



**CENTER FOR GLOBAL  
HEALTH DELIVERY–DUBAI**  
HARVARD MEDICAL SCHOOL

# PROCEEDINGS

**Global Consultation on Best Practices  
in the Delivery of Preventive Therapy  
for Household Contacts of Patients  
with Drug-Resistant Tuberculosis**



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# **Global Consultation on Best Practices in the Delivery of Preventive Therapy for Household Contacts of Patients with Drug-Resistant Tuberculosis**

## **PROCEEDINGS**

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# Part 1.

## Introduction: Laying the foundation for a paradigm shift

### 1.1 GLOBAL POLICY CONTEXT

On April 12-13, 2015, 51 experts in tuberculosis gathered for the Global Consultation on Best Practices in the Delivery of Preventive Therapy for Household Contacts of Patients with Drug-Resistant Tuberculosis (Figure 1). The meeting was hosted by the Harvard Medical School Center for Global Health Delivery–Dubai, in Dubai, United Arab Emirates. The aim was to convene key specialists and leaders in the field to share experiences with delivering preventive therapy in both child and adult household contacts of patients with drug-resistant tuberculosis— in other words, delivering treatment for suspected or confirmed TB infection in these individuals to prevent disease.<sup>1</sup> In this meeting report, the term “infection treatment” is used, instead of “preventive therapy,” “prophylaxis,” or “chemoprophylaxis.”

This meeting was convened against the backdrop of unacceptably slow progress against tuberculosis (TB) on the global level over the last 50 years. Despite the implementation and improvement of TB programs throughout the world, the disease continues to cause a disproportionate amount of disease and death, even though effective treatments have been available since the 1940s. Today TB is the number-one killer of people living with the human immunodeficiency virus (HIV), and the disease remains one of the biggest killers of adults worldwide overall. Each year, an estimated 9 million people develop TB disease, and approximately 1.5 million people die from the disease. Before TB patients die, they transmit TB bacteria through the air to others in their families and communities.

The evidence strongly supports the widely held perception that TB is a disease of the vulnerable and the socially and economically marginalized. Children in particular have been systematically neglected in TB research and public health pol-

icy. This is due to both technological limitations and the manifestation of the disease in children. Current diagnostic tools cannot reliably detect both TB and drug-resistant TB among children. TB often presents differently in children, who typically have more subtle symptoms and radiographic abnormalities, and are more likely to have extra-pulmonary disease. Compounding this, children cannot reliably produce sputum for testing and determination of drug resistance.

On a policy level, about 30 years ago, a one-size-fits-all approach was adopted and emphasized by international policy bodies and aid donors with poor results, particularly in the area of childhood TB and the emergence of drug-resistant strains. The directly observed therapy short course (DOTS) strategy encouraged first and foremost the treatment of the most infectious cases of TB, de-emphasizing children, HIV co-infected patients, and those suffering from TB outside the lungs. It emphasized passive case-detection and a focus on drug-susceptible disease, while ignoring transmission within health care settings.

Exacerbating the limitations of this policy frame, the approach during this time for finding TB cases relied on passive case finding, which fails to diagnose the many other contacts surrounding sick individuals who may be sick or infected. The cumulative data from over 50 years of TB projects has demonstrated that passively waiting for sick individuals to seek treatment while not implementing systematic interventions in their households or communities will consistently fail to stop the TB epidemic on local and global levels (Figure 2).

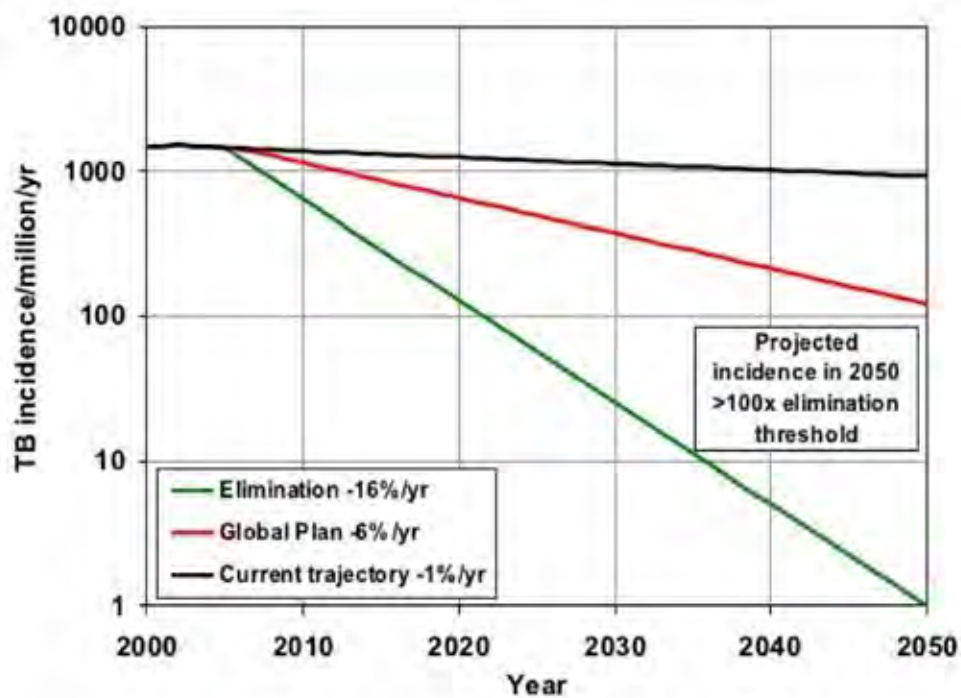
<sup>1</sup> The meeting agenda and list of participants can be found in Appendices A and B.

**Figure 1. Global convention of expertise: Map of participants' settings**



Source: Becerra presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

**Figure 2. Global Plan will not eliminate TB by 2050**



Source: Dye. Imperial College London, 2009



Crucially, this approach fails in its lack of attention to the most vulnerable populations, including children who live with tuberculosis patients.

As a result of the limited scope and passive operational approach of these global policies and recommendations, the overall global situation is relatively unchanged over the last three decades; despite modest progress against drug-susceptible tuberculosis, more of the circulating strains are now resistant to available drugs. As a result, many groups are now focusing on the household as well as the places where sick people seek care. They are looking to advance a pragmatic agenda in these high-risk groups wherein programs will be able to more promptly identify children and other adults sick with tuberculosis, and to connect them with appropriate treatment

rapidly, thereby improving individual outcomes and reducing community-based TB transmission. From this perspective, implementing the delivery of infection treatment is a necessity, not a luxury.

The group of specialists gathered in Dubai was convened with the following objectives: to present and discuss new evidence, both published and unpublished, in this area; to synthesize findings from the accumulated body of observational and experimental data; to consider points of consensus and contention; and to outline potential steps forward to integrate a fully comprehensive package for preventing TB disease in household contacts, particularly when the patient has drug-resistant TB disease.

## **BOX 1-1 TUBERCULOSIS AND DRUG-RESISTANT TUBERCULOSIS BASICS**

### **What is tuberculosis (TB)?**

Tuberculosis (TB) is a disease caused by bacteria that are spread from person to person through the air. TB usually affects the lungs, but it can also affect other parts of the body, such as the brain, the kidneys, or the spine. In most cases, TB is treatable and curable; however, persons with TB can die if they do not get proper treatment.

### **What is multidrug-resistant tuberculosis (MDR-TB)?**

When a TB bacteria is resistant to a drug, that means that drug can no longer kill the bacteria. Multidrug-resistant TB (MDR-TB) is caused by an organism that is resistant to at least both isoniazid and rifampin, the two most potent TB drugs. Without these two drugs, TB treatment regimens are longer, more toxic, and can be less effective.

### **What is extensively drug-resistant tuberculosis (XDR-TB)?**

Extensively drug resistant TB (XDR-TB) is a type of MDR-TB that is resistant to both isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Because XDR-TB is resistant to the most potent TB drugs, patients are left with treatment options that are much less effective.

MDR-TB and XDR-TB are of special concern for persons with HIV infection or other conditions that can weaken the immune system. These persons are more likely to develop TB disease once they are infected, and also have a higher risk of death once they develop TB disease.

Source: <http://www.cdc.gov/tb/publications/factsheets/drtb/mdrtb.htm>

**Table 1. Drugs used to treat multidrug-resistant tuberculosis**

Type	Drug	Abbreviation
First-line drugs	Ethambutol	E
	Pyrazinamide	Z
	High-dose Isoniazid	H
Injectable drugs	Kanamycin	Km
	Amikacin	Am
	Capreomycin	Cm
Other second-line drugs with anti-TB activity	Ethionamide	Eto
	Prothionamide	Pro
	Cycloserine	Cs
	Terizidone	Trd
	Para-aminosalicylic acid	PAS
	Linezolid	Lz
	Thioacetazone	T
	Bedaquiline	
	Delamanid	
Drugs of unclear efficacy	Clofazimine	
	Clarithromycin	
	Amoxicillin-clavulanate	

## 1.2 ORGANIZERS' RATIONALE AND GOALS FOR THE MEETING<sup>2</sup>

At its core, the decision to implement a program of infection treatment in household contacts requires weighing the evidence for doing so in the face of uncertainty. The meeting was planned to draw upon the experiences of program providers who have implemented or are planning to implement programs to treat individuals who have been exposed and likely infected with drug-resistant TB by another individual in their homes, in order to try and prevent progression to disease.

The primary objective of the two-day meeting was to harness the discussion that took place during the meeting in order to highlight points of clarity and work toward establishing clear guidance for the provision of treatment for presumed drug-resistant TB infection in household contacts of drug-resistant TB patients.

Mercedes Becerra stated that the goal to frame this discussion was not to protect children exposed to drug-resistant TB in the home for a lifetime, but to capitalize on the window after finding one person in a house sick with drug-

resistant TB: given sufficient resources, what practical steps can be taken to ensure that there will be no more cases of TB disease in that home for the next 2-3 year period?

## 1.3 REASONS FOR LACK OF CLEAR GUIDANCE ON INFECTION TREATMENT<sup>3</sup>

James Seddon set the stage for the workshop by examining reasons for the lack of clear guidance on infection treatment at present. He emphasized the need to clearly quantify the burden of MDR-TB exposure so that it is not summarily dismissed as a niche problem. An estimated 2 million children under 15 years of age are infected with MDR-TB strains worldwide, and they have a high risk of developing MDR-TB disease (Table 2).

In higher-burden TB settings, the proportion of children aged <15 years in the total TB burden is significantly higher than in low-burden settings. In 2002, Peter Donald ventured that this trend is due to countries in the developing world having a relatively higher number of children in the population, coupled with a greater force of infection

<sup>2</sup> This section is based on the presentation by Mercedes Becerra, Associate Professor, Harvard Medical School, Boston, MA, U.S.

<sup>3</sup> This section is based on the presentation by James Seddon, Clinical Lecturer, Imperial College London, U.K.

such that children become exposed at a younger age when they are at a higher risk of developing disease.<sup>4</sup> Further, the proportion of TB that is MDR-TB in adults is similar to the proportion in children (Figure 3).

Existing guidance for MDR-TB preventive therapy is limited, inconsistent, and lacking consensus regarding care, according to Seddon. Recommendations vary widely, ranging from

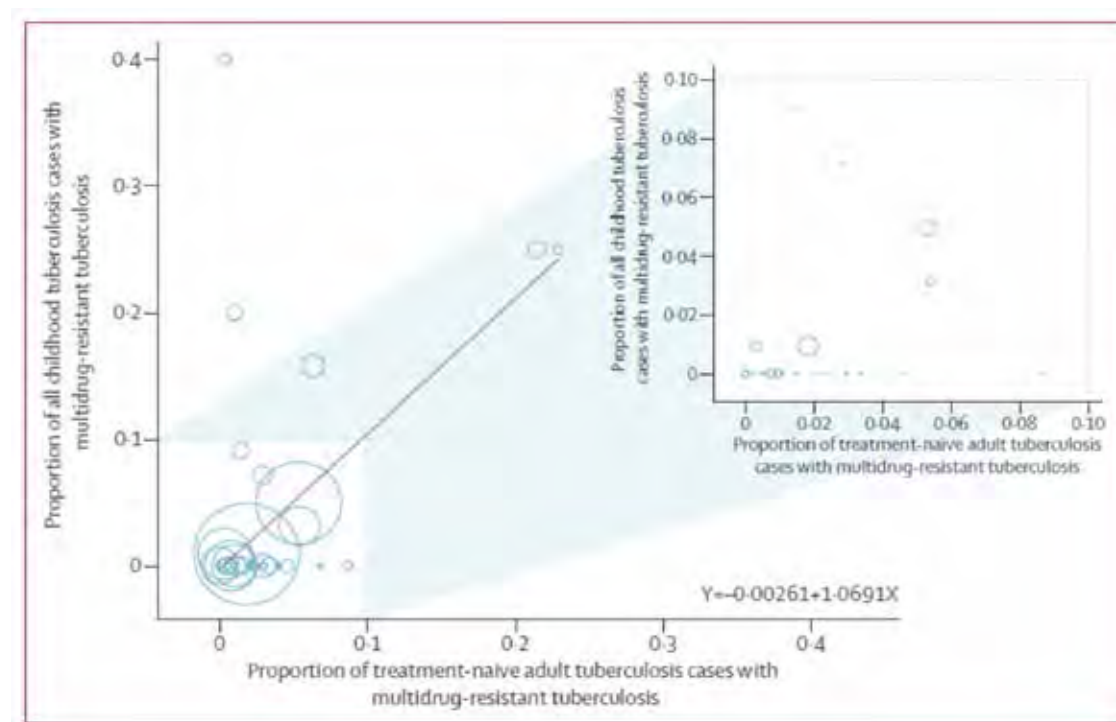
no treatment for children exposed to MDR-TB (World Health Organization guidance), to recommendation to treat them with agents to which the source case strains are susceptible (United States guidance), to using either high-dose isoniazid, or isoniazid, or no treatment (South Africa guidance).

**Table 2. Burden of TB and MDR-TB among children aged <15 years**

	All TB	MDR-TB
Disease incidence	851,691	29,809
Infection incidence	9,415,243	329,534
Infection prevalence	65,254,045	2,283,892

Source: Table adapted from Seddon presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai. Adapted from Dodd et al. *Lancet* 2014.

**Figure 3. Proportion of treatment-naïve adult TB cases with MDR-TB vs. proportion of all childhood TB cases with MDR-TB**



Source: Jenkins et al. *Lancet* 2014

<sup>4</sup> Donald PR *Curr Opin Pulm Med* 2002.

### 1.3.1 Balancing act: Benefits and drawbacks of treating presumed MDR-TB infection

Seddon identified several important concerns entrenched in the discourse about the use of infection treatment when the infection is thought to be MDR-TB, and sought to balance each of them with corresponding benefits of providing infection treatment.

A primary concern is toxicity, particularly to the fluoroquinolones and especially in children. However, he cited several larger studies suggesting that toxicity should be placed in the appropriate context: adverse events are more common in older children and adults with comorbidities, and severe adverse events are relatively rare.

Another concern is the unclear efficacy of MDR-TB infection treatment. A number of studies with smaller cohorts investigating the use of isoniazid for MDR-TB contacts have shown that isoniazid does not work for treating MDR-TB infection; however, emerging evidence suggests that other drugs may be effective for the treatment of infection in adults and children exposed to MDR-TB.<sup>5</sup>

Concordance is another topic of concern—specifically, the chance that, if a patient's close contact becomes sick with TB, whether that individual will have the same strain and matching drug-susceptibility profile as the first patient. Several studies, however, have confirmed high rates of strain concordance within households,<sup>6</sup> particularly when:

- The source case is infectious, and there are no other identified source cases
- The source case has intense interaction with the contact
- The contact has limited social activity outside the household
- The contact is very young

Seddon noted that the setting's incidence rate may be inversely related to the strain concordance rate. Put simply, close contacts in low-burden settings may have higher rates of strain concordance.

Yet another concern is that infection treatment will lead to the emergence of drug resistance. Existing evidence indicates that the use of isoniazid to treat TB infection does not lead to the emergence of resistance to isoniazid in contacts who subsequently develop TB disease. While resistance propagation after treatment with levofloxacin is a concern, Seddon pointed out that the expanded use of levofloxacin for MDR-TB infection treatment would be dwarfed by the use of fluoroquinolones for other conditions.

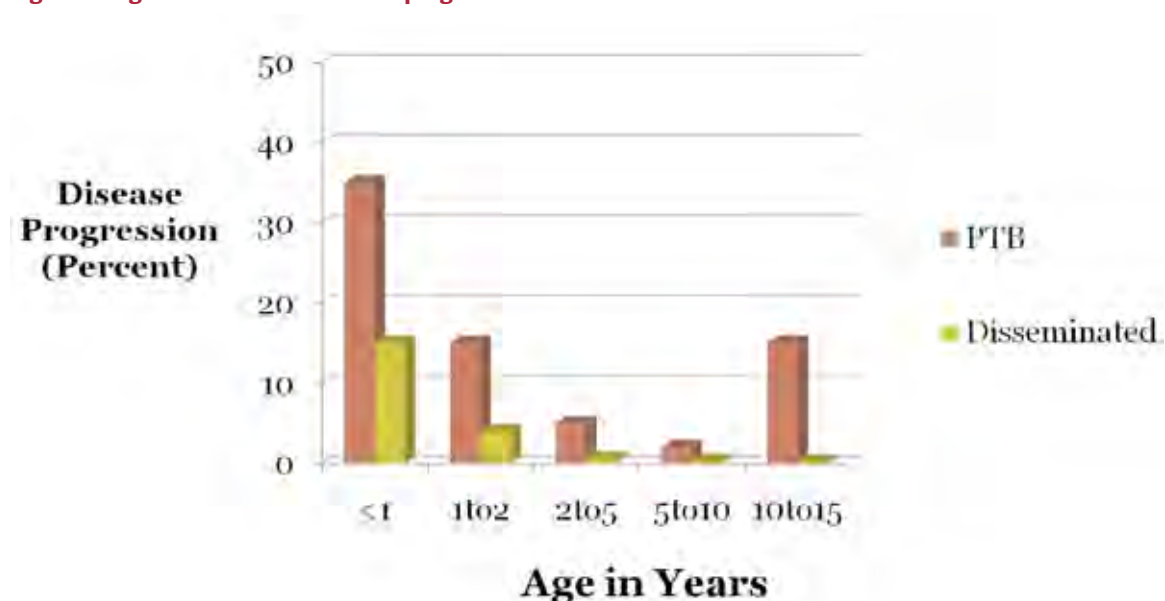
Another argument made against the use of infection treatment is the ostensibly low risk of progression-to-disease for patients who do not receive it; however, Seddon explained that quantifiable risk factors exist at every juncture between exposure, infection, disease, and outcome. One such factor is age-related risk (Figure 4).

Some feel that priority should be given to treating cases of smear-positive MDR-TB over the provision of prevention. However, Seddon noted the high cost of treating MDR-TB versus preventing it.

<sup>5</sup> Schaaf et al. *Pediatrics* 2002; Feja et al. *Pediatr Infect Dis J* 2008; Seddon et al. *Clin Infect Dis* 2013; Bamrah et al. *Int J Tuberc Lung Dis* 2014; Adler-Shohet et al. *Pediatr Infect Dis J* 2014

<sup>6</sup> Parr et al. *Clin Infect Dis* 2014; Grandjean et al. *Int J Tuberc Lung Dis* 2011; Schaaf et al. *Pediatrics* 2002; Teixeira et al. *Int J Tuberc Lung Dis* 2001; Wootton et al. *Pediatrics* 2005; Schaaf et al. *Pediatr Infect Dis J* 2000

**Figure 4. Age-related risk of disease progression**



**Abbreviation:** PTB, pulmonary TB

Source: Marais et al. *Int J Tuberc Lung Dis* 2004

### 1.3.2 Planned trials for MDR-TB infection treatment

Seddon noted briefly three double-blind randomized controlled trials that are being planned that would expand the knowledge base to guide preventive treatment in contacts of MDR-TB patients:

- TB-CHAMP will compare levofloxacin versus placebo in children aged <5 years in South Africa.
- ACTG 5300 (PHOENIX) will compare levofloxacin and isoniazid versus isoniazid alone in child and adult contacts.
- V-QUIN will compare levofloxacin versus placebo among adult and child contacts in Vietnam.

Moving forward, Seddon posed the question of how much— and what kind— of evidence should be required to start clinical treatment. As observational evidence continues to mount, randomized controlled clinical trials are gearing up but their results will not be compiled and analyzed for three years or more. Seddon stressed that the gap between starting clinical treatment now, versus after the trials have been reported, rep-

resents several million infected individuals going untreated.

### 1.3.3 Key points from discussion

Gail Cassell<sup>7</sup> drew attention to the strong evidence for the high efficacy of isoniazid infection treatment to prevent TB disease, and raised the conundrum that drug-susceptibility testing data may not be sufficiently reliable as to justify replacing isoniazid for treating infection in contacts. Jeffrey Starke<sup>8</sup> and Seddon concurred that if the efficacy of levofloxacin is demonstrated for MDR-TB, there is every reason to think that it would also work for drug-susceptible TB. Domingo Palmero<sup>9</sup> noted that he has experience with levofloxacin working well for treating drug-susceptible TB.

Starke commented that there are large-scale clinical trial data (>100,000 people studied) for use of isoniazid in treating drug-susceptible TB. Some of the children in the trials had what would now be considered TB disease; they were treated safely with isoniazid alone with no evidence of resistance. He emphasized that before those trials were carried out, there was a push in

<sup>7</sup> Gail Cassell, Harvard Medical School, Boston, MA, U.S.

<sup>8</sup> Jeffrey Starke, Baylor College of Medicine, Houston, TX, U.S.

<sup>9</sup> Domingo Palmero, Hospital Dr. F.J. Muñiz, Buenos Aires, Argentina

the pediatric community to use isoniazid to treat TB infection in children despite lack of evidence from randomized controlled trials. He argued for the importance of working in concert with manufacturers, such as levofloxacin manufacturer Macleods, to introduce pediatric formulations of TB drugs that will not only improve efficacy of TB therapy for children (e.g., scored tablets rather than syrups) but to generally improve the efficacy of drugs included in TB clinical trials.

Given the difficulty of diagnosing TB disease in children, Iqbal Master<sup>10</sup> expressed concern that a two-drug prophylaxis regimen might compromise the use of those two drugs in future. Seddon replied that in cases where the MDR-TB disease is subtle enough for diagnosis to be missed, a regimen to treat infection will likely be efficacious as treatment for disease, and in only a small number of cases will their resistance profiles be affected.

With respect to the study design of the three planned trials, Joseph Burzynski<sup>11</sup> and Salmaan Keshavjee<sup>12</sup> both raised the question of why a placebo arm would be included when there is a possibility of isoniazid-sensitive TB among study participants. Seddon agreed that this was a valid question, but questioned the widespread applicability of any particular study's concordance data for clinical trial design and noted that similar ethical challenges were found throughout TB trials. Given that, he emphasized maximizing the rigor and clarity of research outcomes in study design.

Aamir Khan<sup>13</sup> called for reflection on the overall effectiveness of programs that target only household contacts of MDR-TB cases; while appropriate for low-prevalence settings, in high-prevalence settings such a program will benefit those in the home, but may not have the greater impact necessary on a broader scale. Seddon replied that wider-scale screening would indeed be beneficial in high-burden settings, but would require significant resources to implement. In terms of prioritizing interventions to achieve the highest yield possible, targeting

households leads to a very high rate of identification of individuals who require treatment for both disease and infection.

## 1.4 KEY CONCEPTS IN CONTACT INVESTIGATION<sup>14</sup>

Burzynski outlined four key concepts underlying contact investigation:

1. Determine infectious period of the index patient
2. Determine extent of TB exposure
3. Concentric circle approach
4. Evaluate and treat contacts

### Determine the infectious period of the index patient

The infectious period is the time during which a TB patient is the most likely to transmit *M. tuberculosis* to others. Figure 5 illustrates a theoretical contact investigation timeline for an infectious patient.

### Determine the extent of TB exposure

Exposure occurs when a person spends time with an individual sick with TB disease during the sick person's infectious period. After determining who was exposed to the index patient during the infectious period, the relative extent of contacts' exposure helps to determine who among them should be tested. Estimating the extent of an individual's TB exposure is a largely subjective task, but key considerations include the degree of infectiousness of the index patient and the environment in which the exposure occurred.

### The concentric circle approach

The New York City Bureau of TB Control utilizes a concentric circle approach to conduct contact investigations (Figure 6).

<sup>10</sup> Iqbal Master, King Dinuzulu Hospital, Durban, South Africa

<sup>11</sup> Joseph Burzynski, Bureau of Tuberculosis Control, New York City Department of Health and Mental Hygiene, New York City, NY, U.S.

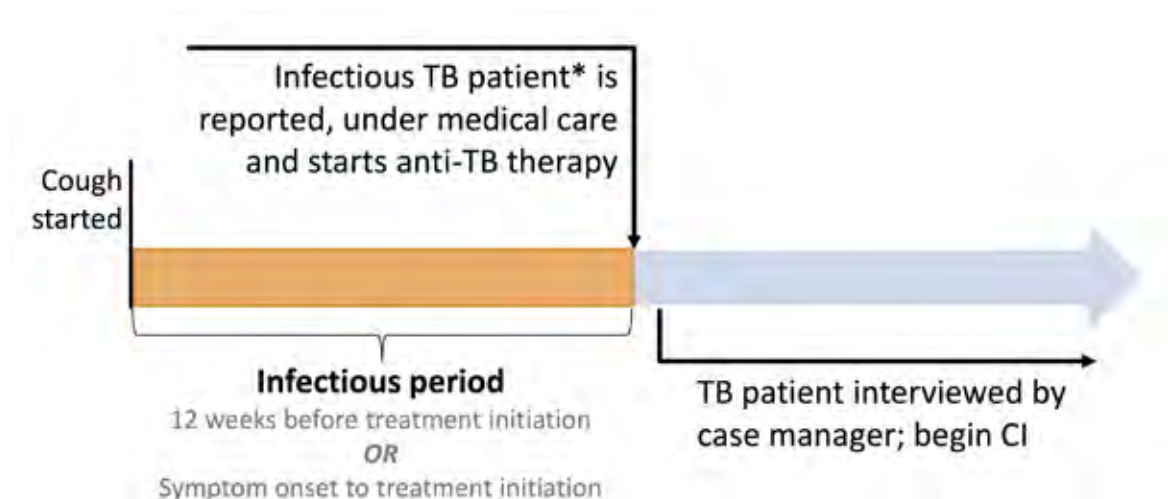
<sup>12</sup> Salmaan Keshavjee, Harvard Medical School, Boston, MA, U.S.

<sup>13</sup> Aamir Khan, Interactive Research and Development, Karachi, Pakistan

<sup>14</sup> This section is drawn from the presentation of Joseph Burzynski, Director, Bureau of Tuberculosis Control, New York City Department of Health and Mental Hygiene, New York City, NY, U.S.



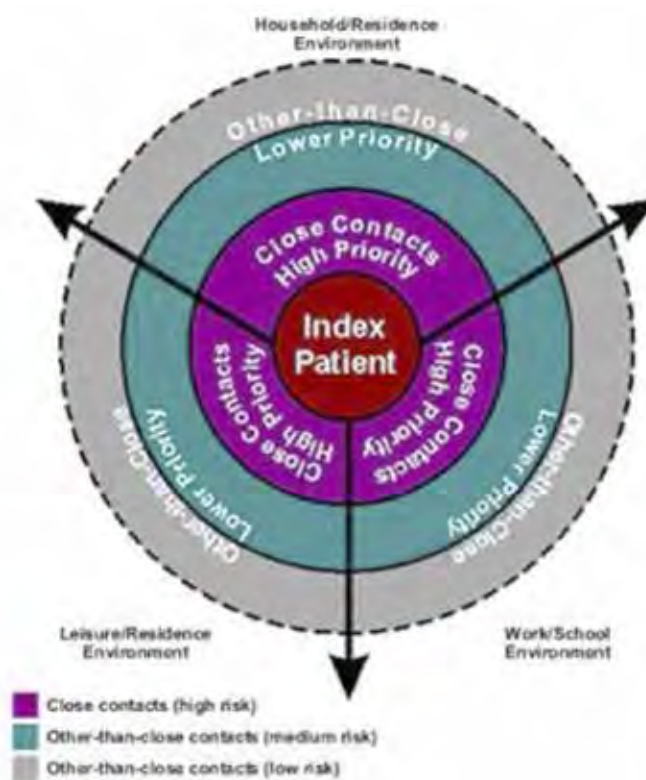
**Figure 5. Determining the infectious period of the index patient in a contact investigation (CI)**



**\*Infectious patients = respiratory/smear culture positive OR cavities on chest X-ray**

Source: Burzynski presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

**Figure 6. The concentric circle approach for TB contact investigations**



Source: CDC Self Study Module on Tuberculosis

The first step is to classify the index case's contacts, with a general threshold of more than eight hours of contact per week for defining a "close" contact, in contrast to those contacts with less than eight hours of contact who are classified as "other-than-close."

The next step is to test the closest circle of contacts and assess evidence of transmission, and then expand the investigation to the next circle as needed.

### Evaluate and treat contacts

Evaluation of contacts may involve symptom screening, testing for TB infection, and/or chest x-ray. TB infection treatment is then initiated according to the physician's evaluation.

## 1.5 FAMILY-CENTERED APPROACH: FRAMEWORK FOR MANAGING CHILDREN EXPOSED TO DRUG-RESISTANT TB<sup>15</sup>

Starke opened his presentation with reference to a 1963 publication that presages current dialogue about the importance of child contact tracing in eradicating TB. Conducted by one of the pioneers in the arena of family-centered contact tracing, Katherine HK Hsu, it calls for public health officials to conduct intensive TB contact investigations with a view to delivering chemoprophylaxis to children and adolescents.<sup>16</sup>

### 1.5.1 Family-centered contact tracing as part of a continuum

Starke shared the following graphic to show the full continuum of TB care as well as opportunities for intervention at key points (Figure 7).

As shown, family-centered contact tracing aims to identify recently exposed and infected children, offering crucial opportunities to:

- Prevent the establishment of TB infection
- Prevent TB infection from progressing to disease
- Detect TB disease earlier, when it is easier to treat and cure
- Prevent dissemination and hospitalization

Such a strategy also represents the only opportunity to determine drug susceptibility for 50% to 70% of children with TB disease— because of difficulty producing sputum— and 100% of children with infection, according to Starke. An especially high yield procedure is testing the adult visitors, including parents, for children in clinics or in hospital with suspected tuberculosis. Because the incubation period of tuberculosis can be short— only a few weeks to months— in young children, the adult from whom they acquired the infection may not yet have been diagnosed and may be one of the adults with the child in the hospital. At Texas Children's Hospital in Houston, Texas, U.S., performing chest radiographs on adults accompanying the children with suspected tuberculosis to the hospital has consistently yielded a 15% return, or a tuberculosis case rate of 15,000 per 100,000. He emphasized that no other TB screening program provides higher yield for disease than health care facility contact tracing for children with suspected tuberculosis. Also, finding an adult with pulmonary tuberculosis who has been with the child helps to establish the diagnosis in the ill child.

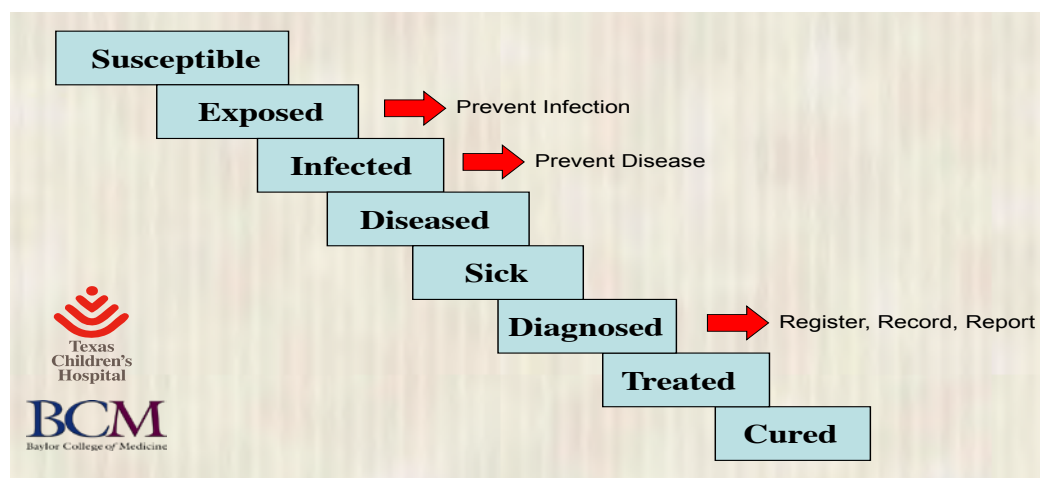
With respect to concerns about the lack of data from randomized controlled trials to establish the efficacy of treatment of tuberculosis infection for child contacts, Starke noted the long history of implementing interventions prior to establishing proof of their efficacy by randomized controlled trials when ample case-control and other data are available (e.g., BCG).

<sup>15</sup> This section is based on the presentation by Jeffrey Starke, Professor, Baylor College of Medicine, Houston, TX, U.S.

<sup>16</sup> Hsu KH. *Am J Public Health Nations Health* 1963



**Figure 7. Transitions in tuberculosis**



Source: Starke presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

### 1.5.2 Results from studies on contact tracing

Starke presented selected results from a set of studies on contact tracing. A two-year study followed 761 household contacts in Uganda, half of which were under 5 years of age.<sup>17</sup> The investigators reported a 10% prevalence of TB disease among child contacts (71% of which were culture positive). There were no reported cases of disseminated disease, which Starke speculated could have been the result of early intervention.<sup>18</sup> Nearly all (483/490; 99%) of the children who were treated with isoniazid (infection treatment) did not develop TB disease during follow up.

A 2012 review<sup>19</sup> of the yields of household contact investigations among child contacts<sup>20</sup> reveals a significant yield for TB disease—not just infection—among children <5 years of age. Across the 11 studies, the yield for TB disease among children in that age group ranged from 3.2%-16.4%. A 2013 study<sup>21</sup> in the Western Cape of South Africa reported rates that were even higher for child contacts (aged <5 years) of adults with MDR-TB: 44.7% (102/228) had TB infection and almost 15% (15/102) had TB disease at the start of the study.

Even when contact investigations are being carried out, many child contacts do not receive appropriate treatment. A 2011 study<sup>22</sup> reported the percentages of missed opportunities for treatment among children with documented TB exposure less than 5 years of age as nearly 44% (146/333).

A 2011 publication<sup>23</sup> in the *Lancet* exposed the significant burden of TB in households with MDR-TB and XDR-TB. This large four-year retrospective study strongly suggested that transmission occurred in households and caused TB disease. A more recent systematic review and meta-analysis of 25 studies from 11 countries is consistent with these observations (Figure 8).<sup>24</sup>

<sup>17</sup> Jaganath et al. *Clin Infect Dis* 2013

<sup>18</sup> He noted that characteristics of the index case were not associated with disease in the contacts.

<sup>19</sup> Triasih et al. *J Trop Med* 2012

<sup>20</sup> In India, Pakistan, Thailand, Indonesia, Lao, Cambodia, and the Philippines.

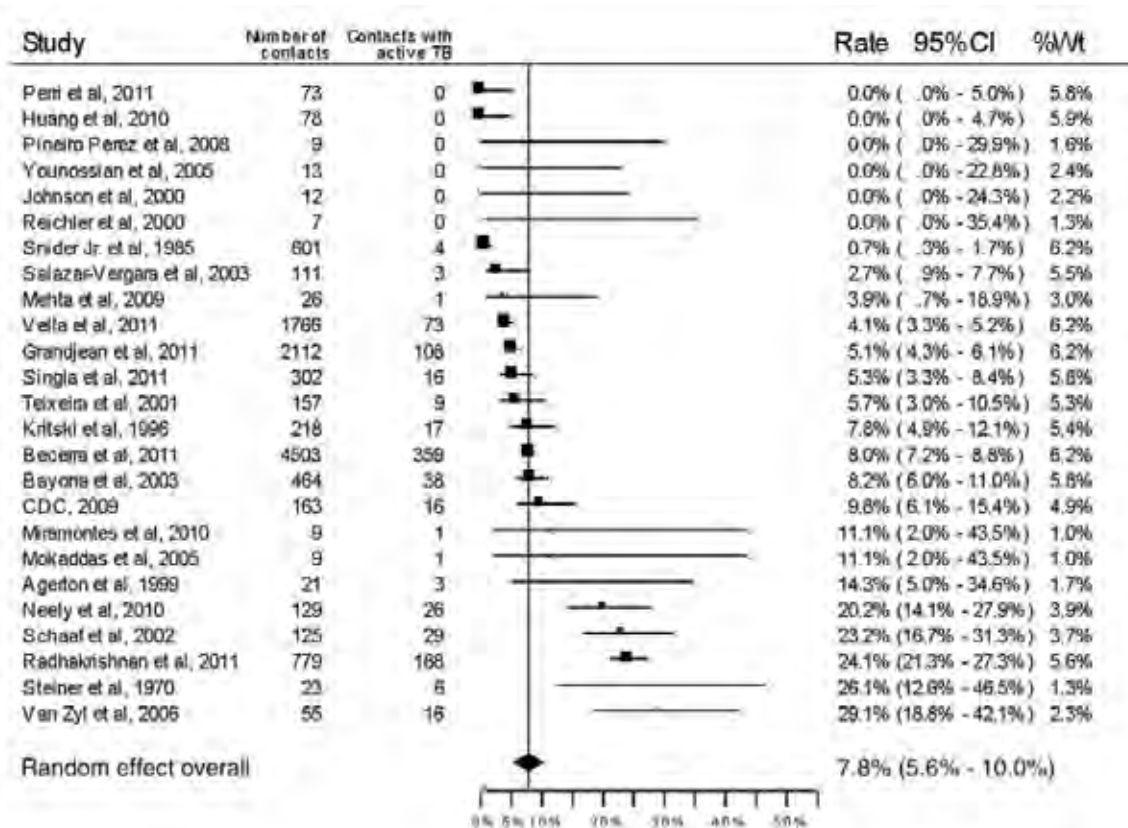
<sup>21</sup> Seddon et al. *BMC Infectious Diseases* 2013

<sup>22</sup> Preez et al. *Annals of Tropical Paediatrics* 2011

<sup>23</sup> Becerra et al. *Lancet* 2011

<sup>24</sup> Shah et al. *Clin Infect Dis* 2014

**Figure 8. Forest plot for secondary cases of active tuberculosis among household contacts of drug-resistant tuberculosis source cases.**



**Abbreviations:** CDC, Centers for Disease Control and Prevention; CI, confidence interval; TB, tuberculosis; Wt, weight.

Source: Starke presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

### 1.5.3 Importance of family-centered contact tracing for drug-resistant TB

Starke emphasized that family-centered contact tracing offers benefits directly to the individual (e.g., accurate diagnosis and appropriate treatment), but those benefits also extend to the family, with regard to access to directly observed treatment and other support services, support for each other during treatment, the psychological effect of preventing loved ones from contracting the disease, and a sense of empowerment over the disease. Concomitant benefits extend even further beyond the family and to society at large, in the prevention of future disease, and to national TB programs, which can benefit from accurate case finding, prevention, and cost containment. He declared

that in his opinion, contact investigations offer the most “bang for the buck” when taking into account the important dimensions of risk, motivation to treat, drug resistance, and directly observed treatment.

Starke described how they treat child contacts of drug-resistant TB patients in Houston, after ruling out TB disease in those children. Most commonly treated for infection are household contacts <5 years of age, child contacts who are immunocompromised, or older children known to be recently infected in school after exposure to someone with infectious drug-resistant TB. If a child has been exposed but has a negative test of TB infection, the child is treated for exposure awaiting the results of a repeat test

for TB infection. The original regimen used in this program to treat exposure/infection was pyrazinamide plus ethambutol, which was then switched to ciprofloxacin. Today, the program treats TB exposure with a regimen of levofloxacin for an average of 10 weeks before repeating the test of infection. If the test is negative, this treatment is discontinued. If the source case isolate is resistant to INH but susceptible to rifampicin, then the child is treated with rifampicin alone for 4 months. If the source case isolate is MDR-TB, then the child is treated with levofloxacin alone for 9 months. Over the past 20 years, Starke estimated that the Houston program has treated around 100 child contacts for exposure/infection with the various regimens he described, and none of those children has developed TB disease.

#### 1.5.4 Key points from discussion

Participants requested that Starke explain the specifics about how his program tests for TB infection. Both interferon-gamma release assays (IGRA) and tuberculin skin tests (TST) are used, depending upon the circumstances. IGRA is valuable if the child has had the BCG vaccine for differentiating between TB infection and cross-reaction with BCG; he is comfortable using either test for children aged <2 years. To further explain, he used the example of a household with a patient with drug-susceptible TB. Everyone in the household gets a TST or IGRA, with a positive result indicating infection and warranting evaluation and appropriate treatment. Children <5 years of age with a negative TST are classified as having “tuberculosis exposure” because it can take up to 10 weeks after exposure for a child to test positive on the TST. Because young children get sick with TB faster, they are treated with “window prophylaxis,” meaning that infection treatment is provided during the window of time needed to determine if the skin test is reliable.

Responding to the question of whether children and adults have sufficiently different natural histories to warrant differentiating treatment between the two, Starke called for a relative-risk approach to TB infection: categorizing people according to tiers of relative risk to prioritize

for evaluation and treatment<sup>25</sup> (with immunocompromised people of all ages as the lowest hanging fruit). He emphasized that programs treating disease and programs delivering infection treatment are not mutually exclusive; they should inform and improve each other, while embracing opportunities to evolve and change for the better.

Hind Satti<sup>26</sup> argued that some national TB programs should be held more strictly accountable for program flaws that are not attributable to funding problems. To illustrate, she referred to recipients of Global Fund support that consistently underspend on drug procurement and countries that procure isoniazid for treating drug-susceptible TB infection, but the isoniazid goes unused and expires. She further cited examples in which national TB programs fail to implement programs supported by existing data, such as community-based TB screening, infection treatment, and treatment for pediatric TB cases (with or without HIV co-infection). Farhana Amanullah<sup>27</sup> reported similar experiences with national TB programs in several countries in Asia that had procured the drugs required to treat drug-susceptible TB, but these drugs were being used improperly or not at all.

<sup>25</sup> He noted that the American Thoracic Society is currently adopting just such an approach as it reframes all of its statements about TB infection and disease.

<sup>26</sup> Hind Satti, Partners In Health, Maseru, Lesotho

<sup>27</sup> Farhana Amanullah, Indus Hospital, Karachi, Pakistan

### **BOX 1-2 SYNOPSIS: WEIGHING THE BENEFITS AND CONCERNS ABOUT TREATING TB INFECTION IN CONTACTS OF MDR-TB PATIENTS**

Should infected contacts of MDR-TB patients be treated? Concerns about infection treatment are reasonable, but they need to be weighed against the benefits of treatment. Key concerns include:

- No standard length of treatment has been established, and there are few evidence-based recommendations for the treatment of presumed MDR-TB infection in exposed contacts; no randomized controlled trials have been completed.
- The risk of treating needs to be considered relative to the risk of not treating: if it is not feasible to provide treatment to completion, it risks the development of further resistance.
- There are concerns about the toxicity of second-line drugs.

In counterpoint, there are an important set of benefits to treating TB infection in exposed contacts:

- Treating MDR-TB infection may be safer and more effective than treating MDR-TB disease.
- Some experts believe it is better to treat MDR-TB while the bacterial burden is low.
- Treatment decreases the likelihood of progression to TB disease. Many infections are not “latent” but are “active,” and vulnerable patients (e.g., young children, immunocompromised persons, and elderly people) can progress rapidly to life-threatening forms of TB. In some cases, it is possible to treat TB infection before the person becomes immunocompromised.
- Treatment prevents severe consequences of clinically active MDR-TB disease for the patient, the community, and the TB program.
- The prevention of future cases of TB disease facilitates lower rates of future transmissions to vulnerable populations.

## Part 2.

# Country-specific experiences and future plans for providing infection treatment

### 2.1 MDR-TB INFECTION TREATMENT IN CHILDREN: EXPERIENCE FROM CAPE TOWN, SOUTH AFRICA<sup>28</sup>



#### 2.1.1 Drug-resistance surveillance in South Africa (2003-2013)

Simon Schaaf described how the 1990s saw the introduction of MDR-TB treatment for adults in South Africa, but there was a dearth of information about MDR-TB in children. Because it was believed to be less infectious than drug-susceptible TB, children were believed to be at low risk for MDR-TB. However, an initial set of studies was launched in 1994 to survey drug-resistance

patterns in children with TB, to screen children aged <5 years in households with MDR-TB cases, and to confirm transmission between adults and children with DNA fingerprinting.

He presented the results of five consecutive drug-resistance surveys carried out between 2003 and 2013 (Table 3).



**Table 3. Results of 5 consecutive drug-resistance surveys in South Africa**

	Period 1 2003-2005	Period 2 2005-2007	Period 3 2007-2009	Period 4 2009-2011	Period 5 2011-2013
Characteristics					
All culture+ cases	323 (%)	291 (%)	294 (%)	340 (%)	324 (%)
Median age (years)	2.5	2.75	2.1	2.4	2.7
Boys	173 (53.6)	154 (52.9)	156 (53.1)	177 (52.1)	166 (51.2)
Previous TB Rx*	59 (18.3)	65 (22.3)	50 (17.0)	59 (17.4)	36 (11.1)
HIV test done**	243 (75.2)	174 (59.8)	217 (73.8)	288 (84.7)	300 (92.6)
HIV-infected***	64 (26.3)	49 (28.2)	63 (29.0)	63 (21.9)	46 (15.3)
DST results					
All culture+ cases	323 (%)	291 (%)	294 (%)	340 (%)	324 (%)
DST done <sup>a</sup>	320 (99.1)	285 (97.9)	292 (99.3)	340 (100)	324 (100)
Any DR	41 (12.8)	43 (15.1)	45 (15.4)	49 (14.4)	41 (12.7)
INH mono-R	22 (6.9)	22 (7.7)	15 (5.1)	19 (5.6)	20 (6.2)
RMP mono-R****	0	2 (0.7)	4 (1.4)	6 (1.8)	6 (1.9)
MDR-TB*****	19 (5.9)	19 (6.7)	26 (8.9)	24 (7.1)	15 (4.6)

<sup>a</sup> Further percentages based on number of DST results

Abbreviations: DST, drug-susceptibility test; DR, drug resistance; INH mono-R, high-dose isoniazid mono-resistance; RMP mono-R, rifampicin mono-resistance

#### Significant differences:

\*Significant decrease in previous treatment 2<sup>nd</sup> vs. 5<sup>th</sup> period: OR 2.62 (1.66-4.15) p<0.001

\*\*HIV tests done (2<sup>nd</sup> compared with 5<sup>th</sup> period): p<0.001

\*\*\*Significant decrease in HIV prevalence from high to low: OR 2.20 (1.43-3.38) p<0.001

\*\*Significant differences: RMP mono-R increase from 1<sup>st</sup> to 5<sup>th</sup> period: p = 0.03 (Fisher exact 2-tailed)

\*\*\*Significant decrease in MDR-TB from 3<sup>rd</sup> to 5<sup>th</sup> period: OR 2.01 (1.04-3.88): p=0.04

Source: Table adapted from Schaaf presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

Schaaf highlighted the notable trend of increased rifampicin resistance rates among children with TB surveyed in the Western Cape, which rose from no cases in 2005 to almost 2% of cases by 2011. The percentage of HIV tests done among children with TB has increased markedly to above 92% in 2013 compared to just under 60% in 2005-2007. Rates of HIV co-infection have roughly halved since the 2007-2009 period. The percentage of retreatment cases has similarly decreased by half between 2005 and 2013. The proportion of pediatric cases that are MDR has decreased almost by half (8.9% of cases to 4.6% of cases) between 2009 and 2013.

#### 2.1.2 Possible reasons for decrease in pediatric MDR-TB rates in Cape Town, South Africa

Schaaf cited several possible explanations for the decrease in MDR-TB. The first is the implementation of active case finding of child contacts of adult MDR-TB cases, with early identification of disease before the children become culture-positive. Second is the initiation of infection treatment in children who have been exposed to or infected with MDR-TB. Because TB is an opportunistic infection for children living with HIV, programs aimed toward prevention of mother-to-child transmission of HIV and the early introduction of anti-retroviral treatment were cited by Schaaf as an explanation for

<sup>28</sup> This section is based on the presentation of Simon Schaaf, Professor, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.

reduced rates of MDR-TB over time. Further, more rapid diagnosis of drug-resistant TB with Xpert MTB/RIF, as well as early initiation of appropriate second-line TB treatment, may decrease the period of infectiousness among adults in contact with the group.

Schaaf reviewed several studies conducted by him and his associated researchers. A study<sup>29</sup> from 2000 that highlighted the importance of contact tracing found that most childhood contacts of adults with MDR-TB are likely to be infected by these MDR-TB source cases. This study concluded that child contacts of adults with MDR-TB should be treated according to the drug-susceptibility test patterns of the likely source cases' *M. tuberculosis* strains unless the child's own strain has drug-susceptibility test results that indicate otherwise.

In a study<sup>30</sup> that followed child contacts of adult MDR-TB cases for 30 months, children treated with combination regimens including two or three drugs (pyrazinamide, ethambutol, ethionamide, and/or ofloxacin) had a lower incidence of TB disease than children who were not on infection treatment. The study also confirmed transmission of MDR-TB infection— and the occurrence of MDR-TB disease (almost all within a 12-month window)— to children in close household contact with adult MDR-TB cases. The results of the study informed regimen design for MDR-TB prevention practice in South Africa.

A follow-up prospective study<sup>31</sup> then evaluated the safety, tolerability, adherence, and outcomes of one of these regimens: a three-drug MDR-TB infection treatment regimen (high-dose isoniazid, ethambutol and ofloxacin). The study also evaluated the outcomes of this infection treatment regimen to prevent TB disease. The regimen was well tolerated and few children developed TB disease or died if adherent to therapy. The authors argue that the provision of infection treatment to vulnerable children following exposure to MDR-TB should be considered.

Schaaf also reviewed and shared the results from a study investigating reasons for non-attendance at pediatric MDR-TB specialty clin-

ics,<sup>32</sup> as well as a study analyzing the limited benefits of two models of decentralized TB care in children, despite an increase in the number of contacts evaluated.<sup>33</sup>

### **2.1.3 Current treatment practice in Western Cape, South Africa**

Schaaf described the current treatment practice for MDR-TB infection treatment in the Western Cape: to provide a regimen of high-dose isoniazid, ethambutol, and levofloxacin for six months to child contacts of MDR-TB source cases aged <5 years and to HIV-infected children irrespective of their ages. The follow-up period is a minimum of 12 months, because most incident TB disease cases tend to occur within 12 months of exposure to the index case (>90%). This practice has been rolled out to the clinic level, so doctors providing TB care can prescribe infection treatment and manage follow-up. If doctors suspect that a patient has active TB disease, the patient is referred to a specialized MDR-TB clinic for care. Children who are in contact with XDR-TB or pre-XDR-TB cases with fluoroquinolone resistance receive only high-dose isoniazid as an infection treatment regimen, as well as follow-up for a minimum of 12 months.

He described how the system has changed from a nurse-driven, specialized TB service to nurses that rotate every six months (due to concerns over exposure to TB/MDR-TB). The drawbacks of this change are that the nurses may lack experience in treating TB and it does not foster the opportunity to develop personal rapport with patients: this lack of continuity of care is a key problem.

### **2.1.4 Current challenges and needs**

Schaaf continued by identifying current challenges, with a primary concern being the excess number of drugs given for infection treatment: there is an urgent need for an infection treatment regimen comprising a single drug. Isoniazid and ethambutol are not effective in many cases and carry a possible risk of adverse events.

Given that adults sick with MDR-TB are currently often treated solely on the basis of their Xpert MTB/RIF results, Schaaf contended that this

<sup>29</sup> Schaaf et al. *Pediatr Infect Dis J* 2000

<sup>30</sup> Schaaf et al. *Pediatrics* 2002

<sup>31</sup> Seddon et al. *Clin Infect Dis* 2013

<sup>32</sup> Seddon et al. *Public Health Action* 2012

<sup>33</sup> Zimri et al. *Public Health Action* 2012

does not provide enough guidance for managing their contacts appropriately due to increasing rifampicin mono-resistance as well as the possibility of pre-XDR-TB and XDR-TB disease. While contact tracing and adherence to infection treatment is presumably better for MDR-TB contacts in Cape Town than it is for drug-susceptible TB contacts, the fact remains that most child contacts are not accessing infection treatment.

He outlined a set of current needs related to managing MDR-TB for patients and their contacts:

- Drugs for infection treatment that are child-friendly, such as lower mg-size (or properly scored) and dispersible tablets for providing appropriate doses to young children
- A single-drug infection treatment regimen for MDR-TB contacts, with efficacy confirmed by randomized controlled trials
- Effective infection treatment for XDR-TB (or fluoroquinolone-resistant) contacts
- Rapid drug-susceptibility testing, at least for isoniazid and the fluoroquinolones<sup>34</sup>
- Community-level management of all high-risk contacts of MDR-TB and XDR-TB cases for screening, treatment of disease, and treatment of infection

### 2.1.5 Key discussion points

Master commented on concerns surrounding the issue of discordance, noting that some households have family members with different resistant TB strains spanning both MDR-TB and XDR-TB, and questioning the bearing that patients presenting with mixed isoniazid mutations would have on Schaaf's recommendation for the use of isoniazid to treat infection. Further, in Master's experience, drug resistance could not be confirmed in 15%-20% of cases, raising concerns about treating patients unnecessarily. Finally, he sought advice as to how to deal with cases of discordance between results of Xpert MTB/RIF and conventional drug-susceptibility testing. Schaaf replied that in cases of discordant results in children, they request gene sequencing to confirm the presence of mutations.

Once a child has been identified as having TB disease in a household with an MDR-TB patient, he or she is managed as if they have MDR-TB. Before initiating disease treatment they perform as many cultures as possible to establish whether the strain is drug-susceptible or drug-resistant. If it is drug-susceptible, the patient is treated for drug-susceptible TB disease with the option of adding levofloxacin to cover the possibility of exposure to MDR-TB contacts.

Master also highlighted the challenges of implementing a program of pediatric infection treatment in TB programs whose resources are already limited. Schaaf noted that, despite the South African's National TB Advisory Committee's decision not to provide pediatric infection treatment, the Western Cape has a policy of doing so.

Richard Brostrom<sup>35</sup> contended that it is impossible to provide safe infection treatment to children without more resources, but emphasized the cost efficiency of providing infection treatment relative to the cost of treating a case of MDR-TB disease.

Schaaf acknowledged two further issues related to the use of Xpert MTB/RIF. The first is that in many cases, a provider receives an Xpert MTB/RIF result, but never receives a conventional drug-susceptibility test result because the culture is never positive. This issue can arise when cultures are sent in too late. Once TB treatment is started in children, the chance of getting a positive culture is markedly lower, while the Xpert may remain positive because it does not need live organisms to be positive. If culture is negative and Xpert MTB/RIF is positive for rifampicin resistance, no information is available about resistance to isoniazid or second-line anti-TB drugs. This makes it difficult to provide the best management for the patient.

The second problem is that many people do not realize that Xpert MTB/RIF is only a test for initial diagnosis, not for follow-up; Schaaf cited cases of false positives for rifampicin resistance in follow-up, and even after treatment, despite negative cultures. Essentially, once a patient is on treatment, the Xpert result may remain positive for a long time, and if the genetic material

<sup>34</sup> Xpert MTB/RIF only informs about rifampicin resistance.

<sup>35</sup> Richard Brostrom, Centers for Disease Control and Prevention, Honolulu, HI, U.S.



becomes minimal, the Xpert result may eventually show rifampicin “resistance” — which could be false. So Xpert is not a test for follow-up after starting TB treatment to monitor if patients respond to treatment.

Another clarification Schaaf added was to urge healthcare providers not to rely on tuberculin skin-testing or IGRA to decide about treating infection or not. This is because infectious markers measured by these tests can take up to three months to become positive after TB exposure. If the tuberculin skin test or the IGRA is positive, then the patient should be treated for TB infection once TB disease is excluded; however, if these test results are negative in a TB-exposed child, the child should still be treated for TB infection if definite contact with an infectious source case is known. TB infection may be present with a negative tuberculin skin test or negative IGRA, as it takes time for the test to become positive after TB exposure. Further, in

some young children or immunocompromised children, the results of these tests may remain negative, but this should not deter providers from treating the child for TB infection.

Acknowledging the difficulties inherent in extrapolating from a specific scenario to a broader global context, Palmero raised the topic of increased mono-resistance to rifampicin. Schaaf noted that this trend is evident in the adult population (where it is strongly associated with severe HIV disease) as well as the pediatric one— this has underscored the need to further understand the mechanism of rifampicin monoresistance development. Contributing factors may include rifampicin not being taken regularly with isoniazid, compromised immune systems, and low concentrations of rifampicin in the blood. He recommended ensuring daily treatment of rifampicin and isoniazid, coupled with higher doses of rifampicin (>600 mg<sup>36</sup>).

## 2.2 TREATMENT FOR TB INFECTION IN CHILDREN AND ADULTS EXPOSED TO MDR-TB IN BUENOS AIRES, ARGENTINA<sup>37</sup>



<sup>36</sup> Schaaf explained that recommendations of dosing rifampicin at less than 600 mg were made on the basis of cost, not efficacy or safety.

<sup>37</sup> This section is based on the presentation by Domingo Palmero, Chief, Pulmonology Division, Hospital Dr. F.J. Muñoz, Buenos Aires, Argentina.

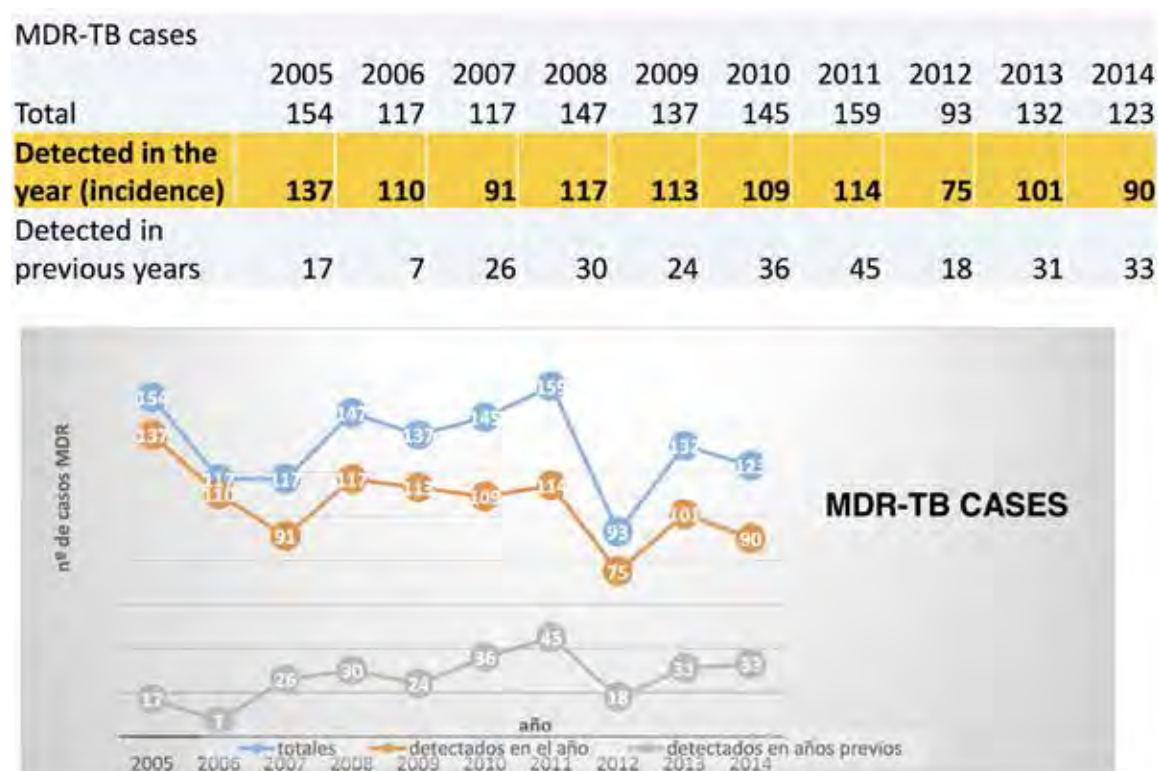
### 2.2.1 MDR-TB statistics in Argentina

Palmero reported on a program for treating presumed MDR-TB infection in Buenos Aires, Argentina. Between 2005 and 2014, Argentina's National TB Program reported that 1,324 MDR-TB cases were detected countrywide, with those notified cases concentrated primarily in Buenos Aires and its metropolitan area<sup>38</sup> (Figure 9).

In the same period, a total 95 cases of XDR-TB were detected, peaking at 15 cases in 2011 and dropping to 5 cases in 2012, before increasing again to 10 cases in 2014.

Palmero noted that relatively few of the patients with MDR-TB were children aged  $\leq 15$  years ( $n=33$ ; 2.5%). Figure 10 illustrates the low level of resistance to fluoroquinolones in this patient group.

**Figure 9. MDR-TB burden in Argentina, 2005-2014**

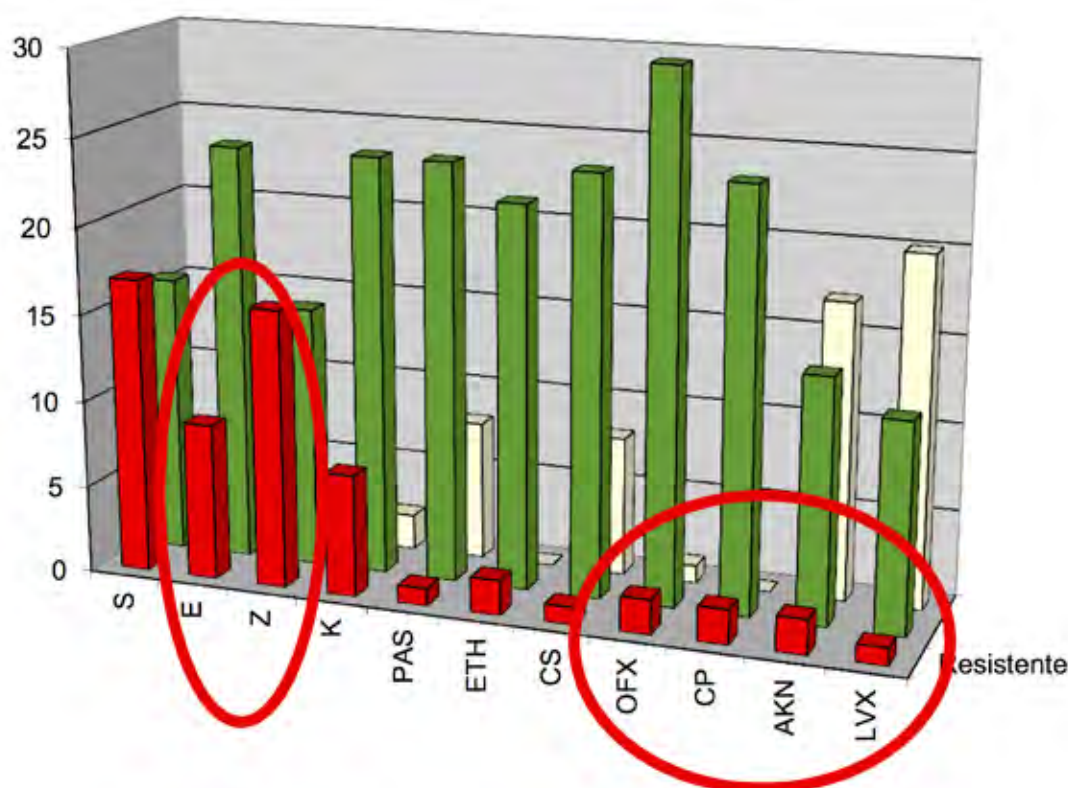


**Blue line:** total cases; **orange line:** cases detected that year; **grey line:** cases detected in previous year

Source: Palermo presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

<sup>38</sup> Buenos Aires has a population of approximately 3 million. Over 50% of TB cases were migrants as of 2013.

**Figure 10. Additional resistance profile in children aged  $\leq 15$  years with MDR-TB in Argentina (2005-2014)**



**Red bars:** resistant; **green bars:** sensitive; **yellow bars:** not done

**Abbreviations:** S, streptomycin; E, ethambutol; Z, pyrazinamide; K, kanamycin; PAS, para-aminosalicylic acid; ETH, ethionamide; CS, cycloserine; OFX, ofloxacin; CP, AKN, amikacin; LVX, levofloxacin

Source: Palmero presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

### 2.2.2 Drug-resistant TB disease diagnosis and contact management

Currently, most cases of drug-resistant TB disease in Argentina are diagnosed using the proportion method in solid media culture; rapid phenotypic (BACTEC MGIT 960) and molecular (line probe assay and Xpert MTB/RIF) diagnostic methods have limited availability and are thus used infrequently. Patients whose resistance profile to fluoroquinolones is not known are treated with levofloxacin as the first option.

Argentina's national guidelines (2013) recommend the use of isoniazid to treat infection only for drug-susceptible TB contacts aged  $<15$  years, but not for MDR-TB contacts. The Argentina Pediatric Society (updated 2010) recommends that MDR-TB contacts be referred to a specialized center, where the use of two susceptible drugs should be considered.

As of March 2015, there are 3 referral hospitals in Buenos Aires for pediatric drug-resistant TB.<sup>39</sup> All three hospitals maintain follow-up of contacts at home, generally for two years. With regard to infection treatment, the Hospital Muñiz-Institute Vaccarezza has had guidelines in place since 2011 that allow for providing 6-12 months of infection treatment to high-risk contacts (i.e., children, immunosuppressed patients, people who have had prolonged contact with a source case, and those with recent TST conversion) in cases with preserved susceptibility to first-line drugs. The suggested regimen options are: (1) pyrazinamide and ethambutol, or (2) pyrazinamide and a fluoroquinolone.

Following an outbreak of drug-resistant TB among children in 2009, Hospital Gutiérrez now provides quinolone infection treatment for

<sup>39</sup>Hospital Muñiz-Institute Vaccarezza (Dr. Sandra Inwentarz); Hospital Elizalde (Dr. Norma González); Hospital Gutiérrez (Dr. Cristina Cerqueiro).

children aged <6 years and immunosuppressed patients. Between 2005 and 2013, the hospital evaluated 81 children between the ages of 1 month and 15 years; these children were close contacts of patients with MDR-TB/XDR-TB disease. Among the 59 contacts without TB disease, 23 patients with immunosuppression and/or under 6 years of age received regimens for infection treatment of either: (1) fluoroquinolone and ethambutol or pyrazinamide, or (2) ethambutol and pyrazinamide. None developed TB disease or MDR-TB disease. To Palermo's knowledge, none of the children who received infection treatment in Argentina had developed drug-resistant TB disease after two or more years of follow up.

### 2.2.3 Current challenges and ways forward

Palmero identified a key problem of inconsistent resistance patterns between the index case and others in the same household, suggesting that resistance patterns are useful but not reliable indicators. In the same vein, he expressed concern about the reliability of drug susceptibility testing for ethambutol, pyrazinamide, and second-line drugs other than fluoroquinolones and injectables. He cautioned about the possible threat of amplified resistance among people already sick with TB disease in whom disease is not recognized who would receive a regimen only to treat infection.

The high cost and limited availability of fluoroquinolones and other second-line drugs are obstacles to convincing policy makers about the utility of infection treatment. He stressed that more evidence is needed to overcome the resistance of national TB programs toward implementing a policy of infection treatment for MDR-TB contacts.

Palmero concluded that the use of fluoroquinolone infection treatment is feasible for MDR-TB contacts who are children aged <5 years or immunosuppressed children aged <15 years. He suggested providing infection treatment, preferably supervised, for at least six months. If the

index case is resistant to isoniazid and rifampicin and susceptible to ethambutol, pyrazinamide, and fluoroquinolones, then he proposed a prophylactic regimen of either (1) ethambutol and pyrazinamide, or (2) ethambutol, pyrazinamide, and a fluoroquinolone. He underscored the challenge of ensuring treatment adherence, noting that it is difficult enough for regimens for the treatment of MDR-TB disease and even more so for infection treatment regimens.<sup>40</sup>

### 2.2.4 Key discussion points

Referring to Palermo's point about the resistance of Argentina's National TB Program to quinolone-based infection treatment on the basis of cost, Courtney Yuen<sup>41</sup> noted that this seems at odds with quinolones' status as a widely prescribed class of medications for treating respiratory diseases. Palermo responded that while patients do not pay for the medications in Argentina's health system, there is a practical difference between treating a single patient for 1-2 weeks and treating infection in a large cohort of patients for 6-9 months.

Keshavjee questioned why, despite presenting data showing that performing infection treatment interventions prevents people from getting the disease, Palermo situated the cost of quinolones (which can be obtained at relatively low cost in other parts of the world) and national TB programs' resistance as qualifiers to strongly recommending a policy of infection treatment.

Master requested clarification as to whether high-dose levofloxacin resistance is the same as that for moxifloxacin or ofloxacin. Palermo replied that the therapeutic range of ofloxacin is very low. Levofloxacin and moxifloxacin both have high-dose therapeutic ranges, but levofloxacin has a single-level mechanism of resistance while moxifloxacin has dual levels of resistance.<sup>42</sup>

<sup>40</sup> Palermo noted that this is a particular problem for children aged < 8 years living without a stable family structure, and questioned the possibility of implementation of an adequate supervised infection treatment.

<sup>41</sup> Courtney Yuen, Brigham and Women's Hospital, Boston, MA, U.S.

<sup>42</sup> He cited a report by a bacteriologist at his reference lab that 17% of the isolates resistant to ofloxacin are susceptible to levofloxacin, and >30% of those resistant to levofloxacin and ofloxacin are susceptible to moxifloxacin.



## 2.3 CONTACT INVESTIGATIONS AND TREATMENT OF PRESUMED MDR-TB INFECTION IN NEW YORK CITY<sup>43</sup>



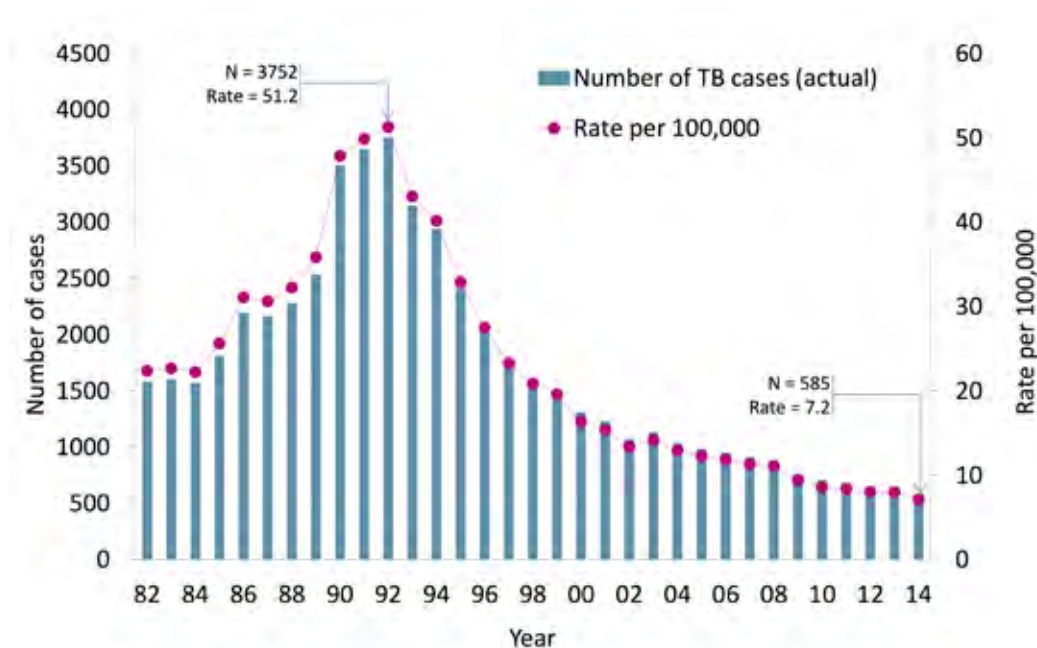
### 2.3.1 Context: TB epidemic in New York City

Joseph Burzynski described how New York City experienced an epidemic of TB cases that gained momentum during the latter half of the 1980s before peaking in 1992. Due to the efforts of the Bureau of TB Control to identify patients and ensure treatment adherence, the number of TB cases in New York City fell from more than 3,700 cases in 1992 to less than 600 cases in 2014 (Figure 11).

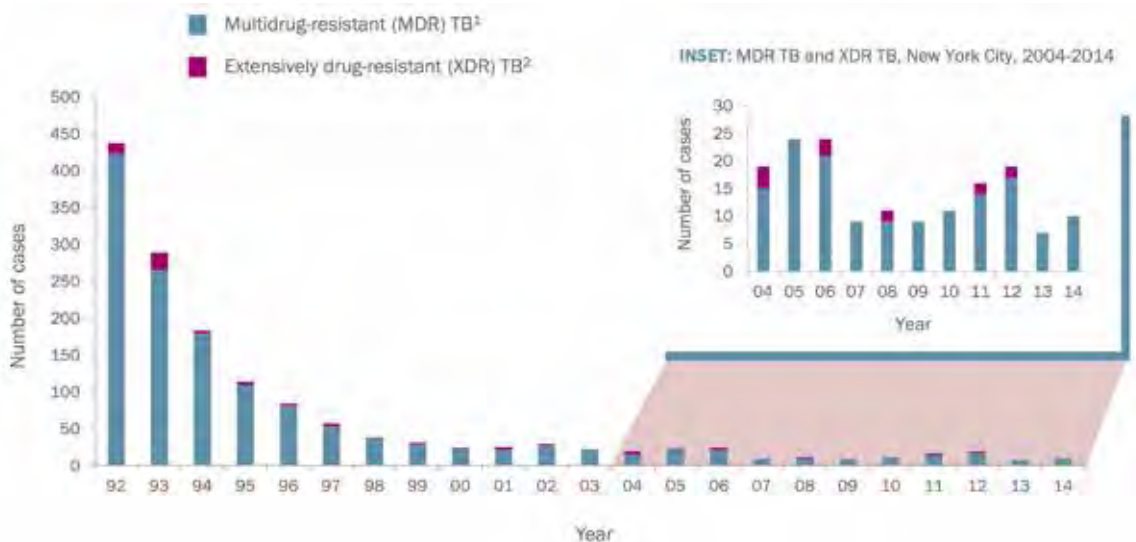
The incidence of multidrug resistance among those cases of TB exhibited a similarly marked decline during the same time period, dropping from almost 450 MDR-TB cases in 1992 to 10 MDR-TB cases in 2014, none of which were determined to be extensively drug resistant or XDR-TB (Figure 12).

Noting that the incidence trend is not decreasing as quickly anymore, Burzynski suggested that this could be due to the wider range of venues for transmission where interventions could be performed. Reduction efforts are more difficult now (for instance, TB and MDR-TB now primarily affect the immigrant community in New York City), so they may be facing what he termed a “new normal.”

<sup>43</sup> This section is based on the presentation by Joseph Burzynski, Director, Bureau of Tuberculosis Control, New York City Department of Health and Mental Hygiene, New York, NY, U.S.

**Figure 11. Tuberculosis incidence in New York City (1982-2014)**

Source: Burzynski presentation at April 2015 tGlobal Consultation hosted by HMS Center for Global Health Delivery–Dubai.

**Figure 12. Multidrug resistance among tuberculosis cases in New York City (1992-2014)**

Source: Burzynski presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

### 2.3.2 Objectives of the New York City Bureau of TB Control

The New York City Bureau of TB Control has two primary objectives:

1. To identify all individuals with suspected and confirmed TB disease and ensure their appropriate treatment, ideally on directly observed therapy.
2. To ensure that individuals at high risk for progression from TB infection to TB disease complete treatment for TB infection and do not develop TB disease.

Burzynski emphasized that contact investigation should be a key component of any TB control strategy. Contact investigations seek to identify individuals who have recently been exposed to an infectious TB case and who, if they are infected, have high risk of progressing to TB disease. The fundamental goals of contact investigations are threefold:

- To find cases of TB disease
- To disrupt the chain of transmission by treating TB disease
- To identify and treat contacts without TB disease who have TB infection

Burzynski outlined several additional factors that were crucial in quelling New York City's TB epidemic. All patients receive close case management and directly observed therapy, with an individualized treatment regimen based on drug susceptibility testing<sup>44</sup> for cases and contacts. The Bureau of TB Control is also tasked with improving infection control in congregate settings and providing physician expertise to community-based health care providers. Regular cohort review is an important means of maintaining accountability for case management and moving away from the mindset of blaming the "negligent patient" for defaulting from treatment.<sup>45</sup>

### 2.3.3 Challenges and benefits of contact investigations

Burzynski explored some of the major challenges associated with contact investigations, the first of which is its dependence upon TB patients' willingness to share information with authorities such as government workers (this can be a particular problem among the immigrant community). Determining the extent of a given contact's exposure to the MDR-TB source case can also be difficult, because household contacts are not always the most exposed and exposure beyond the venues of household, workplace or school can be difficult to establish due to the complexity of social networks.

However, Burzynski stressed that, despite their attendant challenges, evidence shows that contact investigations are worth the effort. He cited a 2012 study<sup>46</sup> that supports the use of contact investigations to facilitate TB case finding and the identification of individuals at high risk of progression to disease. Further, the study suggests that treatment of TB infection, even if adherence is incomplete, prevents patients from developing TB disease.

He suggested that individuals exposed to someone with infectious TB may benefit from treatment for TB infection, including those exposed to MDR-TB cases. A recent observational study of 50 MDR-TB contacts who received a moxifloxacin-based regimen as infection treatment demonstrated that the regimen was generally well tolerated and that after nine years of follow-up, no other TB cases with the outbreak strains had occurred among the contacts.<sup>47</sup>

### 2.3.4 Challenges of treating TB infection

Burzynski explained that the barriers to delivering infection treatment for drug-susceptible TB and drug-resistant TB are largely similar in important ways. Deciding which individuals to treat requires identifying the contacts of people sick with TB, assessing their relative extents of

<sup>44</sup> Drug-susceptibility testing is mandatory for all culture-positive cases.

<sup>45</sup> Physicians are required to report on their patients' treatment plans at regular intervals. Each TB case has an assigned case manager, who must present their case management, recording, and contact investigations for review by the director of the TB program every 3-4 months; each manager is accountable for contacts who are not evaluated and/or treated.

<sup>46</sup> Anger et al. *Clin Infect Dis* 2012

<sup>47</sup> Trieu et al. *Emerg Infect Dis* 2015

exposure, and determining prior TB infection status and/or other comorbidities. The challenge of convincing patients and physicians to commit to treatment of TB infection applies for both drug-susceptible TB and drug-resistant TB, as do questions of how best to monitor infection treatment (due to large loss to follow-up) and how to lower the risk of re-infection.

Less analogous, noted Burzynski, are issues concerning the best infection treatment regimen to use, how long to treat, and access to medication. While regimen choice for treating infection for both drug-susceptible TB and drug-resistant TB can be challenging when the susceptibility of the infecting strain is unknown, decisions about treating presumed drug-resistant TB infection are constrained by access to timely and accurate drug-susceptibility test results. High cost and lack of consistent supply are further barriers to access and provision of medications for treating drug-resistant TB infection. Major challenges linked to treating drug-resistant TB infection (but not drug-susceptible TB infection) revolve around the lack of evidence for treatment efficacy and potential drug toxicity. To conclude, Burzynski reiterated the value of contact investigations for finding cases of TB disease among those screened, as well as finding and treating those individuals with TB infection who are at the highest risk of developing TB disease.

### **2.3.5 Key discussion points**

Palmero sought clarification regarding the age of contacts being treated by the Bureau of TB Control. Burzynski explained that all contacts of MDR-TB patients are evaluated regardless of age, and that the Bureau of TB Control treats MDR-TB infection with fluoroquinolones (when available) in all contacts who accept this treatment.

Khan wondered why it is the case, given that compelling evidence from program settings such as the New York City Bureau of TB Control

regarding contact investigations and standards of care have been available for years, that policy recommendations have been so slow to follow (e.g., 2012 guidance from the WHO). Burzynski observed that the WHO has only recently focused upon the impact of contact investigations in prevention and stated it directly in its policies. The emphasis has traditionally been on case finding and treatment, with contact investigations receiving less attention.

Jennifer Furin<sup>48</sup> remarked that policy is often based not upon evidence, even when it is available, but instead upon costs and perceptions about implementation. For new drugs recently approved for the treatment of TB, the evidence demonstrating the utility of adding those drugs onto MDR-TB therapy was clearly reviewed, yet global policy recommendations are not to add them into regimens but to substitute them (subject to expert opinion).

Becerra stressed that trials are not the only evidence that should be considered; data from carefully controlled prospective observational cohorts provide a wealth of valuable information that should be considered. Starke concurred, urging the group to act now on the basis of observational evidence while incorporating early lessons from more rigorously designed randomized controlled trials.

<sup>48</sup> Jennifer Furin, Harvard Medical School, Boston, MA, U.S.



## BOX 2-1 APPLICATION OF TOOLS IN DIVERGENT SETTINGS: CONSIDERING THE “SIGNAL TO NOISE RATIO”

Throughout the proceedings, participants raised a key point regarding the universality of specific tools in differing epidemiological, economic, and demographic settings.

The phrase “signal to noise ratio” was used throughout to indicate the epidemiological reality— the statistical and therefore programmatic complexity of working in a high-burden setting, vs. a low burden one. Within this, a program manager, clinician, or epidemiologist must consider common co-infections, questions of acquired vs. primary resistance, and demographic particularities (e.g., migrant worker driven) of the TB situation in a given setting. This complexity led some participants to question at times whether models implemented successfully in the U.S. and Europe are applicable to higher burden, more resource limited settings.

Despite the well-founded sentiment of this skepticism, the organizers throughout urged participants to consider how all tools might be used in concert where appropriate, absent resource constraints or the seemingly insurmountably complex challenge present in high-burden settings. They argued that only after this intellectual exercise was conducted would the group be able to systematically lay out the ideal package of comprehensive TB prevention and treatment for their site, uninhibited by “path dependence,” or the urge to choose from previously available programmatic tools, rather than those that are actually the most effective. As a result of this exercise, some tools may be prioritized and others, though effective, may only be implemented when efficient and appropriate.

### An example of a tool on the edge: Associate investigations

Jeffrey Starke of Baylor College of Medicine described the benefits of a form of targeted testing called associate investigation, or “reverse contact tracing”: identifying and evaluating close contacts of children and adolescents with TB infection or disease, aimed at working backwards from index case to original source case. While the yield of finding cases of TB disease may be low, especially among mobile populations such as recent immigrants, the yield of finding TB infection is 30% to 40% in the U.S. He stressed that this is effective only if the index child was tested due to risk. This sort of approach would be of limited help to those in high-burden settings, but should be included in the “toolbox” of a TB program as they proceed to near-elimination levels.

**Table 4. Associate investigations for children with TB infection**

Location	Year	No. of associates	Positive TST n (%)	TB cases
San Francisco	1986	831	330 (40)	3
New York City	1993-1995	659	210 (32)	0
New York City	1996-1998	668	198 (30)	3
San Diego	2001-2002	713	292 (41)	0
Ft. Worth	1990-2001	87	31 (35)	2

**Abbreviation:** TST, tuberculin skin test

Source: Table adapted from Starke presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

## 2.4 THE MANAGEMENT OF MDR-TB CONTACTS IN THE UNITED KINGDOM AND EUROPE<sup>49</sup>



Seddon presented the results of investigations into current practices for managing MDR-TB contacts in the United Kingdom and throughout Europe.

### 2.4.1 Management of pediatric contacts of MDR-TB in the United Kingdom

Clinicians in the U.K., according to Seddon, are currently treating relatively few child contacts of MDR-TB cases. He cited a 2013 study<sup>50</sup> that performed a retrospective audit of a four-year period between 2006-2010, querying UK pediatricians as to whether they had managed any cases of pediatric MDR-TB and about their management of child contacts of MDR-TB cases. Of the 23 children identified, eight were uninfected and untreated, and eight of the 12 infected children identified were given a two-drug infection treatment regimen for six months (all 12 were well at two-year follow-up).<sup>51</sup>

### 2.4.2 Perspective of Public Health England

Public Health England conducted a retrospective study (January 2011 – December 2014) in which clinicians who had managed an MDR-TB case were asked about their management of child contacts. Of the 232 (77%) who responded, 96 (41%) indicated that they had identified child contacts. Those who provided further details about the child contacts revealed that 158 (91%) children were screened for TB disease, 156 (90%) were screened for infection, and 34 (22%) were infected.<sup>52</sup>

Seddon noted that 37 respondent clinicians did not give any infection treatment to the child contacts, while 12 clinicians reported providing infection treatment to child contacts with a general follow-up period of two years.<sup>53</sup>

<sup>49</sup> This section is based on the presentation by James Seddon, Clinical Lecturer, Imperial College London, U.K.

<sup>50</sup> Williams et al. *Pediatr Infect Dis J* 2013

<sup>51</sup> Children were less likely to receive infection treatment if the source case was resistant to several drugs

<sup>52</sup> IGRA, tuberculin skin testing, and a combination were used.

<sup>53</sup> Six gave 3RH; six gave a combination of isoniazid, rifampicin, pyrazinamide, ethambutol, ofloxacin, levofloxacin, and moxifloxacin.

### 2.4.3 Survey of MDR-TB treatment practice in Europe

Seddon reported that there are an estimated 74,000 adults in Europe (according to the WHO's geographical definition) with pulmonary MDR-TB, which means that close to 150,000 children may be exposed to MDR-TB each year.

To investigate how MDR-TB child contacts are managed in Europe, an email survey was sent out to clinicians who might be managing MDR-TB contacts: there were 72 respondents from 25 European countries (28 from Eastern Europe and 44 from Western Europe).

Their responses exhibited variability on virtually all levels, which can be taken to represent the wide spectrum of current practices in Europe and to reflect the consequences of having a poor evidence base and inconsistent guidance about treating MDR-TB contacts. The results indicate that in Europe, the following specific practices are highly variable:

- Means of screening for children: chest radiograph, IGRA, tuberculin skin testing, or nothing at all were reported.
- Making decisions about which children should receive infection treatment: reported factors include age and immunosuppression status; 30 respondents indicated that no children received infection treatment.
- Drugs and regimens used for treating MDR-TB infection: responses included single drug, multidrug, standardised, tailored, first-line drugs, and second-line drugs
- Duration, investigations, and schedule for follow up

### 2.4.4 Key discussion points

Cassell pointed out a knowledge gap with respect to why a small proportion of people infected with TB go on to develop TB disease: assuming that one-third of the world's population is infected with TB, an estimated 10% will develop disease.

She suggested a strategy of following people who are infected to find out more about the factors that may contribute to the likelihood of progression. Keshavjee and Schaaf noted that there are specific groups already known to have high risk for progression (e.g., children, people recently infected, immunosuppressed persons, people with silica exposure or COPD); they held that these existing categories can guide immediate decisions about prioritizing infection treatment. Yuen highlighted the need for more risk-benefit analyses to address current needs, as much of the progression-to-disease data originates from studies carried out in specific populations in the pre-chemotherapy era, when risk groups and risk factors were likely different than they are today.

Schaaf noted that in his experience, many policy makers are only interested in data from peer-reviewed publications; he urged participants to publish their data to build a strong body of collective evidence for the use of infection treatment in MDR-TB contacts. Keshavjee remarked upon the wealth of observational data drawn from 25 years of treating MDR-TB disease, suggesting that decision-makers may be missing an important opportunity to improve TB outcomes sooner than later by placing a higher premium on data from randomized controlled clinical trials than observational data. Starke agreed, arguing that it is not possible to conduct large-scale randomized controlled trials on MDR-TB infection treatment for a host of reasons (lack of funding, patients, sites, and so on) and that waiting for an ideal amount of "perfect" evidence is not a justifiable reason for inaction: he stressed that anything with any benefit and little harm is worth doing.

**Table 5. Survey results: provision of infection treatment for MDR-TB child contacts in Europe**

Respondent Characteristics		Given	Not given	Odds ratio (95% CI)	p-value	Adjusted OR* (95% CI)	p-value
Experience treating TB patients (years)	<10	13	10	Ref	0.83		
	>10	29	20	1.12 (0.41-3.06)			
Specialist TB doctor	No	28	13	Ref	0.05	Ref	0.51
	Yes	14	17	0.38 (0.14-1.04)		0.69 (0.23-2.09)	
Consultant-level doctor	No	6	7	Ref	0.33		
	Yes	36	23	1.83 (0.54-6.22)			
Number of MDR-TB child contacts per year	<3	19	12	Ref	0.66		
	≥3	23	18	0.81 (0.31-2.10)			
Country of respondent	Eastern Europe	10	18	Ref	0.002	Ref	0.014
	Western Europe	32	12	4.80 (1.59-14.5)		4.07 (1.33-12.5)	

Source: Table adapted from Seddon presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

## 2.5 MDR-TB ELIMINATION IN CHUUK: A CASE FOR TREATING MDR-TB INFECTION<sup>54</sup>



Photo Credit: Richard Brostrom

Sapna Bamrah Morris, Richard Brostrom, and Dorina Fred presented their experiences in mitigating an outbreak of MDR-TB in Chuuk State, Federated States of Micronesia, as a case study demonstrating the efficacy of providing treatment for MDR infection.

### 2.5.1 Epidemiology and background on the MDR TB outbreaks in Chuuk Island

Chuuk State is one of the Federated States of Micronesia (FSM), which are located west of the Marshall Islands. The Marshall Islands have the second highest rate of TB in the world. In 2007, four cases of MDR-TB were reported to the U.S. CDC and to WHO: one patient with TB disease as a result of an MTB strain that was resistant to isoniazid, rifampicin, and ethionamide (3-drug-resistant Manila strain) and three patients with TB disease as a result of an MTB strain resistant to isoniazid, rifampicin,

pyrazinamide, ethambutol, and streptomycin (5-drug-resistant Beijing strain). The four patients were sent home with standard TB disease treatment, as second-line medications were not available in FSM at this time.<sup>55</sup> The understaffed TB program in Chuuk, lacking MDR-TB treatment experience and hampered by fragile infrastructure and limited resources (e.g., power, water, and roads), faced a one-year delay in the acquisition of medications to treat cases of MDR-TB disease.

By 2014, the MDR-TB outbreak<sup>56</sup> in Chuuk comprised 24 cases of the 5-drug-resistant strain and 17 of the 3-drug-resistant strain; 17 (41%) of those were pediatric patients aged <15 years.

A summary of the respective treatment regimens the Chuuk TB program used to treat patients sick with the 3-drug-resistant and 5-drug-resistant strains is provided in Table 6.

<sup>54</sup> This section is based on the presentation by Sapna Bamrah Morris (Medical Officer, Division of TB Elimination, U.S. CDC, Atlanta, GA, U.S.), Richard Brostrom (Chief, Hawaii TB Control Branch, U.S. CDC, Honolulu, HI, U.S.), and Dorina Fred (Medical Officer, Chuuk TB Program, Chuuk TB Program, Medical Officer, Weno, Chuuk, Federated States of Micronesia).

<sup>55</sup> Four of the first five known cases died within an eight-month period.

<sup>56</sup> Factors such as crowded living conditions in Chuuk involving large, multi-generational families contributed to the spread of MDR-TB.



**Table 6. MDR-TB treatment regimens used in Chuuk outbreak**

Medication <sup>a</sup>	3-Rx Res (I,R,ETH)		5-Rx Res (I,R,P,E,S)		Months
	Peds	Adults	Peds	Adults	
amikacin/capreomycin	✓	✓	✓	✓	6-9
ethambutol	✓	✓			18-24
pyrazinamide	✓	✓			18-24
levofloxacin	✓		✓		18-24
moxifloxacin		✓		✓	18-24
ethionamide/prothionamide			✓	✓	18-24
para-aminosalicylic acid	✓	✓	✓	✓	6-12
cycloserine	✓	✓	✓	✓	18-24

<sup>a</sup> All patients received vitamin B6.

**Abbreviations:** Peds, pediatric cases; I, isoniazid; R, rifampicin; ETH, ethionamide; P, pyrazinamide; E, ethambutol; S, streptomycin

Source: Bamrah Morris, Brostrom, and Fred presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

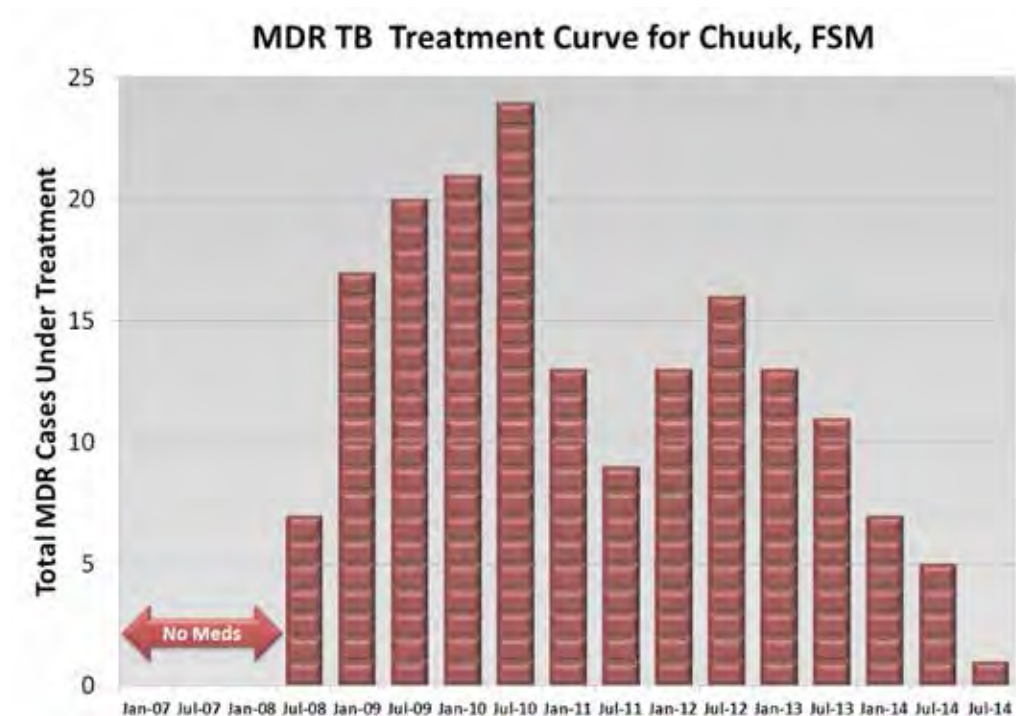
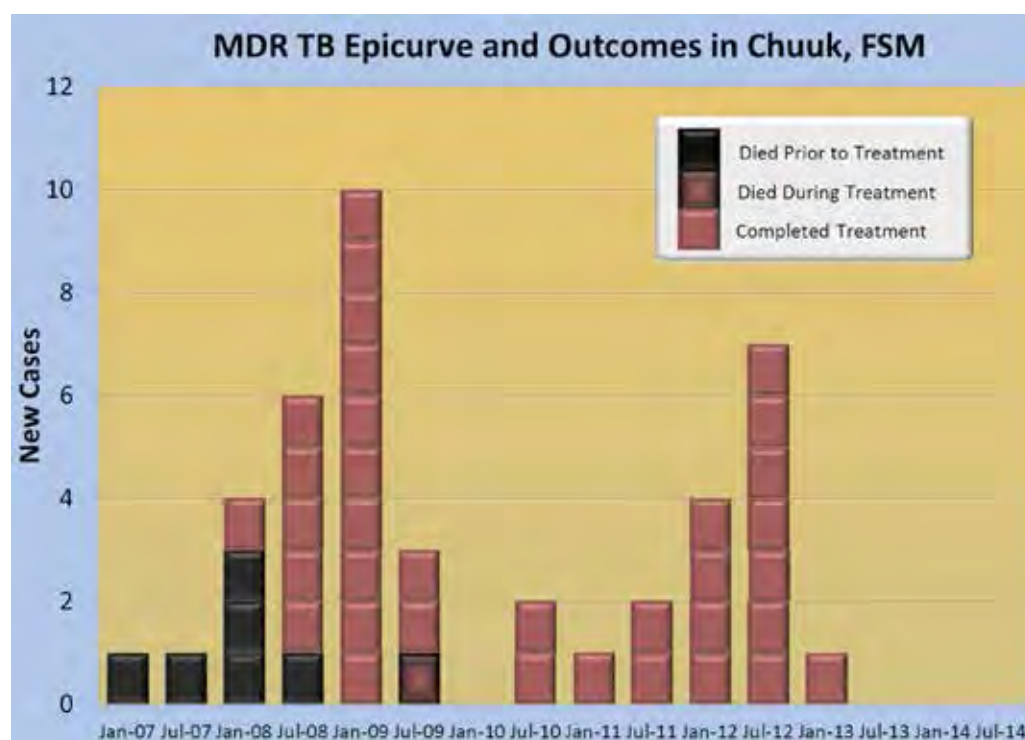
By January 2009, five people had died from MDR-TB, 15 were being treated for MDR-TB disease, and 21 more had yet to be diagnosed. As of February 2015, 34 of the 35 eligible<sup>57</sup> patients successfully completed MDR-TB disease treatment (97%) and none had relapsed.<sup>58</sup> No new MDR-TB cases had been diagnosed in the preceding two years.

The MDR-TB epi curve, outcomes and treatment outcomes in Chuuk between January 2007 and July 2014 are represented in Figure 13.

<sup>57</sup> Excluding cases who were untreated and died prior to arrival of second-line drugs and cases who were still on MDR-TB treatment.

<sup>58</sup> However, the presenters reported that in April 2015 a previously unidentified contact of the source case has been found to be sick with the same strain of 5-drug-resistant TB.

Figure 13. MDR-TB epi curve, outcome, and treatment curves in Chuuk



Source: Bamrah Morris, Brostrom, and Fred presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

### 2.5.2 Review of the management plan for treating MDR-TB infection in Chuuk

In response to the MDR-TB outbreaks on Weno Island in Chuuk, a contact investigation was initiated in July 2008 in which 232 household contacts were identified and evaluated. Household contacts were defined as individuals who had a meal or had spent a 24-hour period in the house of someone with MDR-TB disease. Tuberculin skin testing was used to determine evidence of infection.<sup>59</sup>

Bamrah Morris outlined the key objectives framing the plan to follow a cohort of contacts receiving treatment for MDR-TB infection. These objectives were: to determine feasibility of implementing this infection treatment and follow-up in a resource-limited setting; to study the tolerability of these infection treatment regimens; and (potentially) to study the efficacy of the MDR-TB infection treatment regimens by evaluating treatment outcomes and following the individuals treated for 36 months after exposure.

The plan for managing contacts exposed to MDR-TB in Chuuk included:

- Treatment for MDR-TB infection with directly observed therapy for one year
- Fluoroquinolone-based regimens (children received a fluoroquinolone and either ethambutol or ethionamide)
- Monthly questionnaires completed by field workers for symptom screening, number of missed doses, and referrals to public health clinic
- Quarterly visits by healthcare provider
- Biannual chest radiograph and clinical evaluation
- Contacts to be followed for two years after completion of the MDR-TB infection treatment regimen, or three years after exposure and initiation of the MDR-TB infection treatment regimen

Bamrah Morris highlighted several key principles that should be considered when the decision is made to treat TB infection in contacts of MDR-TB cases, emphasizing that the efficacy of infection treatment is largely contingent upon adherence to and completion of the infection treatment regimen. To reduce the risk of developing XDR-TB disease, it is critical to exclude TB disease before beginning a regimen to treat infection. Before deciding to treat infection, the likelihood of infection with an MDR-TB strain—and risk of progression to MDR-TB disease—needs to be assessed. Finally, the regimen for treating infection should be based on the drug-susceptibility test results of the strain of the source case.

### 2.5.3 Effect of significant procurement delays

The planned program encountered delays for initiating infection treatment attributable to several factors, both anticipated and unanticipated: hiring and training workers to provide directly observed therapy, obtaining vehicles, and delays in drug procurement.<sup>60</sup>

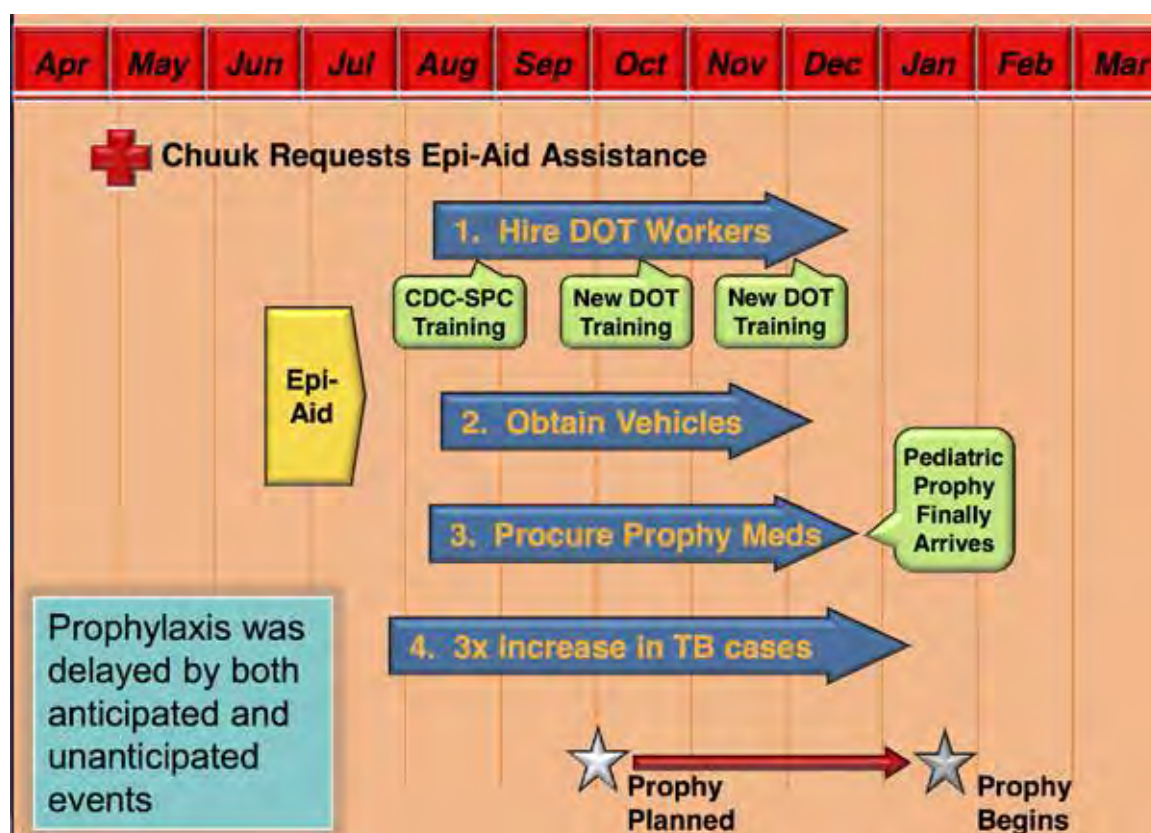
The delay in drug procurement was a significant barrier (Figure 14).

<sup>59</sup> During the ensuing discussion among participants, Bamrah Morris clarified that 90% of those treated for TB infection had positive tuberculin skin test results; the rest were pediatric contacts. There were no cases of TB disease among the contacts with negative tuberculin skin tests.

<sup>60</sup> Pediatric drugs for treating TB infection were ultimately procured privately because the cost of obtaining them from the United States was prohibitive, and they were not able to be obtained from the Global Drug Facility.



**Figure 14. Delays for initiating treatment for TB infection**



Source: Bamrah Morris, Brostrom, and Fred presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

During the window of almost nine months between the initial request from assistance from CDC's Epi-Aid and the initiation of infection treatment in the children, there was a three-fold increase in TB cases. During the first six months, one out of every seven (5/34) pediatric household contacts (aged  $\leq 15$  years) awaiting treatment for MDR-TB infection developed MDR-TB disease.

#### 2.5.4 Results of MDR-TB infection treatment in household contacts in Chuuk

Of the 105 MDR-TB contacts who initiated treatment for infection (43 of whom were aged  $< 18$  years), 93 (89%) completed the treatment—including 25/26 (96%) of pediatric cases  $< 12$  years of age.<sup>61</sup> Fifty-two patients reported adverse events but nonetheless completed treatment.<sup>62</sup>

Bamrah Morris reported that none of the contacts treated for MDR-TB infection had developed TB disease at 36 months after treatment initiation.<sup>63</sup> While this outcome contributes meaningfully to the mounting body of observational evidence about the efficacy of treating MDR-TB infection, she cautioned that treatment effectiveness remains difficult to demonstrate with the low number of contacts in the Chuuk cohort, and without randomized controlled trials to show efficacy.

She stressed that there are further important outcomes to be gleaned from the experience in Chuuk. A high percentage of those treated were adherent to and completed infection treatment; regimens were safe and tolerable. From an operational perspective, the Chuuk program shows that it is in fact possible to deliver treatment for MDR-TB infection via directly observed therapy.<sup>64</sup>

<sup>61</sup> 12 patients discontinued due to pregnancy, adverse events, and loss to follow up.

<sup>62</sup> Most common adverse events were nausea ( $n=112$ ; 44%) and headache/dizziness ( $n=112$ ; 44%). Tendon/joint pain—a common concern with fluoroquinolone treatment—was less common in this cohort, reported by 21 patients (4%).

<sup>63</sup> Two contacts who refused infection treatment did develop MDR-TB disease.

<sup>64</sup> Mase et al. *Am J Respir Crit Care Med* 2012

### 2.5.5 Operational challenges and keys to success

The presenters examined some of the operational challenges and keys to success experienced during the Chuuk program's delivery. Firstly, the Chuuk government responded proactively to the epidemic by declaring a public health disaster, setting up an MDR-TB task force, and recruiting and educating community leaders. This facilitated overcoming structural barriers to program initiation such as staffing required to provide directly observed therapy and capacity limitations. The operational strategy was to design a best-practices model (rather than a randomized controlled trial), which was informed by Chuuk's unwillingness to take part in an "experimental" infection treatment program.

From a financing perspective, the presenters explained that the costs for the program component to treat MDR-TB infection were not calculated separately from the overall MDR-TB treatment program, so the marginal increase of adding the infection treatment component into the existing MDR-TB program was modest.<sup>65</sup> For example, the program used existing directly-observed-therapy infrastructure and local clinical staff were trained to deliver infection treatment.

A positive consequence of the program in Chuuk was capacity development across the Pacific region, such as improved technology (e.g., lab, chest radiograph, and molecular diagnostics) and the development of a multi-agency regional MDR-TB support network. Because none of the islands in the region could individually afford to keep MDR-TB drugs in stock, they used Global Fund support to develop a Pacific stockpile of second-line drugs (for treating MDR-TB disease, not as yet for treating MDR-TB infection). Subsequently, an emergency two-month supply of MDR-TB drugs was available with no delay for an outbreak in Guam.

### 2.5.6 Key discussion points

Given Chuuk's island locale, Master raised the issue of how universally some of the factors contributing to the success of its MDR-TB

program would map onto programs situated in other types of geographical settings, particularly those with highly mobile populations.

With regard to the longer-term impact of health systems' strengthening, Khan questioned whether the system would be vulnerable to failing again when the U.S. CDC program is gone. Noting that MDR-TB can be a sentinel for a broken or inadequate healthcare system, Brostrom responded that they made concerted efforts throughout the intervention to rebuild a sustainable healthcare system. In that vein, he recounted how officials in Chuuk's national program have remarked that the response to the MDR-TB outbreak was a significant boon to Chuuk Hospital. Bamrah Morris continued by underscoring the substantial and far-reaching difference that just a few people working on the TB program made in the community at large.<sup>66</sup> Once the community saw the success and helpfulness of the TB program, their enthusiasm dominoed to other areas of care.

David Moore<sup>67</sup> raised the possibility that, due to the procurement delays, the TB cases being prevented may actually have been exposed to secondary cases rather than index cases. Bamrah Morris conceded that this could be true, but that it was impossible to confirm because the initial cases were deceased.

Even though none of the contacts who received TB infection treatment developed TB disease, 15% of the patients do not have defined outcomes; Moore questioned whether they may have died, or left the island and developed TB disease. Bamrah Morris replied that the latter possibility is more likely, but because the U.S. CDC genotypes every TB case, that agency would have recognized the same strain elsewhere.

Several participants proposed that a program of MDR-TB prevention should not be an add-on to an existing overstretched treatment program, but rather a stand-alone operation, supported by sufficient staffing and funding, and perhaps community-based.<sup>68</sup>

<sup>65</sup> The U.S. Department of the Interior provided more than USD 2M, the majority of which went toward MDR-TB disease treatment (e.g., second-line drugs, facilities, vehicles, and staff for directly observed therapy) rather than for the treatment of MDR-TB infection

<sup>66</sup> For instance, she referred to provision of basic education about germ theory to the index patient's family, who believed TB to be a supernatural act of the devil to punish the patient for wrongdoing.

<sup>67</sup> David Moore, London School of Hygiene and Tropical Hygiene, London, U.K.

<sup>68</sup> Yuen cautioned that many clinicians are overburdened and may lack the expertise to build such community-based programs. Other experts, such as those in public health, should be consulted to guide the design process when possible.

Participants also discussed challenges related to second-line drug procurement. At the time of the Global Consultation there was a policy (now under review) that the National TB Program should supply a letter of approval for private healthcare entities to receive quality assured second-line drugs through the Global Drug Facility mechanism. Keshavjee noted that the paperwork requirements for private hospitals and clinics to secure drugs through the Global

Drug Facility mechanism posed a significant barrier feeding into procurement delays in several countries. Satti held that in her program setting in Lesotho, the National TB Program was able to supply this paperwork to private entities without significant difficulty. It was agreed that it is not always the case that this paperwork is forthcoming in a timely manner from national TB programs to private entities.

## **BOX 2-2 POST-EXPOSURE PROTOCOL FOR MDR-TB: A HOW-TO GUIDE FOR MANAGING HOUSEHOLD CONTACTS**

Jennifer Furin provided a progress report on the development of the forthcoming manual *Post-Exposure Protocol for MDR-TB: A How-To Guide for Managing Household Contacts*, which is forthcoming in 2015 from the Sentinel Project on Pediatric Drug-Resistant Tuberculosis. The rationale for this “how-to” manual is multifaceted. It was planned to fulfill the unmet need for practical, explicit guidance about how to manage household contacts of patients with drug-resistant TB (much of it could also apply to households of patients with drug-susceptible TB). All existing guidelines mention the necessity of urgent contact evaluations for households where someone has been diagnosed with drug-resistant TB, but in practice “contact tracing” is often considered an extra activity and is thus not prioritized.

The manual focuses on providing a step-by-step approach to interventions for persons who have been exposed to drug-resistant TB in the household setting. It draws upon models of successful post-exposure protocol interventions for other infectious diseases (e.g., HIV and rabies).

Overview of content for the *Post-Exposure Protocol*:

- Part I: General overview; for ease of reading, supporting evidence is provided in an annex
- Part II: How to implement the intervention in household settings
  - Identify and screen all household members of a person diagnosed with drug-resistant TB disease
  - Evaluate and refer all symptomatic contacts to determine who requires treatment for TB disease
  - Offer preventive interventions to those without TB disease, including infection treatment, ongoing monitoring, and other support
- Part III: Programmatic considerations

Structurally, it contains a range of practical components. Protocol items serve as the main point of the intervention, and action items elaborate specific activities such as how to define households, symptom screening, and frequency of evaluations. “Making it count” tips include such advice as basic recording and reporting tips. The manual also provides implementation tools (e.g., algorithms and forms) and it differentiates between ideal and essential components of interventions.

## 2.6 COMMUNITY-BASED MANAGEMENT OF PERSONS EXPOSED TO DRUG-RESISTANT TB IN THE HOUSEHOLD: KHAYELITSHA COMMUNITY PROJECT<sup>69</sup>



### 2.6.1 Context in Khayelitsha

Jennifer Furin reported on the program for community-based management of household contacts exposed to drug-resistant TB in Khayelitsha, South Africa.<sup>70</sup> Khayelitsha is a township in the Cape Flats region of Cape Town with an estimated population of about 500,000, many of whom are migrants. It is a setting with high burdens of both MDR-TB and HIV, with more than 200 MDR-TB patients per year.

Khayelitsha's context poses a set of challenges with regard to the provision of preventive services for drug-resistant TB. Treatment outcomes for drug-resistant TB are poor, with a 45% success rate and 40% loss to follow-up. Maintaining follow-up in general is difficult, with respect to both patients treated at clinics and household contacts. Outreach staffing is difficult and has a high turnover rate. Much of the community is highly mobile, with many living in informal housing.

Furin described how older children (between 5 and 14 years of age) are at particular risk in the community, and there are few targeted interventions for this population. She posited that the high risk of progression to TB disease in children under 5 years of age contributes to a lack of intervention for children over the age of 5 years. Elsewhere, children over 5 years of age who live with drug-resistant TB patients have also been shown to have high risk of TB disease.<sup>71</sup> She emphasized the urgent need to address high-risk children aged 5-10 years who have smear-positive TB but are HIV negative.

### 2.6.2 Overview of community-based outreach to households

Furin provided an overview of the community-based management program for drug-resistant TB household contacts in Khayelitsha. The first step is to identify an individual diagnosed with drug-resistant TB, followed by obtaining permission to visit the person's household. She noted that multiple visits to the household may be required to assess all exposed contacts.

<sup>69</sup> This section is based on the presentation by Jennifer Furin, Lecturer, Harvard Medical School, Boston, MA, U.S.

<sup>70</sup> Run by Médecins Sans Frontières (MSF)-Khayelitsha in partnership with BCH/Tygerberg Children's Hospital and the NDoH, Provincial Health Services, City of Cape Town

<sup>71</sup> Amanullah et al. *Int J Tuberc Lung Dis* 2014

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The comprehensive household assessment is multi-faceted, including:

- HIV testing and counseling
- Conducting detailed exposure risk profiles, symptom screenings, and basic exams
- Facilitating evaluation for symptomatic contacts
- Devising follow-up plans with symptomatic contacts
- Providing ongoing assessments of household members for 12-24 months, both for follow-up and for “newly identified” contacts

The program also focuses on special interventions for adolescents, who have a high mortality risk in the population.

Several key issues related to this program have yet to be resolved. The ideal timing and frequency of household visits needs to be determined, as does the optimal use of infection treatment. The program is also seeking to maximize the role of community nurses in a decentralized setting, as well as integrating and coordinating with planned trials.



## 2.7 DRUG-RESISTANT TB CONTACT MANAGEMENT: EARLY PLANS FROM KARACHI<sup>72</sup>



Farhana Amanullah and Hamidah Hussain described early-stage plans for a program to treat household contacts of drug-resistant TB patients in Karachi, Pakistan. The Indus Hospital in Karachi is the largest private-sector childhood TB reporting center, housing a TB program that has enrolled and treated more than 14,000 drug-susceptible TB patients and more than 2,400 drug-resistant TB patients to date. The results of this planned community-based program of contact evaluation and management within drug-resistant TB households will ultimately inform Pakistan's national TB program.

The program is committed to the principles that prompt evaluation, monitoring, and infection treatment for household members of drug-resistant TB patients is not only possible, but necessary to avert preventable cases of the disease and thus preventable deaths. Given that household contacts of drug-resistant TB patients have a high risk of infection and recent infection is a risk factor for progression to disease, they noted that the risk is higher for children and the immunocompromised, who tend to develop TB

disease faster and are more likely to develop fatal forms of the disease.

### 2.7.1 The Indus Hospital TB program: Plans for treating TB disease and TB infection among child contacts

Between January 2008 and January 2013, 192 child contacts of drug-resistant TB patients were screened and evaluated, revealing that 9% of those children had TB disease (40% of whom had culture-confirmed drug-resistant TB).

Amanullah and Hussain outlined a study to be carried out during 2015-2016 among drug-resistant TB household contacts in the Karachi slums of Korangi and Landhi. Patients from those two areas make up 22% of the overall drug-resistant TB cohort, with around 150 new patients enrolled each year and a treatment success rate of 76%. They noted that female patients between the ages of 15 and 24 years represent the largest proportion of this cohort (Figure 15).

The planned protocol is to screen children aged <5 years for TB disease, and for those 5 years of

<sup>72</sup> This section is based on the presentation by Farhana Amanullah, Pediatric TB Consultant, Indus Hospital, Karachi, Pakistan, and Hamidah Hussain, Director for TB Technical Assistance, IRD, Karachi, Pakistan.



age and older to test for infection using tuberculin skin tests. Skin-test positive contacts, as well as any person with more than one suggestive symptom, will be further evaluated to rule out TB disease.

Trained workers will then perform household contact investigations (ideally home-based) around consecutively diagnosed drug-resistant TB patients until 100 households have been identified. Contacts will be screened for symptoms and have height/weight measured, and those aged  $\geq 5$  years will receive tuberculin skin testing.<sup>73</sup>

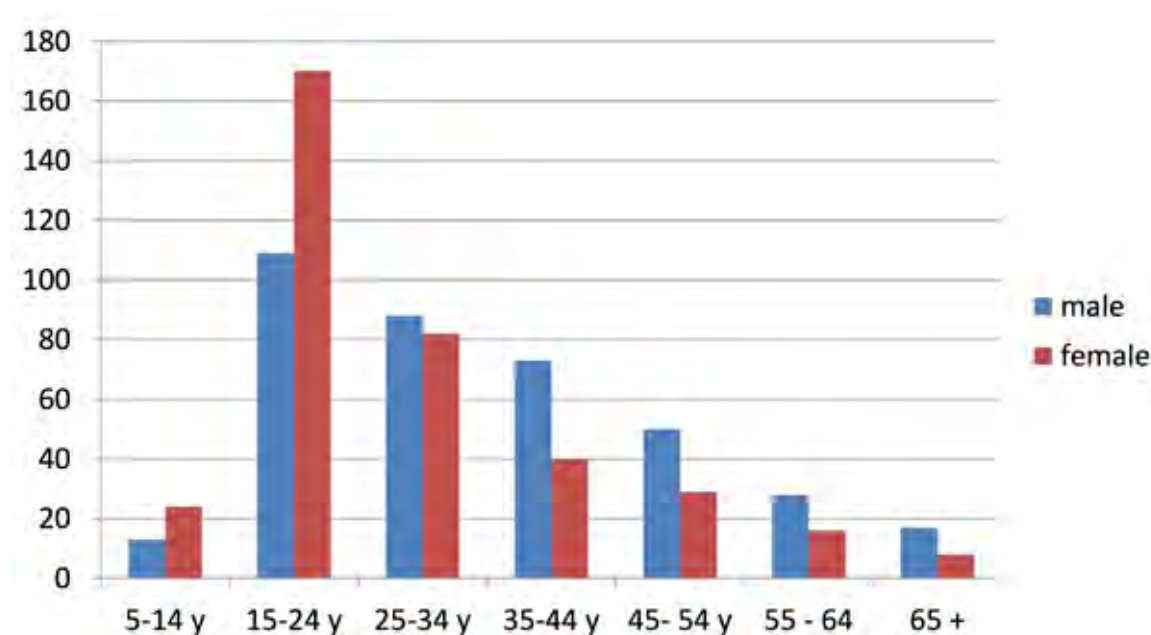
The plan includes the provision of treatment for presumed drug-resistant TB infection for all children aged  $<5$  years, as well as all individuals who have evidence of TB infection, and/or those who are immunocompromised due to being malnourished, HIV-positive, or having diabetes. Infection treatment is planned to last

for six months, with field workers responsible for directly observed therapy and monthly questionnaires, and physician evaluations every two months.

Drug-susceptibility testing reveals that patients in the Indus Hospital program have high rates of resistance to fluoroquinolones (ofloxacin resistance in nearly 60%).<sup>74</sup> This will inform regimen design, which will be individualized to the index patients' respective drug-susceptibility patterns. The regimen will likely include 2-3 drugs to which the index patient strain is sensitive.

The presenters flagged several potential challenges to screening and treatment delivery that may impact the planned program. Poor treatment adherence and completion rates are a concern, as are poor follow-up rates, the risk of adverse events arising from infection treatment, and the risk of potential re-infection.

**Figure 15. Age and gender distribution of drug-resistant TB patients at the Indus Hospital TB Program**



Source: Amanullah and Hussain presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

<sup>73</sup> Contacts will be referred to physicians if they: are  $<5$  years of age; are immunocompromised; have a positive result on the tuberculin skin test; or have one or more suggestive symptoms.

<sup>74</sup> During the ensuing discussion, Amanullah clarified that this percentage applied to the group tested for resistance to any second-line drug; changing the denominator to be all MDR-TB patients generates a rate that is slightly less than 30% resistant to fluoroquinolones and 10% resistant for ethionamide.

## 2.8 HOUSEHOLDS EXPOSED TO DRUG-RESISTANT TB: NOTES FROM THE FIELD IN FREE STATE, SOUTH AFRICA<sup>75</sup>



Limpho Ramangoaela reported on the experience working with households exposed to drug-resistant TB in a program housed in the Dr. J.S. Moroka Hospital Drug-Resistant TB Unit, Free State, South Africa. The program aims to support households exposed to drug-resistant TB by providing support to the index patient, screening and educating household contacts about TB and drug-resistant TB, and empowering patients to be able to take charge of their treatment with the view to improving treatment adherence and preventing loss to follow up.

A central concern highlighted by Ramangoaela is the struggle of drug-resistant TB patients on two fronts: dealing with the treatment itself, and dealing with families who reject the patients because they do not understand what drug-resistant TB treatment entails. Many patients have had to default or interrupt treatment due to lack of family support. This encompasses the emotional, financial, and physical domains; it is further compounded by the fact that many patients are the family breadwinners. Fear— and lack of education about drug-resistant TB and infection control practices— all contribute to the spread of drug-resistant TB within households.

Patients are often diagnosed and followed up primarily in clinics and there are resource limitations at programmatic level, which have led to the discontinuation of key components such as directly observed therapy, contact tracing, injection teams, and community health care worker groups.

### 2.8.1 Screening of household contacts

There has been a steady increase in the rates of drug-resistant TB transmission to contacts of index patients, which has underscored the need to intensify screening efforts<sup>76</sup> in households. The general aim is to incorporate regular screening of contacts into patient support visits in the home with the view to improving adherence to infection control practices and providing infection treatment to those who require it.

South Africa currently lacks an adequate system to deliver directly observed therapy. Ramangoaela explained that the goal is to restructure the hierarchy of drug-resistant TB management by transferring the responsibility for drug-resistant TB treatment from the clinics to patients and their families<sup>77</sup> (as has been successfully implemented with anti-retroviral treatment for HIV). However this can happen effectively if

<sup>75</sup> This section is based on the presentation by Limpho Ramangoaela, Medical Officer, Dr J S Moroka Hospital DR-TB Unit, Thaba Nchu.

<sup>76</sup> The South African Department of Health currently uses a screening tool (adapted from the WHO tool) at facilities. South Africa.

<sup>77</sup> To be supplemented with commonly used methods such as pill bottles, reminders, treatment buddies, and support from health care workers (particularly for patients in the intensive phase).

there are community health workers supporting the patient.

### **2.8.2 Support to patients**

The system of patient support currently spans multiple arenas, beginning when a patient is admitted and continuing throughout treatment:

- Offering assistance from a Provincial Clinical Review Committee to facilitate patient support by bringing different stakeholders to assist with financial and social support (Social Development department) and housing (housing and settlements department).
- Educating family members about the disease and how they can support the patient.
- Carrying out monthly follow-ups at the drug-resistant TB Unit.
- Encouraging patients by providing rewards in kind for positive behaviours related to treatment and celebrating key treatment milestones, like conversion of sputum from negative to positive, completion of the intensive phase, and completion of treatment.
- Assisting with coordination of patient support groups and involvement of community-based organizations and community health worker groups.

Ramangoela continued by describing future plans to reinforce case finding efforts by screening all contacts of index patients and providing infection treatment as needed, particularly to risk groups such as patients immunocompromised by circumstances such as malnutrition, diabetes mellitus, cancer, pregnancy, or age (young and old). Additional plans include further education on TB disease and infection control in households and capitalizing on the decentralization model. This includes management of patients at the clinic level and involving non-governmental organizations and community-based organizations to support the patient with injections and directly observed therapy in general.

## 2.9 MANAGEMENT OF PEDIATRIC MDR-TB CONTACTS IN SWAZILAND<sup>78</sup>



**Table 7. Epidemiological background in Swaziland**

Population	1,200,000
TB Incidence per 100,000 (n)	1,382 / 100,000
HIV prevalence (among population aged 18-49 years)	31%
HIV co-infection rate (%)	74%
Children on drug-susceptible TB treatment (%)	10%
MDR-TB among new cases (%)	7.7%
MDR-TB among re-treatments (%)	33%
Children on MDR-TB treatment (%)	?

Source: Ustero presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.  
Adapted from WHO 2013

Pilar Ustero reported on the program to manage pediatric MDR-TB contacts in Swaziland, a small country located in southern Africa. It currently has the highest rates of TB/HIV prevalence in the world (Table 7).

### 2.9.1 Implementing a dedicated clinic for MDR-TB child contacts

Ustero described the family-centered, comprehensive approach to health care delivered in three clinics by Baylor College of Medicine Children's Foundation-Swaziland. Since 2008, the clinics have treated more than 800 children

less than 14 years of age sick with TB. With an increased number of children with known drug-resistant TB contacts arriving to the clinic with advanced undiagnosed MDR-TB, the urgent need for a dedicated clinic for implementing services for MDR-TB contacts precipitated the initiation of steps toward that goal in February 2015.

Key steps for implementation have so far included identifying children who have had current or recent exposure to MDR-TB among current patients and developing the appropriate protocol

<sup>78</sup> This section is based on the presentation by Pilar Ustero, Physician, Global Childhood Tuberculosis Program, Baylor College of Medicine and Texas Children's Hospital, Mbabane, Swaziland.

**Table 8. Results of implementation of services for MDR-TB contacts in Swaziland**

Child contacts identified (n)	25
Source cases identified from child contacts (n)	13
Average age (years)	6.6
Children aged <5 years (n, %)	10/25 (40%)
HIV status	
Non-reactive (n, %)	20/25 (80%)
Reactive (n, %)	4/25 (16%)
Pending (n, %)	1/25 (4%)
Average time since the index case started MDR-TB treatment (months)	16 months
Positive screening (n, %)	8/25 (32%) <sup>a</sup>
Share bed or room at night (n, %)	22/25 (88%)

<sup>a</sup> 6/8 had Xpert MTB/RIF testing (MDR-TB not detected); no chest X-rays up to date

Source: Table adapted from Ustero presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

(in conjunction with Stellenbosch University) for a clinical SOP, risk assessment, and eliciting information from the index case. Financial barriers to care have been addressed by offering transport reimbursement and free chest radiographs.

Ustero reported that implementing the MDR-TB clinic has thus far identified 13 source cases from 25 child contacts (Table 8).

Drug-susceptibility test results are currently available for only 4/13 (30%) source cases:

- Two cases were sensitive to rifampicin and resistant to isoniazid, pyrazinamide, ethambutol, and streptomycin
- One case was resistant to all first-line drugs
- One case was resistant to rifampicin and isoniazid and sensitive to ethambutol, pyrazinamide, and streptomycin

### **2.9.2 Challenges for implementing drug-resistant TB infection treatment in Swaziland**

Ustero outlined several challenges that Swaziland's program faces in diagnosing MDR-TB in children. Firstly, Xpert MTB/RIF misses 30% of cases of drug-resistance in the country.<sup>79</sup> Further, there is generally poor access to drug-susceptibility testing that leads to delays in diagnosis. There is a lack of health facilities able to admit children sick with MDR-TB, coupled with reluctance on the part of many clinicians involved in drug-resistant TB care to start presumptive treatment for TB disease in children.

Ustero emphasized that waiting to confirm MDR-TB is too late. But efforts to implement infection treatment for drug-resistant TB are hampered by lack of routine and standardized contact tracing for TB patients and the absence of either national or international guidelines for infection treatment. In that vein, the infection treatment regimen needs to be standardized due to lack of access to drug-susceptibility test results of source cases. However, the limited access to MDR-TB drugs is a further constraining factor. The "knowledge gap" for childhood MDR-TB is also a key problem that parlays into a lack of confidence among clinicians about how to

<sup>79</sup> Sanchez-Padilla et al *N Engl J Med* 2015



manage pediatric MDR-TB cases and contacts.

### 2.9.3 Next steps in program implementation

Next steps for the program in Swaziland are the opening of a one-stop clinic for the diagnosis of childhood TB in May 2015, and the rollout of free MDR-TB treatment. In terms of policy, advocates at the national level will need to push for national guidelines that include the provision of infection treatment for MDR-TB contacts; at the international level, similar guidelines are needed. On a programmatic level, needs include improved efficiency in contact tracing and follow-up of child contacts of MDR-TB cases in existing MDR-TB clinics.

## 2.10 KEY POINTS FROM GROUP DISCUSSION ON COUNTRY-SPECIFIC PLANS (2.5-2.9)

Moore commented that in many settings, malnourished children are put on treatment for TB disease rather than infection treatment, because TB is thought to be a cause of malnutrition for many patients. Amanullah agreed that it can be difficult to ascertain whether TB is the cause of malnutrition or vice versa. At Indus Hospital, the TB Program does receive a number of referrals for evaluation from their malnutrition clinic and before starting a patient on TB infection treatment, they strive to be as diligent as possible in ruling out TB disease with further imaging.

Moore also questioned whether employing mobile technology might provide a means to reduce the number of face-to-face visits required with patients. Furin reported that, in South Africa, they have recruited celebrities to “send” automated text reminders regarding therapy adherence. However, she noted the problem of text message fatigue impinging upon the effectiveness of such strategies, particularly among adolescents. She suggested surveying the patients themselves (rather than healthcare providers) about the most effective ways to deliver reminders.

Furin sought advice about how to persuade provincial and national-level health services to provide infection treatment for groups of patients who are not considered to be “high-risk” ac-

cording to various guidelines, specifically citing children over the age of 5 years who are not HIV infected. Starke countered that in the United States, data-driven guidelines (other than those set forth by WHO) state that all children with TB infection are treated because they are considered to be at risk. The data demonstrate that older children and adolescents are in fact at high risk—albeit relatively lower risk—but that their risk is high enough that they warrant treatment from the perspectives of health, adverse events, and cost.

Furin noted that many of the TB program directors and administrators with whom she regularly engages are not particularly receptive to hearing about the guidelines of the United States. To remedy this, proactive efforts should be made to convey the importance of the long-term benefits of infection treatment. She raised a related concern that academic papers on the topic often conclude that infection treatment for MDR-TB in high-risk population “may” be an effective intervention; this diminishes such papers’ impact and utility in convincing national TB programs to effect change. Imran Zafar<sup>80</sup> suggested that a useful strategy for convincing TB program managers might be a cost-benefit approach, emphasizing the return on investment in terms of the cost of TB infection treatment compared with the cost of treating TB disease.

On the topic of empowering families to help patients complete therapy, Burzynski remarked that, in New York City, the TB program tends to avoid involving families due to concerns about conflicting interests between sympathy for the patient undergoing treatment versus public health concerns about stopping further TB spread. He noted a tension between helping individual patients to do what is best for them and the public health impact of non-adherence to therapy. Ramangoela described the strategy of involving a trusted family member to empower and entrust with responsibility to assist the patient, with guiding principles of disclosure and destigmatization. Zafar suggested motivating families by framing the treatment as ensuring a family’s safety from drug-resistant TB.

Khan recommended developing the proper

<sup>80</sup> Imran Zafar, Interactive Research and Development, Karachi, Pakistan



tools, such as a contact registry, before scaling up case-finding and infection-treatment interventions. Ustero commented on the issue of tools in expanding capacity to follow-up and report, noting that it is impractical to strive for perfect reporting of *all* data. She stressed focusing on what is needed to provide the best possible care by striking a balance between essential indicators that must be recorded and the practical realities of the setting.

Schaaf reported that the resistance rate to fluoroquinolones in the Western Cape is 35% and that ethambutol resistance is a problem because the intolerability of the drug among both children and adults drives poor treatment adherence. He underlined several current needs with respect to drug resistance:

- Using line probe assays to further refine the exact place of ethambutol within treatment regimens when isoniazid resistance is present
- Developing a more rapid test for fluoroquinolone resistance
- Investigating the use of high-dose isoniazid for patients sick with TB strains with mutations indicating resistance to low-dose isoniazid
- Finding new options for addressing fluoroquinolone resistance

With reference to the perception that young children are not infectious, Yuen noted that the same cannot be argued convincingly with regard to adolescents, particularly in communities where they go to work or school in congregate settings. Perhaps this could be used to argue that they are a group that should be treated for TB infection to prevent TB disease, due to a high risk of their spreading TB when they become sick.

Palmero recommended focusing exclusively on infection treatment for MDR-TB contacts only, not pre-XDR or XDR, because there are no effective infection treatment regimens for the latter two. Given the absence of guidelines for use of the new drugs in children, Khan argued that there is a strong public-health need to develop new approaches to prevent pre-XDR-TB

and XDR-TB cases. Cassell concurred about the need to address the spread of XDR-TB on both the new-drug and policy levels, because the frequency of XDR-TB is still largely unknown. Furin reported that, in Kwazulu-Natal, more than 80% of XDR-TB cases are in new TB cases who have never been treated,<sup>81</sup> which indicates XDR-TB is being spread. She reiterated that balancing the risks and benefits of supporting XDR-TB patients is crucial. According to Grigory Volchenkov,<sup>82</sup> drug-susceptibility testing data indicate that 10% of MDR-TB patients in Vladimir have XDR-TB.

Yuen queried the group at large about treating TB infection in XDR-TB contacts; in the United States they are followed clinically. Cassell suggested that if an XDR-TB patient is susceptible to one or two antibiotics, their contacts might benefit from treatment of TB infection. Furin concurred about the need to accelerate the timeline for developing XDR-TB infection treatment.

Iqbal commented that Xpert MTB/RIF has increased patient numbers in his program dramatically, consequently placing even more strain on the system and leading to decentralization of care. However, he suggested that decentralized patients may be more likely to default. Furin noted that many patients default due to difficulties tolerating the months-long regimen, which is yet another reason to argue for infection treatment that can prevent disease.

<sup>81</sup> Shah et al. *CROI* 2015

<sup>82</sup> Grigory Volchenkov, Vladimir TB Control Center, Vladimir, Russia

### BOX 2-3 MEDICATION COSTS: ECONOMY VS. LUXURY

Brostrom emphasized that parsing the economics of MDR-TB disease treatment serves as a significant incentive to promote effective infection treatment in high-risk household MDR-TB contacts (Table 9).

**Table 9. Medication cost comparison**

Category	Pan-sensitive TB		MDR-TB	
Cost <sup>a</sup> to treat active case (GDF-USD)	21.00		5,822.00	
Preventive regimen	INH (6 months)	RIF (4 months)	LFX (6 months)	MFX (6 months)
Cost to treat TB infection (GDF-USD)	360	8.40	12.87	115.20
Ratio of costs, infection treatment vs. treatment of active case	0.17	0.40	0.002	0.02
Number of infected cases treated per cost of treating one active case	5.8	2.5	452.5	50.5

<sup>a</sup> All costs from GDF Catalog, [www.stoptb.org/gdf/drugsupply/drugs\\_available.asp](http://www.stoptb.org/gdf/drugsupply/drugs_available.asp), accessed March, 2015

**Abbreviations:** INH, isoniazid; RIF, rifampicin; LFX, levofloxacin; MFX, moxifloxacin

Source: Table adapted from Bamrah Morris, Brostrom, and Fred presentation at April 2015 Global Consultation hosted by HMS Center for Global Health Delivery–Dubai.

Referring to Global Drug Facility catalogue prices as of March 2015, Brostrom directly compared the cost of treating MDR-TB disease with the cost of the provision of infection treatment:

- 458 people can receive levofloxacin infection treatment for the cost of treating a single case of MDR-TB disease.
- If 15% of pediatric contacts progress to TB disease, and infection treatment is 80% effective in preventing MDR-TB disease, then levofloxacin infection treatment can prevent 58 MDR-TB cases for the cost of treating one MDR-TB case.
- MDR-TB infection treatment with levofloxacin is 80 times more cost-effective than infection treatment with isoniazid in preventing drug-susceptible TB disease.

He explained that applying cost multipliers for the treatment of MDR-TB disease can further increase the cost-effectiveness of treating MDR-TB infection, in terms of avoiding hospitalization costs for MDR-TB treatment, outpatient clinical monitoring costs, home injection costs, and so forth. Further, applying a 50% clinical failure rate for MDR-TB treatment also increases the relative cost-effectiveness of treating MDR-TB infection.

## Part 3.

# Moving toward agreement on priorities, challenges, and tools

Following presentations by expert practitioners and researchers, each day included extensive discussions in break-out groups addressing specific conceptual questions (the “what”) and operational and programmatic questions (the “how”) surrounding two major issues: screening and post-exposure treatment. Immediately building off these discussions, the plenary group convened to discuss and, where appropriate, to synthesize the outputs from these break-out groups. The following is a representation of the plenary group discussions in which groups reported their summary observations and arguments regarding best practices for screening and implementation of post-exposure treatment on a project level and among larger patient populations. The participants drew primarily upon their own practical experiences in managing, studying, and implementing TB programs, but sought to move toward points of agreement in terms of universal challenges and practical clinical and programmatic approaches for the delivery of infection treatment for households exposed to drug-resistant TB.

### 3.1 SCREENING

The first topic considered by the break-out groups centered around the issue of screening, with key areas of focus including: who should be screened to rule out TB disease and evaluate the risk to disease progression; how, when, and where they should be screened; and the programmatic implications of implementation.

Screening was explicated as a two-step process: screening to rule out TB disease and, once TB disease is ruled out, screening for infection in order to determine who would benefit from infection treatment.

The participants identified a set of considerations that underpin decisions about screening methods.

#### 3.1.1 Risk assessment

Risk assessment of contacts should inform which contacts to screen, both for TB disease and for infection. The relative risk of various kinds of contacts is variable, highlighting the need for country-specific and operational analyses. Primary care physicians should identify individuals who have high-risk comorbidities for screening to rule out TB disease and initiate infection treatment.

#### 3.1.2 Who should be screened?

Participants offered a host of suggestions toward establishing guidance about who should be screened. The plenary group largely concurred about the need to more actively screen population groups that are at high-risk for progression to disease, or who are likely to have poor outcomes if they do become sick with TB. The break-out groups suggested the following recommendations about who to screen:

- All household contacts of the drug-resistant TB index case should be screened for infection and disease using symptoms, chest radiograph, and tuberculin skin testing.<sup>83</sup>
- All child contacts aged <5 years of age should be screened for disease using symptoms, examination and chest radiograph if possible.<sup>84</sup>
- Child contacts >5 years of age who are symptomatic.
- Additional high-risk groups:
  - Immunocompromised patients
  - HIV-positive patients
  - Pregnant women
  - Malnourished patients
  - Patients with diabetes mellitus
  - Patients with COPD

<sup>83</sup> A participant noted that for older people, it can be difficult to determine if a positive tuberculin skin test result is attributable to recent contact or lifetime exposure to persons sick with TB. Others argued that the positive result indicates that the person is definitely infected with TB, so treatment with levofloxacin should be beneficial regardless.

<sup>84</sup> In settings without access to chest radiographs, screening can be supplemented with behavioral observation and monitoring children's weight.

### BOX 3-1 DEFINITIONAL CHALLENGES DELINEATING HIGH-RISK GROUPS: THE “HOUSEHOLD” AS AN EXAMPLE

How to best define a household contact is a key consideration. The concept of a household is highly context-specific, spanning a broad spectrum of relatively fluid definitions among and within different program settings. Depending upon the setting, the designation of “household” often extends beyond the physical structure and the individuals who live there full-time, to encompass meaningful relationships in which time is spent with one another. Key questions to consider include who spends time in the home (and for how many hours), how many people intermittently eat or sleep there, and so forth. Beyond households, additional venues for transmission such as social networks and places of employment can vary widely in high-prevalence versus low-prevalence settings.

One group suggested that screening should target population groups rather than particular patients, with the aim of screening every individual in high-risk groups and providing infection treatment to all individuals in whom TB disease has been ruled out. The TB program in Vladimir, Russia, adopts this type of approach, placing patients who are HIV positive at the highest priority, followed by socially vulnerable groups such as the homeless, psychiatric patients, and those with alcohol and/or substance use.

#### 3.1.3 Implementing screening

The break-out groups offered a range of concrete suggestions and needs concerning the implementation of a screening program:

- To carry out household screening, recruit and train a team of dedicated complementary healthcare workers who receive salary and travel support
- Delegate 1 worker per approximately 50 households, depending upon the size of the geographical area to be covered
- Implement some form of verbal screening for entire households

For drug-resistant TB contacts:

- Implement household screening using the forthcoming *Post-Exposure Protocol*
- Use a questionnaire for initial screening, and then if necessary: chest radiograph, IGRA, culture, and drug-susceptibility testing

One break-out group strategized by outlining a minimal set of responsibilities for healthcare workers in screening households with a drug-resistant TB source case:

- Provide verbal screening and risk assessment at home to rule out TB disease in adults
- Request a chest radiograph in clinic for children aged <5 years
- While in the clinic,<sup>85</sup> children and adults should be evaluated by the medical officer; based on their symptoms and exam the clinician can recommend the next treatment step
- Use tuberculin skin testing if available
- Sputum culture and chest radiograph should be considered the minimal set of diagnostic tools, with add-ons such as tuberculin skin testing as program resources allow

<sup>85</sup> Incentives for patients and family members to come to clinic should be provided (e.g., transportation assistance).

Another group prioritized screening tools in terms of complexity, noting the first two options are available in virtually any setting regardless of resource limitations:

1. Verbal screening (or questionnaire) to assess symptoms
2. Referral to a physician as needed
3. Chest radiograph
4. Tuberculin skin testing
5. Bacteriological culture

Recommendations regarding frequency of testing for household contacts:

- Provide tuberculin skin testing at baseline, month 3, and every 6 months until the index case completes treatment
- Perform chest radiograph at baseline and month 3, then at one year if required

With respect to referrals, healthcare workers refer to pediatrician at the TB clinic (highlighting the need to coordinate services between TB and pediatric programs).

In medium- to low-resource settings:

- Physician refers the contact investigation to the TB program
- TB program sends personnel to make home visit
- Suspected cases are referred to a physician

### 3.1.4 Programmatic implications of screening

Much of the discussion with respect to the issue of implementing screening concentrated on the need to employ different people to implement screening than those who are responsible for treating TB disease, and the programmatic implications of this need. In this context, the pivotal role of community healthcare workers was a fruitful ground for discussion. In some settings, there are already systems in place of community healthcare workers who are already familiar with households and individuals in the community due to their work in the arenas

of drug-susceptible TB, HIV, family planning, nutrition, and so on. When such systems are already in situ, especially with a component for TB disease treatment, participants suggested that incorporating household contact screening into the existing program might not impose an excessive burden.<sup>86</sup>

However, others commented that given the number of household members that may need to be screened, coupled with an overreliance upon community healthcare workers, some circumstances may require a separate dedicated screening program.

The role of such workers in the TB program in Lesotho was used as an instructive example. In that program, dedicated community healthcare workers are essential for implementing household screening; they enter households and baseline screen all household contacts of the index case. They fill out forms for each contact that are entered into an electronic database. The workers are also responsible for provision of directly observed therapy for the index case, and during each of those visits they also solicit information about whether anyone else in the household has TB symptoms.

A participant commented on the potential problem of overloading healthcare workers. In an Ethiopian project supported by TB REACH, they identified 50,000 people in one year and collected sputum smears for testing, then supervised treatment for 2,500 patients. The team was willing to do the work because they felt invested in contributing to something valuable. From the MDR-TB perspective, employing the healthcare worker model and moving away from relying exclusively on more costly staff is worth considering, but many different models of task-shifting were considered appropriate, dependent upon the MDR-TB burden.

Further programmatic implications include provisions for training and compensating support staff, coordination of services, and resources to facilitate testing.

<sup>86</sup>It was noted that because approximately 5% of TB cases have MDR-TB, the marginal cost of adding on an MDR-TB household screening program to an existing TB program would be small in terms of personnel and resources required.

### BOX 3-2 THE IMPACT OF TERMINOLOGY IN BUILDING CONSENSUS FOR A LEXICAL SHIFT

A recurring thread of discussion throughout the workshop was the impact of terminology when differentiating between the state of persistent immune response to *M. tuberculosis* ("latent TB infection"; "TB infection") and progression to TB disease (or "active TB disease").

Participants worried that the semantics of the term "latent TB infection" denotes a lack of urgency or importance to treat. In fact, it may actually be an inaccurate or misrepresentative term for children and the immunocompromised. Rather than a binary distinction between latent TB infection and active TB disease, TB infection and disease (particularly among children) are better understood as a spectrum. This might be effectively addressed by encouraging the universal adoption of less conceptually dichotomous terminology.

Participants raised concerns that this change might cause confusion for program managers and clinicians using guidance from bodies such as WHO and the U.S. CDC that continue to use the term "latent TB infection." To address this would require convincing international policy makers and authors of global guidelines of the value of this lexical shift. Notably the U.S. CDC has recently decided to use the term "TB infection" rather than "latent TB infection."

#### 3.1.5 Challenges regarding screening: Could attempts at reform create new barriers?

Some participants expressed concern that guidelines requiring chest radiographs would be a barrier to decision-making about infection treatment in resource-limited settings, due to problems of cost, access, and availability. For instance, people may travel to have a chest radiograph done and radiologists are needed to interpret them (computer technology is available, but not widely so in resource-limited settings where access to basic resources such as electricity remains a challenge).

A participant remarked that while contact investigations yield a large number of patients proportionally, and infection treatment for MDR-TB makes sense conceptually, there are high numbers of MDR-TB patients with primary resistance (as opposed to having acquired resistance via previous treatment attempts). He urged the group to consider how many of those patients would be found eventually by other means when they or their family members become sick.



## 3.2 POST-EXPOSURE TREATMENT

### 3.2.1 Who should receive post-exposure treatment?

In considering the question of who should receive post-exposure treatment if TB disease is ruled out, participants were generally in agreement that infection treatment should be provided to those individuals who are at the highest risk of progression to disease.

The following recommendations were offered:

1. In a household with a drug-resistant TB index case, infection treatment should be given to:
  - Child contacts <5 years of age regardless of their tuberculin skin test results
  - People of any age with a positive tuberculin skin test result
2. At minimum, infection treatment should be given to all household contacts of drug-resistant TB index cases who are aged <5 years and people of any age who are immunocompromised. Preferably, infection treatment would also be given to children <15 years of age and people of any age with a positive tuberculin skin test result.
3. Analyze the epidemiological disease patterns of the specific setting and then identify high-priority groups to receive infection treatment, which may include:
  - Members of high-risk households
  - HIV+/immunocompromised patients
  - Malnourished patients
  - Children aged <5 years, followed by children aged <15 years
  - People with chronic illnesses

In the context of discussion about how to proceed in the absence of a test for infection (such as a positive tuberculin skin test result), a participant commented that under such circumstances being a household contact ipso facto is infection, thus any child and adolescent household contacts are all infected and should

be prioritized. Discussion ensued about whether, in the absence of a test for infection, all adult household contacts should receive infection treatment. Of concern is that the risk-benefit profiles for children and adults differ, with fluoroquinolones being more tolerable for children than older people. However, there is not enough data available to determine an age cut-off for this differential risk.

Participants noted that prior to determining who to treat for infection, it is important that once a commitment is made to give infection treatment to anyone in the household that everyone in that household needs to be followed for outcomes. Any such household also needs to be part of a cohort, or registry, which is followed prospectively for an appropriate length of time.

### 3.2.2 Infection treatment regimen, duration and follow-up

The break-out groups contributed several sets of recommendations while working toward the objective of establishing agreed-upon guidance for infection treatment:

- Provide a 3-drug regimen of high-dose levofloxacin; either high-dose isoniazid or ethionamide; and ethambutol<sup>87</sup>
- Provide levofloxacin only for six months. During treatment, follow up with a health professional with visits at Week 2, Week 4, and then monthly thereafter with nurses. Physician visits to take place at treatment start, Month 3, and Month 6.
- Provide a 2-drug regimen for three months, with follow-up period of one year.
- Provide infection treatment for six months, including a visit every two weeks with a doctor and every month with a nurse. Follow up twice a year for 18 months. Use a checklist to evaluate adverse events and refer to the physician as needed.
- Treat drug-resistant TB patients until the index case is culture negative and all other infectious TB sources have been removed from the household through effective treatment. Implement infection treatment using directly observed therapy followed up every month

<sup>87</sup> The participants raised concerns about the suitability and efficacy of ethambutol for infection treatment, due to its low level of bacteriostatic activity and the high rates of resistance (>60%) reported in South Africa.

while patients are on treatment, and every 3-6 months thereafter.

Ultimately, the plenary group deliberated the relative benefits and disadvantages of two specific regimen options for infection treatment:

1. Treat with levofloxacin only for six months if fluoroquinolone susceptibility is known, or if there is a low fluoroquinolone-resistance background. Treat with moxifloxacin for six months if resistance to ofloxacin is known, or if there is a high fluoroquinolone-resistance background.
2. Provide levofloxacin and high-dose isoniazid for six months.

The rationale for the possible addition of isoniazid to an infection treatment regimen is that contacts of MDR-TB patients may not only be infected with MDR-TB, but potentially with drug-susceptible TB strains as well. Isoniazid would treat any concurrent drug-susceptible TB infection, and there is a chance (though not supported or refuted by evidence as yet) that isoniazid may be active against some MDR-TB organisms in high doses.

This generated further reflection among the group about the ideal infection treatment regimen. Primary concerns centered on the toxicity of high-dose isoniazid (and whether it would be safer to use levofloxacin alone), juxtaposed with the preponderance of evidence that exists supporting the efficacy of 2-drug regimens in practice as the infection treatment of choice. It was suggested that a useful research question would be to compare regimens of levofloxacin and high-dose isoniazid versus levofloxacin alone.

The group generally concurred that the “must-have” minimum follow-up period after the completion of infection treatment should be at least one year.<sup>88</sup>

### 3.2.3 Implementing infection treatment

Recommendations and programmatic implications:

#### Treatment literacy

Patients should be counseled so that they understand what MDR-TB is, why it needs to be treated, and how to reduce the chance of spreading infection.

#### Procurement of drugs

Procure drugs through the national TB program, but if drugs are difficult to obtain through the Global Drug Facility mechanism, give local clinics the ability to procure for themselves.

#### Administration of infection treatment

While it is relatively straightforward to task directly observed therapy workers with asking about symptoms and making decisions about who needs a chest radiograph, deciding if someone needs treatment for TB disease or treatment for TB infection is more complicated. This means that enough providers will be required who have been trained to screen for TB disease; in addition to physicians, appropriately trained nurse-clinicians might fill this role.

If infection treatment is implemented as an add-on to existing TB programs in households, have healthcare workers administer TB medications at the same time and place as other medications.

Another option is to utilize self-administered therapy with context-dependent accompaniment (e.g., clinic or household-based), which should be close and involve supervision at regular intervals. This could be supplemented with checklists, reminders, and other tools.

#### Program and staff monitoring

The impact of the infection treatment program should be evaluated and monitored on an interim basis by cross-checking names on the household contact register with those on the

<sup>88</sup> Discussion among the participants as to the appropriate follow-up period led to the suggestion that adults should be followed up annually for up to three years. When a child has recent exposure, progression to disease will probably occur within the first year, thus after completing infection treatment a one-year follow-up period is likely to be sufficient. However, because the risk for progression to disease for adults extends for a longer time period the contention is that a longer follow-up period is in order.

TB register, to see if identified contacts have developed TB disease and to determine if there is variance according to whether they accepted or declined infection treatment. The registry could serve an important function of measuring success by a standard such as completion of infection treatment. From a long-term perspective, the key indicators of program success should be a decrease in the number of TB patients, paired with an increase in the success rate of treatment, given that cases will be found sooner and therefore experience better outcomes.

Another key recommendation is that clinics should self-monitor with operational research. A participant emphasized that there is a role for observational evidence and a role for clinical trials, yet having the former does not obviate the need for the latter to determine good regimen design principles. However, randomized controlled trials cannot provide the information produced by operational research, which can guide how to best implement a given model in a particular setting.

Monitoring the performance of staff is a program component that often receives little attention. Suggestions for doing so included a system of regular ride-alongs to ensure and improve compliance by support staff tasked with the provision of directly observed therapy, and using a registry to track individualized completion rates.

It was also suggested that electronic medical record systems should be implemented if feasible. However, in resource-limited settings that preclude the use of electronic data collection systems, with records located physically in clinics or with staff, the suggestion was made to add information about TB screening and treatment history to a “Road-to-Health”-style card, or a card which the patient maintains containing a variety of health information. Road-to-Health cards are typically used for children who may seek healthcare services from many different providers. These cards serve the purpose of following the patient from provider-to-provider so all providers are aware of the patient’s medical information.

### 3.3 TOWARD A CONSENSUS STATEMENT

As detailed above, at the conclusion of each day the group found consensus on the key challenges facing successful screening programs and implementation of successful infection treatment in households exposed to drug-resistant strains. Principles and recommendations for how programs can address these challenges are outlined in a consensus statement emerging directly from this global consultation.<sup>89</sup> The group reached near consensus on the prioritization and ideal response to these challenges, with any differences largely being a matter of emphasis, timing, or implementation methodologies. These points of contention also often included concern about how “best practices” from wealthy health systems with low tuberculosis prevalence can be applied in resource-constrained settings, given the particular epidemiological “signal-vs-noise” dynamics, as well as strategic political considerations. Despite this, the group moved forward under the assumption that the two-day meeting had shone a light on a clear pathway to effective prevention of TB in households exposed to drug-resistant TB in the near future.

<sup>89</sup> Seddon et al. *Harvard-Dubai Center Policy Brief* 2015.

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## Appendix A.

# Agenda and questions for discussion groups

### FINAL MEETING AGENDA

#### Global Consultation on Best Practices in the Delivery of Preventive Therapy for Households Exposed to Drug-Resistant Tuberculosis

April 12-13, 2015

DAY 1: Sunday, 12 April 2015		
8:30	Shuttle bus will pick up participants at Hyatt lobby	
8:30 – 9:00	Registration	
9:00 – 9:05	Welcome	Salmaan Keshavjee
9:05 – 9:15	Rationale and goals for meeting	Mercedes Becerra
9:15 – 9:45	Introductions	All
9:45 – 10:10	Reasons for lack of clear guidance on preventive therapy	James Seddon
10:10 – 10:15	Questions	
10:15 – 10:45	Experience from Cape Town, South Africa	Simon Schaaf
10:45 – 11:15	Coffee break	
11:15 – 11:30	Questions	
11:30 – 12:00	Experience from Buenos Aires, Argentina	Domingo Palmero
12:00 – 12:15	Questions	
12:15 – 13:15	Lunch	
13:15 – 13:45	Experience from New York City, USA	Joseph Burzynski
13:45 – 14:00	Questions	
14:00 – 14:30	Experience from Houston, USA / Perspectives on family-centered care	Jeffrey Starke
14:30 – 14:45	Questions	
14:45 – 15:15	Experiences from the UK and Europe	James Seddon
15:15 – 15:45	<b>Coffee break (** Group Photo at 15:35)</b>	
15:45 – 16:30	Small group discussions	All
16:30 – 17:30	Large group discussion	All
19:00	Banquet, Hyatt Regency Dubai Creek Heights	All

## FINAL MEETING AGENDA

### Global Consultation on Best Practices in the Delivery of Preventive Therapy for Households Exposed to Drug-Resistant Tuberculosis

April 12-13, 2015

DAY 2: Monday, 13 April 2015		
8:30	Shuttle bus will pick up participants at Hyatt lobby	
8:30 – 9:00	Registration	
9:00 – 10:00	Experience from Chuuk State, Micronesia	Sapna Bamrah Morris, Richard Brostrom, Dorina Fred
10:00 – 10:30	Questions and discussion	
10:30 – 11:00	Coffee break	
11:00 – 12:00	Panel – Plans from four programs	
	11:00 Khayelitsha, South Africa	Jennifer Furin
	11:15 Karachi, Pakistan	Farhana Amanullah, Hamidah Hussain
	11:30 Free State, South Africa	Limpheo Ramangolela
	11:45 Mbabane, Swaziland	Pilar Ustero
12:00 – 12:15	Questions	
12:15 – 13:15	Lunch	
13:15 – 13:30	Developing field guidance: A post-exposure protocol for households	Jennifer Furin
13:30 – 13:45	Questions	
13:45 – 14:45	Small group discussions	All
14:45 – 15:15	Coffee break	
15:15 – 17:00	Large group discussion	All
17:00 – 17:30	Wrap-up and adjourn	Mercedes Becerra



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## QUESTIONS FOR DISCUSSION

### Global Consultation on Best Practices in the Delivery of Preventive Therapy for Households Exposed to Drug-Resistant Tuberculosis

April 12-13, 2015

#### **12<sup>TH</sup> APRIL - THE 'WHAT'?**

(6 groups – 3 groups to cover screening and 3 to cover post-exposure treatment)

##### **Screening**

1. Who should be screened to rule out disease? What groups?
2. How should they be screened? When? Where? With what?
3. Who should be screened to evaluate risk of progression to disease? How should they be screened? When? Where? With what?

##### **Post-exposure treatment**

4. Who should receive post-exposure treatment?
5. What should be used for post-exposure treatment in each group? What drugs? How often? What dose? What duration?
6. How should those receiving post-exposure treatment be followed up? For how long? How often? What tests to do at each follow up visit? Who do they need to see at follow up? How should those not receiving treatment be followed up?



## QUESTIONS FOR DISCUSSION

### Global Consultation on Best Practices in the Delivery of Preventive Therapy for Households Exposed to Drug-Resistant Tuberculosis

April 12-13, 2015

#### **13<sup>TH</sup> APRIL - THE 'HOW'?**

(6 groups – 3 groups to cover screening implementation and 3 to cover post-exposure treatment implementation)

##### **Implementing screening**

1. How to implement household screening? Resources required? Personnel required? Programmatic implications?
2. How to rule out TB disease? Tools needed? Resources needed? Site of screening (home/clinic/hospital)? Types of investigations? Programmatic implications? Who refers to whom?
3. How to evaluate risk of disease progression? Tools? Tests? Personnel? Site of evaluation?

##### **Implementing post-exposure treatment**

4. How to give post-exposure treatment? Counselling? Consent? Supervision? Drug supply? Programmatic considerations? Personnel?
5. Following up contacts? Frequency of monitoring? What to do at monitoring? Investigations? Evaluation of adverse events? Duration of follow up?
6. How to monitor and evaluate? Recording and reporting? How to budget for staff? Work plan of staff? How to monitor impact of intervention? Role of research vs. surveillance?

## Appendix B.



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### LIST OF PARTICIPANTS

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April 12-13, 2015

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## **ABOUT THE HARVARD MEDICAL SCHOOL CENTER FOR GLOBAL HEALTH DELIVERY–DUBAI**

The Harvard Medical School Center for Global Health Delivery–Dubai is addressing some of the most pressing health challenges in the region by focusing on research, medical education, and training that promises to improve 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, established by Harvard Medical School in Boston and Dubai in 2014, is a hub for policy formulation and analysis that is optimizing the last phase of health care delivery, ensuring that care providers have the systems and tools necessary to alleviate human suffering caused by disease. The Center does not provide patient care but focuses exclusively on research and training.

The Center aims to:

- Promote research and education focused on the delivery of high-quality healthcare for communicable and non-communicable diseases in Dubai and the region.
- Highlight and foster interdisciplinary collaborative research and education around health delivery with the Harvard Medical School Department of Global Health and Social Medicine and other Harvard faculty in Dubai and the region.
- Create a hub for discussion, research, analysis, and policy formulation focused on health concerns of critical global importance.



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