and what should not be done to fight TB.

South Africa has one of the highest burdens of drug-resistant TB (DR-TB) in the world, yet it outperforms the global standard of treatment initiations by more than two-fold (see Figure 3-1). More than 13,000 cases of rifampicin-resistant (RR) TB and multidrug-resistant TB (MDR-TB) were diagnosed in the country in 2018 alone, representing about 7% of the global burden of those two forms of TB.[30] However, South Africa initiated treatment for 77% of DR-TB cases in 2018, far exceeding the global proportion of MDR-TB cases initiated on treatment in 2017 (25%). South Africa has had even more success treating people with XDR-TB, with a success rate of 58% among more than 600 people who started second-line treatment in 2016.

Figure 3-1: Burden of drug-resistant TB: worldwide and in South Africa



Source: Ndjeka presentation; World Health Organization 2018a

3.1.1 Overview of drug-resistant tuberculosis in South Africa

South Africa is the source of 60% of the DR-TB burden in its region. Historically, attempts to treat DR-TB in the country have been associated with poor patient outcomes, which have been exacerbated by a constrained health system and poor tolerability of DR-TB treatment. These programs have been consistently weakened through (1) reliance on hospital-based care and

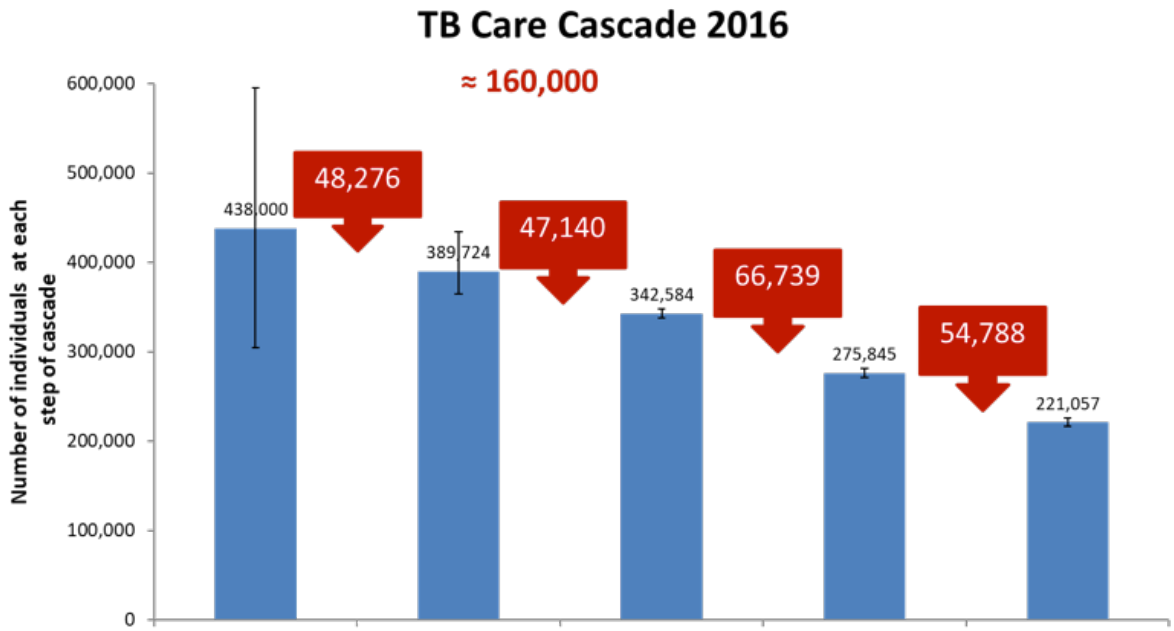
30 World Health Organization 2018a

injectable drugs, (2) long delays in treatment initiation, and (3) insufficient capacity.

South Africa has come a long way in the treatment of DR-TB since the first epidemics were reported in the mid-1990s, Ndjeka explained. South Africa declared TB a national emergency in 1996 and the DOTS protocol was implemented nationwide, although treatment was not standardized across the country. Throughout the 1990s, there were around 2,000 cases of MDR-TB each year; these cases were accompanied by costly hospitalizations. The first national TB surveys, conducted in the 2000s, estimated that 3,300 cases of MDR-TB had emerged since the mid-1990s. In 2001, South Africa was one of the first countries to roll out second-line treatment for MDR-TB on a national scale. An outbreak of XDR-TB at a rural hospital in KwaZulu Natal in 2006 demonstrated the threat posed by MDR-TB. By 2010, the number of patients diagnosed with MDR-TB had increased to around 8,000 per year.

Today, South Africa is at the forefront of DR-TB research and treatment initiation conversion. The introduction of improved diagnostic tests—including line probe assay testing (LPA) in 2009 and GeneXpert in 2011—has contributed significantly to quantifying the DR-TB burden in South Africa. However, the MDR-TB burden in the country has continued to grow and is a major issue—19,000 cases of MDR-TB were reportedly diagnosed in 2016. While South Africa has provided MDR-TB treatment to thousands of people, a gap remains between the number of cases diagnosed and individuals receiving second-line treatment. Figure 3-2 illustrates the significant loss of patients at each step in the TB care cascade, which reflect the challenges of screening for, diagnosing, and successfully treating TB in South Africa.

Figure 3-2: Estimating the "missing" TB and DR-TB patients in South Africa



Source: Ndjeka presentation

3.1.2 Tuberculosis and drug-resistant tuberculosis case-finding strategies

3.1.2.1 Introduction of GeneXpert in South Africa

GeneXpert, used in South Africa since 2011, has been a critical tool for finding TB cases. Before GeneXpert was available, South Africa used microscopy to test for TB. This testing was conducted at hospitals and some community health centers, with assistance from sample transportation contractors who would bring samples to and from testing facilities. However, it could take more than two months to diagnose and initiate treatment for one MDR-TB patient. This system took in over 1 million microscopy samples each year, with the few TB culture laboratories also performing phenotypic drug susceptibility testing.[31] When GeneXpert was introduced in South Africa, it was determined that there should be one TB testing site (sometimes one combined TB and HIV testing site) in each province. 54 technicians were trained to handle the initial workload of GeneXpert testing.

When GeneXpert was first introduced in 2010, it was chosen as the initial testing method for all individuals suspected to have TB. The objectives were to simplify the screening process and to eliminate the need to develop a more complex screening algorithm to determine who is eligible for GeneXpert testing. GeneXpert was used to update the screening algorithm, but it did not replace microscopy, which is still used for follow-up testing.[32] The roll out of GeneXpert in 2010 aimed to place the machines at all TB microscopy sites (requiring 258 machines), which was achieved by the third year of the roll out. Multiple physical challenges were encountered in acquiring and installing the new GeneXpert machines throughout South Africa—for example, many hospitals did not have an entryway large enough to fit the machines into the building. Sites that did not have GeneXpert machines were instructed to continue using the smear microscopy screening algorithm until GeneXpert became available, which created a split in screening algorithms during the transitional period. Ultimately, the implementation of GeneXpert greatly increased South Africa's testing capacity, because some GeneXpert machines can process 48 samples simultaneously in just 2 hours.

3.1.2.2 Finding missing cases in South Africa

Ndjeka explained that, even after most sites had access to GeneXpert, TB cases were still being missed by South Africa's screening efforts. Researchers established that each year, about 80,000 cases of TB were going undetected in South Africa. The primary strategy for finding these missing cases is to further expand the screening and testing campaigns with a goal of finding 80,000 additional cases each year. This goal has been divided into province, district, and sub-district goals so that each site has its own target for case-finding. South Africa uses the number of people tested for TB as an independent surrogate measure that can indicate if screening has increased and explain potential reasons for a lack of case-finding.[33] South Africa purchases and uses over 50% of the GeneXpert cartridges sold globally; the positivity rate is around 10%. Using this estimated positivity rate, sites can estimate how many people they need to test to meet their case detection goals. To meet their national goal of finding 80,000 cases, South Africa must administer around 3 million GeneXpert tests.[34]

3.1.3 Treating tuberculosis and drug-resistant tuberculosis

South Africa has historically faced many challenges in treating TB, Ndjeka explained. These challenges include (1) long wait times for treatment admission, (2) long distance transportation for treatment and follow-up, (3) negative

31 For more information, see Appendix 11
32 For more information about South Africa's screening algorithm, see Appendix 7.
33 Epidemiological data from 2017 was used as baseline, number of people tested and positivity rates. NHLS provides quarterly reports with the percentage tested against that target.
34 For more information about South Africa's GeneXpert testing targets, see Appendix 8.

social and economic impacts of treatment, (4) risk of in-hospital transmission, and (5) poor outcomes of DR-TB cases.

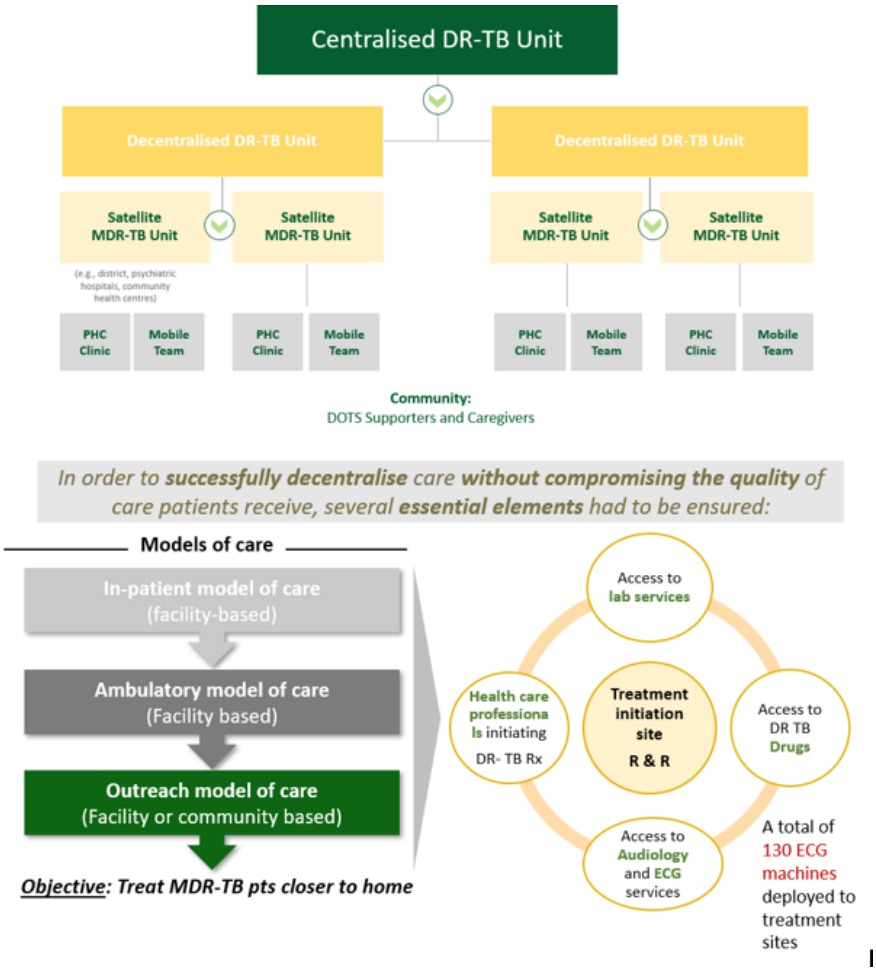
3.1.3.1 Development of decentralized MDR-TB care

To address these challenges, South Africa developed a model[35] that is patient-centered and designed to decentralize MDR-TB care, with a goal of having one MDR-TB treatment unit in each sub-district (see Figure 3-3). In order to successfully decentralize care without compromising the quality of care that patients receive, several essential elements had to be ensured (see Figure 3-3). The model also seeks to accommodate patients' needs and abilities through flexible admissions policies. For example, some patients can come to the health facility, while other patients need care in their homes. The program has designed MDR-TB care to offer patients choices and provide welcoming accommodations for those who will be staying in TB wards for treatment; the Global Fund has helped fund the creation of comfortable, accommodating, hotel-like TB wards.

In addition to creating more accommodating hospital environments for MDR-TB patients, South Africa has trained nurses to initiate MDR-TB treatment in communities where there are not enough physicians to manage patient treatment. This task-sharing alleviates the burden on patients to travel to health facilities and eliminates a barrier to treatment for those who would otherwise refuse to initiate MDR-TB treatment. An assessment of this task-sharing showed that it did not adversely impact treatment outcomes for MDR-TB; the outcomes of doctor-managed and nurse-managed treatment were similar.[36]

35 This model was developed between 2009 and 2011 through a series of workshops and policy meetings that culminated in a technical committee meeting at the National Health Council in 2011.
36 Farley et al 2017

Figure 3-3: Decentralized model of care for DR-TB



Source: Ndjeka Presentation

3.1.3.2 Management of ototoxicity

The MDR-TB treatment program includes efforts to strengthen ototoxicity management, said Ndjeka, because it is very difficult to test and monitor for hearing loss in patients. Best practices in audiology include early detection of any changes in patients' hearing sensitivity and the use of devices to assess the basal component in the cochlea, which is the primary target for destruction in hearing loss. The devices required to manage ototoxicity are sensitive up to 16,000 Hz. Devices used in other settings are only sensitive up to 8,000 Hz; the less sensitive devices are not as useful for the management and prevention of ototoxicity caused by TB treatment. Conventional hearing loss measurement is designed to measure hearing loss once symptoms of hearing degradation are apparent. However, once symptoms of hearing degradation are apparent in TB patients, it is too late to manage or prevent ototoxicity. Ototoxicity management requires that hearing degradation be detected before hearing loss symptoms are observed. Using highly sensitive, portable hearing testing devices, patients receiving treatment in hospitals can have their hearing routinely assessed in their hospital beds. The use of portable machines for ototoxicity management also supports the aim of decentralizing TB care. South Africa has implemented a plan to strengthen its ototoxicity management policies, ensuring that all DR-TB patients have access to hearing testing during treatment. The strategic objective of this plan is to conserve the hearing of all patients on injectable DR-TB drugs by

using various hearing testing devices provided by CDC, TB program partners, and centralized TB care sites.

3.1.3.3 Introducing bedaquiline to the drug-resistant tuberculosis treatment program

Ndjeka explained that bedaquiline was introduced to South Africa's DR-TB program in three phases. The initial phase was the development of the bedaquiline clinical access program (BCAP), which involved developing bedaquiline protocols, obtaining ethical approval, and conducting a literature review. This process was carried out by a collaborative public-private working group. Once protocols were developed, the working group developed and implemented bedaquiline training protocols. Finally, BCAP was introduced in five hospitals and prepared for scale-up to all provinces.[37] The BCAP phase began in 2012; the program enrolled 200 pre-XDR-TB and XDR-TB patients between 2013 and 2015. Phase two was the scale-up of the BCAP to all provinces in South Africa, which was completed in 2015 and 2016. More than 1,000 patients received bedaquiline treatment during the scale-up phase. During this phase, clinics acclimated to the BCAP protocols and use of bedaquiline was effectively integrated into the province-level TB care system. Phase three, which began in 2017, involves decentralizing BCAP. Because DR-TB care had already been broadly decentralized, it was relatively straightforward to decentralize BCAP by leveraging the existing channels of district-level care.

Lack of expert guidance from WHO or other global actors led to challenges in implementing, scaling-up, and decentralizing BCAP. To address these difficulties, South Africa consulted with an independent group of experts to draft a new protocol to guide clinicians on the use of bedaquiline for treating DR-TB.[38] Shortly after South Africa began working on these efforts, WHO released an interim policy guideline on the use of bedaquiline that added value to the South African protocol.[39]

3.1.3.4 Policy framework for introducing shorter, injectable-free DR-TB regimens

South Africa observed excellent treatment outcomes associated with the use of bedaquiline, Ndjeka noted. Consequently, policymakers felt that it was irresponsible to continue treating patients with injectable-agent-based regimens that have lower treatment success rates. In 2015, they developed a policy framework for the introduction of new drugs and drug regimens for the management of DR-TB in South Africa. The policy was designed (1) to serve as a useful tool for health care workers, TB program managers, civil society, and people with DR-TB, (2) to provide a clear plan for new drug introductions, and (3) to provide clinical details on eligibility and referral mechanisms for participating patients. The document and the specific details of implementation were updated as new evidence became available. In 2018, WHO released a rapid communication calling for the removal of injectable agents from all DR-TB regimens.[40] In response, South Africa developed interim clinical guidelines for implementation of injectable-free regimens for rifampicin-resistant TB in adults, adolescents, and children.[41] This new policy provides detailed guidance on the composition of new patient regimens and eligibility criteria, based on the rapid communication by the WHO. It also provides guidance on recording and reporting requirements as well as guidance on the management of HIV and RR/MDR-TB coinfection in patients.

These updated guidelines brought changes to both the shorter and longer regimens for RR/MDR-TB:

37 For more information about the introduction of bedaquiline in South Africa, see Appendix 9.
38 Republic of South Africa Health Department 2015
39 World Health Organization 2013
40 World Health Organization 2018b
41 Republic of South Africa, 2018. Interim clinical guidance for the implementation of injectable-free regimens for rifampicin-resistant tuberculosis in adults, adolescents and children. The interim guidelines are available athttp://www.tbonline.info/media/uploads/documents/dr_tb_clinical_guidelines_for_rsa_september_2018.pdf (accessed December 10, 2019).

- Shorter regimen (4-6 months intensive phase): bedaquiline (6 months) + high-dose isoniazid + linezolid (2 months) + levofloxacin (6 months) + clofazimine + pyrazinamide + ethambutol
- Shorter regimen (5 months continuation phase): levofloxacin + clofazimine + pyrazinamide + ethambutol
- Longer regimen (6-8 months intensive phase): bedaquiline + linezolid[42] + levofloxacin + clofazimine + thiazolidinedione
- Longer regimen (12 months continuation phase): levofloxacin + clofazimine + thiazolidinedione

These new regimens cured over 70% of XDR-TB cases in South Africa. The use of linezolid in these regimens presents a risk of peripheral neuropathy, so those on linezolid regimens must be monitored throughout treatment. Full blood count and neutrophil count are also monitored in these patients.

Meetings to discuss the introduction of the shorter regimen began in 2016, with provincial TB managers and other healthcare workers involved in planning for the implementation. The roll out of the shorter regimen was delayed by a lack of clofazimine availability,[43] but South Africa worked to solve the clofazimine supply issues. In early 2017 only two provinces had begun using the shorter regimen but by the end of 2017, all provinces in South Africa were using the shorter regimen for all patients eligible to receive it. More than 3,000 patients in South Africa have been treated for DR-TB using the shorter regimen.[44] As of June 2018, the first fully comprehensive national cohort of patients was being treated with the shorter regimen.

3.1.3.5 Bedaquiline expansion program

In 2018, South Africa developed the bedaquiline expansion program. The program brought changes to the regimen and supplementary training materials. The initial plan was to introduce bedaquiline at two of the biggest health facilities in each province. Readiness to implement in additional facilities was assessed based on factors including human resources; laboratory services and access to first-and second-line line-probe assay (LPA); supply security (a key metric being 2-month stock of bedaquiline and linezolid); and ECG and audiometer availability.

The bedaquiline expansion program planned to scale-up bedaquiline treatment with a provincial approach. Key activities included:

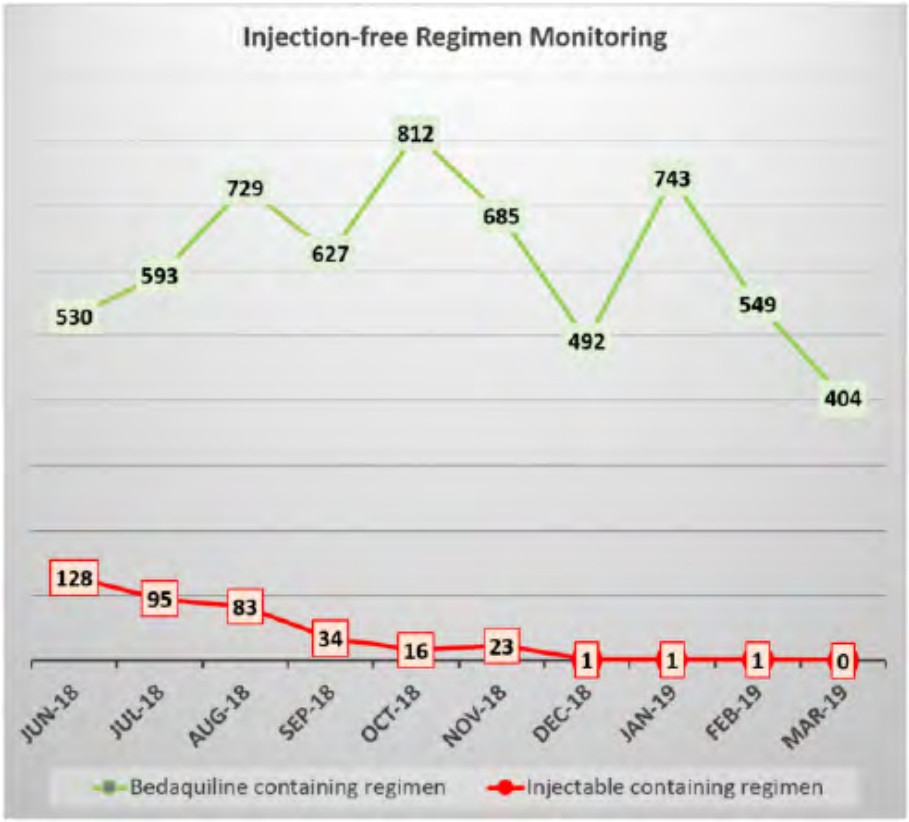
- Close monitoring of implementation on a daily basis
- Drafting readiness assessment checklists for provinces
- Identifying additional resources required to accomplish this project
- Supporting provinces in drafting their plans (the Department of Health provides templates and conducts meetings with each province to support scale up)
- Contracting cardiologists to consult and support provinces in maintaining the cardiac safety of patients (including clinical discussions, review of complex cases, audits, and in-service training)
- Ensuring access to drug availability as the bedaquiline expansion program is implemented
- Monitoring and evaluation[45]

The bedaquiline expansion program was a success, reported Ndjeka. Figure 3-4 shows that in March 2019, the number of patients being treated with injectable-based regimens reached zero. The South African TB program has benefited from academic research that utilized South Africa's database containing over 120,000 DR-TB records. Despite many gaps in the data, they still provide valuable insights for South Africa's TB program. For example, one study

42 Linezolid monitoring is essential, including full blood count and neutrophil count.
43 Provinces were advised that if clofazimine could not be obtained, they should continue using the old, longer regimen.
44 For more information about the introduction of the shorter regimen, see Appendix 15.
45 For an overview of the data flows, responsibilities, and feedback structures, see Appendix 16.

observed a significant reduction in mortality among patients on bedaquiline-based regimens.[46] Another study observed a 73% treatment success rate for XDR-TB and pre-XDR-TB patients using bedaquiline.[47] These insights were revealed through database research and record-keeping over time. Controlled randomized trials are very important, he noted, but countries should also proactively collect and analyze data from ongoing interventions to guide their actions while they await the completion of trials.

Figure 3-4: Injection-free regimen monitoring in South Africa (2018-2019)



Source: Ndjeka presentation

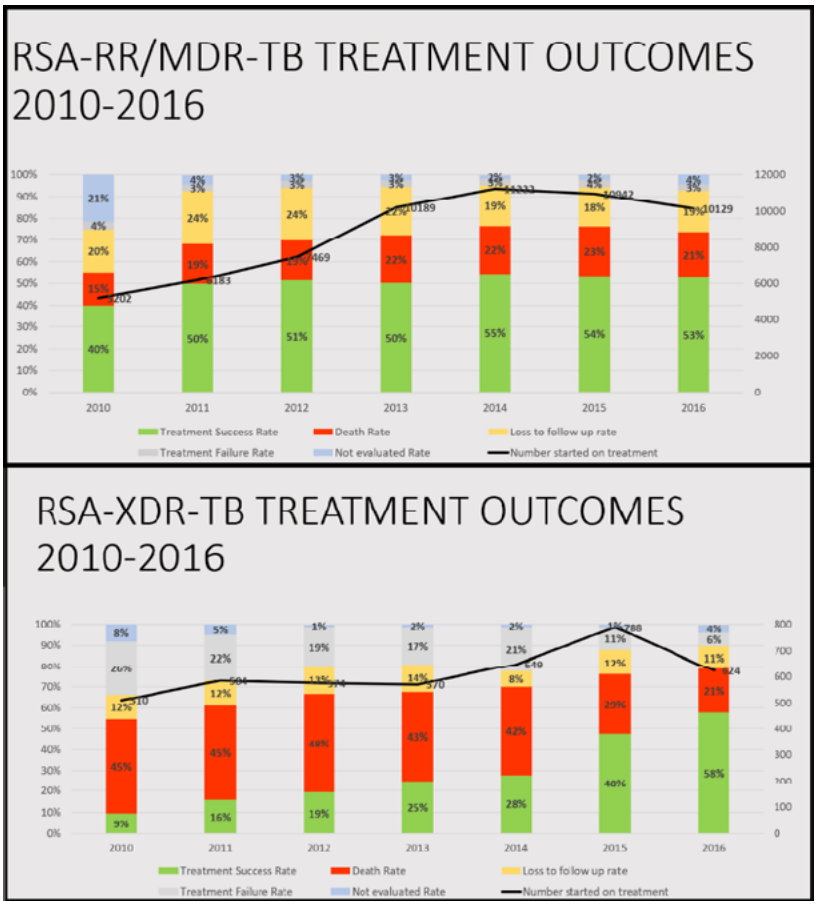
3.1.3.6 RR/MDR-TB treatment outcomes in South Africa

Ndjeka described how treatment outcomes for MDR-TB and XDR-TB have improved since the introduction of these new policies, beginning in 2011. Figure 3-5 illustrates the RR/MDR-TB and XDR-TB treatment outcomes in South Africa between 2010 and 2016. The number of RR/MDR-TB patients treated has expanded significantly since 2010 and the treatment success rate for RR/MDR-TB treatment has increased consistently since 2011. The treatment success rate for XDR-TB has improved substantially since 2011, with the XDR-TB mortality rate falling from 45% in 2010 to 21% in 2016.[48] Changes in the methodology of mortality tracking have led to a more accurate assessment of XDR-TB and RR/MDR-TB mortality rates in recent years. Figure 3-6 shows that treatment success

46 Schnippel et al 2018
47 Ndjeka et al 2018
48 More detail on long-term regimen treatment outcomes in South Africa in 2016 is provided in Appendix 17.

rates continued to rise in 2017.[49] South Africa's target success rate is 75%; the excellent results of bedaquiline-based regimens give planners confidence that they can achieve this target. In 2017, 6% of patients were not evaluated. He suggested that there are likely unevaluated treatment successes that would contribute to South Africa's treatment success target if they can find ways to improve their evaluation rates. Ndjeka remarked that he is encouraged by the results and analyses from the efforts to improve MDR-TB and XDR-TB treatment. The provincial-level, district-level, and national-level results all indicate improvements toward South Africa's goals for treating DR-TB.

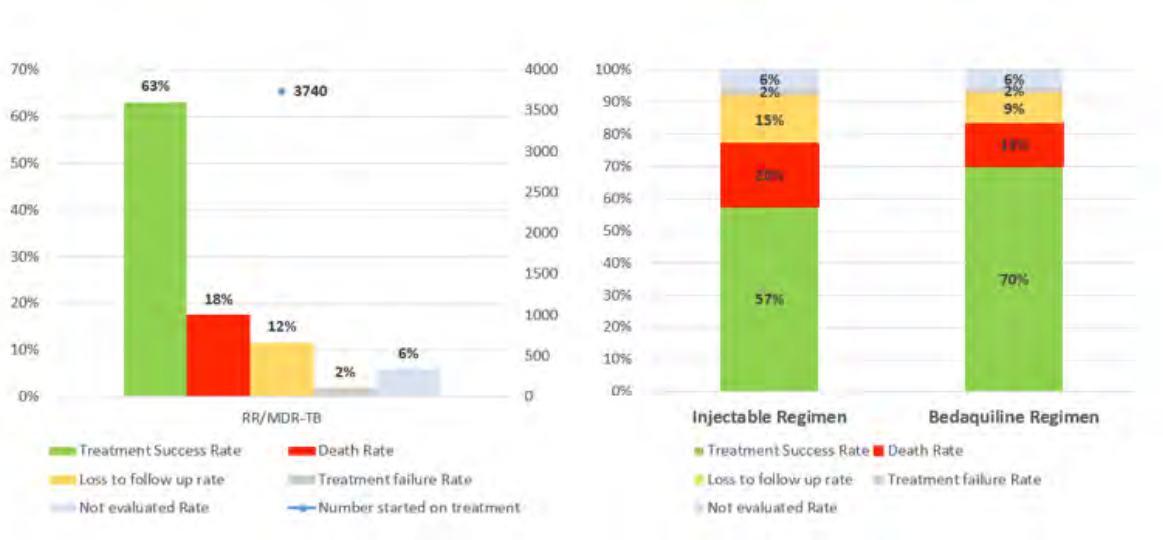
Figure 3-5: MDR-TB and XDR-TB treatment outcomes in South Africa (2010-2016)



Source: Ndjeka presentation

49 More detail on short-term regimen treatment outcomes in South Africa in 2017 is provided in Appendix 18.

Figure 3-6: Shorter regimen treatment outcomes in South Africa (2017)



Source: Ndjeka presentation

3.1.4 Introduction of preventive therapy into DR-TB treatment guidelines

Ndjeka explained that in the past, clinicians' only option for preventive therapy was to use isoniazid. During TB treatment training, providers often inquired about preventive therapy, but there was a lack of acceptable options. Once South Africa discontinued the use of injectable treatments, attention was turned to revamping the guidelines for preventive therapy. International consultants were enlisted for technical assistance to support the creation of revised guidelines that, for the first time in South Africa, included guidelines on preventive therapy.

Box 3-1 provides the options for high-risk RR-TB contacts—particularly children aged <5 years and older children with HIV—that are set forth in the guidelines, pending the future findings from randomized controlled trials. Clinical monitoring of these high-risk groups is needed, regardless of whether therapy was initiated. Six-month preventive therapy regimens were offered to these high-risk groups. If the source case's M. tuberculosis strain is susceptible to fluoroquinolones, the preventive therapy regimen could include a third-generation fluoroquinolone (ideally levofloxacin) together with another drug that is likely to be efficacious; possibly ethambutol or high-dose isoniazid.

South Africa has established a network of experts who consult with clinicians digitally. This system has been very effective and will be used to help with the implementation of preventive therapies. Adherence to preventive therapy is a major concern, leading to concerns that a multidrug regimen may lead to low rates of completion. However, patients are more likely to adhere to treatment when they are taking fewer medications. For this reason, high-dose isoniazid for 6 months could be considered for contacts exposed to fluoroquinolone-resistant MDR-TB, despite limited evidence. He added that South Africa is evaluating delamanid and is currently planning to provide it to 3,000 contacts by the end of 2020.

Box 3-1. Options for high-risk RR-TB contacts (particularly children aged <5 years and older children with HIV)

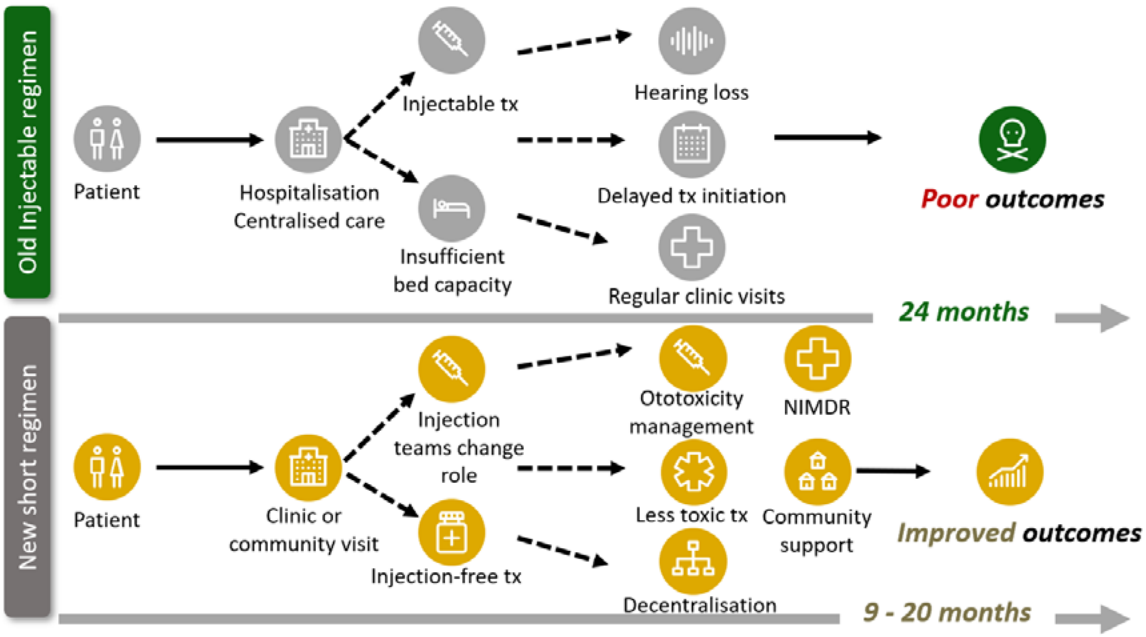
- Clinical monitoring, without therapy, and close follow-up to detect incident TB disease early.
- Offering the option of a 6-month preventive therapy regimen. If the source case's M. tuberculosis strain is susceptible to fluoroquinolones, such a regimen could include a third-generation fluoroquinolone (ideally levofloxacin) together with another drug that is likely to be efficacious, and possibly including ethambutol or high-dose isoniazid.
- Other regimens that may be considered in consultation with pediatric experts include:
- Three-drug regimen of ethambutol, high-dose isoniazid, and levofloxacin for 6 months when contacts have been exposed to MDR-TB with documented quinolone susceptibility.
- Single-drug regimen of isoniazid (normal-or high-dose) for 6 months when contacts have been exposed to rifampicin mono-resistant TB, where susceptibility to isoniazid is confirmed. This is also an option for contacts exposed to patients diagnosed with RR-TB based on a positive GeneXpert MTB/RIF or Ultra that is rifampicin-resistant but LPA-negative/inconclusive and/or culture negative.
- Single-drug regimen with high-dose isoniazid (15-20 mg/kg) for 6 months when contacts have been exposed to MDR-TB with inhA mutation only; this could be considered for contacts exposed to fluoroquinolone-resistant RR-TB.
- Single-drug regimen of levofloxacin for 6 months when contacts have been exposed to MDR-TB with katG mutation only and documented quinolone susceptibility.

3.1.5 Summary and conclusion

Ndjeka concluded with a summary of key drivers of improvements in treatment outcomes in South Africa, including strong partnerships between the national department of health, researchers, and implementing partners, as well as the creation of the National Clinical Advisory Committee. Engagement with provinces has strengthened ownership and expedited buy-in. Another key driver has been the progressive stance on the implementation of innovative drugs, regimens, and diagnostics methods.

Ongoing engagement with key stakeholders has expedited patients' access to the most up-to-date and effective treatment technologies; continued collaboration and engagement is critical in maintaining the best care for patients. Because strict reliance on WHO guidelines is not a sufficient TB control strategy, he emphasized that countries must develop their policies beyond the minimum recommendations provided by WHO. Stakeholder engagement and monitoring of program outcomes contribute to the success of programs not only by virtue of the programs being implemented, but also by the impact of word-of-mouth testimonies. Province leaders and politicians who become aware of a program's success will talk to their colleagues about the program, increasing buy-in nationally. Programs that are initially implemented at a small scale can particularly benefit from this effect. Figure 3-7 shows how the MDR-TB treatment program was developed in response to patient needs. The changes to and reduction of the use of injectable treatments was a major part of the new MDR-TB treatment plan, but the introduction of less toxic regimens, community support, and contact tracing have also contributed to the improved outcomes. Box 3-2 provides an overview of Ndjeka's key takeaways from the experience in South Africa.

Figure 3-7: Injectable regimen vs shorter regimen



Source: Ndjeka presentation

Box 3-2. Key takeaways from the experience in South Africa

- GeneXpert is a TB diagnostic tool, not a DR-TB diagnostic tool.
- The use of GeneXpert in all TB presumptive cases is necessary, NOT a luxury.
- The use of LPA is a requirement; failure to rule out pre-XDR-TB among all DR-TB cases is unethical.
- Decentralization of DR-TB care has been necessary to treat all DR-TB patients in South Africa.
- The systematic use of portable audiometers (while injectables were in use), ECG machines, and laboratory testing helped effectively decentralize DR-TB care.
- The introduction of new and repurposed drugs has been very helpful.
- Through effective collaboration and seeking technical assistance, South Africa was able to develop a strategy for preventive therapy.

3.1.6 South Africa's policies on the use of bedaquiline

Hemant Bogati, Médecins Sans Frontières, France, asked whether South Africa has used bedaquiline 'off-label' after the initial 6-month treatment regimen and, if so, about the rationale for this decision. Ndjeka reiterated that the routine use of bedaquiline does not extend beyond the 6-month regimen that is included in nearly all DR-TB treatments in South Africa. Expert committees are willing to approve the use of bedaquiline beyond the 6-month regimen if there is good reason; some patients in South Africa have been approved to use bedaquiline for longer than six months. For example, many

TB patients with HIV have been exposed to many agents and have developed resistance to many drugs. Consequently, once the intensive phase of treatment is complete and bedaquiline is taken out of the regimen, the remaining drugs are sometimes not strong enough to maintain the efficacy of the treatment. Some patients being treated with the shorter regimen have been approved to take bedaquiline for 9 months.

Milo Richard, Programme National de Lutte contre la Tuberculose (PNLT), Haiti, questioned why South Africa's policy is to discontinue the use of bedaquiline after six months if a patient's treatment has been successful for the first 6 months. Ndjeka explained that patient treatments are designed and evaluated in consideration of each patient's resistance profile. There is a risk of developing resistance associated with treating DR-TB. If patients become smear-positive during DR-TB treatment, they may have developed new resistances over the course of treatment—it can become very challenging to manage such cases. The policy of using bedaquiline for only 6 months was designed with these concerns in mind. Patients who need to continue taking bedaquiline for longer than 6 months are permitted to do so on a case-by-case basis.

Muhammad Rafi Siddiqui, Institute of Chest Diseases, Kotri, Pakistan, asked about the threat of developing and spreading bedaquiline resistance when patients taking bedaquiline are lost to follow-up. Ndjeka acknowledged that South Africa has a 9% lost to follow-up rate. Before the implementation of bedaquiline regimens, the lost to follow-up rate was 20% and in some areas, 1 in 3 patients were lost to follow-up. While 9% loss to follow-up is an issue, it also represents an improvement. Since the use of injectables was still ongoing until March 2019, the lost to follow-up rate still measures some of those patients who were on injectable-containing regimens. He expressed confidence that as the cohort of patients who were treated with injectable drugs age out of the outcome data, the lost-to-follow-up rate will continue to decrease. The outcome data in 2021-2022 will start to show the true outcomes of bedaquiline-containing regimens, allowing for a more accurate assessment of the threat of bedaquiline resistance. Regardless, more drugs should be developed because TB treatment cannot rely on bedaquiline for the next 5-10 years. A variety of effective, safe drugs needs to be available in order to prevent the development of drug resistance, he said.

3.1.7 Benefits for tuberculosis patients in South Africa

Karl Le Roux, Zithulele Hospital, South Africa, commented on the impact of the changes made to TB treatment in South Africa. The introduction of GeneXpert and LPA were very impactful and effective; the emphasis on decentralization, or the provision of care in a patient's community, has also been very beneficial. In the past, many patients refused care because they did not want to leave their families and travel to a large TB hospital. Richard asked whether South Africa provides social assistance for their TB patients. Ndjeka explained that in South Africa, social assistance is provided by the Department of Social Development in collaboration with the Department of Health. All patients (not just people with TB) in South Africa who require social assistance receive food, cash, and other forms of assistance. Similar forms of social assistance are also available to individuals aged >65 years and to those who do not have jobs.

3.1.8 What makes South Africa different?

Aamir Khan, Interactive Research & Development, Pakistan, remarked that South Africa has consistently been ahead of global policy recommendations in their TB policies. From decentralizing TB care to nationwide GeneXpert testing to the elimination of injectable regimens, South Africa consistently made large-scale decisions without waiting for WHO recommendations. Khan asked what factors empowered South Africa to act without reliance on global policy directives. Ndjeka pointed out that, in the early 2000s, South Africa created a chief director of TB. This change meant that TB care was prioritized and represented in the national government. After this change, the director general of TB and colleagues attended ministerial meetings and advocated for TB at the highest govern-

mental level. Ndjeka pointed to the fact that his own boss reports directly to the deputy director general of TB; this short chain of command makes a difference for implementing and developing new policies to fight TB. The decision to prioritize TB required political commitment and the government of South Africa is now fully invested in fighting TB. Parliament mandated that provincial directors should report directly to parliament on HIV and TB every three months. The members of parliament also care about TB. For example, if ototoxicity increases in South Africa, parliament will question it. The government's interest strengthens every aspect of TB care, including the funding of academic research and the facilitation of effective partnerships.

Jennifer Furin, Harvard Medical School, USA, commented that South Africa is very open to partnerships in dealing with TB. In many settings, TB control is about controlling not just the disease but also about controlling the health system. WHO wants to control what countries do; countries want to control what doctors do; and doctors want to control what patients do. This system has had negative effects on controlling the disease. South Africa has been successful in independently assessing their own data, considering WHO guidelines, and then making decisions based on the information available. In doing so, South Africa has created a unique atmosphere of collaboration where all voices are heard, particularly the voices of civil society and affected communities.

3.2 ZERO TB KARACHI: THE DRUG-RESISTANT TUBERCULOSIS STORY

Aamir Khan, Interactive Research & Development, Pakistan, discussed the Zero TB Karachi program. He highlighted the program's approach to DR-TB management and efforts to provide preventive treatment to contacts of DR-TB patients. He noted that much of what has been done in Pakistan is based on experiences from other countries. Pakistan (population 200 million) has about 525,000 incident TB cases and 27,000 incident MDR-TB cases annually, with about 55,000 people dying from TB each year in Pakistan. Although TB control has been a problem in Pakistan, the national response to TB has been strong in the past, with national access to DOTS and smear microscopy testing. The national TB program has a history of engaging the private sector that has been built upon by the Zero TB program.

3.2.1 Pakistan's Zero TB Initiative

In Pakistan, the Zero TB Initiative is primarily being carried out in three large urban centers: Karachi (population 16-22 million), Peshawar (population 5-6 million), and Quetta (population 3 million). Khan explained that the Zero TB Initiative has benefited from the Global Fund's support of comprehensive TB control.[50] Karachi and Peshawar are Zero TB cities; in Quetta, they are carrying out active case-finding and treatment, with preventive treatment soon to be provided. The Zero TB program will be in full force in these three large city-centers in 2020.

Pakistan's Zero TB Initiative also works in 32 rural districts. The approach in these rural areas was less comprehensive than the approach in the larger cities, but active case-finding was employed in these rural areas. In order to roll out Zero TB in three cities and 32 rural districts, the program has employed 1,200 staff. In Karachi, over 3 million people were screened symptomatically before the introduction of mobile X-ray vans. Once Global Fund funds were available, the 55 mobile X-ray vans and an additional 70 fixed X-ray machines were deployed at various sites. In nearly two years, over 1 million people were screened with these X-ray machines. In total, over 61,000 TB patients were notified through these screening efforts, and over 4,000 contacts were placed on preventive therapy. Figure 3-8 shows the search, treat, prevent chakra which was developed to coordinate the many levels of

50 The Global Fund supported the initial roll out of Pakistan's Zero TB program in Karachi in 2016 and the expansion of the program to Peshawar and Quetta in 2018. Both the initial phase (2016-2017) and the expansion phase (2018-2020) were funded by the Global Fund; at each phase, US$40 million was provided for all TB control efforts in Pakistan. The Zero TB programs Khan discussed in Karachi, Peshawar, and Quetta did not cost US$80 million. He emphasized that implementers should not require such funding to implement similar programs in their countries.

the Zero TB program. Each major component of the comprehensive approach was broken down into sub-components, so that it was very clear how each team needed to focus their efforts and how these efforts fit into the conceptual framework of TB elimination.

Figure 3-8: Search Treat Prevent TB Free Karachi Chakra

Source: Khan presentation

3.2.1.1 Enhancing services in the public and private sectors in Karachi, 2016

Initially much of the Zero TB program focused on the private sector, but it became clear to Zero TB planners that there must be investment in public sector facilities in the three Zero TB cities. Before the roll out of the program, planners ensured that public sector facilities had improved capacity to screen, test, treat, and prevent. The program established a variety of TB care sites in the public sector, including national TB reporting sites, FAST sites, PMDT sites, childhood TB sites, comorbidities management sites, and post-exposure treatment sites. Additionally, the public sector was enhanced with ultraviolet germicidal irradiation lights, mobile digital X-ray vans, and GeneXpert machines. Public health facilities were also strengthened by the addition of more than 300 dedicated field and medical personnel across all sites. TB control is augmented in similar ways in the private sector, for example, through partnership with not-for-profit organizations. Zindagi Centers are used as centralized testing and treatment sites in low-income communities, where many patients prefer to seek care from private providers. Zindagi Centers are networked with numerous private facilities in these communities to offer community members free TB services, including testing, treatment, and preventive therapy. Through these enhancements, people living in slums in Karachi had access to TB care through private care providers. These patients could be screened, registered through the call center database, and referred to care in a not-for-profit or public sector hospital. The program was able to deliver and monitor comprehensive care to such patients.

3.2.1.2 Public outreach and communication

The comprehensive approach used in Pakistan included intensive communication efforts, Khan explained. The outreach campaigns included athlete endorsements, social media engagement, stigma-reduction efforts, and awareness campaigns to ensure that communities were knowledgeable about the free services available. In a social intervention implemented alongside the medical intervention, young girls were educated about symptoms, free testing, and other messaging about TB to bring awareness into every household.

3.2.1.3 Lessons from the past

In 2016, no other programs were using large-scale mobile X-ray screening and there were no contemporary examples of how to teach the public about mobile X-ray vans. However, Zero TB planners were able to learn from the experiences of mobile X-ray screening efforts conducted over 50 years ago. For example, images from mobile X-ray screening campaigns from showed that there was no need for people being screened to disrobe. This informed the design of the X-ray vans and circumvented the complication of dealing with cultural sensitivities regarding disrobing in Pakistani culture. Important knowledge and experiences from historical X-ray screening efforts were never incorporated into present initiatives; however, in this case, the Zero TB planners were implementing lessons that had been learned in the past.

Khan remarked that many features of comprehensive TB care that have been carried out in wealthy countries have never been carried out in many countries in Asia, Africa, and South America. This motivated and inspired the Zero TB planners in Pakistan to develop the most comprehensive, large-scale program possible. They were determined not to accept the inferior, ineffective interventions designed for poor countries. Rather, the Zero TB planners in Pakistan were determined to deal with TB in a comprehensive way, just as North America, Japan, and other wealthy nations have for decades.

3.2.1.4 X-ray screening in Pakistan

The X-ray vans were equipped with artificial intelligence tools that issued a probabilistic score to each X-ray image indicating whether individuals should receive further testing, Khan explained. This technology relieved the burden of staffing radiologists at the 50+ sites where mobile X-ray vans were deployed in communities. Individuals with abnormal X-rays were tested with GeneXpert. Khan emphasized that it would be inap-

propriate to put this kind of effort into screening with X-ray only to use an inferior test—such as smear microscopy—to confirm whether an individual has TB. Once a person has been screened with an X-ray and flagged for further testing, it is worth the additional cost to use an accurate test, such as GeneXpert. Individuals with abnormal X-rays were also provided printouts of their X-rays so that they could bring them to their physicians wherever they chose to seek care. X-ray vans were also deployed in prisons, outside hospitals, and in very remote areas of Pakistan.

3.2.1.5 Social enterprise scale-up in Pakistan

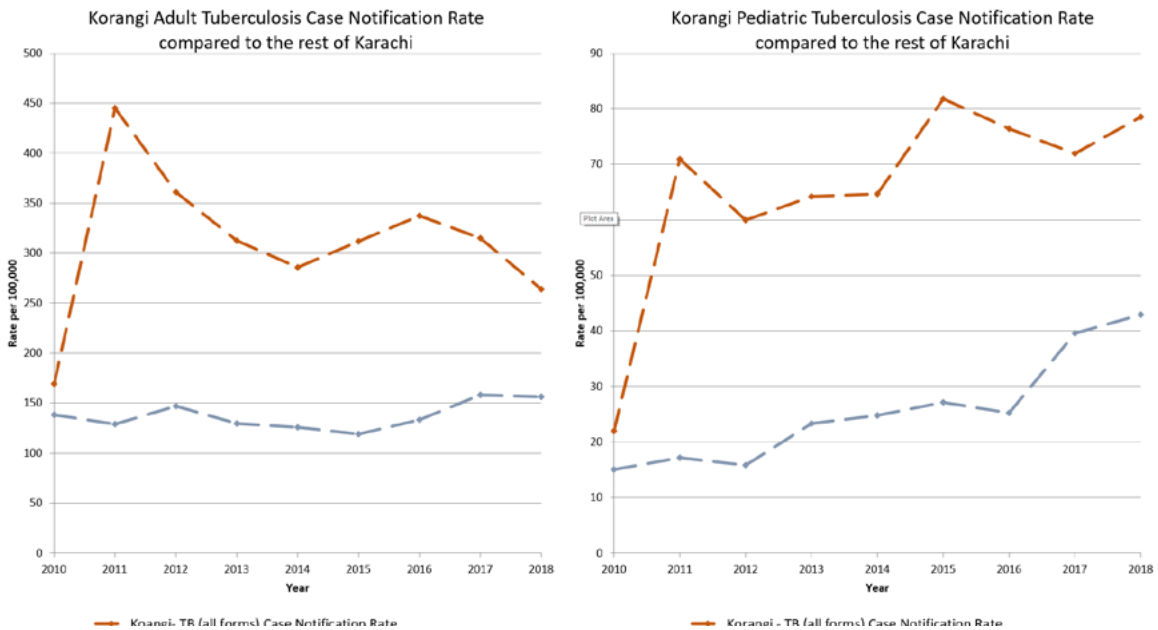
The Zero TB Initiative in Pakistan helped to build a network comprising over 60 Zindagi Centers in three provinces, Khan said, including 28 centers in Karachi. The network of Zindagi Centers helped Pakistan notify and properly manage the care of patients who were being treated in the private sector. This network was made possible by a variety of investments in the public, private, and not-for-profit sectors.

3.2.1.6 Comprehensive tuberculosis control and tuberculosis notifications in Pakistan

Khan explained that in 2011, Zero TB began working in Korangi. He noted that the Indus Health Network, one of the primary Zero TB partners in Pakistan, is based in Korangi. Figure 3-9 shows that there was a peak in case notifications in children and adults in Korangi in 2011. Among adults, this peak was followed by a plateau and subsequent decline, but the rest of Karachi is still increasing at a slower rate. In children, the notification rate has climbed continuously since 2011. Khan suggested that this is because TB in children has never been targeted in Pakistan before; eventually, the notification rate for children should peak and begin to decline as it has for adults. The trends in Korangi mirror the trends observed around the world when comprehensive TB care is implemented. When active case-finding begins, notification rates increase. As comprehensive TB control is carried out, notifications eventually plateau, then begin to decline. These declines reflect not only the impact of active case-finding, but also of treatment and preventive therapy. Khan recommended the use of the Stop TB Partnership Field Guides, which were developed by some of Zero TB Pakistan's partners. These guides were designed to help planners design and develop comprehensive TB programs.[51]

51 For more information about the Stop TB Partnership Field Guides, see https://stoptb-strategicinitiative.org/elearning/ (Accessed September 30, 2019)

Figure 3-9: Notification rates in Korangi compared to the rest of Karachi



Source: Khan Presentation

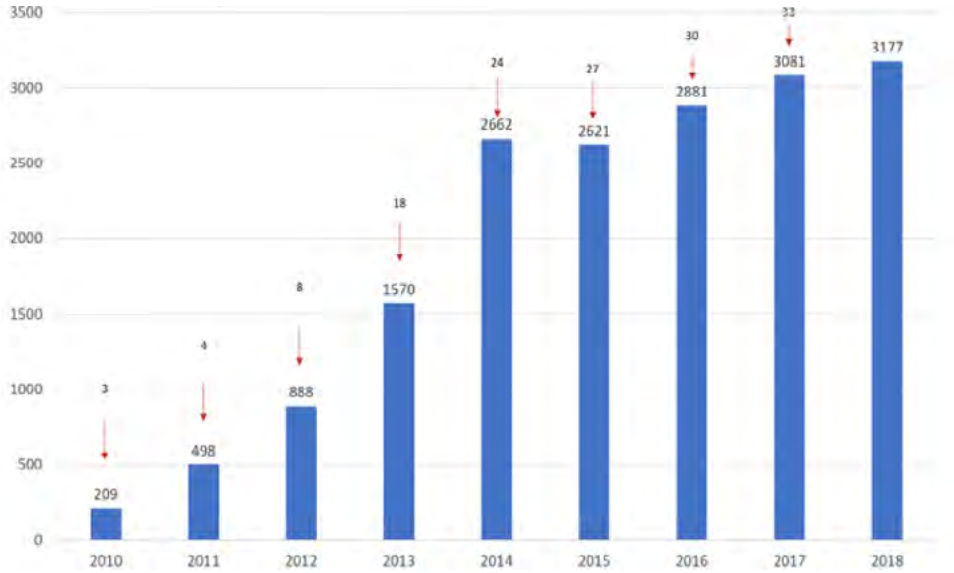
3.2.2 Drug-resistant tuberculosis in Pakistan

3.2.2.1 Drug-resistant tuberculosis in Pakistan

Pakistan has the fourth highest burden of DR-TB in the world. About 3,000 MDR/RR-TB patients were notified in 2017, representing about 11% of the estimated 27,000 incident MDR/RR-TB cases and 20% of the 15,000 cases expected among notified TB cases. In 2017, 120 XDR-TB cases were notified, which accounts for about 4% of the DR-TB cases in Pakistan. In the past, Pakistan has struggled to screen the necessary number of people required to detect the expected number of DR-TB cases. Figure 3-10 shows that as more DR-TB treatment sites have been established, more DR-TB patients have been put on treatment; still, this number has plateaued in recent years. This plateau reflects the late scale up of GeneXpert and the rigid testing algorithms used in Pakistan's screening process.

Since 2011, GeneXpert testing has been expanded widely across Pakistan. Pakistan now has 336 GeneXpert testing sites, seven drug susceptibility testing (DST) labs, 11 culture labs, and 5 BSL-3 labs. Despite the high capacity for testing in Pakistan, there simply are not enough people being screened in Pakistan to find the estimated undetected DR-TB cases in the country. Within the Indus Health Network, which covers the three Zero TB cities and an additional 32 rural districts, all individuals have access to the full range of tests required to detect DR-TB. Since 2007, the network has continuously increased the diagnostic capacity of their labs, which now have access to QuantiFERON (QFT-plus) testing. This diagnostic capacity is available to all agencies that need to access it. Since Zero TB roll out began, the number of tests conducted per year has increased drastically, rising from 192 tests in 2007 to 83,882 in 2018. Most of these tests are GeneXpert tests, but they include culture and DST tests as well. Khan emphasized that in order to detect DR-TB, countries need to not only enhance their capacity to test, but also need to increase the number of tests actually conducted.

Figure 3-10: DR-TB Patient enrolments in Pakistan, 2010-2018



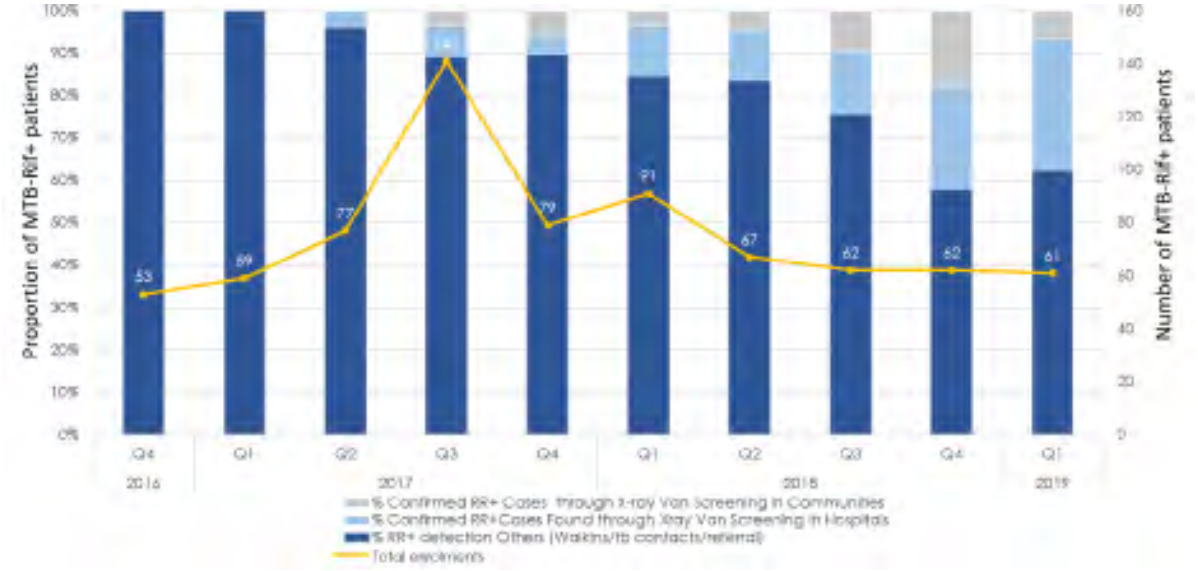
Note: Arrows indicate number of operational DR-TB treatment site
Source: Khan Presentation

3.2.2.2 Strategies for detecting drug-resistant tuberculosis

Khan described the impact of mass X-ray screening on DR-TB case detection in Pakistan. Figure 3-11 shows that in 2016, the majority of DR-TB was detected through walk-ins or patient referrals. The majority of such cases were in patients who were symptomatic. As mass X-ray screening was deployed throughout Karachi, the proportion of DR-TB detected through X-ray screening grew significantly. In 2018, as much as 40%-50% of DR-TB was detected each quarter through X-ray screening. This increase in case detection represents patients who may not have been detected otherwise. Even among patients who might have been detected without X-ray screening, X-ray screening detected these patients earlier in their community, reducing the transmission of disease.

The increased use of X-ray screening and the uptake of GeneXpert testing as the first test for those with abnormal X-rays has been very impactful. Active screening has been conducted in the households and communities of DR-TB patients, with 1%-2% of DR-TB contacts identified by the program as having active disease. The majority of the 324 DR-TB contacts identified in Karachi and Kotri are enrolled in ongoing observational studies. The addresses of XDR-TB and MDR-TB patients were used to map DR-TB hotspots in Karachi. X-ray screening camps, called 'mop-ups', were then strategically deployed in these hotspots. The yields from these X-ray screening efforts were also monitored.

Figure 3-11: Proportions of patients with rifampicin-resistant TB identified through X-ray-based active case-ginding and passive case-finding in Karachi, Pakistan (Q1 2016-Q1 2019)



Source: Khan presentation

3.2.2.3 Treating drug-resistant tuberculosis

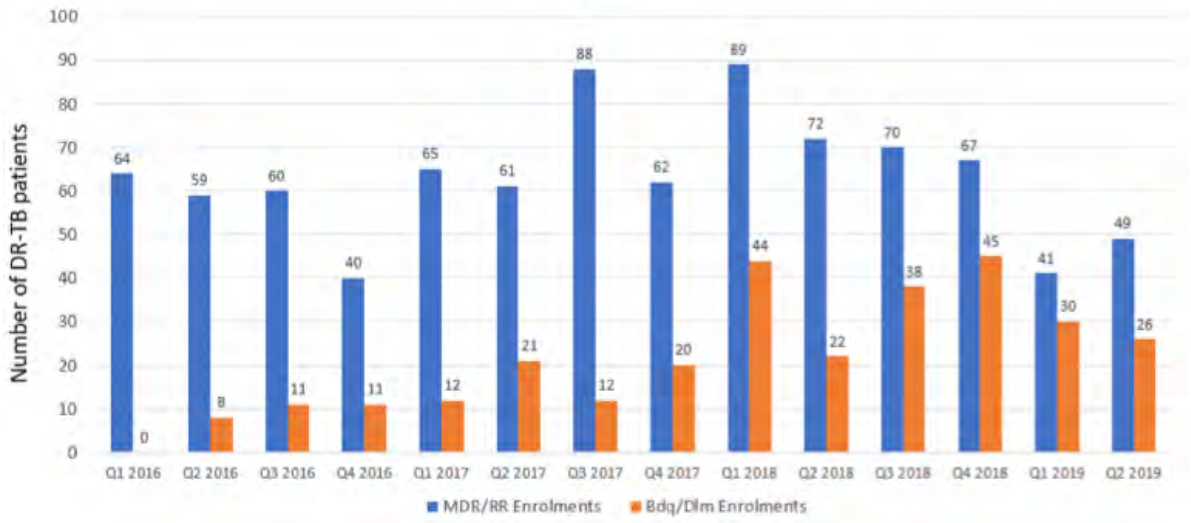
Khan explained that active case-finding enables the use of specialized strategies for treatment. These strategies include (1) increasing treatment and diagnostic access and options, (2) responding to special populations, (3) training the health workforce to diagnose and manage DR-TB, and (4) increasing operational research capacity to identify optimal regimens for DR-TB patients. To manage the DR-TB burden in Karachi, a new DR-TB treatment site was introduced; there are now four DR-TB treatment sites in Karachi. Since 2016, DR-TB enrolments in Karachi have plateaued. It is possible that this plateau reflects the number of people being screened each year; it is also possible that this plateau reflects that early detection is limiting the increase of DR-TB cases or that people are seeking care for DR-TB in the increasing number of treatment sites outside of Karachi.

Data from Karachi's DR-TB program reveals that females aged 5-24 years are more than twice as likely to have DR-TB than males in the same age range. Khan noted that this trend has been well documented in the region. Special interventions will be needed to address this heightened burden of TB among younger women.

3.2.2.3.1 Increasing therapeutic options with bedaquiline and delamanid

Through the partnerships facilitated by the endTB Initiative, the program in Karachi was able to offer bedaquiline and delamanid to DR-TB patients who otherwise would have been offered regimens that are less-desirable. Because bedaquiline and delamanid are new drugs with limited WHO recommendations, planners in Karachi had to balance the concerns of funders, the government, and other partners in order to implement the use of these new drugs. These new drugs were introduced over time through various means beginning in May 2016. Most of their consumption has taken place under operational research conditions. Figure 3-12 shows that the proportion of DR-TB patients that have access to these new drugs has increased since 2017. Making newer, better drugs available to DR-TB patients is an important aspect of DR-TB treatment that has not yet been implemented broadly in Pakistan.

Figure 3-12: Introduction of bedaquiline and delamanid in Karachi through endTB initiative



Source: Khan presentation

3.2.2.3.2 Treating DR-TB among children

Khan noted that 9% of DR-TB patients in Karachi are under 15 years old. Treating children for DR-TB can be especially challenging and raises special considerations. Treating children for DR-TB requires collaborative care delivered by pediatricians and DR-TB physicians. Additionally, pediatricians must be trained to manage DR-TB among their patients. Diagnosing DR-TB in children requires special diagnostic tools, but through Global Fund support, Karachi was able to secure a CT scan machine specifically for diagnosing TB in children. They offered free CT scans to all children in Karachi referred for TB diagnosis. This very expensive diagnostic tool would have otherwise been a barrier to diagnosing DR-TB in children. Because of the issues related to treating DR-TB in children, it is essential to evaluate children who have been exposed to DR-TB to detect disease as promptly as possible.

3.2.2.3.3 Treating extrapulmonary TB among DR-TB patients

More than 6% of people in Karachi being treated for DR-TB have extrapulmonary TB, which can develop in cervical lymph nodes, the spine, the meninges, or the abdomen. Managing extrapulmonary TB requires a specific sub-set of medical expertise and diagnostic strategies—for example, treating this form of TB requires longer treatment regimens which must be carefully tracked. Khan noted that Pakistan lacks the capacity and resources to deal with extrapulmonary TB in rural sites.

3.2.2.3.4 Treating drug-resistant tuberculosis patients with hepatitis C infections

While HIV is not an issue in the Pakistani setting, treating DR-TB among those with hepatitis C has been challenging in Karachi, Khan remarked. About 10% of MDR-TB patients enrolled in the endTB study were co-infected with hepatitis C, so strategic screening for hepatitis C has been implemented at TB screening sites.[52] Early find-

52 Out of the 147 patients enrolled on bedaquiline-or delamanid-containing regimens in Karachi through the endTB program, 14 (9.5 %) had hepatitis C, 7 (50 %) were tested with PCR, and 3 (43%) had positive results and were started on treatment by a partner hepatitis C program.

ings indicate that 8% of those suspected to have TB were found to have hepatitis C.[53]

3.2.2.4 Preventing drug-resistant tuberculosis

Khan discussed some of the strategies used to prevent DR-TB in Karachi. Key prevention strategies include: (1) the use of early detection and reducing treatment delays to prevent transmission, (2) contact tracing and preventive therapy, (3) diligent and continuous education of patients and contacts, and (4) designing spaces in a way that prevents the spread of infection.

The introduction of GeneXpert testing drastically reduced the time between screening and initiation of treatment for TB patients. In 2012, it could take as many as 28 days after the patient's screen to initiate treatment. Since the implementation of GeneXpert, time to treatment has reduced greatly. Currently, those who test positive for TB are put on treatment within 3 days. Patients who need to wait for GeneXpert results are put on a standard regimen until drug susceptibility is confirmed. This reduced delay prevents TB by decreasing the transmission of disease by those with TB who have been screened but not yet diagnosed or treated; it also reduces the loss to follow-up rate. To reduce the spread of infection, ultraviolet germicidal irradiation lights were installed in high-burden facilities.

3.2.2.5 Data systems and management

Managing TB requires effective data systems, Khan explained. Through the endTB collaboration, the program in Karachi was able to implement Bahmni EMR, a data tool module designed to monitor DR-TB patients' progress and quality of care by capturing detailed clinical and outcome data. This data management tool facilitates the operational research conducted in Karachi and Kotri. The data collected is used for many monitoring and evaluation activities, including:

- tracking missed follow-up and lost to follow-up rates;
- monitoring interim treatment outcomes;
- monitoring culture conversion;
- tracking final treatment outcomes;
- monitoring relapse and reversion;
- tracking contact screening in households;
- categorizing risk groups for targeted interventions; and
- monitoring concordance of results (DST and LPA).

3.2.2.6 Capacity building, quality, and adherence

At the national and province level, clinical review committees perform regular audits, participate in case discussions, review extraordinary clinical situations, guide regimen selection, and review other program decisions. These committees comprise a mix of generalists, specialists, and senior and junior medical practitioners to create an educational and mentoring environment. Field-based teams are used to support treatment adherence through regular contact with patients and their families. These field-based teams also report on adverse events, counsel patients, and provide mental health support.

3.2.3 Social responses to tuberculosis control in Pakistan

Khan remarked that planners in Pakistan knew that they needed large-scale action to bring TB control to every household in Pakistan. An adolescent health leadership course was developed to recruit young women in Pakistan as community health advocates. Over 20,000 young women in grades 8 and 9 from public sector schools in poor communities were enrolled into the program and given hours of training on communication skills, leadership, self-awareness, health, planning, and community-based TB detection. Each of these women was then deployed to screen 20 houses in their neighborhoods; they would then bring women and children from their communities to X-ray screening camps and help manage the screen-

53 The general population prevalence of hepatitis C in Pakistan is 4.8%.

ing process. This program led to the screening of 70,000 women and children. The success of the program overwhelmed the screening capacity of the program, requiring operators to run GeneXpert tests 24/7 to keep up with the incoming specimens. After a year of screening, these young women were invited to a special event which was attended by the chief minister of the province, celebrities, and singers. The success of this program and the special event have led to government commitments to expand this community screening program to another 600 public sector schools. The efforts of these young women had a huge impact, both in terms of detecting disease and in terms of creating community and governmental buy-in. This program also spread the key messages of stigma reduction and free access to TB care throughout their communities.

Khan pointed out that TB is impacting the lives of young women disproportionately, so it follows that the team working in Karachi should be made up of many young women. The future of TB control in Pakistan is in the hands of these women who represent the group most vulnerable to the disease. Changing the narrative of TB control in Pakistan has been an important step in bringing about changes to TB outcomes in Pakistan.

Khan noted that partnership is another crucial aspect of the success of TB control in Pakistan. The models and strategies used in Pakistan have been developed through lessons learned in other countries. The Zero TB approach was developed by studying the disparities between TB treatment in poor and wealthy countries. Khan closed by emphasizing that it is not acceptable to deliver inferior care on the basis of a nation's wealth. The Zero TB model has implemented every successful strategy that has been used in wealthy settings such as North America, Europe, and Japan, rather than the inferior strategies that have been offered to poor countries in the past. Khan expressed hope that other countries will utilize the experiences from Pakistan in developing comprehensive TB care in their settings.

3.2.4 Community volunteers in Pakistan

Nerges Mistry, Medical Foundation of India, asked about the development and staffing of the field-based support teams in Karachi. Khan explained that many of these team members are high-school educated individuals who are trained in basic program management, ethics, and communication skills. These teams are trained in a brief 2-3-week training program and then monitored in the field. The teams tend to be composed of women who live in the communities. The community volunteers are deployed based on where they are most likely to be successful in their tasks. For example, men are sent to certain areas where women would be less likely to gain access. Community volunteers are provided a basic stipend. Many young women who were involved in community advocacy through their high schools are recruited preferentially for these community volunteer positions. This is done because these young women already have valuable training and experience, and the program organizers want to offer economic opportunities to this cohort of young women.

3.2.5 Selecting the first Zero TB city

Mohammad Khaled Seddiq, National TB Program, Afghanistan, asked why Karachi was chosen to be the first Zero TB city. Khan explained that Karachi was selected in part because of the logistical complexity of developing and implementing the Zero TB program. The team in Korangi had been working on TB for 10 years when they began the process of scaling-up for the rest of Karachi. It was practical to start scaling up the Zero TB program in a familiar environment where there was existing infrastructure and workforce. However, it has taken longer to expand the program to places like Peshawar because there were not pre-existing teams in those settings with experience in dealing with TB.

3.2.6 Case notification rates in Korangi

Seddiq asked why the case notification rate for children in Korangi increased while the case notification rate for adults decreased. Khan explained that adult notifications spiked and then declined because of increased focus on adult case-finding in Korangi. The spike was achieved through extensive case-finding implemented through multiple programs, which included X-ray screening and preventive treatment. Since the spike, notification has been decreasing in Korangi, although notification rates have continued to rise in the rest of Karachi. The notification rates in children represents the sporadic focus on childhood TB. Initially, there was not a focus on childhood TB, but the Indus Health Network became a de facto referral center for children sick with TB. Once childhood TB was specifically targeted by the Korangi program, the notification rate went up dramatically. It is suspected that there is still more TB among children in the area, and numbers are likely to continue rising. Khan emphasized that increasing notification rates are not a bad thing per se; they indicate that the program is getting better at detecting TB. He expressed confidence that eventually notification rates among children will go down.

3.2.7 The disparity in tuberculosis rates between men and women in the region and coinfection

Seddiq asked about the disparity between TB in men and women in the region. Khan explained that, in South Asia and in parts of the Middle East, disparities in TB rates between men and women have been well documented and are likely related to social and biological factors. It seems that younger women are either exposed to TB more frequently or are progressing to TB disease more rapidly. One theory is that this may be related to vitamin D deficiency associated with women covering themselves from sunlight more so than men; it may also be related to the fact that many young women are caregivers and have limited time to access health care. Additionally, many young women may be undernourished because of the culture of preferential male feeding. Further hormonal and age-related biological factors may also contribute to the high rate of TB among young women. This trend is observed in Jordan, Afghanistan, and parts of Pakistan, but neither India nor Bangladesh have observed this trend.

Maxo Luma, Partners In Health, Liberia, asked about the rate of HIV coinfection among young girls in Pakistan. He suggested that there may be some connection between coinfection rates and the disparity in TB rates between women and men. Khan pointed out that this region is unique in that it has a very low burden of HIV; he estimated that less than 2% of TB patients in Pakistan are co-infected with HIV. It is unlikely that comorbidities of any kind will be the underlying factor driving the disparity in TB rates between men and women; rather, the disparity in the region is likely related to social and biological factors.

3.2.8 Media involvement in Pakistan's Zero TB program

Patrice Joseph, GHESKIO, Haiti, asked about the role of the media on Pakistan's Zero TB program. Khan acknowledged the importance of the media for Pakistan's program. For example, the mobile X-ray vans generated government and media interest wherever they went; there would often be inaugural ceremonies that generated awareness and community involvement. The community advocacy of the high-school-aged women also created "buzz" in the communities. For the first time, the city experienced a sustained awareness and interest in the effort to fight TB in Karachi. The program benefited from free publicity through these activities, but they also paid for national advertising campaigns on radio, television, and print media.

3.2.9 Sustainability and the comprehensive approach to TB control

Peter Nyasulu, Stellenbosch University, South Africa, asked about the sustainability of the Zero TB program in Karachi. Programs often bring about positive impact, but there is always the accompanying challenge of maintaining

those changes over time. Khan acknowledged that nothing in TB control is truly sustainable. Whether countries receive external funding or appropriate government funds to implement these programs, once the funding is diverted away from these efforts, the activities of the programs will be discontinued. The program in Karachi did not, however, require any more funding than would have been granted to Pakistan. The novel approach in Pakistan was to strategically target a small geographic area with full force, rather than to implement limited, less-intensive interventions across a much broader geographic area. He emphasized that the program in Karachi utilized a new approach rather than new money. In terms of sustainability, Khan asserted that the cost of not dealing with TB is immense. For example, the burden of TB among young women can negatively impact fertility and health outcomes in ways that would be very difficult to calculate. He also pointed out that the reason older approaches to dealing with TB have produced recurring costs is simply because they are ineffective. In contrast, a successful approach to TB should become less costly over time as TB rates begin to decline. The targeted, high-intensity approach needs to be implemented broadly in Pakistan. Khan expressed confidence that this approach will yield the desired results within 10-20 years, just as it has in other settings where these strategies have been implemented.

3.2.10 Preventive treatment of tuberculosis infection in Pakistan

Karl Le Roux, Zithulele Hospital, South Africa, asked about the LTBI treatment criteria and regimen. Khan explained that for DS-TB rifampicin and isoniazid are used for preventive therapy. For DR-TB, high-dose levofloxacin and ethionamide are used.

3.2.11 Optimizing GeneXpert coverage

Charles Sandy, Ministry of Health and Child Welfare, Zimbabwe, asked how GeneXpert testing coverage has been optimized in Karachi, given the relatively small number of GeneXpert machines available. Khan explained that the majority of GeneXpert machines in Pakistan have been purchased in the public sector. All GeneXpert devices are connected through GXAlert, which tracks how many machines are operational and the throughput of each machine. The system also transmits tests results to the central database in Islamabad. These data indicate that GeneXpert machines are currently underutilized in the public sector but 'overutilized' in the private sector. This disparity results from the different approaches to testing. In the private-sector Indus Health Network sites, anyone with abnormal X-ray or referred by a physician is given a GeneXpert test. In the public sector, smear microscopy is used before GeneXpert. The current challenge is in the testing algorithm, he said, not in the testing capacity. The government has recently agreed to loosen the criteria for GeneXpert testing such that all people with abnormal chest X-rays will be tested with GeneXpert. He was hopeful that the GeneXpert machines will be more effectively utilized moving forward. However, if all of Pakistan were using the same testing algorithm as the Indus Health Network, then Pakistan would indeed need more GeneXpert machines.

4 Post-exposure management of persons exposed at home to MDR-TB

4.1 TREATMENT OF INFECTION FOR RIFAMPICIN-RESISTANT TUBERCULOSIS: THE CASE FOR ACTION

Jennifer Furin, Harvard Medical School, USA, reviewed the need and rationale for the treatment of TB infection, also referred to as 'preventive therapy.' She explored data on the elevated risk of TB disease among household contacts of people with RR-TB and shared global experiences in administering RR-TB infection treatment, with reference to possible regimens that can be used to treat RR-TB infection. She also described several randomized trials being conducted to study the treatment of this infection and addressed some common barriers to treatment. Finally, she explained how post-exposure management of household contacts is an optimal starting point for treating RR-TB infection.

4.1.1 Tuberculosis pathology: who is at risk and who should be treated?

Furin emphasized that what has been referred to as 'preventive therapy' is really the treatment of an infection. Those exposed to TB have been infected with a small quantity of bacteria. For this reason, the terminology 'treatment of TB infection' is preferred. The conventional training for TB treatment teaches that there are 'latent' and 'active' forms of TB disease, but this framework is long outdated—TB pathology should be thought of as a spectrum. Individuals with very low quantities of bacteria in their lungs usually have good outcomes with single-or dual-agent therapy; people with higher bacillary burden are sicker and require different forms of treatment. Figure 4-1 shows the conventional labels of 'active' and 'latent' TB superimposed on the spectrum of disease.

4.1.1.1 High-risk situations for TB infection

TB recommendations often assign risk of acquiring TB disease to groups, such as people living with HIV and children aged <5 years. However, rather than focusing on "high-risk individuals," it may be more useful to focus on identifying high-risk situations. The level of risk in any situation is determined by (1) the characteristics of the individual with TB disease, (2) the exposure environment, and (3) the characteristics of the exposed individuals. The judgment cannot be made based solely on the attributes of those who have been exposed, Furin emphasized. Higher-risk characteristics of persons living with TB disease include the presence of smear-positive, cavitary TB disease and the presence of laryngeal TB disease. Higher-risk characteristics of exposure environments include limited airflow and prolonged, close contact with a person living with TB disease.[54] For instance, a child that shares a bed with his or her mother who is ill with TB is living in a higher-risk environment; a person riding on a bus for one hour with a person living with TB is in a lower-risk environment. Higher-risk characteristics of individuals exposed to TB disease include younger age, malnutrition, and immunosuppression.

4.1.1.2 Testing for infection and predicting who will develop disease

Testing for TB infection is problematic, Furin explained. Tests such as TST and IGRA are designed to detect an immune response to TB, but for those with compromised immune systems, these tests are not very useful. People who cannot mount immunological responses to TB are at the greatest risk of developing TB disease, but because TST and IGRAs require a functional immune response, they perform most

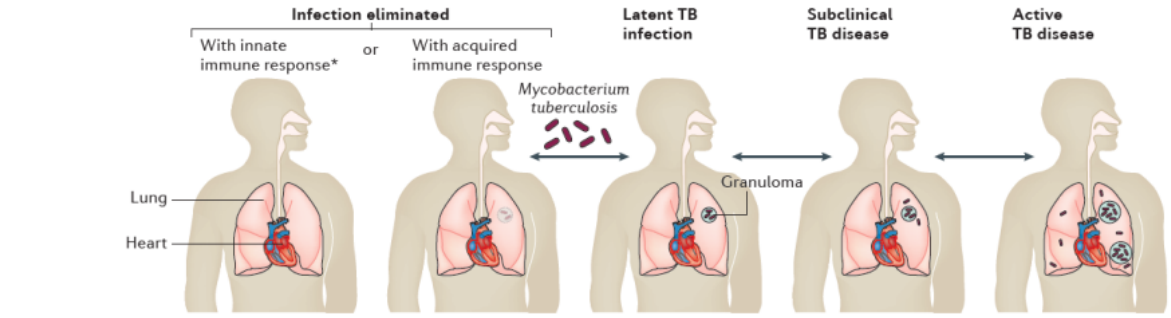
54 Furin addressed the frequent concern about TB transmission on airplanes. Studies have found that there is very low risk of transmission on flights less than 8 hours in duration. For flights longer than 8 hours, the risk is primarily for those sitting within two rows of the person with TB.

poorly in those at highest risk. She suggested that exposure scales may be useful for determining who is infected with TB. Although exposure scales have not been widely validated, individuals who score high on exposure scales should be treated for TB infection.[55] Emerging data shows that socioeconomic predictors also have value for determining who to treat.

Beyond identifying risk and detecting infection, additional methods are needed to predict who among the estimated two billion people worldwide who have TB infection will go on to develop active disease. If the individuals who are most likely to progress to active disease can be identified consistently, the burden of delivering treatment for TB infection would be greatly reduced. Unfortunately, there is currently no way to accurately determine who will develop active TB among those with TB infection. Better science is needed to make such predictions and multiple ongoing studies are investigating this issue.[56] It is likely that the characteristics of the mycobacteria will have a role in predicting who will develop active TB. The characteristics of the exposed individual are also likely to have an impact—e.g., age, malnutrition, immune status, and macrophage function—in making some people more able to clear the TB infection than others. Timing of exposure also plays a role; most people who develop active TB after being infected do so within 2 years of infection. Thus, more recent exposures are more likely to progress to disease. Socioeconomic factors also play a role in who progresses from infection to disease.

Numerous factors contribute to the potential risk of developing TB disease. Figure 4-2 shows the relationships between different characteristics of hosts and environments in determining the risk of developing TB disease. Furin noted that simplified algorithms that merely identify children aged <5 years and individuals living with HIV are insufficient because they miss a large number of people who would benefit from treatment of TB infection.

Figure 4-1: The spectrum of tuberculosis



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Notes: TB = tuberculosis; TST = tuberculin skin test; IGRA = interferon-gamma release assay
Source: Furin presentation

55 Mandalakas et al 2012
56 Saunders et al 2017

4.1.2 Treatment of tuberculosis infection saves lives

The value of treatment of TB infection has been well documented,[57] Furin stressed, so there is no room to question whether the treatment of TB infection saves lives. The literature from DS-TB studies shows a clear and lasting mortality benefit across multiple populations in both high-burden and low-burden settings. Benefits of TB infection treatment have been observed after a single course of treatment, even in settings where re-infection is likely. The mortality benefit persists for at least 5 years. The risk-benefit analysis is clear for DS-TB: the issue is one of resources, not science or evidence. TB clinics are overwhelmed and adding the treatment of TB infection to the workload for providers is challenging. This likely contributes to why, in many settings, treatment of TB infection is not offered or offered only to children aged <5 years and individuals living with HIV.

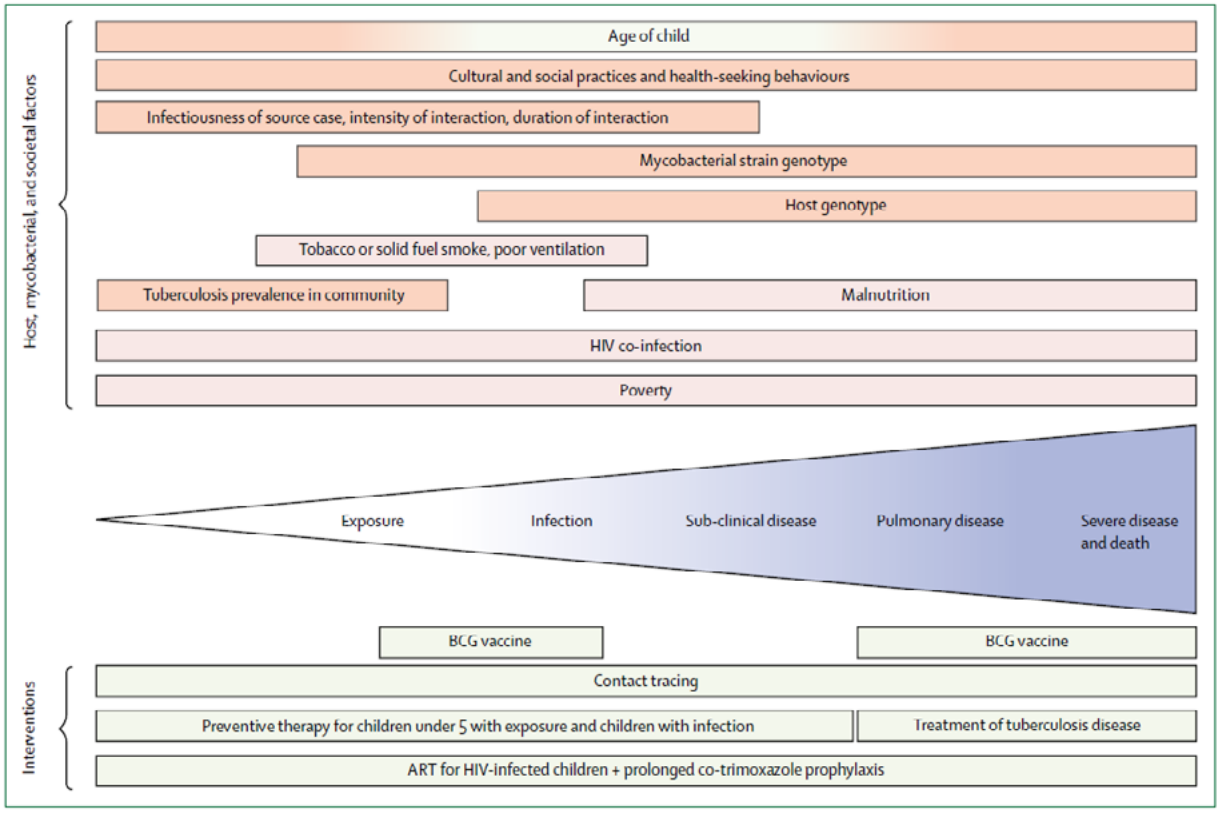
Furin asserted that the same principles apply to the treatment of RR-TB infection as DS-TB: treatment of infection saves lives. An estimated 1.2 million people are exposed to RR-TB in their homes every year and an estimated 19.1 million people are infected with RR-TB worldwide.[58]

People in wealthy countries are treated for TB infection, whether they have been exposed to RR-TB or DS-TB. In the US, for example, individuals who were in a shopping mall when an individual with RR-TB was in that shopping mall will be tracked and offered treatment for RR-TB infection.

The risk-benefit analysis for RR-TB also favors treatment of infection. While DS-TB treatment is not easy, it is far better and more likely to be successful than RR-TB treatment. However, only about 20% of people with active RR-TB are found and cured; the treatment success rate for RR-TB is only 55%-65%. Further, the medications used for RR-TB are associated with multiple permanent adverse effects. The catastrophic costs and psychosocial toll of RR-TB are higher than that of DS-TB.[59] The ideas that RR-TB is not as transmissible as DS-TB or that RR-TB is not as virulent as DS-TB are also outdated notions. Multiple studies show higher rates of TB disease when a household member has RR-TB. This could be due to a longer period of time without adequate therapy for the first person in the household who was diagnosed with RR-TB.[60] It is clear that people who have been exposed to RR-TB need intervention.

57 Danel et al 2015; Getahun et al 2010; Gomes et al 2013
58 Knight et al 2019
59 Shringarpure et al 2016
60 Shah et al 2014

Figure 4-2: Schematic representation of risk factors and protective interventions in pediatric interactions with *Mycobacterium tuberculosis*



Note: Red background denotes risk factors, green background denotes protective factors, and orange denotes factors that can be either protective or increase risk. ART = antiretroviral therapy
Source: Furin presentation
Data Source: Basu Roy et al. 2019

4.1.3 Global experiences in treating drug-resistant tuberculosis infection

Furin pointed out that in high-income countries, individuals exposed to RR-TB are routinely treated for TB infection.[61] A recent study found that wealthier nations in the WHO European region treat DR-TB contacts, while the less wealthy nations in the region do not.[62] This gives rise to the question of whether standards are being applied based on wealth or based on evidence. When the US CDC was asked to intervene during a DR-TB outbreak in Chuuk, they provided patients with treatment of TB infection. People who received and completed treatment for infection did not develop disease, but among those who refused or were unable to complete treatment of TB infection, three individuals developed DR-TB.[63] She added that the Desmond Tutu TB Centre's work in South Africa has shown that treatment for DR-TB infection is effective and well tolerated.[64]

Colleagues at the US CDC conducted a meta-analysis that found a 90% reduction in the incidence of DR-TB in settings where treat-

61 Harvard Medical School Center for Global Health Delivery -Dubai 2015, Denholm et al 2012
62 Turkova et al 2017
63 Bamrah et al 2014, Mase et al 2016
64 Seddon et al 2012; Seddon et al 2013a; Seddon et al 2013b; Zimri et al 2012

ment of infection was offered.[65] Most regimens used fluoroquinolones as the base and many regimens included another drug. In addition to the reduction in TB disease, the study found that treatment for DR-TB infection was cost effective. This evidence contributed to WHO's recommendation that people exposed to DR-TB should be offered treatment of infection.

4.1.4 Treatment regimens for drug-resistant tuberculosis infection

Furin suggested that uncertainty about which drugs to use may be one reason that treatment of RR-TB infection is not being widely offered. For DS-TB, there is a well-known selection of drugs to use. For RR-TB infection, however, there is less consensus about which drugs to use. A third-generation fluoroquinolone should almost always be included in regimens for treatment of RR-TB infection. Multidrug regimens have typically been used to treat RR-TB infection, but the use of fewer drugs in regimens is associated with fewer side effects and better adherence. Multidrug regimens were used in the past because it would take months to get DST results—so providers often felt uneasy putting contacts on a single-drug treatment while waiting for the results—but such delays are no longer an issue as susceptibility testing improves. Fluoroquinolone can treat both DS-TB and RR-TB infection. If a patient has been exposed to fluoroquinolone-resistant TB, then delamanid may be a good option for treatment of infection.

4.1.5 Disclosure counseling

Disclosure is a high-risk activity that has not been appropriately addressed in TB treatment, said Furin, and she underscored the importance of counseling patients on the risks of disclosure. Healthcare providers often advise patients to "go home and tell your family that you may have given them TB. They must come and get checked to see if you made them sick." This is a significant, unnecessary, and potentially dangerous burden to place on a person with TB. Some patients experience domestic violence or are kicked out of their homes after disclosing their TB disease to family members. Disclosure counseling has been well developed in HIV treatment, she noted, and TB care providers need to work on providing better disclosure counseling for TB patients.

4.1.6 Ongoing randomized trials for treatment of RR-TB infection

Furin shared three ongoing trials that are likely to further inform the optimal treatment for RR-TB infection, although the results are not expected from these studies for at least a few years. She noted that preventive therapy is usually discussed in the context of households, because it is difficult to randomize by individual.

V-QUIN is a cluster-randomized controlled trial investigating the effects of 6 months of levofloxacin compared with placebo being conducted in Vietnam. Household contacts of patients with RR-TB of any age can enroll in the study within 3 months of contact. Initially, contacts were required to be over 15 years of age to enroll, but now all ages are permitted to enroll in the study. To date, 1,653 of the targeted 2,006 participants have been enrolled. Results are expected in late 2022.[66]

In South Africa, TB-CHAMP is another cluster-randomized trial comparing 6 months of levofloxacin monotherapy with placebo. The study was initially planned to test delamanid, but it was too difficult to get approval because the safety data on children aged <3 years is not yet available. The trial is studying child contacts of individuals with active RR-TB aged <5 years; they may add older children and individuals with HIV to the study at a later point. Approximately half of the target population has been enrolled and results are expected in 2023.[67]

PHOENIx (ACTG 5300) is a multi-site trial being conducted in Botswana, South Africa, Thailand,

65 Marks et al 2017
66 For more information about V-QUIN, see https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369817 (accessed September 12, 2019).
67 For more information about TB-CHAMP, see http://www.isrctn.com/ISRCTN92634082 (accessed September 12, 2019).

Brazil, and Peru that is comparing the use of delamanid to isoniazid over 6 months of treatment. The trial is enrolling household contacts of all ages, although children aged <2 years will be enrolled last after the safety data for delamanid becomes available. The trial began enrolment in July 2019 and results are expected in 2024. The trial is using isoniazid as a control because of ethical concerns raised about giving placebo to household contacts of patients with RR-TB. Isoniazid was selected for the control based on early data suggesting that isoniazid may benefit those exposed to RR-TB if given at higher doses.[68]

4.1.7 Barriers to treatment of drug-resistant tuberculosis infection

Furin described five key barriers to treatment of drug-resistant tuberculosis infection: (1) safety of fluoroquinolones, (2) generation of fluoroquinolones-resistant TB, (3) situations where contacts may have been exposed to drug-sensitive tuberculosis, (4) possible exposure to fluoroquinolone-resistant tuberculosis, and (5) people do not come to the clinic.

4.1.7.1 Barrier 1: Safety of fluoroquinolones

Concerns about the safety of fluoroquinolones are a common barrier to the provision of treatment of RR-TB infection. Years ago, there was a study that observed potential adverse effects of fluoroquinolones in dogs' cartilage, so providers have long advised that children should not be given fluoroquinolones. Furin explained that this information is outdated: multiple cohorts of children have been successfully treated using fluoroquinolones without any permanent damage to their joints.[69] Overall, fluoroquinolones are safe drugs for treating RR-TB infection and are associated with fewer and less serious adverse events than isoniazid.[70] She pointed out that isoniazid, in fact, has a black box warning, yet it is frequently used for the treatment of TB without concern. It is likely that fluoroquinolones will be found to be safer than isoniazid, which can cause fatal fulminant hepatitis.

4.1.7.2 Barrier 2: Generation of fluoroquinolone-resistant tuberculosis

It is common to hear concerns that the use of fluoroquinolone will lead to cases of fluoroquinolone-resistant strains of TB. Among the cohort of those who have been treated for RR-TB infection using a fluoroquinolone, no cases of fluoroquinolone resistance have been reported. Similar concerns were raised as isoniazid became widely used to treat TB infection. Thus far, isoniazid resistance among people treated for TB infection using isoniazid is very low. Any resistance that has been developed can likely be attributed to the presence of active disease or a high bacillary burden at the time of treatment for TB infection. It is extremely unlikely that a clinician will see a wave of fluoroquinolone-resistant TB disease after treating patients for DR-TB infection with fluoroquinolones.

4.1.7.3 Barrier 3: Contacts may have been exposed to drug-sensitive tuberculosis

Furin reiterated that fluoroquinolones should be effective for DS-TB and RR-TB infection; however, it is possible that some contacts of patients with RR-TB have been previously exposed to DS-TB. Exposure to DS-TB may be more likely in adults and older child contacts who may have been exposed to DS-TB at school or work. To ensure successful treatment of whatever infection is present, some clinicians may choose to treat patients using both fluoroquinolones and high-dose isoniazid. Such a regimen would eliminate any concern about whether individuals were exposed to RR-TB or DS-TB.

68 For more information about PHOENIx, see https://actgnetwork.org/study/a5300b-mdr-tb-households (accessed September 12, 2009).
69 Recently, the European Medicines Association issued a warning about the use of fluoroquinolones to treat pneumonia in elderly patients. However, this was a very specific finding among a specific population where alternative drugs were available.
70 Schaaf et al 2016

4.1.7.4 Barrier 4: Possible exposure to fluoroquinolone-resistant tuberculosis

Furin noted that in some settings, fluoroquinolone resistance is as high as 50%. In many cases, there may not be fluoroquinolone-susceptibility testing results, or the results may not be available immediately. However, it is essential to begin the treatment of RR-TB infection as soon as possible and clinicians are not advised to withhold treatment while waiting for susceptibility testing. It is also possible that a patient with fluoroquinolone-susceptible TB may develop fluoroquinolone resistance during treatment. This discovery can cause complications for that patient's contacts if the contacts are being treated for infection with fluoroquinolones. When fluoroquinolone resistance is a concern, delamanid can be used for the treatment of RR-TB infection. However, access to delamanid is limited in many settings. This is a difficult barrier to overcome in settings where fluoroquinolone resistance is common, but these difficulties should not prevent clinicians from providing treatment to individuals who have been exposed to RR-TB.

4.1.7.5 Barrier 5: People do not come to the clinic

Most patients with RR-TB are advised to bring their household contacts to the clinic, but many of those contacts never visit the health facility for evaluation. A study conducted in Cape Town, South Africa, found that the most common reason that contacts do not come to health centers is that they do not have the means of transportation required; the second most common reason was a lack of symptoms. Mothers may not wish to send their seemingly healthy children to the health clinic, especially when doing so will take them away from school or work. Respondents also expressed concern about sending their children to a health facility where they may be exposed to TB. This attitude reveals the psychological impact of TB and how difficult it is for many parents to accept that they may have caused their children to be sick. This barrier underscores the critical importance of disclosure counseling and careful use of language to explain the contact tracing process to patients. Furin explained that she often tells her patients that 'everyone who breathes the same air may have TB. Everyone breathes, and breathing is how one gets TB. Families living together are breathing the same air, so everyone in the family home is at risk.' Furin advised against using language that suggests that the patient 'gave' their family RR-TB. The way that providers communicate to patients will determine whether they bring their children in for evaluation.

4.1.7.6 Additional barriers

Furin acknowledged that the lack of resources is a common and very challenging barrier to providing treatment for TB infection. Overwhelmed staff may be uneasy about inviting numerous additional patients to their clinics every time a new patient is admitted. Financial resources also constrain efforts to treat TB infection. For example, active TB must be ruled out before treatment for RR-TB infection can be considered. However, ruling out active TB is neither easy nor inexpensive, especially among young people and those living with HIV. Another common barrier is that providers and policymakers may adopt a 'wait and see' attitude of wanting to see evidence from randomized controlled trials before taking action. Although this is a reasonable attitude, waiting for evidence should not render providers powerless or justify inaction, given the good options for treating TB infection that are available now. In many settings, one clinician becomes the designated prophylaxis clinician, which may not be a preferred role. Health care facilities may need to restructure their services to integrate treatment of infection with other RR-TB services. The variety and complexity of regimens and the lack of a single regimen for all cases is another barrier for some clinicians. Unfortunately, the nature of RR-TB requires that the appropriate regimen be used for each case.

4.1.8 Post-exposure protocol for rifampin-resistant tuberculosis

Every person who is treated for RR-TB infection must have active disease ruled out. Furin suggested that ruling out active disease is a great starting point for a post-exposure protocol.

Some programs may not want to treat TB infection or may be unsure about which drugs to use. However, all programs can begin systematically evaluating all contacts for active disease, either in clinics or in their homes. Screening contacts for active disease is part of WHO's guidelines, but it is often not done in a systematic way. The Sentinel Project for Pediatric Drug-Resistant TB has published a guide to help programs manage treatments for RR-TB contacts, offering modular approaches for caring for those who have been exposed to RR-TB. Programs can begin by only screening contacts for disease or by only treating those who have been exposed with the highest risk. Using this guide, programs can begin working on post-exposure management and develop the program further over time.[71]

The term 'post-exposure management' was coined to replace the term 'contact tracing.' In HIV, post-exposure prophylaxis (PEP) is an established protocol. Similarly, if an individual is bitten by a dog and there is concern about rabies, treatment is offered immediately: clinicians would not say 'come back if you get sick.' The mindset in TB care needs to shift from contact tracing to post-exposure management of individuals who have been exposed to an infectious disease. This change of mindset can help providers and it is also more appealing to funders. Further, post-exposure management provides an opportunity for programs to conduct operational research. Programs can collect data and observe how their post-exposure management programs are working in their settings. Furin concluded with a set of key takeaways from her presentation (see Box 4-1).

Box 4-1. Key takeaways about treating rifampicin-resistant tuberculosis infection

For 13 years, WHO has recommended urgent action for those who have been exposed to RR-TB. Now is the time to take action to care for those who have been exposed to DR-TB.

- TB programs have several options to take action:
- Programs should, at least, be screening contacts of RR-TB patients for active disease.
- Programs can begin selectively treating RR-TB infection in at-risk populations using an epidemiology-based regimen.
- RR-TB infection treatment can be widely implemented under carefully monitored operational research conditions (e.g., operational research on effectiveness, safety, and acceptability).

4.1.9 Discussion

4.1.9.1 Workplace contact management

Saleem Kazmi, Pakistan, remarked that it is very difficult to get contacts to come to health care centers in Pakistan and inquired about the importance of workplace contact management. Furin explained that the focus on household contacts is due to the fact that households are high-risk settings. The burden of household contacts alone is overwhelming for many health care systems. There are cases found in the workplace, but it varies significantly depending on the working environment. Workplace contact investigation should be informed by the identification of high-risk exposure settings and the resources available. She compared this approach to 'ring vaccination' for Ebola: Ebola vaccine is not broadly administered; rather, it is

71 To access this guide, visit http://sentinel-project.org/wp-content/uploads/2018/03/PE-Guide_English_V1_Mar2018-1.pdf (Accessed Dec 1, 2019)

given to those within the ring of exposure. Yuen added that the focus on household contacts is a shortcut. Generally, household contacts are at risk and it is an easy group to identify and define. In Peru, Yuen and colleagues are implementing the contact investigation protocol used in the US, which involves a structured risk assessment. A 40-minute conversation with a TB patient can reveal where they spend their time and when their symptoms started. Using this information, investigators can predict who will be at risk or infected. Often, this strategy leads to the identification of household contacts as well as regular visitors, such as family members who spend weekends with the patient. Close workplace contacts are also frequently identified. It requires an investment of time and training to identify and locate these contacts, but this approach increases the number of contacts evaluated.

4.1.9.2 Bridging the equity gap for access to tuberculosis care

Maxo Luma, Partners In Health, Liberia, asked how to bridge the equity gap between developed nations and the developing world in terms of access to interventions that have been shown to work. He also asked about the role of pharmaceutical companies in implementing post-exposure management. He noted that many countries rely on funding from the Global Fund, a funding mechanism that prioritizes the short-term budget and makes it difficult for programs to purchase relatively expensive drugs, like delamanid. Furin acknowledged that the limited availability of evidence is being used as an excuse to tell poorer nations not to use the relatively expensive interventions that are being used in wealthier nations. It is true that there are no randomized controlled trial data to support the treatment of RR-TB infection; however, there is not sufficient evidence to advise against the treatment of RR-TB infection. Operational research is a valuable tool for providing interim evidence. She agreed that the issue of funding is also a very important concern. A 6-month supply of delamanid procured through the Global Drug Facility costs US$1,700. Most funders are not looking at the 10-year impact of their spending; they want to see what can be accomplished in a single year. This is a challenge, because implementing treatment of RR-TB infection is not going to yield an impact for a least 5 years. The UN High-Level Meeting on TB yielded an international commitment to put 30 million people on preventive therapy by the end of 2020 and countries need to be held accountable to this commitment. She advised that the operational research model may also help program organizers bring in new funders, including generous pharmaceutical companies. She cautioned that pharmaceutical companies must be dealt with in a particular way to navigate conflicts of interest. She also advised that all participants can advocate for the reduction of drug prices.

4.1.9.3 Diagnostic biomarkers for tuberculosis

Yatin Dholakia, Foundation for Medical Research, India, expressed his support for the acknowledgment that TB is a non-binary spectrum of disease. He asked about the role of biomarkers in diagnosing TB infection and whether such biomarkers could be used to monitor the progress of TB infection. Furin explained that biomarkers are chemical signatures or imaging findings that can indicate: (1) who may be infected; (2) among those who are infected, who may be at risk for progressing to disease; and (3) if the risk changes over time. Some studies have shown promising evidence of biomarkers for TB, but no biomarkers have yet been tested for predictive value. She speculated that, in 5 years, there may be a simple biomarker that could indicate whether a person is infected and at risk of developing disease.

4.1.9.4 Repeated treatment of infection verses single treatment regimens

Dholakia asked about the possibility of pulsed (repeatedly administered) TB preventive therapy. Furin acknowledged that many people are exposed repeatedly and it is known that administering treatment of TB infection provides a mortality benefit. Among the studies investigat-

ing the benefits of cycled therapy is WHIP3TB,[72] which is looking at the effects of annual cycles of 3HP. Although it may suggest that annual treatment is more effective than single treatment regimens, such evidence should not discourage providers from offering single treatment regimens.

4.1.9.5 Managing the risk of exposure among those who work in health care facilities

Lilit Khachatryan, Ministry of Health, Armenia, asked about how wealthy nations, such as the US, deal with the risk of TB exposure among medical staff. Furin explained that in the US, the approach to this issue is different than in most countries—both because the US has more money than many countries and because the US has very little TB. Healthcare workers are tested with TST annually. If the TST is positive, then health workers are tested with a chest X-ray and offered some form of preventive therapy (usually 3HP, since there is very little RR-TB in the US). If a hospital patient in the US is found to have DR-TB, then all workers exposed to that patient are tested with TST. Since health workers in the US are tested with TST annually, their results can be compared to previous results to determine if they have developed TB infection or disease. Health workers exposed to DR-TB would be offered levofloxacin or levofloxacin in combination with another drug. However, it is much more complicated to deal with this issue in other countries and settings. At this time, it is not well understood whether health workers in DR-TB hospitals should be taking preventive treatment, but people providing care to patients with TB should be closely monitored.

Yuen commented that it would be problematic for countries with higher TB burdens to adopt the guidelines of wealthy nations. Wealthy nations have guidelines in place, but the risk profile in these nations differs greatly from that of high-incidence countries. For example, the US recently eliminated the requirement for intake TST testing among healthcare workers who would not routinely be exposed to a patient with TB, if one were admitted. TB has become such a nonissue in many wealthy nations that it is very unlikely that any healthcare worker would be exposed to a contagious TB patient more than once. It is not appropriate for high-incidence countries to try to use the guidelines of low-incidence countries to develop their policies for monitoring TB among health care workers, she added. People living with HIV in high-burden settings may be more analogous to healthcare workers in high-burden settings, said Yuen.

Furin added that non-healthcare providers who work in healthcare settings, such as cleaning staff, must also be monitored. Cleaning staff spend more time in TB wards than anyone else and there have been high rates of DR-TB among these individuals, so they should routinely be offered assessment and treatment. She also implored her colleagues to wear N95 masks. Doctors and nurses who treat patients with DR-TB are a limited resource and providers should protect themselves from disease to the fullest extent possible. She also pointed out that once patients are on the right therapy, they become non-infectious within 24-48 hours. This is another reason not to withhold the most powerful available regimens from patients. Patients should be given the most powerful available regimen first in order to minimize the risk of transmission within healthcare facilities. The risk of transmission in a healthcare facility is very low if providers (1) have drug susceptibility results, (2) prescribe the correct therapies, and (3) know that patients are taking their medicines. The risk of transmission is greatest before diagnosis is made, making nurses and practitioners in primary clinics more vulnerable than TB specialists.

4.2 SCREENING AND TREATMENT OF CHILDREN AND ADULTS EXPOSED AT HOME TO DRUG-RESISTANT TUBERCULOSIS

Hamidah Hussain and Amyn Malik, both from Interactive Research & Development, Pakistan,

72 For more information about WHIP3TB, see https://clinicaltrials.gov/ct2/show/NCT02980016 (Accessed September 12, 2019)

discussed the preventive therapy program that was implemented under operational research conditions in Pakistan. Hussain described the programs implemented in Karachi and Kotri. Malik reported on two studies that were nested in the preventive treatment programs and investigated questions about preventive treatment for contacts of DR-TB.

Pakistan is a high-burden country, both in terms of DS-TB and DR-TB (see Figure 4-3). Hussain explained that the objectives of the preventive treatment program were:

- To assess the proportion of household members with disease in a household with a pulmonary DR-TB patient at baseline;
- To assess the proportion among those initiated on preventive therapy who completed treatment;
- To assess the risk of development of disease in those contacts twho were ineligible for preventive therapy or those who refused preventive therapy; and
- To assess the proportion of adverse events

Figure 4-3. Estimates of the TB burden in Pakistan (2017)

ESTIMATES OF TB BURDEN,[a] 2017		
	NUMBER (THOUSANDS)	RATE (PER 100 000 POPULATION)
Mortality (excludes HIV+TB)	54 (42–67)	27 (21–34)
Mortality (HIV+TB only)	2.2 (1.1–3.8)	1.1 (0.56–1.9)
Incidence (includes HIV+TB)	525 (373–704)	267 (189–357)
Incidence (HIV+TB only)	7.3 (3.6–12)	3.7 (1.8–6.2)
Incidence (MDR/RR-TB)[b]	27 (17–39)	14 (8.8–20)

Source: Hussain and Malik presentation

4.2.1 Operational research in Karachi, Pakistan

The preventive treatment program began at the Indus Hospital in Karachi and was then expanded to the Institute of Chest Diseases in Kotri. The program in Karachi was designed to evaluate 100 households of TB patients in Karachi, Hussain explained. When an index patient was identified, his or her household was added to the evaluation group. The operational research limited the evaluation population to those individuals who live with a patient who was treated for DR-TB disease at the Indus Hospital in Karachi. The operational research was conducted over a 2-year duration (Q2, 2016 – Q2, 2019).[73] The program began with very restrictive criteria. All household contacts aged <5 years were eligible for treatment. Children aged 5-17 years were eligible if they met 1 of 3 eligibility criteria: (1) the child had a positive TST, (2) the child had an immunocompromising condition, or (3) the child was malnourished (3rd centile or less). Adults aged >18 years were eligible only if they were malnourished or if they had an immunocompromising condition, such as HIV, chronic lung disease, or diabetes.

4.2.1.1 Indus Hospital drug-resistant tuberculosis program procedure

Once a DR-TB patient at the Indus Hospital was identified, providers requested permission to visit the patient's home, Hussain explained. If permission was granted, then a health worker visited the home, enumerated those in the household and asked for their consent to participate in the study. Those who agreed were verbally screened in their homes by the health worker at the time of the initial visit. The entire family was then asked to visit the hospital for further evaluation to rule out TB disease. TB disease was ruled out through chest X-ray, clinical evaluation, and GeneXpert testing if sputum was available. Physicians had discretion to use whatever testing methods they felt were necessary to rule out TB disease. Those who were found to have TB disease were referred for treatment of TB disease. Those who were found not to have TB disease and met the eligibility criteria were offered treatment for TB infection as per the study protocol.[74] To minimize paper records, the program used electronic data capture. Both contact investigation and follow-up were managed using an electronic data capture system.

4.2.1.2 Drug regimens

Hussain described the regimens offered for preventive treatment, which included levofloxacin with either ethambutol or ethionamide. The study designers preferred ethambutol, but midway through the study, ethambutol become unavailable in the desired dosage (the regimen had been designed with 400-mg tablets, but only 100-mg tablets were available). This change

73 Malik et al 2019b
74 For more information, see Appendix 14.

increased the pill burden such that the program designers chose to use ethionamide instead of ethambutol. In cases where the index patient was found to have fluoroquinolone-resistant TB, contacts were given moxifloxacin in combination with either ethambutol or ethionamide. The regimens were administered daily for 6 months.[75]

4.2.1.3 Patient support

The counseling aspect of the program was very strong, said Hussain. Index patients and household contacts were counseled before the preventive treatment was offered. Counseling included explanations of (1) what TB is, (2) how TB is transmitted, (3) the importance of screening contacts for disease, (4) the importance of initiating contacts on preventive therapy, and (5) the importance of treatment adherence. Counseling took place at baseline, at the beginning of treatment, and at follow up. Initially, clinical psychologists were enlisted as counselors. As the program progressed, other health workers with exceptional patient communication skills were selected to counsel patients.

Hussain pointed out that the cost of transportation is a major barrier to treatment. To overcome this barrier, the operational research program included patient enablers. Patients were provided PKR 600 at baseline, at the initiation of preventive therapy, and at every 2-month follow up.

4.2.1.4 Operational research results from Karachi, Pakistan

Hussain explained that, out that of the 800 contacts identified during operational research, only 794 were able to be contacted. Of the 793 contacts who participated,[76] 402 were eligible for investigation for preventive therapy. Among the contacts who were screened, eight were found to be on treatment for DR-TB or DS-TB. All child contacts aged <17 years and adults who fit the eligibility criteria were evaluated for preventive therapy; three of the contacts evaluated were diagnosed with DR-TB. Among those evaluated, 214 contacts were eligible for preventive therapy and 172 of those contacts initiated preventive therapy. Among those who started preventive therapy, 61 were aged ≤4 years, 86 were aged 5-17 years, and 25 were aged ≥18 years. Of these contacts, 121 (70%) completed treatment. Among the 30% of contacts who initiated treatment but did not complete treatment, treatment was taken for between 1 and 5 months.[77] Because of the eligibility criteria of this operational research, the majority of those who initiated treatment were aged <17 years. Among the adults who initiated preventive therapy, 9 women and 15 men initiated treatment, including one man over 65.

Hussain remarked that the primary reason for initiating treatment was malnutrition (weight for age 3rd centile or less). Of the 86 children aged 5-17 years who initiated treatment, 5 were initiated on treatment due to positive TST and 81 were initiated because of malnutrition. Of the 25 adults who initiated treatment, 23 had low BMI (<18.5kg/m^2) and two had diabetes mellitus.

Adverse events were a major concern for the operational research study. Adverse events were categorized by regimen, distinguishing the adverse events caused by ethambutol-containing regimens from those caused by ethionamide-containing regimens. More adverse events were associated with ethionamide-containing regimens (36 adverse events) than ethambutol-containing regimens (28 total events); the difference in adverse events between the two regimens was statistically significant.

4.2.2 Operational research in Kotri, Pakistan

4.2.2.1 Changes from the Karachi protocol

Once operational research in Karachi concluded, the program was expanded and implemented in Kotri, with some modifications. The Kotri operational research program had expanded eligibility criteria and preventive treatment was available for all household contacts of patients with fluo-

75 For more information about the operational research drug regimens, see Appendix 15.
76 One contact refused to participate.
77 For more information about contacts treated, see Appendix 16.

roquinolone-susceptible TB. There was some concern about whether the patient enabler used in Karachi was coercing patients to participate. In Kotri, the enabler was reduced and given on a per family basis. Each family received PKR 500 at the baseline investigation visit, at the initiation of preventive treatment, and at each 2-month follow-up. In this case, the enabler would not cover the cost of transportation for families. This change was made to evaluate questions about coercion, said Hussain.

4.2.2.2 Contact eligibility and treatment initiation

The study in Kotri evaluated 412 contacts from 50 households. All contacts but one agreed to participate and were verbally screened. Among the contacts who were screened, nine contacts were already on treatment for DS-TB. Of the 277 contacts who traveled to the health facility to be investigated, one was diagnosed with MDR-TB. Among the remaining 276 contacts who had been investigated and were eligible for preventive therapy, 175 initiated treatment (32 contacts aged 0-4 years, 65 contacts aged 5-17 years, and 78 contacts aged >18 years). Of those who initiated treatment, 29 people completed treatment, 16 refused treatment, and 130 are still in treatment. Because of the expanded eligibility criteria, the distribution of age among contacts who initiated preventive treatment in Kotri was different than that in Karachi.

4.2.3 Nested studies conducted through operational research in Pakistan

Malik provided an overview of two nested studies conducted through the operational research in Pakistan that was described by Hussain.

4.2.3.1 Pharmacokinetics of levofloxacin in children

One of the nested studies was designed to evaluate whether WHO-recommended doses of levofloxacin are sufficient to achieve therapeutic concentration in children, Malik explained.[78] Two WHO guidelines exist for using levofloxacin to treat children for DR-TB,[79] but two previous studies investigating these guidelines have produced conflicting results. To explore this further, the nested study sampled 24 children aged 2-10 years who had been on levofloxacin therapy for more than 1 month. These children were admitted to the hospital for half of a day. Researchers administered a dose of levofloxacin and conducted blood tests 0, 1, 2, and 6 hours after the dose was consumed. Their levofloxacin concentrations were measured using high-pressure liquid chromatography assay with tandem mass spectrometry detection. Non-compartmental pharmacokinetic analysis was used to measure pharmacokinetic parameters. The children aged <5 years were being treated with 15-20 mg/kg; children aged ≥5 years were being treated with 7.5-10 mg/kg. The study found that only nine children (37.5%) achieved adequate drug exposure. Target serum drug concentration was met in four of the 15 children (26.7%) who were dosed at WHO-recommended levels and four of the five children (80%) who received higher-than-recommended doses (these children received higher doses because of the dosage concentrations available). The study concluded that most children who received WHO-recommended doses of levofloxacin did not achieve adequate drug exposure. The research supports the recommendation made by the Sentinel Project on Pediatric Drug-Resistant Tuberculosis, which calls for 15-20 mg/kg for all children for treatment of DR-TB disease and infection.

4.2.3.2 Comparison of first-line line probe assay with phenotypic drug sensitivity testing

Malik explained that the second nested study had two objectives: (1) to compare the diagnostic performance of the MTBDRplus assay with phenotypic DST in detection of drug resistance and (2) to determine the local burden of KatG and InhA mutations and their implications for diagnosis and treatment. This was a descrip-

78 Malik et al 2019a

79 The 2014 WHO DR-TB treatment guidelines recommend 15-20 mg/kg for children 5 years old and younger and 10-15 mg/kg for children over 5. The 2014 WHO childhood TB guidelines recommend 7.5 – 10 mg/kg for all children.

tive study of 96 consecutive TB patients with isolates resistant to isoniazid from two health centers in Karachi. LPA was performed using GenoType MTBDRplusv2 for genotyping. This study found 98.8% sensitivity for rifampicin resistance, 92.9% specificity for rifampicin resistance, 90.6% sensitivity for isoniazid resistance, 98.8% positive predictive value for rifampicin resistance, and 92.9% negative predictive value for rifampicin resistance. Because strains used for the study were selected based on their isoniazid resistance, researchers could not calculate the specificity or predictive value for isoniazid resistance.

Of the isolates studied, 74% had the katG mutation, 16% had the inhA mutation, and 1% had both mutations. Of the 96 patients in the study, 58 had been treated with isoniazid previously. Among these patients, 10% had the inhA mutation and 83% had the katG mutation. These results indicate that burden of katG mutation is greater than the inhA mutation in the study population. Of 17 patients with ethionamide resistance, 59% had the katG mutation, 29% had the inhA mutation, and 12% were susceptible to isoniazid on LPA.

This study shows that increased use of LPA can inform local programs about isoniazid resistance levels, said Malik. This can help planners decide which drugs to use: if katG mutation is found, then ethionamide can be used; if inhA mutation is found, then high-dose isoniazid can be used. If LPA testing is not available, then ethionamide may be the better choice, since over 70% of patients in this study were found to have the katG mutation.

4.2.4 Discussion

4.2.4.1 The value of pediatric formulations

Yuen commented that Pakistan's findings should not cause too much alarm for those trying to treat TB infection in children. Research from TB-CHAMP has found that pediatric formulations of drugs have greater bioavailability for children.[80] While the levofloxacin dosing recommendations need to be revised, using better formulations may also have an impact.

4.2.4.2 Treatment completion and evaluating efficacy

A participant asked about the 30% of patients who did not complete treatment in the Karachi study. She also pointed out that the study in Pakistan did not collect data about outcomes or effectiveness. She asked Hussain to comment on the question of the effectiveness of preventive therapy. Hussain explained that most of the 30% of patients who did not complete treatment either moved out of the city or did not complete because of adverse events. Others may have discontinued because they did not feel sick or because their index patient completed treatment. Researchers in Pakistan are measuring effectiveness by measuring the development of TB disease among the cohorts that accepted and refused preventive therapy. Follow-up is still ongoing and effectiveness data is expected to be available in early 2020. Jennifer Furin, Harvard Medical School, USA, pointed out that very large samples and long follow-ups are required in order to measure efficacy using the methodology that would be used in a controlled trial. In operational research conditions with smaller sample sizes, researchers must use proxies or alternative measures to describe the efficacy of preventive therapy.

A participant asked about the follow-up protocol for contacts who did not complete treatment or were lost to follow-up, and they asked how contacts who were lost to follow-up would be dealt with should they return for treatment in the future. Hussain reported that the operational research protocol called for extensive investigation of treatment adherence. The contact families were scheduled for monthly follow-ups in their homes conducted by health workers. Additionally, treatment supporters were working with patients on a daily basis and played a role in supporting the treatment of the household contacts. A significant proportion of the household contacts who did not complete treatment moved away from the area or they

80 Seddon et al 2018

suffered adverse events, and chose to discontinue treatment. Those who suffered adverse events were counseled and received follow-up. Once a contact decided to discontinue treatment, healthcare workers respected that individual's decision. When a family or contact discontinued treatment, it was known immediately. Treatment discontinuation due to contacts being lost to follow-up is generally not an issue. If a contact who has discontinued treatment wishes to resume treatment, they can do so, but the treatment would be case-specific. If more than one or two months have elapsed, the clinicians would prefer to start the contact on a new 6-month regimen. If a contact returns to treatment within a month of discontinuation, they can generally pick up where they left off.

A participant asked about how the studies in Karachi and Kotri controlled for treatment adherence. Hussain reported that the TB programs in these hospitals have a treatment support staff for the index patients. These studies worked with these treatment supporters to help support the rest of the family when they were taking preventive treatment. Sometimes the preventive treatment was administered with DOT; sometimes it was self-administered.

4.2.4.3 The need for greater support for contact screening programs

Sivakumaran Murugasampillay, World Health Organization, Zimbabwe, pointed out that the yield rates from contact screening programs are very low. He asked how contact tracing was reported in the 2018 Pakistan annual report. Hussain replied that contact investigation in Pakistan is not very well supported, largely due to a lack of resources, and national efforts to increase contact screening are minimal. Providers generally counsel patients to bring contacts for evaluation, but they make no further effort to evaluate contacts. Contacts are only evaluated if they come to the health facility. Murugasampillay pointed out that the global TB reports do not address the issue of contact screening. This suggests that WHO is not sufficiently concerned about contact screening or about collecting data about contact screening, hence the lack of funding for those efforts. Muhammad Rafi Siddiqui, Institute of Chest Diseases, Kotri, Pakistan, was the lead researcher at the Kotri site and remarked that contact screening needs to be expanded throughout Pakistan in order to increase TB detection.

4.2.4.4 Participation and eligibility

Peter Nyasulu, Stellenbosch University, South Africa, asked why the group of contacts aged 5-17 years was relatively large in the operational research studies in Pakistan. Hussain responded by reiterating the eligibility criteria of the studies. Children aged 5-17 years were a large group in the studies because many were found through contact investigation and were eligible based on criteria. Furin commented that, while the youngest children have the highest risk, the larger group of children aged 5-17 years will likely yield a greater number of cases found. She also remarked that there is a rise in TB risk during adolescence and a similar risk of TB infection among children aged 2-10 years.

Maxo Luma, Partners In Health, Liberia, asked whether any pregnant women were among the contacts treated in Pakistan. Hussain explained that pregnancy was an exclusion criterion for the operational research, so no pregnant women were given preventive treatment in the two studies in Karachi and Kotri. Luma questioned the rationale for this decision, pointing out that there is evidence to support the use of fluoroquinolones and ethambutol for pregnant women. He asked whether researchers in Pakistan would consider treating pregnant contacts in future operational research based on their experiences in Karachi and Kotri. Hussain acknowledged that pregnant women can be treated for DR-TB infection and said that she would like to include pregnant women in future operational research. The programs in Karachi and Kotri used very restrictive eligibility criteria to minimize risk and reduce complications. Carole Mitnick, Harvard Medical School and Partners In Health, USA, remarked that countries developing operational research protocols will face challenging protocol questions, such as how to treat pregnant women. Operational research protocols can be designed to become more inclusive as the program is implemented. For example, a coun-

try starting a new preventive treatment program may design the protocol to exclude pregnant women for the first 6 months. Programs should make these kinds of decisions deliberately with plans to re-evaluate these kinds of questions as the program develops.

A participant asked whether any children evaluated in the study had presumed but unconfirmed MDR-TB. Hussain explained that clinicians were responsible for evaluating contacts and making the DR-TB diagnoses. All the adults in the program and as many children as possible were tested with GeneXpert; the reported cases of DR-TB in the study's findings were bacteriologically-confirmed cases. The three bacteriologically confirmed cases in Karachi were among adults; no cases of MDR-TB were found among children.

4.2.4.5 Ruling out disease in operational research in Pakistan

Furin asked how Pakistan ruled out disease in their operational research. Hussain reported that when the contacts came to the health facility, they were evaluated by the same physician who was treating the index patient. A clinical exam with chest X-ray was conducted for every contact; sputum specimens were collected whenever possible and tested with GeneXpert. Other tests were administered as needed, including CT scans or fine needle aspiration cytology. The program used a standardized diagnostic algorithm, with the cost of these tests borne by the study and facility, not the contacts or patients.

4.2.4.6 Nested study design in Pakistan

Furin asked Malik how the objectives for the nested sub-studies were determined. Malik explained that while the operational research program was being designed, researchers had to choose between ethambutol, ethionamide, or high-dose isoniazid as the secondary drug. One of the nested studies was designed to study population mutation rates to help determine which secondary drug is optimal. Similarly, the question of the other nested study arose as planners investigated therapeutic concentrations of levofloxacin in children. Planners found conflicting reports in the literature, so they decided to nest the pharmacokinetic study into the operational research, because the existing study gave researchers access to a cohort of children they could follow over time. He noted that obtaining consent from parents and drawing blood from children was difficult, however. All children in this nested study had been on treatment for at least one month, so there was some existing rapport between researchers and families participating in this nested study. A counseling component of the study informed families about how the study worked and about the blood samples that would be required. Patient enablers were also offered to the nested study participants.

4.2.4.7 Post-treatment follow-up

A participant asked how post-treatment follow-up was conducted in Pakistan and whether any cases of TB have been found through follow-up. Hussain explained that follow-up is still underway, but the data are not yet available. Thus far, two patients with potential symptoms have been identified through follow-up and are under investigation. Follow-up for the cohorts in these studies will last two years for the cohort in Karachi and 6 months for the cohort in Kotri.

4.2.4.8 Treatment refusal among children and adults

Courtney Yuen, Harvard Medical School, USA, asked whether refusals for treatment tended to be for the whole family or if the children were treated but the adults refused treatment in some cases. Malik remarked that most of those who accepted treatment were children, and most of those who refused were adults. Parents were more likely to consent to having their children treated but refuse treatment for themselves.

4.2.4.9 Ethical questions regarding patient enablers

A participant asserted that patient enablers are coercive in rural, highly impoverished settings. Hussain reiterated that the value of patient enablers they used were very low, not even covering the cost of transportation. Research-

ers do not believe that these enablers had a coercive effect. Yuen asked about how the value of the patient enabler was determined. In other settings, researchers have conducted economic analyses to determine the appropriate value of cash transfers. She maintained that it is unethical to inadequately reimburse patients for the cost of transportation. Hussain reported that PKR600 was the initial value of the patient enabler provided to the index patients by the MDR-TB program. The operational research designers did not want to offer a different patient enabler to contacts than was already being offered to their index cases, so they used the same patient enabler. Both program planners and donors raised objections to these enablers, one of which was that these enablers would not be sustainable at scale. The institutional review board did not have any concerns about the patient enablers.

4.2.4.10 Genome data collection

A participant asked whether the study collected baseline genotype data for index cases or whether Pakistan knows the common mutations among index cases. He also asked whether genotype data will be collected for the two post-follow-up TB investigations to determine whether contacts may have had the disease before the preventive therapy was administered. Malik replied that some reports are available that provide mutation rate data from Pakistan, to which researchers are comparing the nested study data. One of these reports has data for Karachi, allowing researchers to compare their data to data from the same city. LPA is now being conducted routinely for all DR-TB patients. The two post-treatment contacts being investigated will be tested using LPA as per this new routine. Uzma Khan, Interactive Research & Development, United Arab Emirates, added that, for the endTB study cohort, isolates have been being stored for prospective whole genome sequencing. Some of the index patients in the operational research study are members of the endTB study cohort.

4.2.4.11 Recommendation for scale-up

Luma asked whether the researchers working in Pakistan would recommend scale-up of the design used for operational research. Hussain endorsed national scale-up of these programs. Pakistan has a high burden of MDR-TB, so early case-finding and prevention are strong strategies to disrupt disease transmission.

4.2.4.12 Immunocompromising conditions

A participant asked what the most common immunocompromising conditions were among contacts in the studies in Pakistan. Hussain confirmed that diabetes was the most common immunocompromising condition found among contacts.

4.2.4.13 Treating contacts of fluoroquinolone-resistant index patients

A participant asked whether contacts of index patients with fluoroquinolone-resistant TB were excluded from the operational research study. Hussain explained that in Karachi, households with fluoroquinolone-resistant index patients were not excluded; they were treated with moxifloxacin. When the program expanded into Kotri, households with fluoroquinolone-resistant index patients were excluded from preventive treatment. Fluoroquinolone resistance was determined based on DST results.

4.2.4.14 The effectiveness of standardized preventive treatment regimens

A participant asked how effective standardized post-exposure treatment could be in Pakistan, given the potential exposure to multiple DR-TB strains. Hussain conceded that the effectiveness of standardized treatment is unknown. Levofloxacin was used as a standardized treatment for operational research; this is one of the drugs most often being used for this purpose. As more data on resistant strains become available, Hussain hopes that preventive treatment regimens will be adapted.

A participant asked whether the operational research program strengthened the links between patient care and preventive treatment. Hussain replied that the link has been strengthened and there is now a unified model in place. The operational research strengthened contact investigation efforts and the TB care program benefited from better information from contact investigation and treatment.

Furin asked how the Pakistani researchers felt about the choice of drug regimen in the operational research protocol and whether they would choose a different regimen if they were designing a new protocol. Hussain remarked that although levofloxacin resistance in Pakistan is high, clinicians felt comfortable using levofloxacin with a secondary drug. Clinicians preferred a multidrug treatment and the study found that among the secondary drugs used, ethambutol was the better option.

4.2.4.15 Nutritional intervention for malnourished contacts

A participant asked whether the contacts who were malnourished received any nutritional intervention. Hussain explained that the operational research did not include any nutritional intervention. Researchers attempted to raise funds to provide nutritional support to contacts, but they were unsuccessful in rallying broad support for some form of nutritional intervention.

4.2.4.16 Nested studies add value to operational research

Mitnick commented on the importance and value of nested studies, such as the pharmacokinetic study conducted in Pakistan. In the context of the shortcomings of WHO recommendations discussed, she noted that in some cases, recommendations cannot be made due to insufficient evidence. In other cases, recommendations must be made in spite of insufficient evidence—this has been the issue with WHO dosing recommendations. Similar issues have been observed in pharmacokinetic studies of rifampicin doses. Currently, rifampicin, which has been given to hundreds of millions of people, does not meet target pharmacokinetic concentrations. Operational research can add a pharmacokinetic element to gain valuable insight without being subject to the same level of rigor required for a randomized controlled trial with a pharmacokinetic element. Furin added that qualitative nested studies can also be insightful. A study could interview program participants to evaluate the motivations and barriers for contacts who choose to participate in preventive therapy. Hussain agreed, pointing out that when a similar operational research program was implemented in Bangladesh, a qualitative study was used to understand the perceived barriers of contacts, patients, policymakers, and healthcare providers. This study found that patients and contacts were likely to take treatment if their doctors recommended it. Patients and contacts also expressed strong preference for shorter regimens. The program in Bangladesh, which had a completion rate of 97%, used a shorter regimen and trained doctors to communicate about the importance of preventive therapy. This demonstrates how qualitative data can provide valuable information for designing operational research protocols, she noted.

4.3 BEDAQUILINE EFFICACY AND TOLERABILITY FOR MULTIDRUG-RESISTANT TUBERCULOSIS EXPOSURE (BEAT-TB) STUDY

Jennifer Furin, Harvard Medical School, USA, presented the plans for an upcoming trial on the efficacy of bedaquiline: bedaquiline efficacy and tolerability for multidrug-resistant tuberculosis exposure (BEAT-TB). Bedaquiline holds promise as a better option for treating MDR-TB than the current fluoroquinolone-based approach.

Bedaquiline is a diarylquinoline compound with a novel anti-tuberculosis mechanism of action that inhibits mycobacterial ATP synthase. Manufactured by Janssen Therapeutics, the drug received approval from the US Food and Drug Administration (FDA) for the treatment of MDR-TB in December 2012—the first new anti-TB drug to receive FDA approval in more than four decades. Results from trials using bedaquiline to treat MDR-TB disease are encouraging:

- *Bedaquiline has been demonstrated to contribute to a high cure rate[81] and decreased mortality.[82]*
- *Risks of using bedaquiline are thought mostly to be associated with prolonged QT intervals and, similar to the use of fluoroquinolones, are mitigated by the significant mortality benefit of not progressing from infection with MDR strains of TB to active disease.*
- *No association was found between QTc-interval prolongation and death in the clinical studies.[83]*
- *Bedaquiline is well tolerated, has minimal adverse events, and is associated with beneficial outcomes in high-burden settings (South Africa[84]) and low-burden settings (France[85]).*

Overall, bedaquiline is well tolerated, has a high volume of distribution, and a long half-life that makes it a strong potential option for preventive treatment. Because bedaquiline has been shown to contribute to beneficial outcomes for patients with MDR-TB, it is being used in a number of clinical trials for active disease (e.g., endTB, BPaMZ trial, NiX, NEXT, TB-PRACTECAL, STREAM II).

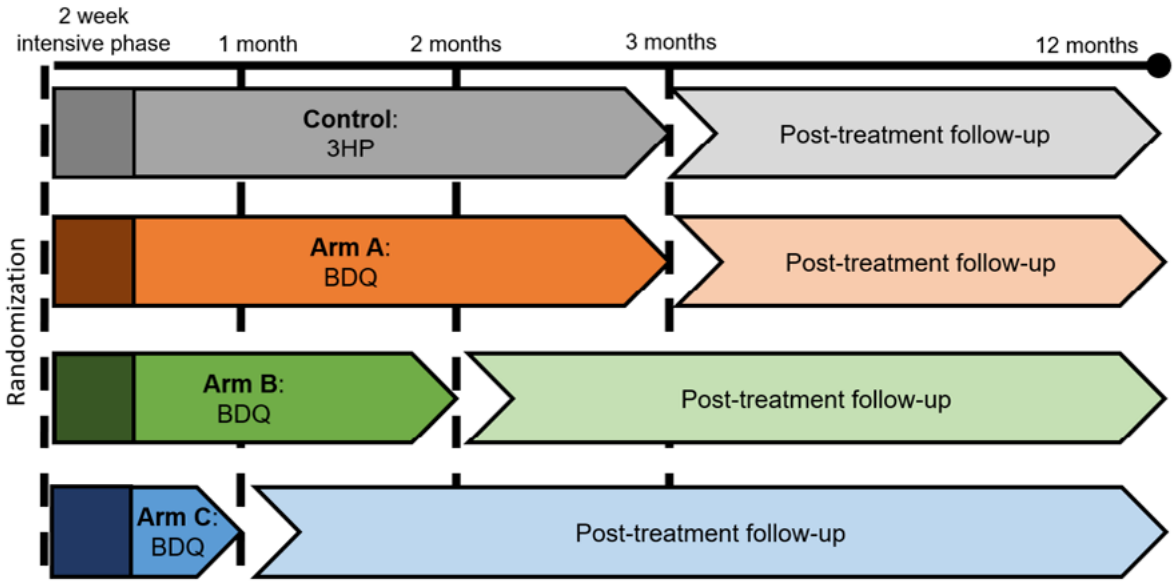
4.3.1 BEAT-TB study design

Furin explained that BEAT-TB is being designed to test bedaquiline's efficacy and tolerability for MDR-TB exposure. It is a phase III, open-label trial will four parallel arms in a cluster-randomized controlled design. Households will be enrolled as clusters equally to each arm. The control arm will receive 12 weeks of rifampicin and isoniazid; the three experimental arms will receive either 4, 8, or 12 weeks of bedaquiline. The study population will include adults aged >18 years who are household contacts of patients diagnosed with MDR-TB. Safety and dosing data are currently available for children aged >6 years, but the study may adapt to include younger populations as more dosing data becomes available.

Figure 4-4 shows the study schema. The four arms will begin simultaneously; post-treatment follow up will begin as each arm completes the treatment phase. Contacts will be treated with the same dosages used for treating DR-TB, with a 2-week intensive lead-in (BDQ 400 mg once per day) followed by 3-times-per week dosing of BDQ 200 mg, with at least 48 hours between doses. All dose administration will be supervised and administered with food and magnesium. Efficacy will be assessed throughout the 52 weeks of participation and tolerability will be assessed during active time on treatment.

81 Diacon et al 2014
82 Although phase IIb trials found excess mortality in the group that received bedaquiline, this mortality was not attributed to bedaquiline by investigators.
83 Diacon et al 2014; Pym et al 2016
84 Ndjeka et al 2015
85 Guglielmetti et al 2017; Guglielmetti et al 2015

Figure 4-4: BEAT-TB Study schema



Source: Furin BEAT-TB presentation

4.3.2 Primary and secondary objectives

Furin reported that one of the primary objectives of BEAT-TB will be to evaluate the efficacy of 4, 8, and 12 weeks of bedaquiline treatment compared to controls receiving 12 weeks of isoniazid and rifapentine for preventing TB disease in adult household contacts of MDR-TB patients. The outcome measure of this objective will be incidence of TB disease at any time during treatment or during the period up to 52 weeks after the date of randomization. The other primary objective of BEAT-TB will be to describe the tolerability (for treatment-related adverse events) of bedaquiline for varying durations. Incidence of participants who have to permanently stop the study drug prior to the end of the treatment period due to a treatment-related adverse event will be used as the outcome measure for this objective. The secondary objectives of the BEAT-TB study are:

1. To compare efficacy of bedaquiline at varying durations to a control of 12 weeks 3HP in reducing all-cause mortality during study treatment and up to a total of 12 months of follow up.;
2. To describe the tolerability (for any reason) of bedaquiline for varying durations;
    a. To describe the incidence of adverse events (grade 2 or higher) and all-cause mortality related to the study drug during treatment and up to 11 months follow up after treatment completion;
    a. To describe the incidence of adverse events (grade 3 or 4) related to the study drug during treatment and up to 11 months follow-up after treatment completion;
3. To compare the drug susceptibility pattern on record of the index MDR-TB case to that of incident TB cases among household contacts;
4. To describe patterns of antibiotic resistance among *M. tuberculosis* isolates in household contacts who develop TB disease;
5. A pharmacokinetic objective will potentially be added to the study.

4.3.3 Inclusion and exclusion criteria

Furin pointed out that clinical studies are very different from everyday clinical settings, in that they have the ability to select who will be treated

and who will not be treated within the study. Clinicians do not have the option to exclude patients based on pre-determined criteria.

Individuals will be eligible to be enrolled as an index case in the BEAT-TB program if they:

- Have been diagnosed with MDR-TB disease, defined as a strain of M. tuberculosis resistant to at least both isoniazid and rifampin, within 4 weeks of patient identification;
- Are 18 years of age or older; and
- Provide signed informed consent.

Individuals will be eligible to be enrolled as a household contact if they:

- Share a dwelling with an index case and are identified within 2 weeks of index case enrolment;
- Are 18 years of age or older;
- Have a TST that is positive (> 10 mm) or a positive IGRA (if person has HIV, they do not need to have a positive TST);
- Are willing to use effective contraception;
- Provide signed informed consent; and
- Live in a dwelling that can be located by study staff and expect to remain in the area for the duration of the study follow-up period.

People will not be eligible to be enrolled as an index case if they have no documentation of MDR-TB diagnosis via DST results. A person will not be eligible to be enrolled as a household contact if they:

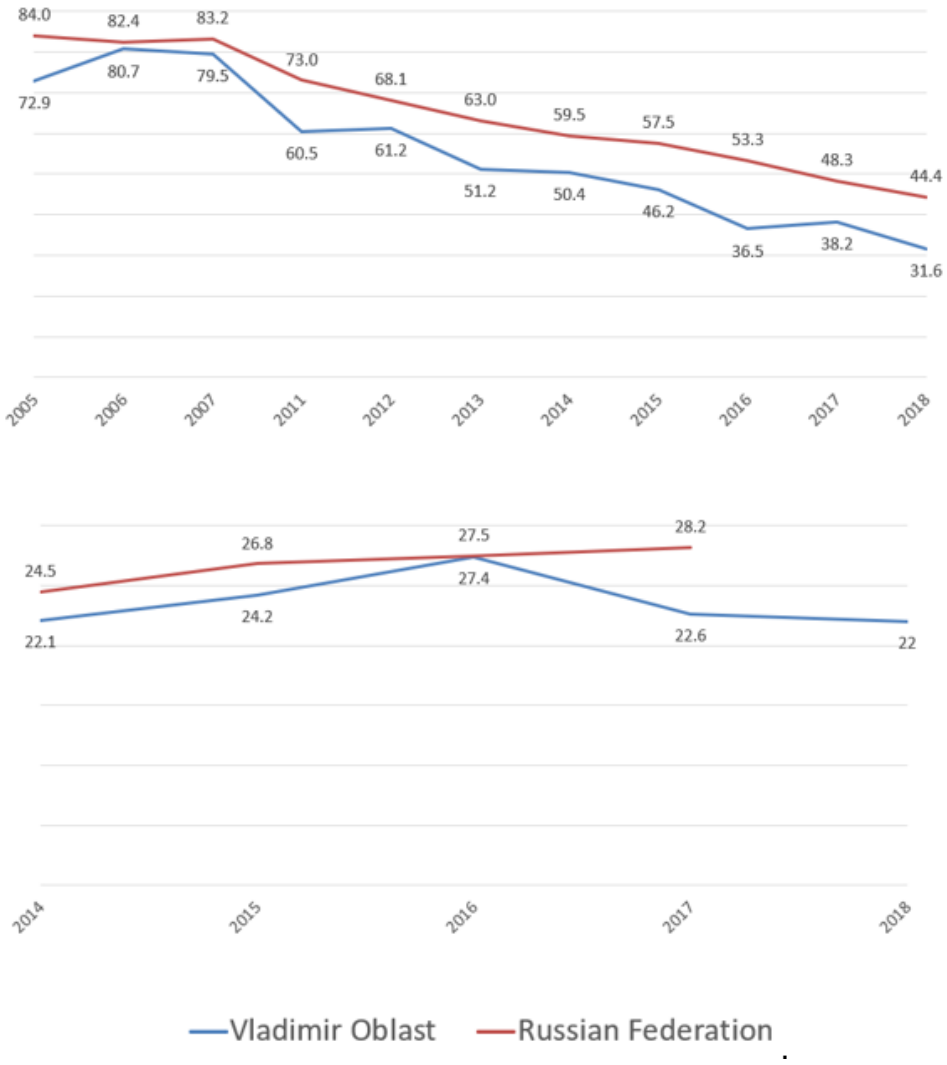
- Have had previous exposure to or resistance to bedaquiline, or known allergies or hypersensitivity to bedaquiline;
- Are a woman currently pregnant, breastfeeding, or planning to become pregnant or breastfeed during the course of the study;
- Are unable to comply with treatment or follow-up schedule;
- Have any condition (social or medical) which, in the opinion of a site investigator, would make participation unsafe;
- Have current suspected or confirmed active TB disease;
- Are currently participating in another trial of a medicinal product;
- Are taking any medication that is contraindicated with the medicines in the trial regimen that cannot be stopped (with or without replacement) or requires a wash-out period longer than 2 weeks;
- Have severe renal impairment requiring dialysis;
- Have hepatitis B or C;
- Have one or more of the following: (a) uncorrectable electrolyte disorders[86]; (b) serum creatinine >3x ULN; (c) AST >3x ULN; ALT >3x ULN; (d) total bilirubin >1.5x ULN (if AST or ALT >ULN) or >2x ULN; or
- Have either of the following cardiac risk factors: (a) QTc interval >500 ms; (b) personal/family history of long QT Syndrome.

4.4 BEDAQUILINE PREVENTIVE TREATMENT IN VLADIMIR, RUSSIAN FEDERATION

Alexandra Solovyova, Partners In Health, Russia, shared updates from TB control efforts in Vladimir City, Russian Federation. In 2018, the Zero TB project began in Vladimir City, the administrative center of Vladimir Oblast which has a population of almost 350,000. Figure 4-5 shows that the TB incidence has been decreasing in Vladimir Oblast and the Russian Federation as a whole; however, the proportion of MDR-TB and XDR-TB had been increasing since 2014. In 2016, the combined proportion of primary TB cases that were either XDR-TB or MDR-TB reached 27% in both Russia and Vladimir Oblast.

86 Uncorrectable electrolyte disorders include: calcium < 7.0 mg/dL; potassium < 3.0 or ≥6.0 mEq/L; magnesium < 0.9 mEq/L.

Figure 4-5: TB epidemiology in Vladimir and Russian Federation



Source: Solovyova presentation

4.4.1 Contact screening in Vladimir Oblast

Solovyeva explained that a contact screening program began in Vladimir Oblast in January 2019. This program has evaluated 635 people who had been exposed to 62 index cases of pulmonary TB. All contacts were evaluated via clinical assessment, TST, and X-ray. The program identified and initiated treatment of four cases of active TB. Among the remaining contacts, 62 had a positive TST. Among these 62 contacts, 45 (73%) initiated preventive therapy.[87]

Contacts who initiated treatment were given regimens determined by the DST of their index case. The 32 contacts who were exposed to DS-TB were treated with 3HP, 3HR, 4R, or 6H. The ten contacts who were exposed to fluoroquinolone-susceptible MDR-TB were treated with a daily regimen of 400 mg moxifloxacin. The three contacts who were exposed to fluoroquino-

87 For more information about the screening algorithm used in Vladimir Oblast, see Appendix 17.

lone-resistant MDR-TB or XDR-TB were treated with bedaquiline for 3 months.[88] Observed treatment is administered either by DOT, VOT, or by a mobile medical team, based on the preferences and life situation of the contact. Upon completion of treatment, contacts will be followed up via clinical monitoring once every 6 months for 2 years after treatment completion.

4.4.2 Treating multidrug-resistant and extensively resistant tuberculosis contacts with bedaquiline

Solovyeva reported that bedaquiline was selected to treat contacts of fluoroquinolone-resistant MDR-TB and XDR-TB based on the availability of drugs and the known resistances among the population in Vladimir Oblast. Of MDR-TB cases, 37% were fluoroquinolone-resistant and of XDR-TB cases, about 80% are resistant to ethambutol and pyrazinamide. Cycloserine and ethionamide were excluded because of their toxicity; delamanid was not considered because it is not registered for use in the Russian Federation.

The program in Vladimir Oblast enrolled seven cases of XDR-TB that were associated with 18 contacts; ten of these 18 contacts were screened. Among the ten who were screened, one contact was found to have active TB and four contacts were found to have LTBI—one refused treatment and the other three were put on the bedaquiline regimen. Those who were screened but did not have LTBI are being followed up for 2 years.[89] Table 4-1 shows the case details for the three contacts treated with bedaquiline regimens, one of whom has completed treatment. Adverse events are monitored monthly via ECG, liver function tests, blood count, TB symptom screening, and metabolic panels. No adverse events have been associated with the bedaquiline regimen.

Table 4- 1: Patients on bedaquiline regimen

	Patient 1	Patient 2	Patient 3
Gender	Male	Female	Female
Age	30	73	40
Date of LTBI treatment initiation	10.04.19	13.05.19	08.07.19
DOT type	VOT	PCA	VOT
Incidence case DST	HREZSKmOfl	HRSEZOflKmAmPas	HRSEZOflAm
Doses has prescribed	44	44	44
Doses taken	44	25	2
Comorbidities	None	Diabetes mellitus with cardiomyopathy, obesity	HIV positive
Frequency of ECG	Monthly	Weekly	Monthly
Treatment completed	Yes	On treatment	On treatment
Adverse events	No	No	No

Note: VOT = Video observed treatment, PCA = mobile team observation
Source: Solovyeva presentation

88 400 mg of bedaquiline per day for 14 days, followed by 200 mg 3 times per week.
89 For more information about the screening of those exposed to XDR-TB in Vladimir Oblast, see Appendix 1

4.4.3 Drug resistance in Vladimir City

A participant asked what may be causing the rise of XDR-TB in Vladimir City. Solovyeva pointed out that while the proportion of XDR-TB in Vladimir City is increasing, the overall number of XDR-TB cases is still small—there were four cases of XDR-TB in 2018. The increasing prevalence of XDR-TB has to do with the epidemiological dynamics in the Russian Federation, where second-line drugs were adopted very early. Furin added that the pattern emerging in the Russian Federation will be common in other countries as well. Throughout the 1990s, the strong emphasis on the use of DS-TB treatment regimens led to situations in which clinicians were advised not to treat MDR-TB. This approach slowly lowered the rates of DS-TB, but it did nothing to address MDR-TB. Models have predicted that if treatment of DS-TB is emphasized to the exclusion of DR-TB, MDR-TB and XDR-TB will eventually become the predominant forms of TB.

A participant asked why 80% of XDR-TB patients in Vladimir City have resistance to ethambutol and pyrazinamide. Solovyeva explained that these resistances are common in Russia because ethambutol has been used as a first-line drug for DS-TB in the region. Furin added that Russia had a very advanced TB program throughout the 1990s. They were then advised to implement DOTS, which does not include DST but relies on an empiric treatment regimen. This led to nearly 100% resistance to isoniazid, rifampicin, ethambutol, pyrazinamide, and later to fluoroquinolones. Those resistant strains developed subsequent to implementation of DOTS and are now being transmitted in communities in many settings with similar histories.

4.4.4 Concerns about the use of bedaquiline for preventive treatment

A participant voiced concern about using bedaquiline as a preventive treatment. He asked whether the use of bedaquiline for preventive therapy will preclude these patients from receiving bedaquiline treatment if they develop active XDR-TB disease. Solovyeva reiterated that active TB is ruled out before any contact is given preventive treatment. Bedaquiline is used as a preventive treatment only if active TB is ruled out with complete certainty. If there is any doubt as to whether a contact has active TB, then the patient is not allowed to be prescribed bedaquiline as a preventive therapy. Furin commented on the notion that clinicians need to 'protect' or 'save' bedaquiline. She remarked that there were similar attitudes when isoniazid preventive therapy was first developed and there is a similar attitude now about levofloxacin. It is critical that clinicians use these drugs responsibly; however, clinicians must not manage this responsibility through rationing or withholding drugs. If a clinician is presented with five XDR-TB cases and can prevent four of them with bedaquiline, that is a beneficial use of bedaquiline. The attitude of withholding drugs is also connected to the fact that there have been very few new drugs developed in the past 50 years. When there were very few antivirals available for HIV treatment, clinicians had the same attitudes about protecting those drugs. Every drug will lead to the development of resistance, so the task for clinicians is to minimize the development of resistance and protect people from disease. Palwasha Khan, Interactive Research & Development, Pakistan, added that DOTS was developed amidst the use of mass chemotherapy to treat DS-TB. It was found that ineffective treatments kept patients chronically ill for a long time, extending the duration of infectiousness. Thus, sub-optimal treatment of TB not only fails to reduce mortality, it promotes the transmission of disease. This pattern must be avoided in DR-TB treatment. If bedaquiline is the most efficacious drug available, then it must be given to patients to prevent the spread of disease.

4.4.5 Results from Vladimir City operational research

Askar Yedilbayev, World Health Organization, Switzerland, encouraged countries to conduct research like the work being done in Vladimir City to fill in gaps in evidence. He asked when preliminary results from the research in Vladimir City will be available. Solovyeva reported that preliminary data is expected to be available in late 2020. The program includes a 2-year follow up period

but, after 1 year of follow up, researchers will be able to report some preliminary data.

4.5 CLOSING DISCUSSION

4.5.1 Is treating tuberculous infection an emergency?

A participant commented that migration studies show that individuals frequently move from high-endemic areas to low-endemic areas. He connected this migratory pattern to the question of whether treatment of TB infection is an emergency or whether it can wait until active TB cases are treated. He pointed out the risk associated with using bedaquiline to treat TB infection in areas with baseline resistance to fluoroquinolone. He asserted that experts in the TB treatment community should re-evaluate whether TB infection is really an emergency. Furin pointed out that the experts who have presented at the meeting—as well as experts around the world—have evaluated the situation and have determined that TB infection is indeed an emergency. She referred to the data presented by Salmaan Keshavjee, Harvard Medical School, USA, showing what happens when only active cases are prioritized. Detection and treatment of TB infection is necessary in order to further reduce the rates of TB. The outstanding questions are related to regimen selection for those who have been exposed to DR-TB. BEAT-TB and the program in Russia are exploring the possibility of using bedaquiline to treat TB infection. Because the efficacy of bedaquiline for treating TB infection is not yet known, bedaquiline must not be used in settings or situations where active disease cannot be definitively ruled out.

4.5.2 Protecting drugs from misuse and the generation of drug resistance

Maxo Luma, Partners In Health, Liberia, remarked that drugs must be made available and used appropriately. In some settings, individuals can freely obtain 1-or 2-week regimens of drugs like rifampicin and isoniazid from private pharmacies, so it is important that these treatments are not used sub-optimally to treat colds, for example. Policies need to ensure that drugs are available in the correct dose for a given situation—in this sense, drugs need to be protected from misuse. Furin agreed, adding that health care systems need to be more accessible to prevent powerful drugs from being dispensed incorrectly by private pharmacies.

Furin emphasized that there is no evidence that the use of drugs to treat TB infection generates resistance to those drugs. Resistance exists naturally with bad clinical practices selecting for resistances to the therapeutic drugs being used. In the past, bedaquiline and linezolid were used as drugs of last resort, but this practice created greater resistance. In order to prevent the development of resistance, clinicians should be using the most efficacious drugs available as soon as possible, which is when they can be most effective. "The strongest regimen, given the first time, is the most effective regimen," she explained. That does not mean that these drugs should be dispensed without caution; there is a safe balance between withholding the most powerful drugs and prescribing them liberally.

4.5.3 Vaccines as an alternative to preventive therapy

A participant asked whether therapeutic vaccines may be an alternative to treating TB infection. Furin acknowledged that therapeutic vaccines are a good idea. When given to a person with TB infection, therapeutic vaccines could boost a person's immunity to help them fight the TB infection themselves. She pointed out that most people with strong immune systems are able to fight TB infection without any intervention. The problem for implementing such a vaccine is that, while the development of such a vaccine is underway, it is far from being a practical reality. Clinicians and policymakers should advocate for the development of TB vaccines, but clinicians should not fail to treat TB infection while waiting for a vaccine. It is important to continue ruling out active disease and to prevent TB disease through treatment of TB infection.

4.5.4 The importance of a comprehensive approach

Sivakumaran Murugasampillay, World Health Organization, Zimbabwe, remarked that there is an overemphasis on 'old' versus 'new' drugs in operational research. These ideas must fit into a comprehensive approach to TB that includes effective surveillance. Operational research is important, but it should start with a good surveillance system and good access to TB care. For example, South Africa's TB program has procured the best drugs available, but compliance is lacking. It is hard to evaluate the causes of resistance without first addressing the issues of access and coverage. Countries need to focus their national efforts on building a comprehensive program, rather than just choosing the best drugs. Furin countered that none of the presenters has been advocating for exclusive focus on drugs. Selecting regimens is an important part of a comprehensive package to manage TB; surveillance can be built in through the development of effective drug regimens. She said that many countries did not begin pharmacovigilance until they began using bedaquiline. Many of the features of a comprehensive package go hand in hand. Rather than postponing any aspect of care in order to develop another aspect, countries should work on these components simultaneously. She agreed with Murugasampillay that national TB programs need to be leading the efforts in each country, which is why a cohort of national TB program leaders have been assembled for this meeting. TB was declared a public health emergency over 25 years ago because the methods that were implemented to deal with TB had not been effective: the stepwise approach recommended in the past simply has not worked. A representative from Pakistan attested that pharmacovigilance will be strengthened through the operational research conducted in Karachi and Kotri. Courtney Yuen, Harvard Medical School, USA, shared that according to colleagues in Papua New Guinea, it was more difficult to build programs incrementally than to build a program all at once. Yuen also pointed out that the US is undertaking new efforts to treat TB infection in all foreign-born residents because existing local TB programs do not have the capacity to deliver this care. The national TB program has determined that a new model and program must be implemented rather than retrofitting the existing system.

Murugasampillay remarked that in the 1960s, 70s, and 80s pharmacovigilance was a priority, but the priority shifted to treatment completion rates once the treatment was oversimplified. This mistake must not be repeated by shifting the priority to DR-TB and the associated new drug regimens. Operational research is important, but it must be done with consideration of the surveillance and information systems available to that program. Many components must come together in unison to constitute a successful, comprehensive TB program; excessive focus on a single component, such as drug selection, can be detrimental. He warned that delivering large quantities of drugs to programs via global funding without ensuring that all the other components of a comprehensive system are in place may distort the focus of TB programs. He suggested that, in order to ensure that the approaches discussed at this workshop are implemented in a balanced manner, programs should be evaluated in terms of indicators that measure access to and delivery of TB care. Such indicators would help to appropriately direct national and global funding toward the development of a comprehensive system of TB care delivery.

Carole Mitnick, Harvard Medical School and Partners In Health, USA, remarked that the strategies discussed at the workshop are intended to be used within the framework of a comprehensive approach to TB care. Resources on developing frameworks for comprehensive TB programs have been made available to all participants. The meeting's subsequent focus on operational research and preventive treatment of DR-TB were not intended to suggest that these topics should be the sole focus of all TB programs. Furin acknowledged that after focusing on the specific issues of operational research and post-exposure management, it is beneficial to reconsider the broader picture of TB care.

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6 Appendices

Appendix 1. Workshop Agenda and Participant List

CENTER FOR GLOBAL HEALTH DELIVERY–DUBAI
HARVARD MEDICAL SCHOOL

Global Consultation on Best Practices in MDR-TB Care

8-11 July 2019

Dubai, United Arab Emirates

Agenda & Participant List

Day 1: Principles of the Zero TB Initiative / Novel MDR-TB Treatment

Day 2: Implementation of Operational Research Conditions and an All-Oral Shorter Regimen

Day 3: Monitoring Under Operational Research Conditions and an All-Oral Shorter Regimen

Day 4: Post-Exposure Management of Persons Exposed at Home to MDR-TB

DAY 1:
Principles of the Zero TB Initiative / Novel MDR-TB treatment

Objectives:

- To understand the components of a comprehensive program to drive down TB rates.
- To understand how MDR-TB care fits into a comprehensive approach.

July 8, 2019		
8:45-9:15	Welcome and introduction	Salmaan Keshavjee Aamir Khan
9:15-10:30	**Session 1: The Zero TB Initiative** Overview of the comprehensive approach overview / Principles of active case finding, treatment, and preventive therapy / Case examples	Salmaan Keshavjee
10:30-11:00	*Coffee break*	
11:00-11:30	Search: You only find what you look for	Courtney Yuen
11:30-12:00	Monitoring and evaluating the comprehensive approach: The Zero TB Initiative's Cascades	Courtney Yuen
12:00-12:30	Discussion	
12:30-1:30	*Lunch*	
1:30-1:45	**Session 2: The comprehensive approach applied in MDR-TB** The challenge of drug resistance and the need for a comprehensive approach	Salmaan Keshavjee
1:45-2:45	Search, treat, prevent for MDR-TB: program experiences (Case 1)	Norbert Ndjeka
2:45-3:15	Discussion	
3:15-3:45	*Coffee break*	
3:45-4:45	Search, treat, prevent for MDR-TB: program experiences (Case 2)	Aamir Khan
4:45-5:15	Discussion	
6:15-7:45	*Dinner, documentary film "UnMasked: We All Breathe" and panel*	

Homework (end of day)

Please write on the papers provided, one reason per piece:

- 3 possible barriers to doing operational research on all-oral shorter regimens
- 3 reasons why it is good to do operational research on the all-oral shorter regimen

Place your responses in the boxes provided by tonight or tomorrow morning

DAY 2:
Implementation of Operational Research Conditions and an All-Oral Shorter Regimen

Objectives:

- Choose an all-oral shorter regimen(s) for your country.
- Write a full first draft of an operational research protocol.
- Understand the role of pharmacovigilance reporting, including different PV reporting options based on your country's conditions.
- Adapt standard data collection forms and the endTB EMR to your country.

July 9, 2019

9:00 – 9:45	**Introduction** • Why do operational research on shorter all-oral regimens? • Review of all-oral shorter regimens currently being tested in clinical trials	Carole Mitnick
9:45 – 10:30	**Choosing an all-oral shorter regimen** • Introduction to the GDI operational research protocol. • Examples of all-oral shorter regimens being implemented under operational research conditions. • Optimum duration of treatment. • Some examples when changes to backbone are needed	Michael Rich
10:30 – 11:00	*Coffee break: Think about if operational research on all-oral shorter regimens is right for your program*	
11:00 – 12:30	**Breakout session 1**: Choosing a backbone oral regimen(s) best suited for your area • Which backbone drugs should make up your all oral STR? • What is the duration of your all oral STR • When are variations to the backbone regimen needed?	Lead: Jennifer Furin
12:30 – 13:30	*Lunch*	
13:30 – 14:30	**Additional important elements to consider of an OR protocol** • Informed consent form. • Identification of eligible patients (laboratory testing, sample transport, etc.). • Eligibility criteria. • Outcome definitions. • Duration of follow-up and visits and tests • When to assess recurrence rate?	Palwasha Khan
14:30 – 15:30	**Other operational research protocols** • TDR/WHO development of a generic DR-TB protocol for all-oral STRs • USAID DESTroy TB	Corinne Merle, Viktoriya Livchits
15:30 - 15:45	Protocol Q&A	All
15:45 – 16:00	*Coffee break*	
16:00 – 18:00	**Breakout session 2**: Working on the different elements of a protocol Identify the elements of the protocol where you need to make some decisions and identify what you need to make the decisions: • Eligibility criteria • Outcome definitions • Primary objectives • Any secondary objective? (not necessary) • Duration of follow-up after treatment • When to assess recurrence rates	Lead: Helena Huerga, Mathieu Bastard
	Dinner at your own leisure	

Facilitators are available after this session until 19:00 to help you with your individual protocol

DAY 3:

Monitoring Under Operational Research Conditions and an All-Oral Shorter Regimen

Objectives:

- Safety monitoring for serious adverse events
- Implementation of EMR for data collection
- Overview of paper forms for simplified data collection
- Review of clinical management

July 10, 2019		
9:00 – 10:00	Monitoring, managing, and reporting on safety • What monitoring schedule is needed- when do you adapt • What level of PV reporting is adapted to your setting • Examples of SAE and SUSAR reporting forms. • Where to report to and when	Cathy Hewison
10:00 – 10:30	*Coffee break: Discuss amongst yourselves how you will collect data in your programme*	
10:30-11:30	Tools for data collection • Introduction to OR data collection forms ("Package 1") • Which data collection tools do you need, examples, can you adapt local forms • Forms, instruction/completion guidelines, list of variables (data dictionary), data analysis tools (database or other) • How to decide on variables (data points) you will collect • Who will collect this data? • Who will analyse the data?	Jennifer Furin, Cathy Hewison
11:30 – 12:30	Breakout session 3: Simplified data collection forms • Adaptation of forms in small groups	Lead: Jennifer Furin, Cathy Hewison
12:30 – 13:30	*Lunch*	
13:30 – 14:30	Data capture and data management • Demonstration of the endTB EMR. • Data capture and cleaning. • Patient confidentiality	James Mbabazi, Mathieu Bastard
14:30 – 15:30	Breakout session 4: Workflow and databases • Group work on databases and EMRs • Workflow- how data will get from the patients into a format that can be analysed. HR considerations etc	Lead: Mathieu Bastard
15:30 – 16:00	*Coffee break*	
16:00 – 17:00	Clinical decision making • What resources can be used to assist decision making (expert committees,) • *Clinical Guide for Management of Patients Taking All-Oral Shorter MDR-TB Regimens*	Uzma Khan
17:00 – 17:45	Case studies	Michael Rich
17:45 – 18:00	Wrap up	Carole Mitnick
18:00 – 20:00	*Dinner*	

DAY 4:
Post-Exposure Management of Persons Exposed at Home to MDR-TB

Objectives:

- To review experiences delivering preventive therapy for MDR-TB.
- To brainstorm approaches to delivering preventive therapy in households of patients receiving shorter regimens for MDR-TB disease.

July 11, 2019

9:00 – 10:00	**Rationale for preventive therapy in MDR-TB contacts and global experience**	Jennifer Furin
10:00 – 10:30	*Coffee break*	
10:30 – 12:15	**Experience from Pakistan**	Hamidah Hussain, Amyn Malik
12:15 – 12:30	**Introduction to afternoon discussion**	Jennifer Furin
12:30 – 13:30	*Lunch*	
13:30 – 15:00	**Facilitated discussion: Challenges to implementation and experience sharing**	Jennifer Furin
15:00 – 15:30	*Coffee break*	
15:50 – 16:10	**Late-breaker: Early experience from the Russian Federation**	Salmaan Keshavjee, Alexandra Solovyova
16:10 – 16:45	**Questions and discussion**	All
16:45 – 17:00	**Wrap-up and next steps**	Jennifer Furin

Participant List

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Summer Intern *HMS Center for Global Health Delivery-Dubai*	Amsterdam *Médecins Sans Frontières (MSF)*
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WEINISCH, Jonathan USA	**WILLIAMS**, Abeda South Africa J&J Global Public Health
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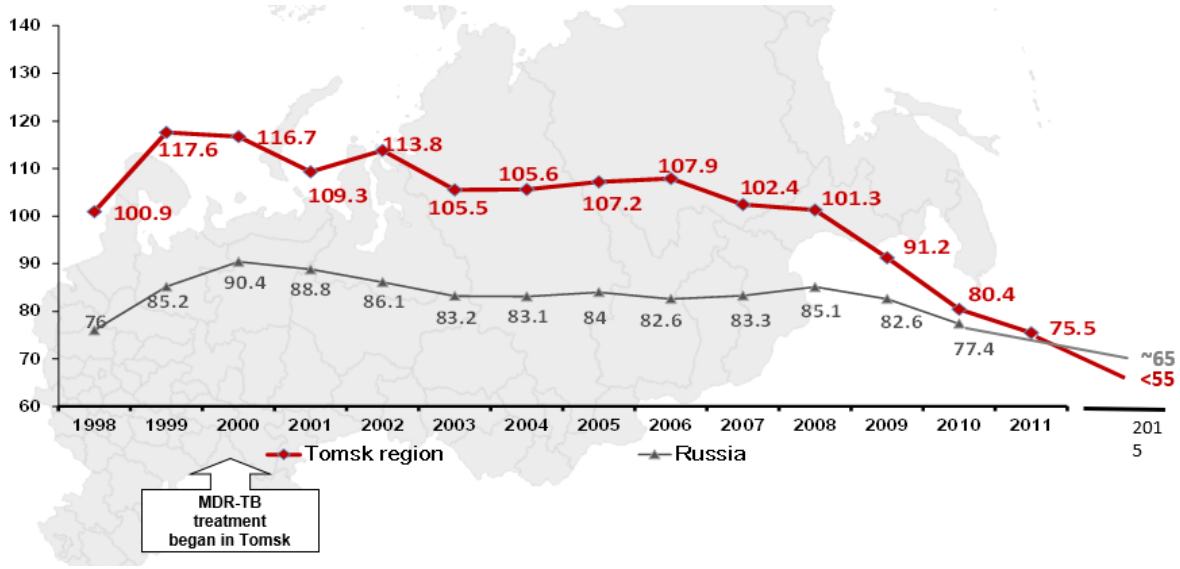
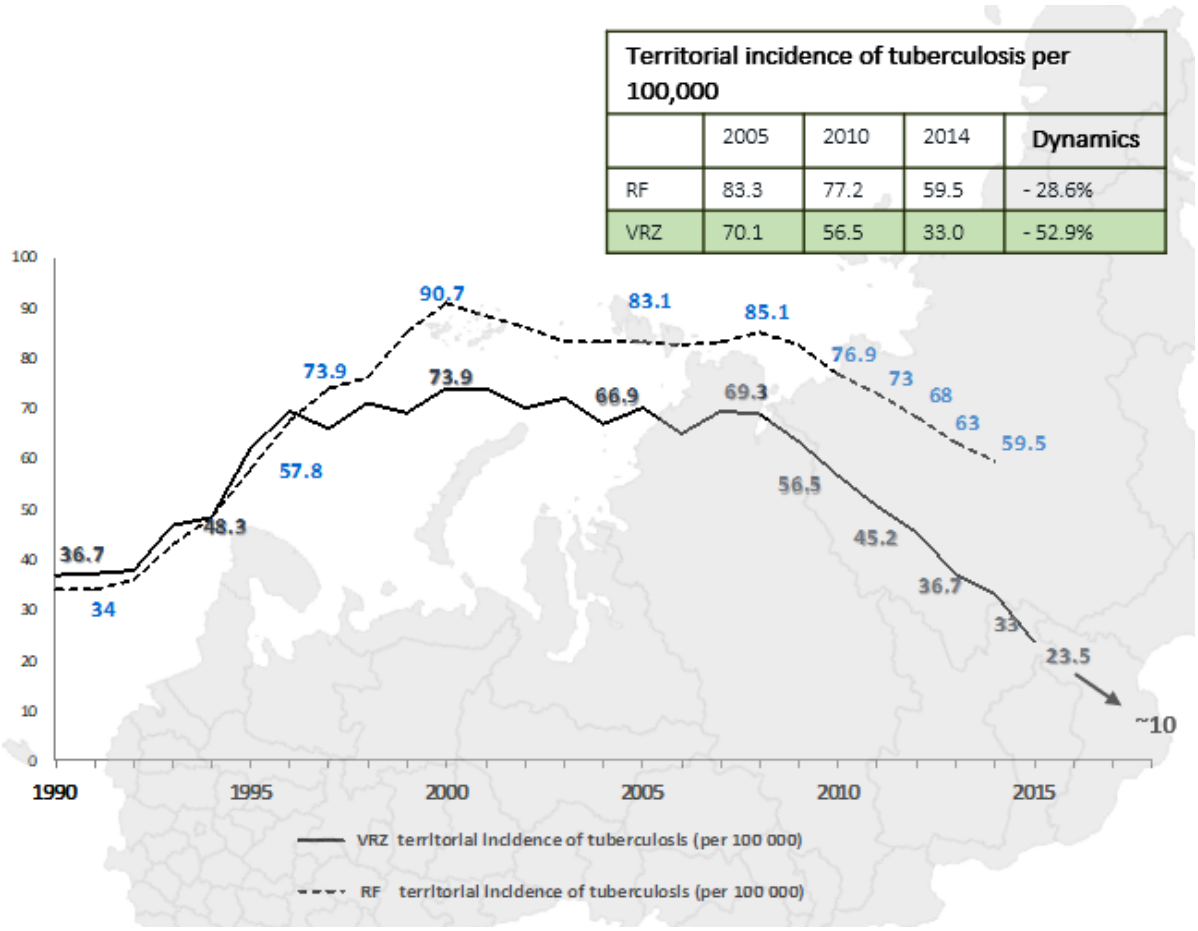
YUEN, Courtney USA *Harvard Medical School*	**ZAMORA**, Gilmer UAE *Harvard Medical School*

Appendix 2. TB incidence per 100,000 population in Tomsk, Russia (1998-2015)



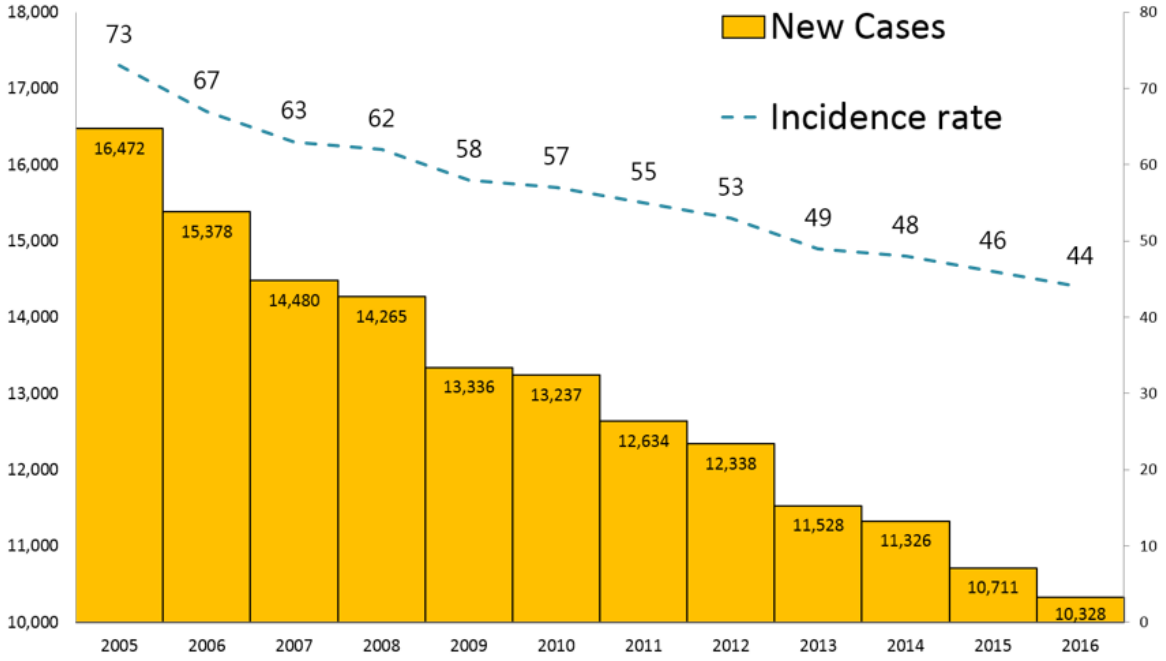
Source: Tomsk Oblast TB Services

Appendix 3. TB incidence per 100,000 population in Voronezh, Russia (1990-2015)



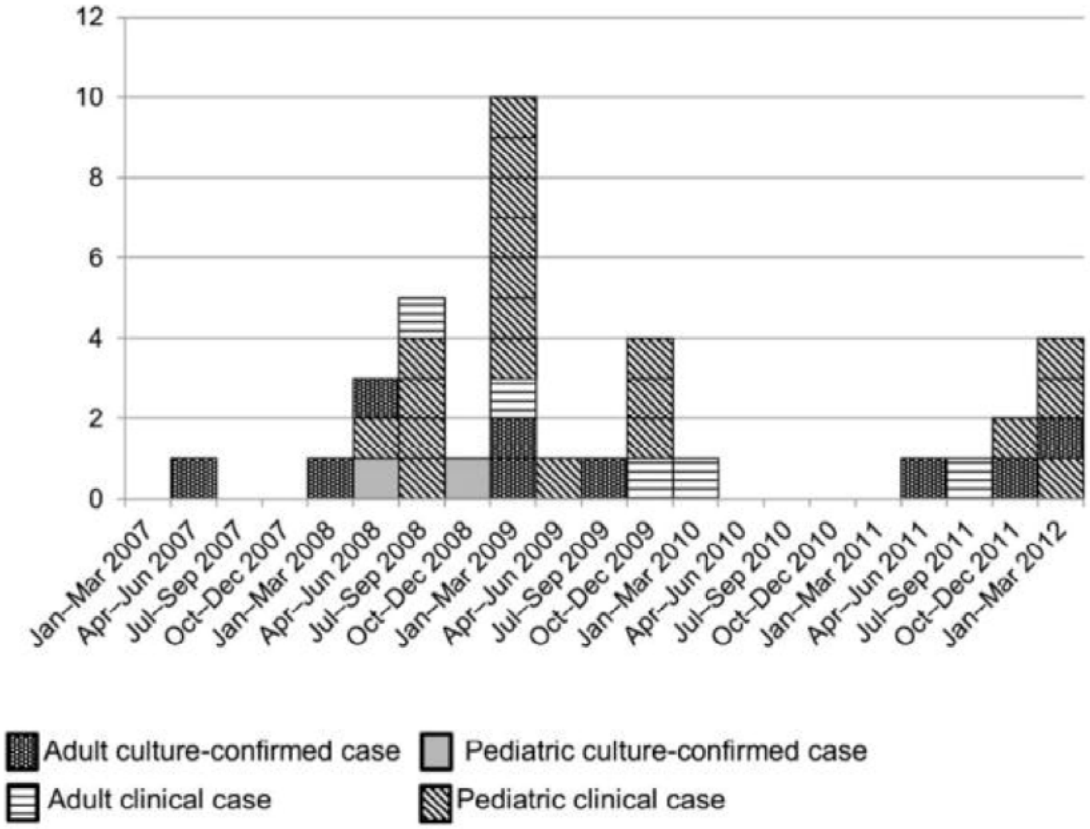
Source: Keshavjee presentation

Appendix 4. TB incidence rate per 100,000 population in Taiwan (2005-2016)



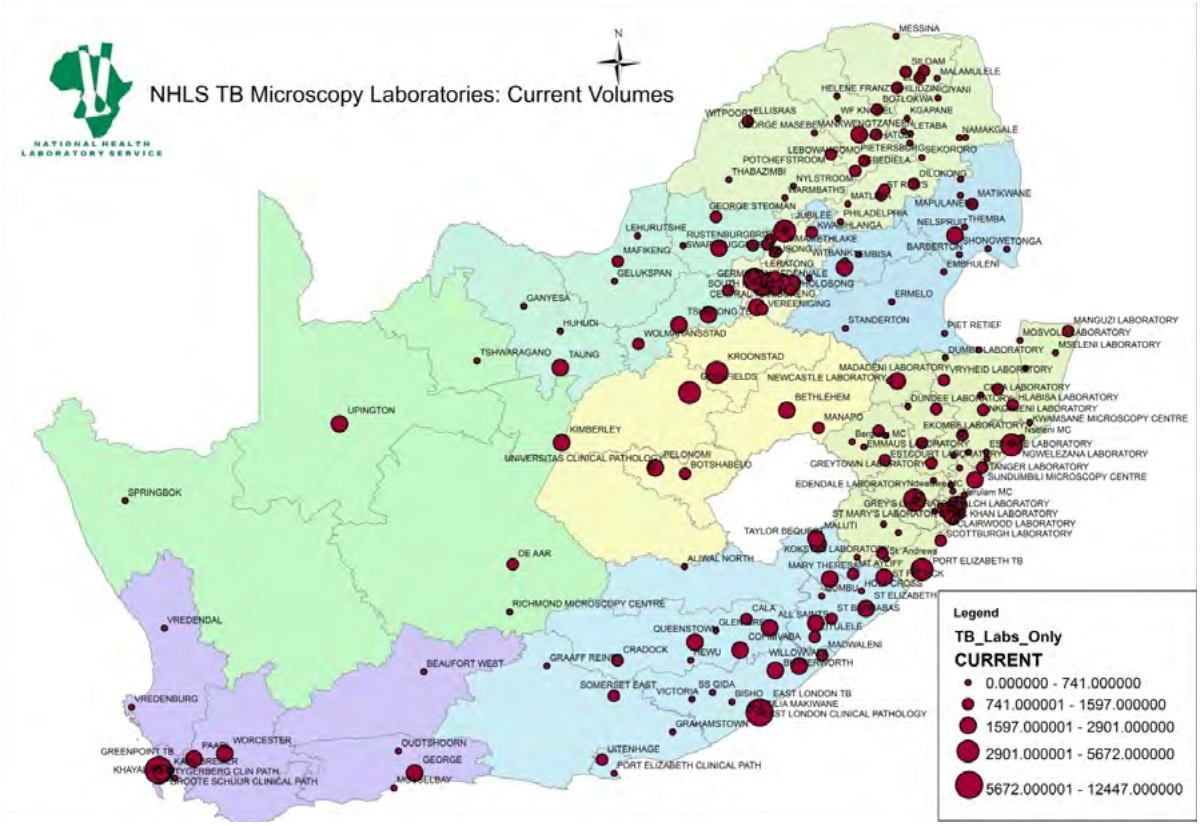
Source: Keshavjee presentation

Appendix 5. TB cases in Chuuk (2007-2012)



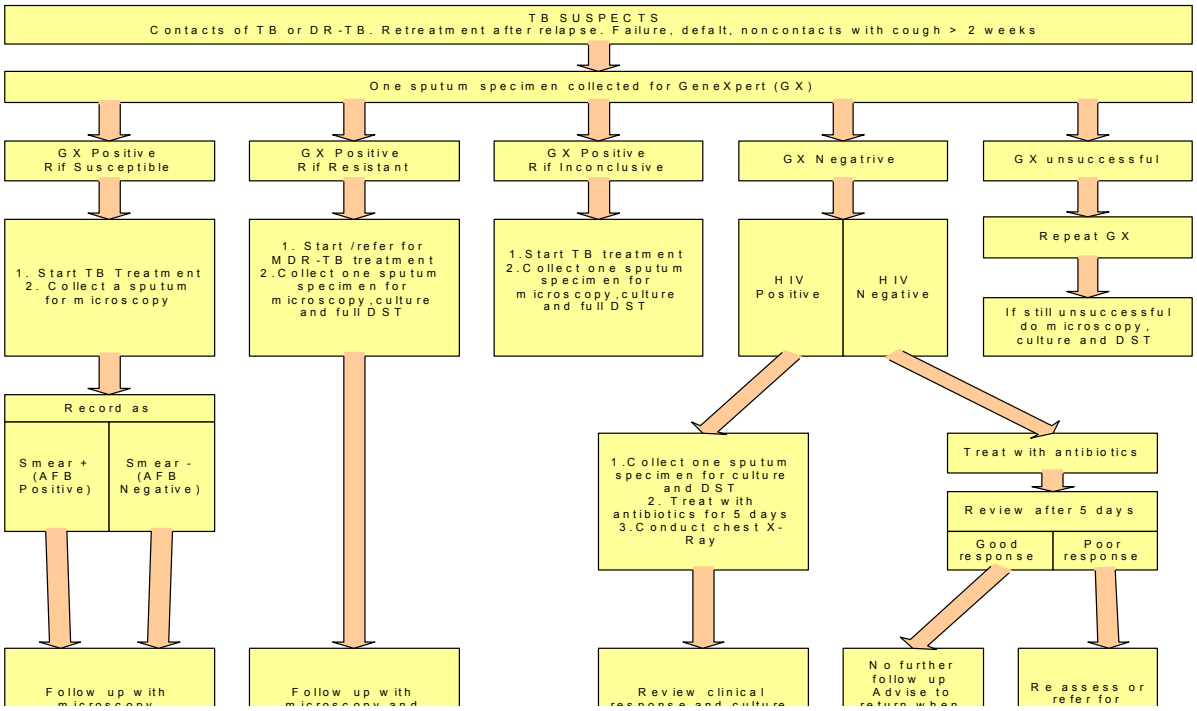
Source: Bamrah et al 2014

Appendix 6: Microscopy sites and smear volumes in 2010



Source: Ndjeka Presentation

Appendix 7: South African TB screening algorithm



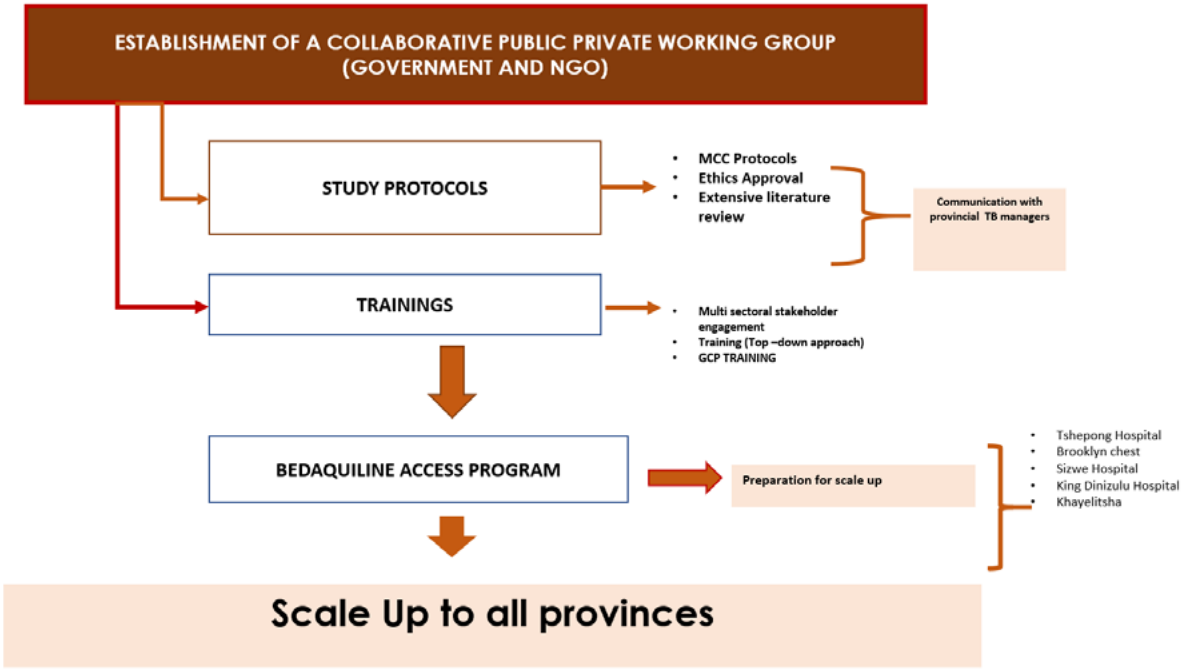
Source: Ndjeka presentation

Appendix 8: South Africa's GeneXpert positivity, testing volume, and targets for 2017-2018

	Missing Cases breakdown			
District/Sub-district	TOTAL PTB CASES 2017	POSITIVITY RATE	TOTAL TESTED IN 2017	TESTING TARGET FOR 2018
Eastern Cape	**45,381**	**10.7**	**384,170**	**571,617**
Alfred Nzo	**3,564**	**10.7**	**38,342**	**44,892**
Matatiele	962	10.7	10,467	12,117
Mbizana	857	10.7	9,298	10,795
Ntabankulu	484	10.7	4,577	6,096
Umzimvubu	1,261	10.7	14,000	15,884
Amathole	**4,913**	**10.7**	**57,470**	**61,884**
Amahlathi	738	10.7	7,982	9,296
Great Kei	188	10.7	1,401	2,368
Mbhashe	1,345	10.7	15,327	16,942
Mnquma	1,210	10.7	17,555	15,241
Ngqushwa	336	10.7	4,310	4,232
Nkonkobe	824	10.7	8,888	10,379
Nxuba	272	10.7	2,007	3,426
>>>>>>>>>>>>				
Mpumalanga	**14,229**	**10.7**	**122,297**	**179,228**
Ehlanzeni	**6,721**	**10.7**	**57,033**	**84,657**
Bushbuckridge	1,443	10.7	13,658	18,176
Mbombela	2,791	10.7	23,238	35,155
Nkomazi	1,546	10.7	11,584	19,473
Thaba Chweu	382	10.7	3,916	4,812
Umjindi	559	10.7	4,637	7,041
>>>>>>>>>>>>				
Grand Total	**231,230**	**10.7**	**2,163,905**	**2,912,564**

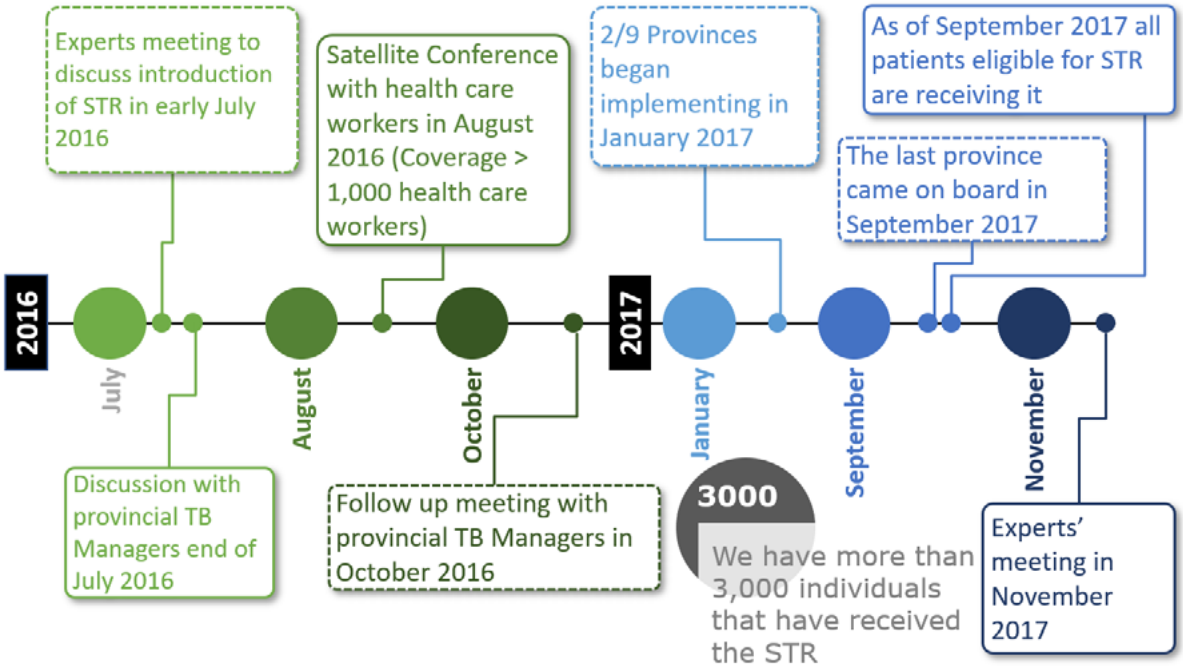
Source: Ndjeka presentation

Appendix 9: The three-stage introduction of bedaquiline into the TB treatment protocol



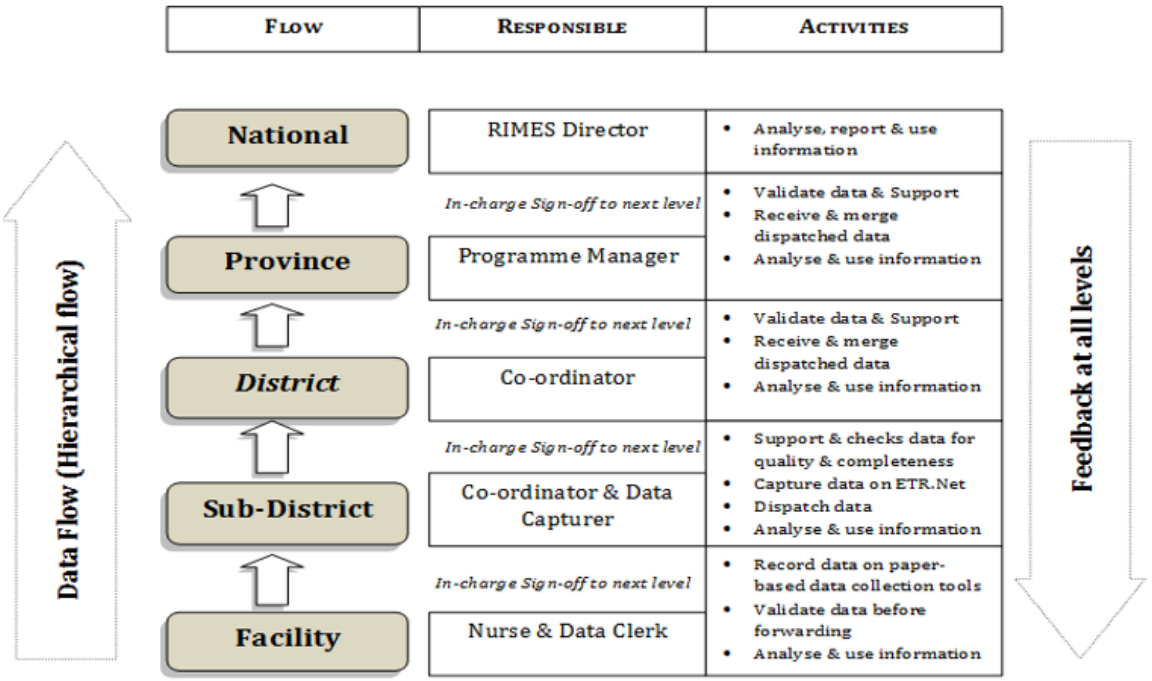
Source: Ndjeka presentation

Appendix 10: Introduction of the shorter MDR-TB regimen



Source: Ndjeka presentation

Appendix 11. Dataflows, responsibilities, and feedback for bedaquiline expansion program



Source: Ndjeka presentation

Appendix 12: Long-term regimen outcomes in South Africa (2016)

	Regimen	Started treatment	Treatment success (%)	Deaths (%)	Loss to follow up (%)	Treatment failure (%)	Not evaluated (%)
MDR -TB	**Injectable**	7132	3645 (51%)	1514 (21%)	1456 (20%)	216 (3%)	301 (4%)
	Bedaquiline	1767	1125 (64%)	240 (14%)	285 (16%)	42 (2%)	75 (4%)
XDR-TB	**Injectable**	93	15 (16%)	38 (41%)	14 (15%)	20 (22%)	6 (6%)
	Bedaquiline	476	321 (67%)	75 (16%)	52 (11%)	13 (3%)	15 (3%)

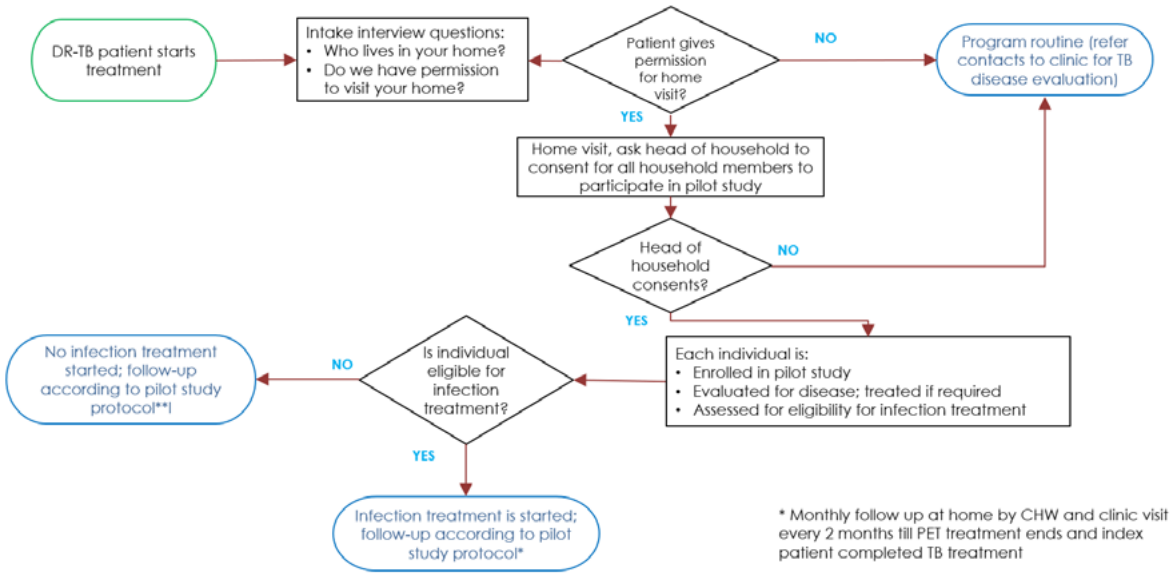
Source: Ndjeka presentation

Appendix 13: Short-term regimen treatment outcomes in South Africa (2017)

Short regimen	Started on treatment	Treatment success (%)	Deaths (%)	Loss to follow up (%)	Treatment failure (%)	Not evaluated (%)
RR/MDR-TB*	3740	2360 (63%)	656 (18%)	433 (12%)	70 (2%)	221 (6%)
Injectable**	1393 (37%)	800 (57%)	275 (20%)	207 (15%)	29 (2%)	82 (6%)
Bedaquiline**	1901 (51%)	1334 (70%)	254 (13%)	176 (9%)	29 (2%)	108 (6%)

** Includes everyone in the register with the diagnosis of RR-TB and MDR-TB started on shorter treatment regimen.*
*** Excludes people for whom it was not recorded whether they received bedaquiline or injectable.*
Source: Ndjeka presentation

Appendix 14: Indus Hospital DR-TB operational research algorithm



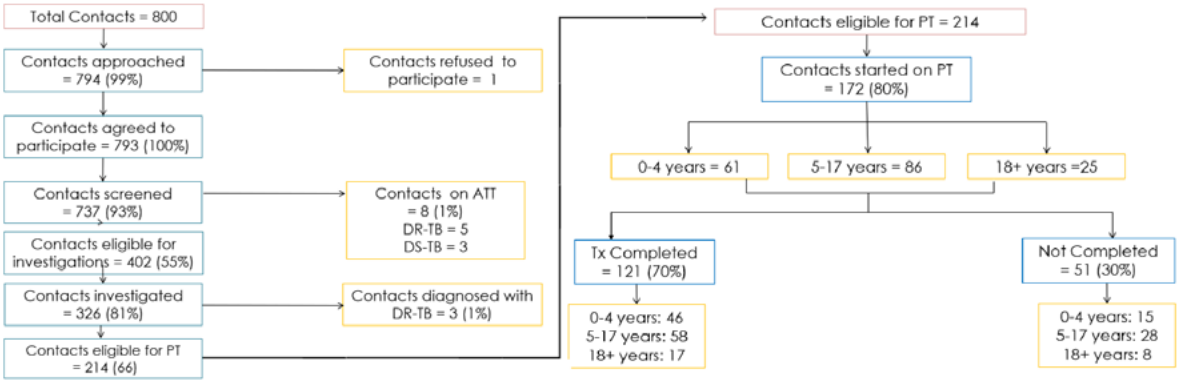
Source: Hussain and Malik presentation

Appendix 15: Indus Hospital DR-TB operational research drug regimens

	Drugs	Dosage	Duration
<5 Years	Lfx and Emb/Eto Mfx and Emb/Eto	Lfx/Eto: 15-20 mg/kg/day Emb: 15-25 mg/kg/day Mfx: 7.5 -10 mg/kg/day	Daily for 6 months
5 - 14 Years	Lfx and Emb/Eto Mfx and Emb/Eto	Lfx: 7.5 -10 mg/kg/day Emb: 15-25 mg/kg/day Eto: 15-20 mg/kg/day Mfx: 7.5 -10 mg/kg/day	Daily for 6 months
≥15 years	Lfx and Emb/Eto Mfx and Emb/Eto	Lfx: 750 -1000 mg/day Emb: 600-1200 mg/day Eto: 500-750 mg/day Mfx: 400 mg/day	Daily for 6 months

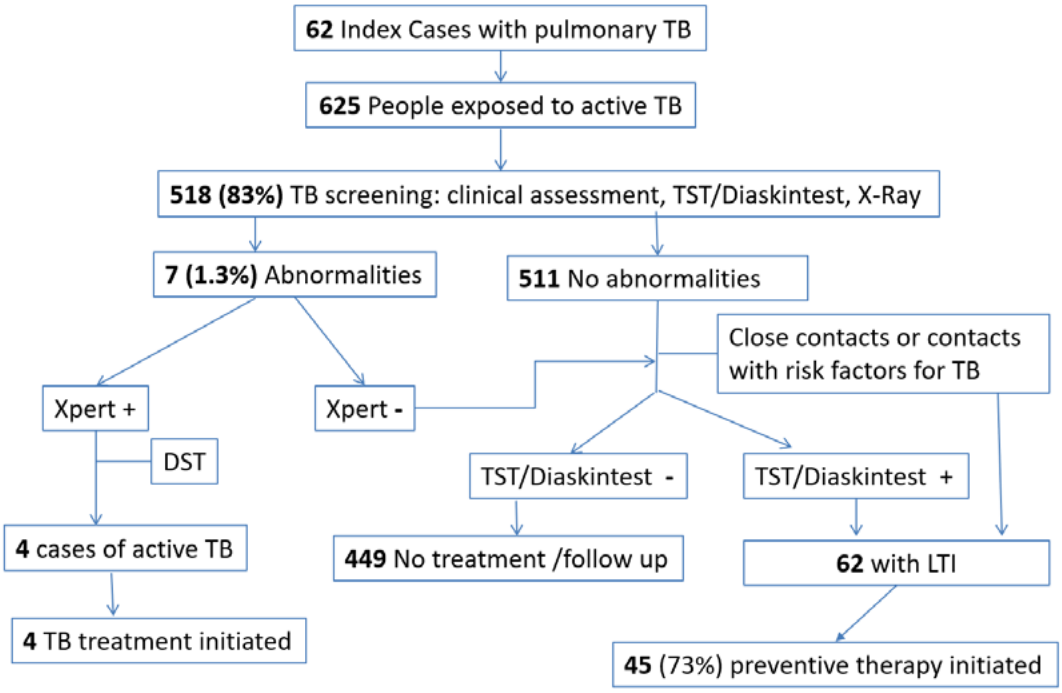
Notes: Lfx = levofloxacin, Emb = ethambutol, Eto = ethionamide, Mfx = moxifloxacin
Source: Hussain and Malik presentation

Appendix 16. Household contacts screened and given preventive treatment (Karachi)



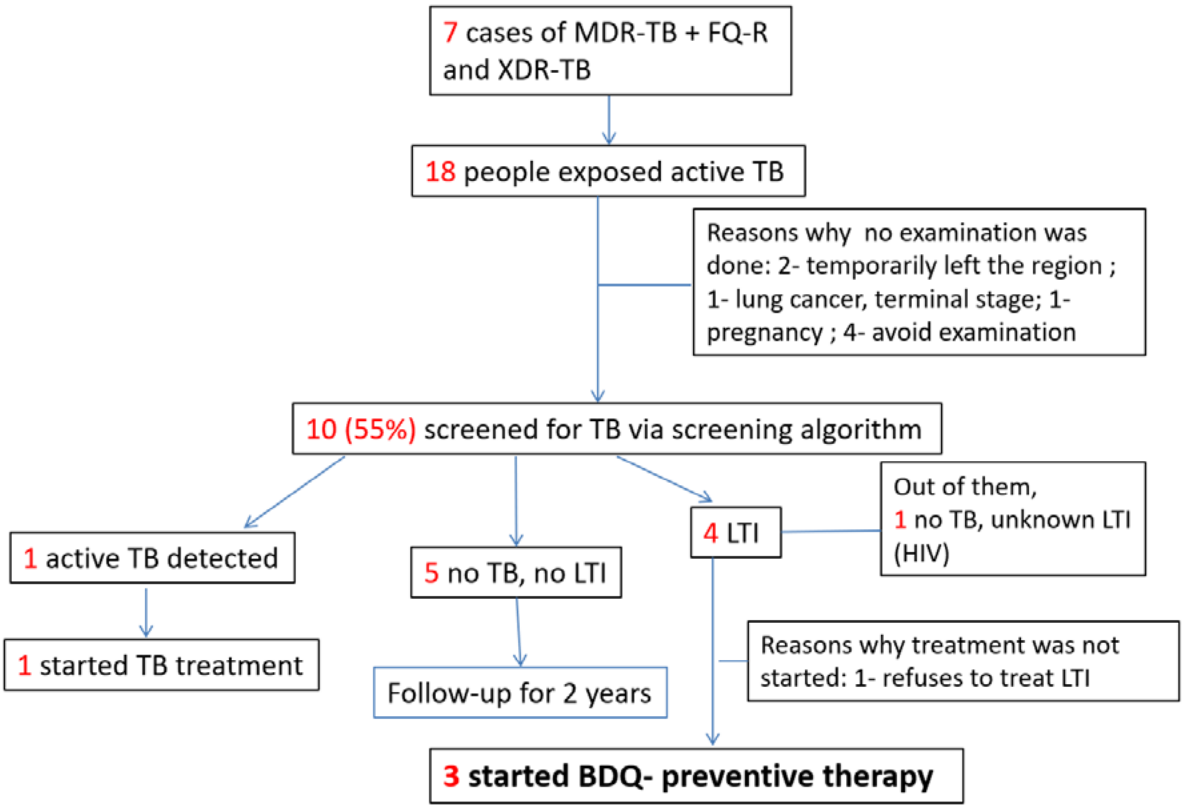
Source: Hussain and Malik presentation

Appendix 17: Contact screening algorithm used in Vladimir Oblast



Source: Solovyeva presentation

Appendix 18: Screening outcomes for those exposed to fluoroquinolone-resistant MDR-TB or XDR-TB in Vladimir Oblast, January 2019



Source: Solovyeva presentation

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ISBN-13: 978-1-944302-25-2