Implementing a Family-Centered Approach to

Post-Exposure Management for Rifampicin-Resistant/Multidrug-Resistant TB:

A FIELD GUIDE

Forward

Rifampicin-resistant/multidrug-resistant tuberculosis (RR/MDR-TB) is a disease that causes a notable amount of sickness and suffering among people diagnosed with the disease and their families. Due to the airborne nature of the disease, when one person in a household becomes sick with RR/MDR-TB, it is vital that all other members receive attention since they all share the same air. These systematic care services for individuals in a household must be structured as "post-exposure management" practices and accessible to all. Based on global estimates, each year there are almost 1.5 million people who need post-exposure management after a DR-TB household exposure. At least 19 million people in the world today should have received such services, but to date, the number reached is nearly zero.

Why are these life-saving interventions not being deployed? While there are a variety of reasons, one is *a lack of practical tools* that guide families, care providers, and programs in how such services can be provided in a comprehensive and compassionate way. While many front-line workers understand the importance of thorough post-exposure management for RR/MDR-TB, they may lack the expertise or the resources to implement such services. Instead, programs often choose a "watch and wait" approach for households where RR/MDR-TB has been newly diagnosed. Such passive approaches will no longer suffice in the current era where commitments to "end TB" require more active approaches, both to find people with RR/MDR-TB at the earliest possible stages of their disease but also to offer preventive interventions to those who have been exposed but whom are not yet sick.

This Field Guide aims to share practical experience gained while implementing post-exposure management for RR/MDR-TB using a family-centered approach. The guide contains practical tools that can be used by providers at multiple levels, by communities impacted by RR/MDR-TB, and by programs and policy makers who must fund and support this work. It is our intention that these tools be adapted to different contexts and settings around the world. We also hope that users will share feedback on the tools so that we can continue to improve them as part of an active community of practice.

The Field Guide has three parts and each section is streamlined for ease of use. Sections also contain additional elements that can be consulted for those who want more details. These include sections where evidence or practices are examined in more detail (signified by a microscope logo) and examples of clinical scenarios or best practices (signified by a chest X-ray logo). Counseling support advice is highlighted with the "handshake" logo.

Millions of people needlessly become sick with and die from TB each year, including drug-resistant forms of TB. Their suffering must push us to act urgently to do all we can to halt this airborne disease. It is our sincere hope that this Field Guide will be a useful tool in the armamentarium we have to fight against all forms TB.

The Field Guide was written and developed by The Sentinel Project for Pediatric Drug-Resistant Tuberculosis (http://sentinel-project.org/) and by Free of TB.

Illustrations by Samkelo Komanisi

Funding support provided by the Government of Japan; other support provided by the United States Agency for International Development.

Preferred Citation: A Family-Centered Approach to Post-Exposure Management for Rifampicin-Resistant/Multidrug-Resistant Tuberculosis: A Field Guide. Boston, MA, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis and Free of TB; July 2024, First edition.

Acknowledgments

The main writing committee for this handbook was: Anja Reuter, Busisiwe Beko, Johnny Daniels, Jean Pannikottu, Elize Pietersen, Lara Wiese and Jennifer Furin. Other contributors included: Ivy Apolisi, Mercedes C. Becerra, Keertan Dheda, Goodman Makhanda, and Jennifer Singler.

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This field guide was developed from a 2018 document called “How to care for people exposed to drug-resistant tuberculosis: a practical guide” led by James Seddon and Meredith Brooks. This resource and the full list of contributors can be found here: https://sentinel-project.org/wp-content/uploads/2018/03/PE-Guide_English_V1_Mar2018-1.pdf

The authors of this Field Guide are thankful to countless people for the time, expertise, and generosity which led to its development. First and foremost, we are mindful of all people impacted by RR/MDR-TB who face multiple challenges with this disease on a daily basis. Their bravery inspires us, and it is for them that we aspire to ensure that TB disease, suffering, and death are prevented. For funding and moral support, we thank the Department of Global Health and Social Medicine at Harvard Medical School and the Stop TB Partnership’s Global Drug Facility (with grant support provided to them by the Government of Japan and USAID). Finally, we thank the men and women who care for people living with RR/MDR-TB around the world. We are incredibly thankful to the PEP Khayelitsha "implementing teams" in the clinics and communities of Khayelitsha, especially to Janet Giddy who led the development and piloting of the contact register in the Annex. The Figure in Annex A was taken from the "Diagnostic CXR Atlas for Tuberculosis in Children" and we are thankful for the work of this group and this exceptional resource. May we all come to know a day when all people impacted by this disease are able to lead healthy and worry-free lives.

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TERMINOLOGY USED IN THE GUIDE

Throughout this document, we will be using some newly adapted terms to better reflect the work that is done after a person has been newly diagnosed with RR/MDR-TB. We consider a contact to be someone who has been around that individual for a prolonged period of time (working definitions of this term are reviewed in the body of the document). Contact tracing will be referred to as "post-exposure management" or just "PEP" (post-exposure package of care). We chose this terminology to underscore that this is a set of essential, integrated activities.

To better reflect advances in understanding the pathophysiology of TB, we use the term "TB infection" rather than "latent TB" and "TB disease" rather than "active TB." "Treatment of infection"' is used instead of "preventive therapy."

Stigmatizing terminology is also avoided. We use "first person diagnosed with RR/MDR-TB"' instead of "index case." We also speak about "shared air" rather than about one person infecting another person.

RR-TB refers to tuberculosis that is resistant to at least rifampicin. MDR-TB refers to tuberculosis resistant to at least both isoniazid and rifampicin. Following WHO convention, we use the term RR/MDR-TB throughout the document.

While these terms may be novel for people working in TB programs, they better reflect current understandings of TB and offer a more clinically sound and dignified way to talk about and think about household RR/MDR-TB exposure.

THE "RR/MDR-TB PEP": OVERVIEW

While caring for people with RR/MDR-TB and their household contacts can seem complex, these are the things that need to be done for them and which we will review in this Field Guide

- Every person diagnosed with RR/MDR-TB should receive counseling and support to disclose their diagnosis to household members.
- Household members of all ages should be assessed for RR/MDR-TB infection and disease. This should be done using exposure scales, symptom assessment, weight, and a basic physical exam offered at a time and in a place convenient for them. They should also be offered HIV counseling and testing.
- Household members with signs and symptoms of possible TB disease should undergo further assessment to rule out RR/MDR-TB disease.
- Household members in whom RR/MDR-TB disease is not likely or has been ruled out should be offered a post-exposure package of care.
- The RR/MDR-TB post-exposure package of care should include: 1) psychosocial support/counseling; 2) medication therapy (usually with six months of levofloxacin); and 3) nutritional supplementation.
- Programs should offer these interventions in an urgent and systematic fashion. This will both improve the detection of RR/MDR-TB cases and prevent TB cases in households where a person has been found sick with TB.

The field guide will review each of these actions in more detail in the following sections.

PART 1: THE WHO, WHAT, WHY AND WHERE OF THE "RR/MDR-TB PEP"

Who developed this field guide?

This is the collective work of many individuals (including front-line health care workers, monitoring and evaluation experts, counselling experts, and researchers) who are a part of the virtual, science-based advocacy network called the Sentinel Project on Pediatric Drug-Resistant Tuberculosis. The guide is modeled on lessons learned from a high RR/MDR-TB burden peri-urban township setting near Cape Town, called Khayelitsha. Here, the PEP was implemented over several years by the Sentinel Project, Médecins Sans Frontières, and the Department of Health of the Republic of South Africa. This was a project known as the "Khayelitsha PEP." While it focused predominantly on adolescents and children (≤18 years), the Khayelitsha PEP team found that delivery of the PEP needs to be family-friendly to be most effective. This means the PEP must be delivered to a complete living unit that includes persons of all ages. Throughout this field, we will note when the tools are specific for children/adolescents and when they can be applied to adults as well.

Who is this field guide written for?

This field guide is written for all cadres of health care workers caring for people with RR/MDR-TB. It is also relevant for policy makers and facility managers, since effective local implementation requires support from management at other levels. It is also written for impacted communities and civil society organizations so they can advocate for these services.

What exactly is the PEP?

The core components of the package are: (1) counseling/psychosocial support for the family of a person who has been newly diagnosed with RR/MDR-TB; (2) evaluation of all household members to assess for TB infections and disease; and (3) provision of treatment for either RR/MDR-TB disease or TB infection to household members

To understand the PEP requires clarity on what happens when TB enters the body. The transmission, infectiousness and pathophysiology of RR/MDR-TB is the same as drug susceptible-TB, so we will only refer to "TB" in this section. An individual becomes exposed to *Mycobacterium tuberculosis* by inhaling the TB germ that is in the air (i.e., if they share the same air with someone who has TB). Following this exposure, one of two things may happen: either (1) the person's immune system may either eradicate the bacillus or try to control it by walling it off; or (2) the TB germ may overpower the immune system and result in TB disease. Disease can sometimes develop immediately after exposure, especially in young children. Other times, the TB germ is initially controlled (sometimes for years) but later overpowers the immune system. This may happen if the immune system is weakened (i.e., due to malnutrition, HIV, cancer, or diabetes, among others). Most PEP interventions focus on eliminating the TB germ from the body after a person has been infected but before he or she becomes sick with TB disease. Additional information on the pathophysiology can be found in Annex A.

The PEP is an RR/MDR-TB **post-exposure package of care** that has been tried and tested in field settings. It is a series of actionable steps that are initiated in response to a person receiving a diagnosis of RR/MDR-TB disease, discussed in Part 2 and summarized in Table 2.1 (p 8).

Why should TB programs deploy the PEP?

There are multiple compelling reasons for programs to deploy an RR/MDR-TB PEP program, including:

- TB prevention is an essential intervention and must be deployed effectively to reach the EndTB goals.
- The PEP is a highly effective active case finding strategy, especially for children and adolescents. Early diagnosis and treatment results in better outcomes and minimizes sequela from TB such as post-TB lung disease.
- Households in which one person has been diagnosed with RR/MDR-TB routinely request measures to prevent RR/MDR-TB in the other persons living there.
- The PEP is effective in preventing RR/MDR-TB and has been recommended by the WHO.
- The PEP is cost effective and can save the health system tens of millions of dollars.

There is compelling evidence to support RR/MDR-TB PEP and a strong recommendation from the World Health Organization (WHO) that **all individuals with household exposure to RR/MDR-TB who are not sick should be offered treatment of infection.** This recommendation is based on two phase III, randomized, placebo-controlled trials comparing six months of levofloxacin with placebo (TB-CHAMP and VQUIN, Box 1A and 1B). When the data from these two studies were combined, a statistically significant 60% reduction in incident TB disease was seen in persons who received six months of levofloxacin compared with placebo. The levofloxacin was also found to be safe and well-tolerated

BOX 1A: TB-CHAMP

Tuberculosis Child Multidrug-Resistant Preventive Therapy Trial (TB CHAMP)

TB CHAMP is a randomized controlled trial that took place in South Africa. The primary objective was to assess the efficacy of six months of daily levofloxacin therapy, compared to placebo, in children exposed to bacteriologically confirmed pulmonary MDR-TB in the household in the past six months. These household contacts between age five years and <18 years had to be either living with HIV or have a positive IGRA.

Baseline screening for contacts included PA and lateral CXR and symptom screen. From 5063 persons with MDR-TB, 922 children were enrolled from 497 households (453 children received levofloxacin).

***Efficacy*:** Levofloxacin was found to be effective at reducing the risk of incident TB. The primary analysis found a hazard ratio(HR) of 0.44 (0.15-1.25 95% CI, P= 0.12; per protocol: 0.50 (0.17-1.45 95% CI, P=0.20)). For children younger than five years, this protection was slightly reduced (HR of 0.54 (0.18-1.16)). *Pooled results with VQUIN (see study description below)*: TB CHAMP and VQUIN results were analysed together using Bayesian analysis. The results of this overall individual patient data (IPD) meta-analysis of TB disease by 54 weeks was a HR of 0.40 (0.17-0.90 95% CI). The number needed to treat to prevent one TB case by 54 weeks was 56 (30-389).

Safety: Levofloxacin was very safe, with fewer grade 3 or higher adverse events in the intervention group than in the group receiving placebo (HR 0.52 (0.16-1.71 95% CI, p = 0.285)). Only six children in the levofloxacin arm discontinued treatment due to an adverse event, compared to one child in the placebo arm.

Other takeaway messages: No cases of fluoroquinolone resistance were detected in participants who developed incident TB disease. While a positive IGRA was used as an inclusion criterion for those over age 5 years, the majority of children with incident TB disease had a negative IGRA. Many fewer participants than expected were IGRA positive at baseline. This suggests the limited use of IGRA's in post exposure management programs.

BOX 1B: THE VQUIN TRIAL

VQUIN Trial

VQUIN was a randomized controlled trial that took place in Vietnam. The primary objective was to assess the efficacy of six months of levofloxacin therapy, compared to placebo, in individuals exposed at home to RR/MDR-TB (dosing and outcomes were aligned with TB CHAMP, which looked specifically at children; additional Bayesian analysis combined data from the two trials). Inclusion criteria specified that household contacts had to have either a positive tuberculosis skin test or conversion to positive for enrolment. 2041 persons were randomized, 1018 received levofloxacin therapy (83% completed therapy per protocol). Median age of persons enrolled was 40 (28-52), and 0.4% living with HIV.

Efficacy: Levofloxacin was found to be effective at reducing the risk of incident microbiologic TB by 45% at 30 months (incidence rate 0.55 (0.19-1.62) 95% CI, P= 0.278), although low event numbers resulted in wide confidence intervals (and a p value that was not significant). Secondary Bayesian analysis with combined results with TB CHAMP at 54 weeks found a 59% reduction in TB disease incidence. The number needed to treat to avert one case of TB was 192 (138-2272 people).

Safety: Levofloxacin was safe and well tolerated. Most persons receiving levofloxacin reported no adverse events at all (87%). There were very few grade 3 or higher adverse events in the intervention group (risk difference 1% (-0.3-2.4, p = 0.140).

Other takeaway messages: No cases of fluoroquinolone resistance were detected in participants who developed incident TB disease. Three times as many co-prevalent TB disease cases as incident cases were found, highlighting the importance of post exposure care as an active case finding strategy.

Another exciting study further supporting active interventions for persons exposed to RR/MDR-TB in the household is the RATIONS trial from India (Box 1C).

BOX 1C: THE RATIONS TRIAL

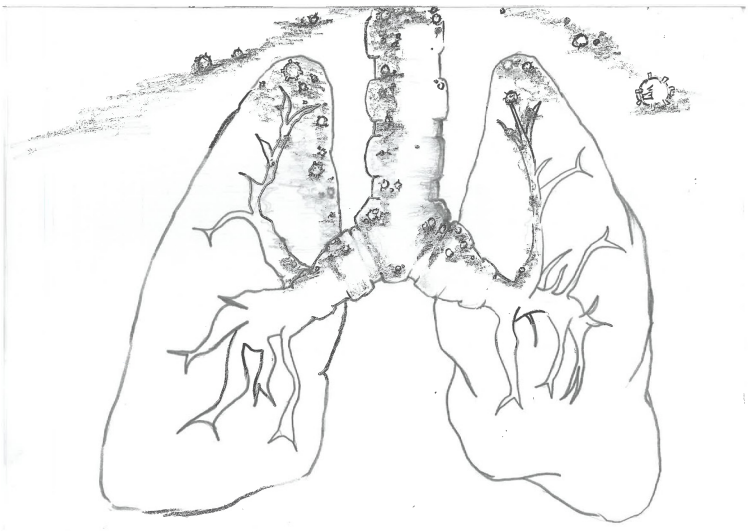
RATIONS Trial

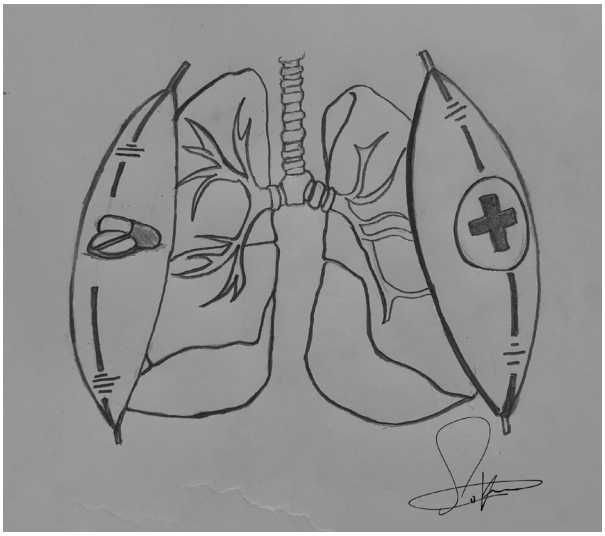
The RATIONS trial was a cluster-randomized study that took place in Jharkhand, India. It assessed the impact of modest nutritional support for household members in the homes of persons who were newly diagnosed with TB. In the control period, only people diagnosed with TB were offered nutritional supplementation for six months while they were on TB disease treatment (1200kcal, 56 grams of protein, and micronutrients). In the intervention period, all close household contacts were also offered a nutritional support package. This package consisted of 750kcal, 23 grams of protein, and micronutrients daily, for a total of six months. The eligibility criteria for the household contacts included living in the same house, eating from the same kitchen for one or more nights, or for frequent and extended periods during the day in the preceding three months and not currently on treatment for tuberculosis. 5328 contacts were enrolled in the intervention period and 4724 in the control period.

Efficacy: Tuberculosis incidence (all forms) in the intervention group had an adjusted incidence rate ration (IRR) of 0·61 (95% CI 0·43–0·85; aHR 0·59 [0·42–0·83]), with an even greater decline in incidence of microbiologically confirmed pulmonary tuberculosis (0·52 [0·35–0·79]; 0·51 [0·34–0·78]). This translates into a relative reduction of tuberculosis incidence of 39% (all forms) to 48% (microbiologically confirmed pulmonary tuberculosis) in the intervention group. An estimated 30 households (111 household contacts) would need to be provided nutritional supplementation to prevent one incident tuberculosis.

Safety: The nutritional support was safe.

Key takeaway messages: Nutritional support is as effective as many medications in preventing the development of TB in household contacts. Nutritional support should be provided to all household contacts for 6 months as a key intervention to prevent TB.





Where should the PEP be deployed?

The PEP is designed to be deployed anywhere that people are diagnosed with RR/MDR-TB. The PEP should be adapted to take into account the local context. Implementing the PEP may seem overwhelming, especially in high-burden TB settings. Our collective experience is that one must decide to start somewhere—no matter how small it may seem.

PART 2: THE HOW OF THE PEP

RR/MDR-TB PEP: a five-action approach

Overall, there are five key actions (Table 2.1) to complete for all households of people newly diagnosed with RR/MDR-TB. We like to think of these as the five fingers on a hand. The hand is reaching out to welcome all people exposed to RR/MDR-TB in their households, and each finger is needed to offer a "handshake of partnership" to those who are at risk. Each action is reviewed in more detail below.

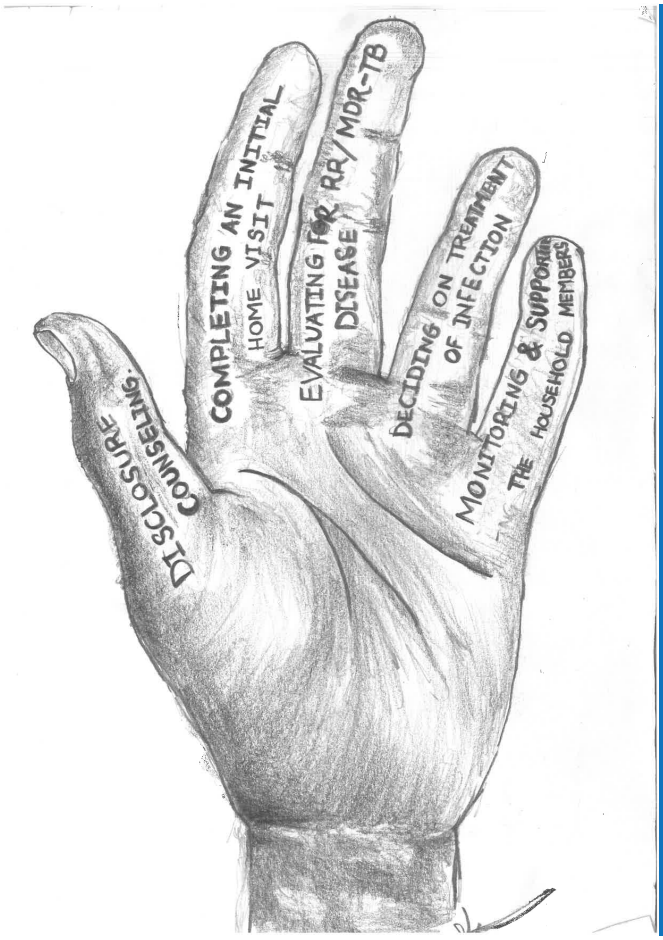


TABLE 2.1: ACTIONS INVOLVED IN PEP

Step / Action	Details
1. Identify close contacts through disclosure counselling	Done by a trained or experienced health care worker or counsellor with the person newly diagnosed with RR/MDRTB and includes: • a review of reasons to disclose RR/MDR-TB status to household members; • a role playing or practice disclosure session; • identification of a trusted person to disclose to first; • selection for site of disclosure (clinic, home); • identification of possible consequences of disclosure; and • development of an action plan following disclosure. *Disclosure counselling could span over more than one contact session depending on the reaction, and receptiveness, of the person who is given a diagnosis of RR/MDR-TB during the interaction.*
2. Perform a home visit (if permission given and visiting the home is acceptable)	Done by a health worker who is familiar with the community and includes: • identifying the time, date, and location of the visit; • avoiding inadvertent disclosure or increasing stigma to family; • identify individuals who have been exposed to RR/MDR-TB at the household level; • identifying socioeconomic family needs.
3. Evaluate for RR/MDR-TB disease (select location of evaluation convenient, and preferred, by contacts)	Done by a clinically trained health worker and includes: • Offering HIV testing; • Plotting weight and height (on growth curve for children/adolescents); • Assessing for symptoms; • Assessing exposure level using formal scale • Performing basic physical examination; • Determining who needs a chest radiograph (posterior-anterior [PA] and lateral) and referring those individuals for services *Transportation support should provided for family to attend any assessments that will be done outside of the home. Testing and CXR done should be done at no charge.*
4. Initiate medication treatment of infection and nutritional support.	Done by a clinically trained health worker and includes: • Levofloxacin for six months for household members exposed to fluoroquinolone-susceptible RR/MDR-TB; • High-dose isoniazid or delamanid as options for contacts exposed to fluoroquinolone-resistant MDR-TB. • Provision of medication treatment in two- or three-month intervals for a total of 6 months. • Provision of nutritional support to all household members in two- or three-month intervals for a total of 6 months.
5. Monitor and support household contacts	Done by a clinically trained health worker and includes: • contacting household members every two or three months until completion of treatment of infection; • refilling medications; • replenishing nutritional packages of support; • supporting adherence as needed • documenting TB status of each household members at the end of 6 months.

ACTION 1: IDENTIFY CLOSE CONTACTS THROUGH DISCLOSURE COUNSELLING

Define a close contact

Programs need a clear operational definition of a close contact of someone diagnosed with RR/MDR-TB so they can offer interventions. It is important to consider contextual social factors when deciding on this definition. For example, some communities may not have such clear distinctions between households. The Khayelitsha PEP defined them as 'all persons who share the living, eating and sleeping space (within the same building) with the first person diagnosed with RR/MDR-TB'. Box 2A gives definitions of household contacts used in other settings.

BOX 2A: EXAMPLES OF HOUSEHOLD DEFINITIONS

Examples of other definitions that can be used to define close contacts:

A definition which makes provision for persons who have had prolonged exposure in a creche, school, or at work may be: 'Anyone who has shared the same enclosed space or living arrangement one or more nights, or for frequent or extended daytime periods before the index case was started on treatment.'

An operational definition that takes into consideration social contacts may be 'Household contacts and close social contacts, including all persons who have been in proximity with the first case for at least 8 consecutive hours on a single day, or for a total of at least 15 hours per week for multiple weeks.'

The **first action** indicated by the PEP involves identifying close contacts during a counselling session(s) with the person newly diagnosed with RR/MDR-TB. Being newly diagnosed with RR/MDR-TB can be overwhelming. In addition to being physically unwell, there are multiple implications of being diagnosed with RR/MDR-TB that include complex long drug therapy, stigma, loss of time from work and potentially catastrophic financial implications. Persons newly diagnosed may also be dealing with feelings of guilt and concern over family members who are at risk of RR/MDR-TB in their home, particularly children. For these reasons, it is extremely important to provide compassionate disclosure counselling (Part 3: Action 1, p 32) and health education as part of post-exposure management.
Action 1 should be done in conjunction with steps 1-2 noted in Table 2.1. A contact register can be extremely helpful in documenting contacts and ensuring that they are followed up [see Part 4: Forms 4.1-4.3 (p 48-50) for an example].

ACTION 2: PERFORM A HOME VISIT

A home visit is an invaluable tool and next step in identifying contacts, as well as identifying additional psychosocial support needs for the first person in the home diagnosed with RR/MDR-TB. Our collective experience from the field is that that there are often more close contacts then initially reported.

It is important to ensure that home visits are only conducted with permission, and where it is acceptable to the first person diagnosed with RR/MDR-TB and their family. A visit from a health care worker can be stigmatizing and lead to inadvertent disclosure to the family or community, particularly if persons conducting the home visit are easily identifiable as a TB health care worker. Home visits should be conducted by someone the person trusts and who is familiar with the community. Home visits should be pre-arranged for a time

convenient for the family. In the Khayelitsha PEP, a valuable lesson learned was for health care workers to arrive in plain clothes and without branded vehicles (so that they are not identified as TB workers). Cadres of staff such as community health workers may be ideal for home visits. For more information on home visits, see Part 3 (p 33-35) of this field guide.

ACTION 3: EVALUATE FOR RR/MDR-TB DISEASE

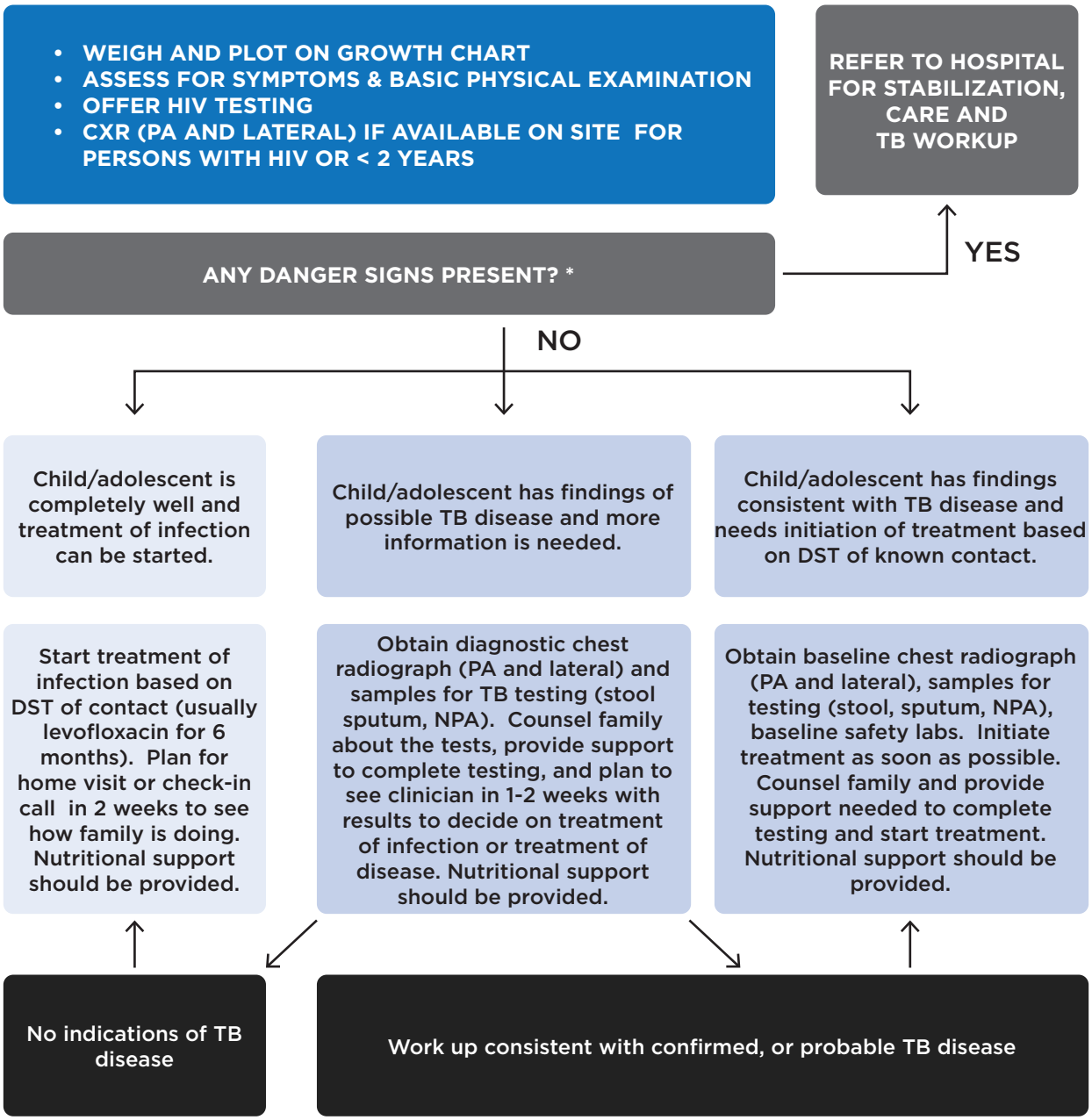
TB programs around the world should already be doing this step as part of the programmatic management of drug-resistant TB, and such evaluation has been recommended by the WHO for more than a decade. Usually, this involves care providers telling the person newly diagnosed with RR/MDR-TB to have their contacts come to the clinic for evaluation. Under such circumstances, it is not surprising that limited action is taken. We suggest that a more person-centered approach to step 3 be followed, as outlined below.

Evaluate close contacts: when and where?

Close contacts should be evaluated at a time and place that is convenient for them. Children and adolescents who are close contacts are often well and may be attending school or creche while their parents are working. Adults who are close contacts may be busy with other job or social responsibilities. For many families, a clinic appointment may interfere with these obligations and could have financial implications. Furthermore, TB clinics are often not child friendly and may be an infectious risk, as this is where persons present for treatment initiation for TB and RR/MDR-TB. It is helpful to provide families with options of where they would like to be evaluated, including their homes or other community venues. Referral to a health facility can be done if further investigation or management is needed. Programs should try to evaluate all household contacts within 1-4 weeks, and sooner if any are reported to be unwell.

Key decision points when evaluating close contacts who are children and adolescents

ALGORITHM 2.1 SUMMARIZES THE MAIN DECISION POINTS WHEN EVALUATING CHILD AND ADOLESCENT CONTACTS FOR RR/MDR-TB.



***Danger signs include:**

- Unable to eat or drink, or vomiting everything;
- Severe dehydration or signs of shock;
- Respiratory distress, obstructed breathing, cyanosis, pallor or decreased oxygen saturation;
- Seizures, neck stiffness or bugling fontanelle or reduced level of consciousness.

A simple screening approach uses a combination of symptoms, weight, and physical examination. CXR can be added for high-risk groups or for people with signs or symptoms of TB (i.e. weight "falling off" usual growth curve, lymphadenopathy on exam). Evaluation should categorize persons into three groups:

1. Completely well where treatment of medical TB infection can be started promptly;
2. Findings indicate possible TB and more diagnostic information is needed; or
3. Findings are consistent with TB disease and treatment of disease should be started promptly.

Children or adolescents with danger signs at any point of an evaluation should be promptly referred to hospital for stabilization, care, and TB workup (and treatment initiation if indicated). Box 2B presents a clinical case demonstrating this approach.

BOX 2B: PATIENT SCENARIO ON DECISION POINTS

Scenario from the field: Decision points in the PEP and family-centered care in action

Nomzuzu (all names changed) is a 43-year-old woman who was recently diagnosed with MDR-TB in Khayelitsha, South Africa. Her brother who lives with her is unwell and bedridden with drug susceptible TB. Nomzuzu has three children that live with them: ages 16, 10, and 2 years. After disclosure counselling and getting permission from Nomzuzu, a nurse visits the family in their home for TB evaluation of the children. A symptom screen and physical exam is done. The 16-year-old girl is well with no TB symptoms and a normal exam and is started on levofloxacin for 6 months on the same day.

The 10-year-old girl, Sixolo, is living with HIV (on antiretrovirals with a last viral load suppressed); she reports a 7-day history of coughing and no other symptoms. On clinical exam she has a temperature of 37.8 C, and her respiratory rate is within normal range. However, she has abnormal breath sounds in the right middle zone. The nurse refers her to the clinic for further CXR and evaluation by a doctor.

The 2-year-old boy—Ludo (formula fed since birth)—is well with no concerns raised by Nomzuzu. However, the nurse hears him coughing. On exam she notes that, although he is a normal weight for age, his weight is unchanged from the last weight done at the clinic 3 months ago. The oral HIV test is negative. Given the nurse's findings, she refers to the clinic for CXR (PA and lateral) and further evaluation.

Nomzuzu attends the clinic with Ludo and Sixolo on the following day for CXRs. The doctor sees both children with the CXR results. Ludo's CXR shows hilar nodes on the lateral film. The doctor counsels Nomzuzu that findings are in keeping with TB disease; the doctor asks if they can return the next morning for gastric washings and RR/MDR-TB treatment initiation. Nomzuzu is also referred to the RR/MDR-TB counsellor and for nutritional support.

Sixolo's CXR shows lobar consolidation, with no visible nodes and a normal cardiac shadow. The doctor suspects either a lobar bacterial pneumonia or TB lobar consolidation. Sixolo is able to produce sputum for Xpert. While awaiting results, Sixolo is started on amoxicillin with clavulanic acid. She returns for results and re-assessment 1 week later. Xpert results are positive for *Mycobacterium tuberculosis*; the RIF result is sensitive and she is started on drug-susceptible TB treatment by the TB nurse.

Follow-up care: Family-friendly follow-up care is provided in which Nomzuzu's and her children's appointments are booked for the same day to minimize her need to travel to the clinic. Ludo's gastric washing results are Xpert negative and so the plan is to complete RR/MDR-TB treatment. Nomzuzu provides feedback on how her 16-year-old daughter is doing with treatment of TB infection and collects medicine refills for her. This allows her to minimize missing school for clinic follow-ups.

More details of this approach are outlined in Table 2.2 below. Special considerations for adults are considered later in this section (p 20).

TABLE 2.2: DECISION POINTS, INFORMATION TO COLLECT, ACTIONS TO TAKE

Decision points	Information to collect / actions to take
Obtain brief medical history and assess for TB symptoms Children—especially young children and children living with HIV—may present atypically, which is why symptom screening alone is not considered a best practice.	The most common presentation of pulmonary TB in childhood is: • a non-remitting (typically >2 weeks) cough, OR • poor weight gain.
	In addition to the traditional four question WHO symptom screen, including • any duration of cough, • fever, • poor weight gain, or • night sweats, it is also helpful to ask about • lethargy, and • reduced playfulness.
	Weight and height should be assessed at • an initial visit after RR/MDR-TB exposure, • with a growth plateau, or • "falling off the curve." Either a growth plateau or falling off the curve raise concern for RR/MDR-TB disease.
Weigh and plot on growth chart. The weight of a child, ideally together with a height, should be regularly plotted on growth charts	All children with a growth plateau or who are not maintaining their curve should be further evaluated for RR/MDR-TB disease • with a complete physical exam, • chest radiography, and • collection of samples for TB testing.
	If malnutrition is identified this should be managed appropriately.
Perform basic physical examination	A clinical exam for a **close contact** should include • vital signs (including respiratory rate and temperature), and • palpating for cervical lymphadenopathy. This can be done by most cadres of staff, including lay health workers.
	Children or adolescents with signs or symptoms of TB disease should be referred for a more complete exam, including • respiratory, • cardiac, • abdominal, • lymph node and • joint/spine examination. This examination should be done by a nurse, clinical assistant, or doctor.

Decision points	Information to collect / actions to take
Test for and treat HIV	Some persons exposed to RR/MDR-TB may be living with HIV and already be on antiretroviral therapy. In such instances, • RR/MDR-TB screening, • treatment of infection, and • treatment of disease should be coordinated with the person's HIV care provider.
	Persons, including children, who do not know their HIV status or who have previously tested HIV negative should be offered • HIV counselling and testing at a time and location that is convenient and confidential. • This testing should be done according to local standards for HIV care.
Consider obtaining a chest radiograph (CXR) CXR can be an important diagnostic tool for TB. **In children** – where only a small proportion of TB will ever be microbiologically confirmed—CXR can be particularly helpful.	Not all household contacts need a CXR.
	CXR should be considered for • all young children (i.e. under the age of 2 years), and • anyone who is immunocompromised, regardless of findings that could suggest TB.
	CXR should be done for all persons with findings that could suggest TB as described above.
	Both a posterior/anterior (PA) and a lateral view should be obtained • to better assess for lymphadenopathy in children under the age of 10 years.
	TB can cause a range of CXR findings, but certain CXR abnormalities are more typical of TB, for example: • hilar lymphadenopathy, • pleural effusion, and • cavitary lesions.
	Some possible challenges with CXR for screening household contacts include: 1. Limited accessibility, 2. Problems with quality, and 3. Difficulties with interpretation.
	CXR must not be a barrier to getting PEP services.
	Programs should consider offering CXR services to those who need it most, for example: • children under 2 years, • persons living with HIV, or • those with signs or symptoms of TB.

Decision points	Information to collect / actions to take
Consider obtaining a specimen(s) for bacteriologic testing with rapid diagnostic	Because of the cost and invasive nature of bacteriological specimen collection, collecting samples in children should be reserved for: • diagnostic purpose for children and adolescents, • who have signs or symptoms of TB, or • who have a worrisome CXR
	For persons who can freely expectorate, the easiest diagnostic test is to send sputum for a WHO-recommended rapid molecular test, i.e. • Xpert MTB/RIF Ultra, or • TrueNAT.
	For younger children and those unable to expectorate, alternatives are: • stool, • gastric aspirate or • a nasopharyngeal aspirate.
	Children/adolescents with HIV can be tested using the urine lipoarabinomannan (LAM).
	Other samples, such as: • lymph node aspirate, and • cerebrospinal fluid can be obtained (depending on the clinical findings) and tested with WHO-recommended rapid molecular tests, • with the exception of pleural fluid.
	Due to the paucibacillary nature of TB in children, most bacteriological testing will be negative.
	Thus, the decision to start RR/MDR-TB treatment should be based on a combination of • history, • symptoms, • examination, and • radiology and not solely on bacteriology results.
	If treatment of disease is started, that treatment should be based on the drug-susceptibility results of known household contacts, given that there is an 80% rate of concordance.
	If bacteriological testing comes back with rifampicin susceptibility, treatment for drug-susceptible TB should be considered.

Decision points	Information to collect / actions to take
Consider an IGRA or TST only in contacts with a low-risk exposure See **Box 2E** for further discussion on tests of infection. See **Box 2F** for an example of an exposure scale.	Tests of TB infection **should not** be routinely offered as part of the PEP, given that they perform poorly in populations at highest risk of developing TB disease.
	Quantified exposure scales can serve as a reasonable proxy for TB infection and several have been validated in prospective studies (see Box 2.7).
	Tests of infection, namely • TST or • IGRA could be considered in populations with more limited contact with the person newly diagnosed with RR/MDR-TB, such as: • persons with exposure outside the household.

A review of CXR interpretation is beyond the scope of this field guide. *The Union's Diagnostic CXR Atlas for Tuberculosis in Children* (https://tinyurl.com/4ja2sf6m) can be a helpful tool as can various telemedicine platforms.

BOX 2C: COMPUTER-AIDED DETECTION

Computer aided Detection

Computer aided detection (CAD) is promising technology in which computers interpret radiographs (instead of people). This technology has been recently recommended as an option by the WHO for the screening of persons over the age of 15 through plain CXR. In time it is likely that software will also be validated for interpretation of CXR in younger age groups.

BOX 2D: RADIATION RISK OF CXR

Fact of Fiction: Concerns about radiation from CXR?

Some patients or clinicians may raise concerns that CXR exposes children to radiation. While it is true that children have a long life expectancy and therefore more time to develop negative radiation-related health effects, exposure to radiation is minimal with newer CXR methods.

On risk-benefit balance, the ill health impacts are likely very low compared to the risk of developing TB disease after a household exposure.

BOX 2E: PEP APPROACH TO IGRA AND TST

Clinical Controversies around the use of IGRAS and tests of infection in PEP

Tests of TB infection include the tuberculin skin test and interferon-gamma releasing assays (IGRAs). These tests measure if there is an immune response to *Mycobacterium tuberculosis*, suggesting that the bacteria has infected the body. TB infection tests cannot distinguish between TB infection and TB disease;cannot predict who will progress to TB disease; and may be negative in people whose immune systems are not functioning, including children and people living with HIV. What is sometimes confusing for clinicians is that although these tests are poor predictors of development of disease, some studies in drug susceptible TB suggest that the efficacy of treatment of infection may be higher in persons with a positive test of infection.

The latter may be one of the reasons why the IGRAs were used as part of the inclusion criteria for VQUIN and TB CHAMP in those over the age of 5 years. In these studies, treating only those persons ages 5 years and above with a positive IGRA was likely done to improve the rigor of the study. And based on these inclusion criteria, many programs may determine that an IGRA (or other test of infection) is needed prior to administering treatment of infection for RR/MDR-TB.

Unfortunately, these tests come with challenges. Skin tests can be difficult to interpret (particularly in populations with HIV or prior BCG vaccination) and require repeat clinic visits. IGRAs require blood draws and are expensive. Other limitations to these tests are that they are often negative in populations who are immunocompromised such as in infants and children, persons with HIV or suffering from malnutrition—ironically the populations at highest risk of developing TB after exposure. Interestingly in TB CHAMP, most children who developed incident TB had a negative IGRA, and few children had positive IGRAs at baseline. This casts doubt on the utility of this test in post exposure management programs. Our experience from Khayelitsha PEP and other field settings is that tests of infection are often barriers to PEP. Well-quantified exposure scales can serve as a proxy for tests of infection and an example of such a scale is included in Box 2F. For these reasons that our preference is not to recommend a TB test as part of PEP.

BOX 2F: EXAMPLE OF A WELL-QUANTIFIED EXPOSURE SCALE

Question	No	Yes
Is the person diagnosed with RR/MDR-TB the household contact's mother?	0 points	1 point
Is the person diagnosed with RR/MDR-TB the household contact's primary caregiver?	0 points	1 point
Does the person diagnosed with RR/MDR-TB sleep in the same bed as the household contact?	0 points	1 point
Does the person diagnosed with RR/MDR-TB sleep in the same room as the household contact?	0 points	1 point
Is the person diagnosed with RR/MDR-TB coughing?	0 points	2 points
Does the person diagnosed with RR/MDR-TB have pulmonary TB?	0 points	2 points
Does the person diagnosed with RR/MDR-TB have a positive sputum smear?	0 points	2 points
Does the person diagnosed with RR/MDR-TB live in the same household as the contact?	0 points	3 points
Does the person diagnosed with RR/MDR-TB see the contact every day?	0 points	3 points
Is there more than one person with TB living in the household of the contact	0 points	4 points
Total points		

A score of 6 or more points on this scale could be used to define TB infection instead of a TST or IGRA

Dealing with diagnostic uncertainty ("possible RR/MDR-TB") in children

Atypical presentations and forms of TB are more common in children than adults. Furthermore, children may not be able to report symptoms, thus their history relies on observations made by caregivers. Thus, there will often be a degree of uncertainty in ruling out RR/MDR-TB disease in children.
Our approach to managing this uncertainty is to work in partnership with the families to weigh the risks and benefits of treating for TB infection or treating for TB disease. When possible, additional evaluations could be considered if they do not place an undue burden on families or lead to lengthy delays. Any additional diagnostic tests should be followed up within 1 – 2 weeks. Where a bacterial pneumonia is in the differential diagnosis, a course of antibiotics can be prescribed (see Box 2G, p 19). Consideration of possible viral pathogens is discussed in Box 2H (p 20).

Sometimes, even at follow up, it may be unclear if the child has RR/MDR-TB disease or not. It is important not to repeatedly delay the decision around treatment of disease or infection as this carries a risk of loss from care. It may be helpful to obtain input from other providers (experts from the Sentinel Project are always available to assist virtually, email patient scenarios to tbsentinelproject@gmail.com). Otherwise, it is best to take a pragmatic decision within a risk-benefit framework (i.e., considering the risk of overtreating RR/MDR-

TB, versus the risk of undertreating it). For children with the following risk factors, in the face of diagnostic uncertainty, it is usually safest to err on the side of treatment of disease.

- Under 2 years old (as this age group is at highest risk of mortality as well as for developing severe TB disease including disseminated or central nervous system forms).
- HIV status: children with HIV are at increased risk of TB disease as well as death.
- Family circumstances: inability of caregiver to monitor for worsening condition and access to emergency care if needed.
- Nutritional status of child: malnutrition has been linked with an increased risk of TB disease, particularly in children with severe acute malnutrition.

Important consideration: children that are started on presumptive treatment for RR/MDR-TB disease should be monitored for treatment response. If their clinical condition does not improve, continue RR/MDR-TB treatment while investigating for other diagnoses as well as other factors that may relate to poor clinical response (i.e., not taking treatment).

BOX 2G: APPROACH TO EMPIRIC ANTIBIOTICS

Clinical Controversy: to give or not to give antibiotics?

In the past, many TB guidelines have recommended a "trial of antibiotics" (usually a broad-spectrum antibiotic that is not effective against TB) for a person with symptoms of *Mycobacterium tuberculosis* disease without sufficient test results to support starting treatment. The reasoning behind this approach is that treatment response to antibiotics could be used to distinguish TB from bacterial pathogens. While antibiotics are appropriate in some persons with TB symptoms (for example, where features are in keeping with a bacterial pneumonia: high fevers and chest findings or lobal consolidation on CXR), a blanket recommendation for all persons with TB symptoms and diagnostic uncertainty to receive a trial of antibiotics is not evidence-based and may contribute to antimicrobial resistance.

Recent data from systematic reviews have found that a "trial of antibiotics'— compared with mycobacterial tests— were below internationally defined minimum performance profiles for TB diagnostics. In addition to being a poor "TB diagnostic test," a randomized controlled trial in children (ages 6 months – 12 years) found that antibiotic (amoxicillin) use in in non-pneumonitic/uncomplicated lower respiratory tract infections did not reduce symptom severity or duration and thus should not routinely be prescribed.

When deciding whether to prescribe antibiotics in a person with TB diagnostic uncertainty, it is important to consider additional factors such as the age of the child. Young infants are at high risk of severe bacterial infections (as well as TB) and so the threshold for prescribing antibiotics should be lower than for other groups. Infants under three months with a possible bacterial infection should always be referred to hospital for septic workup and evaluation for broad spectrum antibiotics, in addition to workup and decision around TB. Another key consideration is that children often have bacterial complications of viral illnesses (for example what starts as a viral upper respiratory infection can result in otitis media)— and these complications may require antibiotics. Finally, it is also important to consider the family's ability to follow up and ability to access acute care and respond to warning signs. Where a family has very poor access to health facilities and acute care, this may warrant a lower threshold for prescribing antibiotics.

BOX 2H: APPROACH TO VIRAL INFECTION

Clinical Case from the Field: Coughing child— viral infection or TB?

A mom who has recently been started on treatment for RR/MDR-TB disease brings her 3-year-old daughter, Nelly, for TB evaluation. Nelly has a 2-week history of cough with no other TB symptoms. She has an appropriate weight for age and an unremarkable clinical exam, except for a few small cervical lymph nodes. The ear, nose, and throat exam is normal. Her HIV test is negative. There are no CXRs available on site.

Evaluation by nurse: findings of possible TB.

Plan: child is sent for PA and lateral CXR at nearest facility and advised to bring stool for Xpert testing. She is provided nutritional support and given a follow up in two-weeks' time.

Two weeks later: CXRs were not able to be done (due to power outages), and mom did not bring stool for Xpert. However, Nelly's cough has resolved and her follow-up exam is normal. Thus, the nurse starts Nelly on levofloxacin preventive therapy for 6 months.

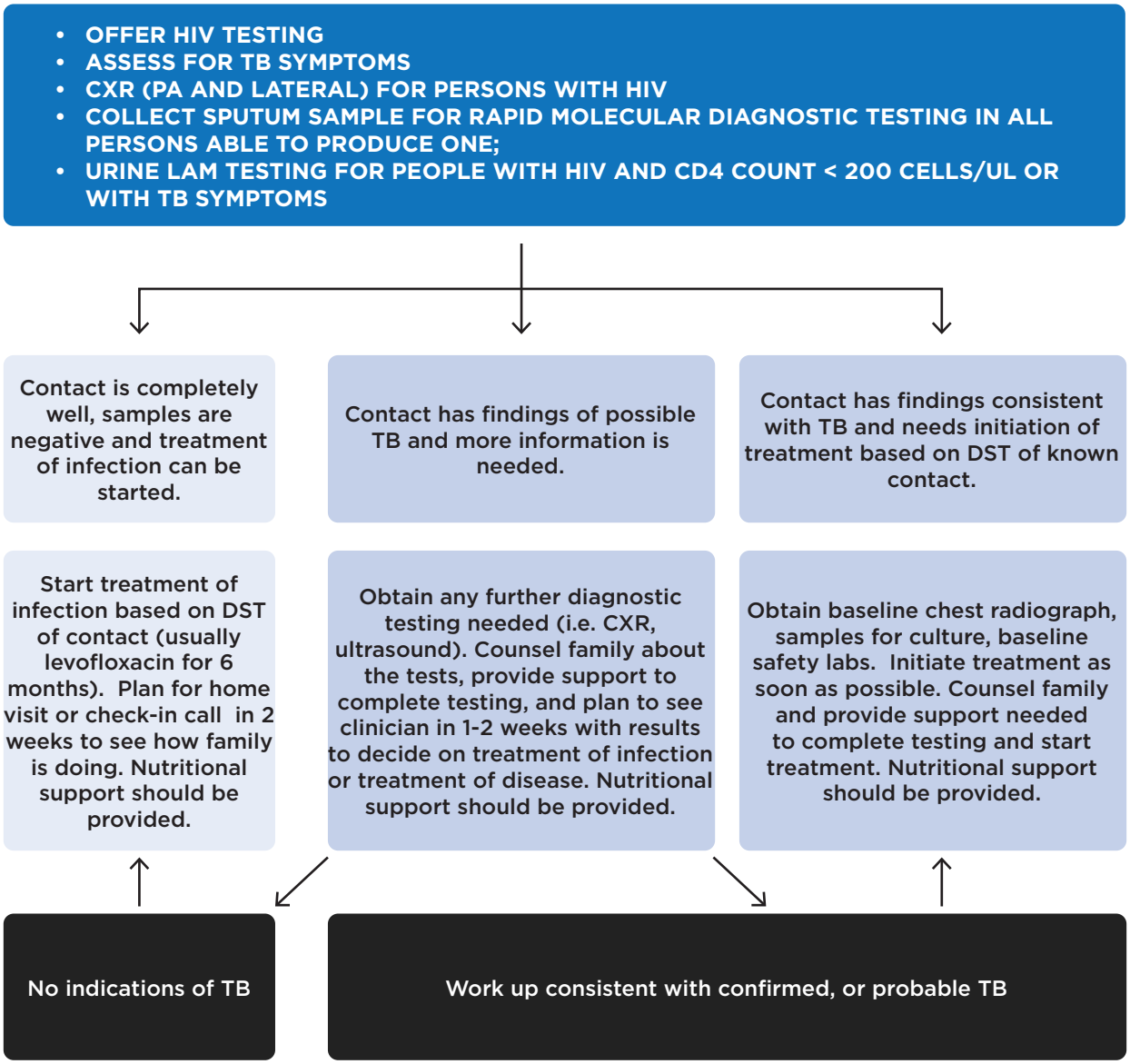
Discussion: Children can have as many as 4-6 episodes of viral upper respiratory tract infections per year, so symptoms such as cough are very common and not sensitive for TB. Most viral causes of cough will be self-limiting and will improve after a week or two, whereas a TB cough will tend to be persistent. In this case the child was low risk (>2 years old, not with HIV, and without warning signs). A follow-up visit was a helpful and appropriate approach to determine if the cough was a symptom of TB or of another childhood illness.

Special considerations in adult contacts of newly diagnosed RR/MDR-TB

Adult contacts of persons newly diagnosed with RR/MDR-TB should also be evaluated for RR/MDR-TB disease using a similar strategy. There are some screenings and assessments, however, that differ in the adult population. In general, unless they are living with HIV, most adults present with classic symptoms of TB, such as fever, cough, weight loss and night sweats. Compared to children, adults are also more likely to have pulmonary TB disease and to be able to produce sputum samples. Additional considerations in adults include:

- Weight should be assessed in all adults as part of the RR/MDR-TB PEP, but weight fluctuations are more common in adults and are not as key in making a TB diagnosis as in children;
- Prior to starting medication treatment of TB infection, tests of infection (i.e. IGRAs) are not required for adults who have had household exposure to someone with RR/MDR-TB disease. Rather, exposure scales could be used to assess risk of TB infection. Please refer to the discussion on this topic in the section on children/adolescents.
- All adults should be asked to provide a sputum specimen for testing using a rapid, molecular diagnostic test. If the person has a negative sputum specimen and does not report any symptoms of TB, then s/he can reasonably be started on treatment of TB infection. If the sputum is tested using a WHO-recommended molecular test, then results should be available within a matter of hours to days. If, for any reason, results are delayed, asymptomatic adults who are completely well could be started on medication treatment of infection even in the absence of sputum test results.

ALGORITHM 2.2 BELOW SUMMARIZES THE KEY PEP DECISION POINTS IN ADULTS



ACTION 4: INITIATE TREATMENT OF INFECTION AND NUTRITIONAL SUPPORT

Household contacts who are assessed and who are unlikely to have RR/MDR-TB disease should all be offered a PEP package. This package consists of nutritional supplementation, medication treatment of infection, and psychosocial counselling (see Algorithm 2.3, page 23 and Part 3 pages 31-42). Medication should be provided with appropriate health education and adherence support (see Part 3, p 31-42). Psychosocial support is reviewed in detail Part 3 (p 31-42).

Nutritional supplementation

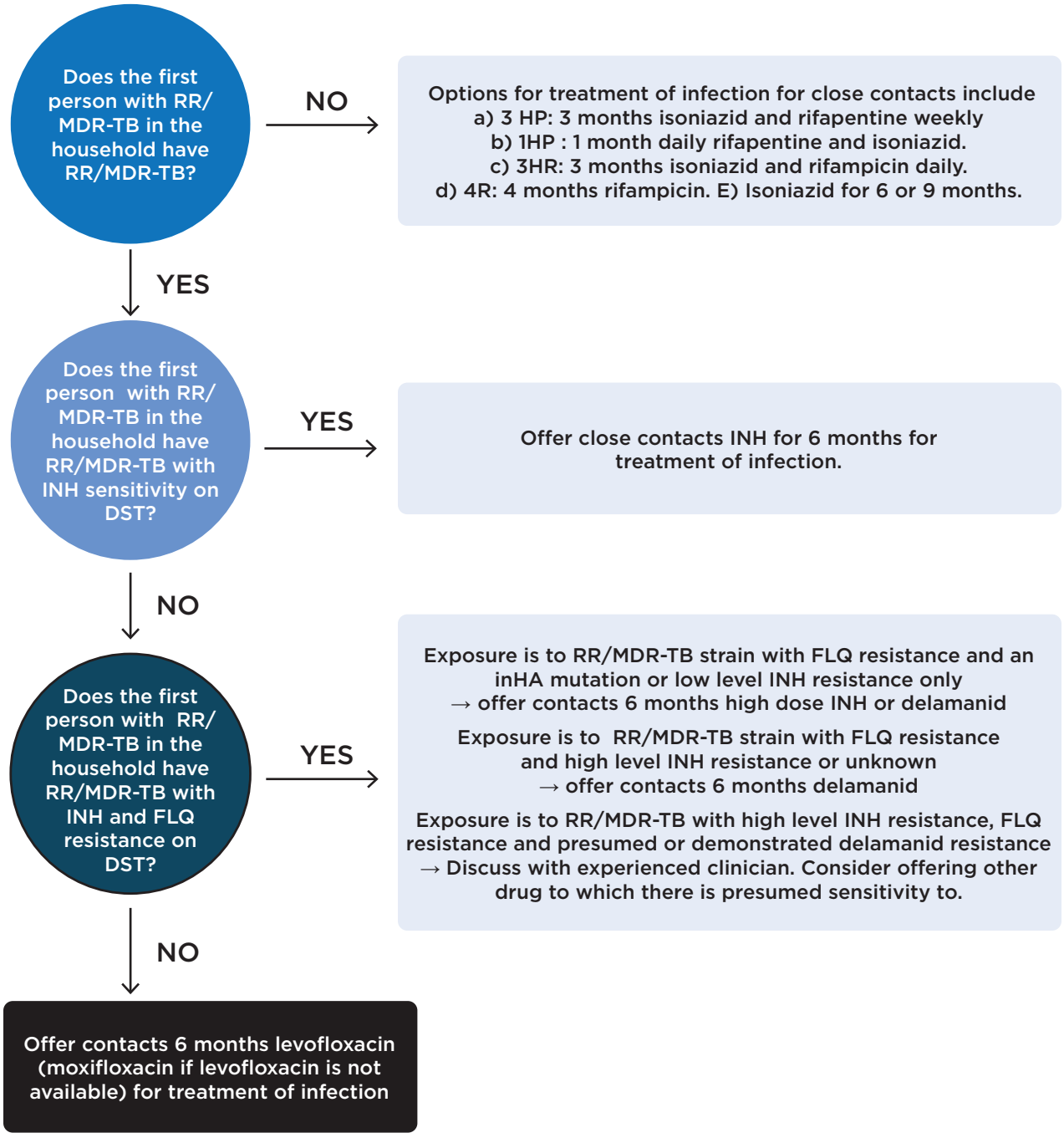
Recently, high-quality data from India have demonstrated that modest nutritional support is effective in preventing TB among household contacts (see Box 1C in Part 1, p 6). Nutritional support is also a valuable incentive for increasing retention in care of persons on TB treatment. Thus, nutritional supplementation is a key component of the RR/MDR-TB PEP. The detailed composition and logistics of nutritional support packages will depend on the context. Support could include cash transfers, food vouchers or food parcels, and these should be provided for the entire household and mirror the components of the RATIONS trial (750kcal, 23 grams of protein, and micronutrients given daily for 6 months).

In the Khayelitsha PEP, a monthly food parcel was distributed to each family. Providing this support has the additional benefit of strengthening the relationship between the health care provider and families. Nutritional support motivates families to remain engaged in care. ***If no other preventive measures are taken, at the very least all household contacts of persons newly diagnosed with RR/MDR-TB should be given nutritional support for 6 months.***

Medication treatment

Algorithm 2.3 is a decision tree that can be used to decide on which medication treatment of TB infection to offer.

ALGORITHM 2.3: DRUG SELECTION FOR MEDICAL TREATMENT OF INFECTION



Guidance on medications for treatment of TB infection, based on the drug-susceptibility profile of the RR/MDR-TB to which the contact has been exposed, is presented in Table 2.3. General consideration before initiating medication treatment of TB infection:

1. It is helpful to screen the person for any contraindication or drug-drug interactions.
2. For children there are very few contraindications to medical treatment.
3. Overall, the drugs commonly used for treatment of RR/MDR-TB infection can be safely used with HIV therapy.
4. There are also very few drug-drug interactions with other medications used for most chronic conditions.

Table 2.3 reviews considerations in deciding on the specific medication to be used in treatment of infection

TABLE 2.3: GUIDANCE FOR CHOOSING DRUGS FOR TREATMENT OF INFECTION

Presumed or confirmed RR/MDR-TB resistance profile of first person diagnosed with RR/MDR-TB, to whom contact was exposed	Choice of medication therapy for close contact
Rifampicin mono-resistant TB with confirmed INH susceptibility	Isoniazid (5-10mg/kg/day) for 6 months OR Levofloxacin (20mg/kg/day—not to exceed 1000mg daily) for 6 months (For weight-based dosing see Table 2.4; p 25)
Multidrug resistant TB with presumed or confirmed fluoroquinolone sensitivity	Levofloxacin (20mg/kg/day—not to exceed 1000mg daily) for 6 months. If levofloxacin not available, use moxifloxacin (10-15mg/kg/day—not to exceed 800mg daily) for 6 months. (For weight-based dosing see Table 2.4; p 25)
Multidrug resistant TB with fluoroquinolone resistance	High dose isoniazid (10-15mg/kg/day) for 6 months if low level isoniazid resistance demonstrated (i.e., *inhA* mutation) OR Delamanid for 6 months (For weight-based dosing see Table 2.5; p 25)
Multidrug resistant TB with high level isoniazid resistance, fluoroquinolone resistance, and presumed or confirmed delamanid resistance	Discuss with an experienced clinician. Short course linezolid for 1 – 2 months may be an option to consider.

TABLE 2.4: WEIGHT-BASED DOSING OF LEVOFLOXACIN

Levofloxacin 100mg scored, dispersible tablets Recommended dosing: 15-20mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**Number of 100mg tablets**	**Number of 250 mg tablets**
1kg	20mg	Mix 100mg tablet in 10ml of water and administer 2ml of mixture immediately	-
2kg	40mg	Mix 100mg tablet in 10ml of water and administer 4ml of mixture immediately	-
3kg	50mg	0.5	-
4-6kg	100mg	1	0.5
7-9kg	150mg	1.5	0.5
10-12kg	200-250mg	2.0 to 2.5	1
13-15kg	300mg	3	1-1.5
16-18kg	300-350mg	3-3.5	1.5
19-20kg	400mg	4	1.5
21-23kg	400-450mg	4-4.5	2
24-25kg	500mg	5	2
26-35kg	750mg	-	3

TABLE 2.5: WEIGHT-BASED DOSING OF DELAMANID

Delamanid Recommended dosing: 3-4mg/kg/day (dose extrapolated from adult dosing for those less than 10 kg) Weight-based dosing			
Weight Band (kg)	**Dose**	**25mg tablet**	**50mg tablet**
3-4.99kg	25mg once daily	1 tablet daily	Half a tablet (0.5 tablet) daily
5-6.99kg	25mg twice daily	1 tablet twice daily	Half a tablet (0.5 tablet) twice daily
7-9.99kg	25mg twice daily	1 tablet twice daily	Half a tablet (0.5 tablet) twice daily
10-15.99kg	25mg twice daily	1 tablet twice daily	Half a tablet (0.5 tablet) twice daily
16-23.99kg	50mg morning, 25mg even	2 tablets morning, one tablet evening	One tablet morning, half a tablet (0.5 tablet) evening
24-29.99kg	50mg morning, 25mg evening	2 tablets morning, one tablet evening	One tablet morning, half a tablet (0.5 tablet) evening
30-49.99kg	50mg twice daily	2 tablets twice daily	One tablet twice daily
> 50 kg	100mg twice daily	4 tablets twice daily	Two tablets twice daily

Note that the 50mg tablet of delamanid when it is crushed, manipulated, or mixed does not result in the same blood levels as the 25mg pediatric formulation. Until the 25mg pediatric formulation is available, the 50mg tablet should be used with caution. Split tablets should not be saved for later administration for time periods longer than 12 hours.

Special consideration when initiating treatment of TB infection for adults, children and special populations.

- **Levofloxacin**

  Levofloxacin was found to be safe and well-tolerated in both the VQUIN and TB CHAMP trial.

  Children: Levofloxacin is safe to use in children of all ages at a dose of 20mg/kg/day. Levofloxacin should be dosed at 20mg/kg/day in children/adolescents. Weight- and age-based doses recommended for levofloxacin are specified in Table 2.4 (p 25)

  Adults: Levofloxacin should be dosed at 15-20mg/kg/day in adults, with a maximum dose of 1000mg daily.

- **Delamanid**

  Delamanid is a nitroimidazole medication which is effective and safe for the treatment of RR/MDR-TB disease. The use of delamanid as treatment of infection is being investigated in the PHOENIx MDR-TB prevention trial, with results anticipated in 2026. It is generally felt to be safe, although it may cause sleep disturbances in children/adolescents. It may be considered as a best clinical practice for people exposed to FLQ-resistant strains of RR/MDR-TB after discussions with them about the risks and benefits.

  Children: Children less than 3 months of age should receive delamanid at a dose of 25mg daily, and this dose should be used regardless of the weight.

  For children age 3 months or older, weight-based dosing as specified in Table 2.5 (p 25)

  Adults: Delamanid is dosed at 100mg twice a day in adults.

- **Other drugs used for treatment of RR/MDR-TB infection**

  Rarely, medications other than levofloxacin or delamanid are needed for treatment of RR/MDR-TB infection as part of a best clinical practice. The most common scenario is where the exposure is to a highly resistant strain of RR/MDR-TB. In these instances, in may be helpful to discuss with experts in the treatment of RR/MDR-TB infection, either locally or via the Sentinel Project (tbsentinelproject@gmail.com).

- **Considerations in special populations**

  Women/people who are pregnant are at high risk of becoming sick from all forms of TB, including RR/MDR-TB. They are usually excluded from studies on TB preventive therapy. For example, there were no pregnant women/people included in the TB-CHAMP or VQUIN studies.

  Pregnant women/people who are exposed to RR/MDR-TB in the household should be assessed for TB disease and, at a very minimum, offered 6 months of nutritional supplementation. The medications used to treat RR/MDR-TB have all been safely used during pregnancy and medication treatment of infection is considered best clinical practice in pregnant women/people as part of a comprehensive PEP. Shared

decision making between the care providers, the pregnant woman/person, and other family members designated by the pregnant women/person is crucial when considering medical therapy.

Newborns whose mothers have been diagnosed with RR/MDR-TB during pregnancy should each have a comprehensive evaluation for congenital TB (Management of Drug-Resistant Tuberculosis in Pregnant and Peripartum People: A Field Guide at https://tinyurl.com/bdctussu).

Once congenital/neonatal TB disease is excluded in the newborn, the newborn should be started on treatment of infection depending on the drug susceptibility profile of their mother. All efforts should be made to access paediatric formulations. If a newborn receives treatment of infection, that child should have their BCG vaccine delayed until 2 weeks after completion of treatment of infection, as infection treatment can make the BCG vaccine ineffective.

Part 4 of this field guide contains sample clinical forms that can be used for treatment of infection initiation and follow up. However, using existing local stationary (sometimes with slight modifications) may be the most effective.

Treatment-Related Adverse Events and Management

Medications used for treatment of infection are generally safe and well-tolerated. It is important, however, for health workers to be aware of potential side effects and respond promptly. Most persons on medical treatment of infection are otherwise healthy people, and even mild side effects may not be considered tolerable. Serious adverse events should be reported to local health authorities, via established channels. Table 2.6 refers to possible side effects from treatment of infection, including suggested management strategies. Management of adverse effects is a key part of follow-up (Action 5; p 29) and will impact the outcome of infection treatment (Table 2.8; p 30).

TABLE 2.6: ADVERSE EVENTS AND MANAGEMENT

Adverse event	Management Strategy	Comment
Nausea/vomiting	• If hepatitis suspected, stop all drugs and refer for urgent assessment • Give medications with food, or space doses throughout the day • Usually diminishes over time	• Can be caused by multiple medications (isoniazid, levofloxacin) • If persistent or accompanied by jaundice, may be a sign of liver toxicity or increased intracranial pressure. • Important to consider TB meningitis as a cause of vomiting
Headache	• Make sure the patient is drinking lots of fluids • Symptomatic management with analgesia	• Can be caused by multiple medications (isoniazid, levofloxacin) • May be a sign of meningitis
Joint pain	• Symptomatic management with analgesia • Topical treatment • Exercise • If on levofloxacin, reduce to lower effective dose	Can be caused by levofloxacin; usually transient
Tendon rupture	• Discontinue drugs; treat symptomatically • Refer for management if tendon rupture	Rare side effect of fluoroquinolones (usually in adults; more common when co-prescribed with corticosteroids)
Rash	• Consult clinician as may need to stop medications if caused by a medication • Topical creams • Antihistamine	Can be caused by multiple medications; consider other causes
Diarrhoea	Uncommon; treat symptomatically	Can be caused by a number of drugs; consider other causes
Liver toxicity	• May include nausea, vomiting, abdominal pain, jaundice, or tenderness over the liver • Stop medication immediately and refer urgently for further investigation and management	Can be caused by isoniazid, delamanid, or levofloxacin
Sleep disturbances	• Change time of day treatment is taken to the morning • Discuss sleep hygiene	Can be an effect of delamanid
Hallucinations, bad dreams, psychiatric effects	• Stop medication if psychotic symptoms or mood dysregulation • For delamanid-associated visual hallucinations in children: if there are no accompanying psychiatric symptoms and child does not find hallucinations distressing, can continue delamanid with close monitoring and see if settles	Can be related to isoniazid or delamanid
Peripheral neuropathy	• May present as tingling or numbness in hands and feet. In younger children may present as stumbling or clumsiness • Discontinue isoniazid and increase vitamin B6	Can be caused by isoniazid

Although the medications used to treat RR/MDR-TB infection are generally safe and well tolerated, the following adverse events should be noted for levofloxacin and delamanid:

- **Levofloxacin may cause**
  - Nausea or vomiting
  - Pain: Joint pain, muscle pain, and (extremely rarely) Achilles' tendon rupture
  - Increased risk of aneurysms or other serious vascular complications in older patients and those with underlying vascular disease
  - Minimal QT prolonging effects (less than 5 m/s). [Moxifloxacin is more likely to prolong the QT interval, so baseline and follow up ECGs could be considered].

- **Delamanid may be associated with**
  - Neuropsychiatric side effects, including nightmares and sleep disturbances. It is important to counsel caregivers and recipients about this.
  - Mild effect on the QT interval, but baseline and follow up ECGs are only needed in people with pre-existing cardiac disease.

ACTION 5: MONITOR AND SUPPORT HOUSEHOLD CONTACTS

The frequency and method of follow up depends on local contextual factors but is usually best accomplished in the community. Unless there are problems, most follow up can be done telephonically, with medication refills arranged in a way that is convenient for the family (i.e. when individuals diagnosed with RR/MDR-TB disease are in the clinic for follow up). Lay health workers and nurses can manage almost all of the follow up and monitoring for people taking RR/MDR-TB infection treatment. Generally, a follow up every two or three months is sufficient (Table 2.7). Follow up should be more frequent in infants, where weight bands are likely to change and medication doses may need to be adjusted.

TABLE 2.7: FOLLOW UP SCHEDULE FOR PERSONS STARTED ON TREATMENT OF RR/MDR-TB INFECTION

Event	M0	M2 or M3	M6
TB symptom screen, basic clinical exam, weight and height	x	x	x
QTcF (ECG) if underlying cardiovascular disease or starting moxifloxacin for treatment of infection	x		
Pregnancy test in females of childbearing age and offer contraception	x		
Counselling and adherence support including assessment of psychosocial needs	x	x	x
Nutritional support	x	x	x
Assessment and management of adverse events		x	x
Assign outcome of treatment of infection			x
Other: Chest radiograph and bacteriological testing to be done if any concerns of incident TB disease			

For most drugs no routine laboratory tests are required. Women/persons of childbearing age should be tested for pregnancy and offered contraception where relevant (particularly if being offered a medication such as delamanid which has only limited use in pregnancy).

Children: At follow up of a child, a health care worker should review test results; re-evaluate the evolution of any TB symptoms (has a cough or fever improved/resolved?); and re-examine the child. The information gained from this should inform a decision to either start RR/MDR-TB disease treatment or treatment of RR/MDR-TB infection. Nutritional support should be provided urgently in any situation where there is a delay in deciding on treatment of infection.

Follow up assessments should include asking about adverse events, adherence, or any new symptoms. Shared medical appointments for multiple family members may be helpful. If persons are in care for HIV or other chronic conditions, follow up should be integrated with these services. Follow up services need to be made as flexible as possible. Offering differentiated forms of follow up (i.e. telephonic, via lay health workers) is likely to be most successful. After a telephonic follow up, medication packages can be sent home with family members or with community health care workers who will visit the household.

Outcome definitions and management of adherence challenges

Typical outcome definitions for persons who have received treatment of infection are listed in Table 2.8.

TABLE 2.8: OUTCOMES FOR PATIENTS ON MEDICAL TREATMENT OF INFECTION

Completed	Patient who has completed treatment of infection
Lost to follow up	Interruption of treatment of infection for >2 months consecutively in a 6-month regimen
Treatment stopped due to adverse event	Where treatment of infection is discontinued due to adverse events or drug-drug interactions; with or without changing regimen
Treatment stopped due to incident TB or RR/MDR-TB	Where treatment is discontinued due to incident TB or RR/MDR-TB disease during any time during therapy
Not evaluated	Transferred to another facility, medical records lost
Death	Patient died while receiving treatment of infection

There is limited evidence on the management of interruption of medical treatment of TB infection. Best clinical practice is to aim for adherence to 80% of prescribed doses. In the Khayelitsha PEP, our practice was to discharge a person 6 months after initiation of treatment of infection, provided they had not missed 8 weeks or more of therapy. If there was an interruption of more than two months, an outcome of loss to follow up was assigned.

Monitoring of close contacts not on medication treatment of infection

In cases where medication treatment of infection is *not started* (i.e. there is no available drug option or person chooses not to take therapy), monitoring should still take place at a similar schedule. The focus of monitoring should be identifying any emergent RR/MDR-TB disease. Providing nutritional support is even more important in individuals who are not on medical treatment of infection.

Psychosocial support

Many households affected by RR/MDR-TB are vulnerable and face huge socio-economic challenges. These can include struggles with substance use disorder, mental health challenges, poverty, food insecurity, relationship complexities, and financial insecurity. Psychosocial and socioeconomic support averts catastrophic family costs related to RR/MDR-TB and improves adherence to treatment of infection. Types of support may include counselling, referral to a psychologist or social worker, peer support, and financial support (including transport allowances) and peer support. See Part 3 (p 31-42) of this field guide for more information on counselling and psychosocial considerations in PEP.

Part 3: SUPPORTING PEOPLE ON PEP

General counselling approach

Working with families after there has been an exposure to RR/MDR-TB can be incredibly fulfilling. It also, however, requires a significant amount of patience and investment on the part of the counseling and health care teams. Each family is unique in terms of the challenges they face and the resources they can call upon while managing RR/MDR-TB. Thus, while there are five key actions in the RR/MDR-TB PEP—each of which has counseling topics (see Box 3A below)—how much information on each topic to cover in a session will depend on what is happening in the family.
This "flexible" counseling approach means that there will not be a standard session(s) or a standard number of sessions held with each family. Rather, the counselor should make sure that the key messages in each topic area have been conveyed to the family, preferably within a month of the diagnosis of RR/MDR-TB being made for a member of the household. Disclosure counseling with the initial member of the household diagnosed with RR/MDR-TB should be done first. This should be followed by counseling for the family members on what to expect after there has been an exposure. The order in which the other topics are covered and the level of detail will be determined in partnership with the counselor and the family.

How should the flexible approach be implemented? This can usually start by having the counselor ask the family members/caregivers if they have any questions. Together, a list of the questions can be made and then a plan for responding to each question can be elaborated. If the family members/caregivers do not have any questions, then the counselor can propose some possible questions and state "these are some questions other families/children/adolescents ask that we might want to talk about together."

After the initial sessions (which address disclosure and "what to expect after exposure"), the counselor should review what has been discussed and then share the key counseling themes with the family member/caregiver and let them know that there are some other important topics that will be reviewed. A plan can be made with the family/caregivers to talk about each theme area in a way that makes sense.

The counselor (either a lay counselor or trained nurse) should also be sure to engage with the child/adolescent in addition to the family members/caregivers. Tips for establishing rapport and building trust with children/adolescents are reviewed in this section.

BOX 3A: KEY COUNSELING ACTIONS

Action 1: *Disclosure counseling.* The counseling focuses on the newly diagnosed individual and should cover important issues in disclosure for people who have been diagnosed with RR/MDR-TB.

Action 2: *Completing an initial home visit.* The counseling focuses on the household members and should cover what to expect at a PEP visit after exposure. Tips for carrying out a successful home visit are also reviewed.

Action 3: *Evaluating for RR/MDR-TB disease.* The counseling focuses on tests that might be done to assess for RR/MDR-TB and should cover strategies for optimal communication with medical providers.

Action 4: *Starting on treatment of infection.* The counseling should cover issues around medication administration.

Action 5: *Monitoring and supporting the household members.* The counseling should cover issues around managing adverse events and for dealing with other psychosocial stresses.

ACTION 1: DISCLOSURE COUNSELING

The process of sharing news about an RR/MDR-TB diagnosis is called "disclosure." Disclosing information about the diagnosis to people in the household is important with a disease like RR/MDR-TB that can be spread in the air. Disclosure can have two main goals. The first is garnering support for the newly diagnosed person so that s/he can have the best chances of success during treatment. The second goal is to encourage other people to protect their own health by getting evaluated for RR/MDR-TB.
Disclosure usually happens in stages and how it happens depends on the preferences and needs of the person who has been newly diagnosed with RR/MDR-TB. When the newly diagnosed individual is prepared for disclosure, the experience can be positive and lead to bonding in the household. When the person is not prepared, then the disclosure can be a negative experience and even lead to serious consequences for the newly diagnosed person, including isolation, discrimination, or even violence in the household.

Activities that should be done in disclosure counseling sessions include:

- Selecting supportive people who can be told first and who can help tell others;
- Role-playing the disclosure with a counselor or other health care provider, including where the conversation will take place, the kinds of information that will be shared, and how questions will be managed;
- Deciding whether or not a health care provider should be present during the disclosure to answer any questions or to provide support;
- Planning what to do if the newly diagnosed individual feels unsafe or worried during the disclosure period;
- Remaining positive throughout the process and reminding others that staying healthy together is a family responsibility and emphasizing the concept of "shared air" as opposed to "person X got person Y sick;"
- Developing an action plan following the initial disclosure session to follow up on any necessary medical or counseling appointments, issues raised during disclosure, and planning for other disclosure sessions that might need to take place.

For additional supplemental health education materials on this topic, see: https://www.treatmentactiongroup.org/wp-content/uploads/2024/02/sharing_your_tb_diagnosis_final.pdf.

ACTION 2: COMPLETING AN INITIAL HOME VISIT.

Ideally, the initial assessment for contacts should be done at the home of the person who has recently been diagnosed with RR/MDR-TB. It is important to adequately prepare for the visit. Tips for carrying out a successful home visit are summarized in Box 3B.

BOX 3B: TIPS FOR THE HOME VISIT

- Ensure that the person newly diagnosed with RR/MDR-TB agrees to be visited in the home and feels safe having the health care providers/ counselors come to the house;
- Arrange to visit the home at a time and date when most of the family members will be present and be sure clear directions and a means for identifying the house are reviewed;
- Always let another team member know where you will be and how they can reach you;
- Wear professional but non-identifying clothing when carrying out the home visit. Avoid carrying bags or tools with logos that could be identifying;
- Make a checklist of equipment and tools you need to have with you during the home visit (i.e. pen, paper, forms, scale, sample containers, register);
- Enter the home politely and respectfully and put on any masks or personal protective equipment inside the home;
- Meet the family on their terms and offer to speak with them in a private place that they feel comfortable in;
- Review follow up plans with the family;
- Do not answer any questions posed to you by neighbors or others in the community;
- Be aware of surroundings and do not take any unnecessary risks. If at any point the visit feels unsafe, end it and make a plan for follow up.

After household members have been told they have shared the same air with someone who has been newly diagnosed with RR/MDR-TB, they may have multiple questions about what to do or expect next. This is a crucial time for health education not only in garnering support for the newly diagnosed individual but also for encouraging household members to also be assessed for RR/MDR-TB. Again, it is important to focus not on "contagion" or "disease spread" but rather on the fact that families share air and living space. For this reason, when one person finds out they are living with RR/MDR-TB, it is important that all members of the household be assessed. Those who are sick can be started quickly on treatment, which improves the chance of returning to health. Those who are not yet sick can be treated for RR/MDR-TB infection.

Activities that should be done in the "what to expect" counseling session include:

- Reviewing ways to support the person who has been newly diagnosed with RR/MDR-TB;
- Planning for where the household members can undergo screening and assessments to determine if they might have RR/MDR-TB disease (i.e. in the home, at another location in the community, or at the clinic);

- Discussing the assessments that will be done (and by whom) for all household members, including an offer of HIV counseling/testing, obtaining weight, screening for symptoms, and carrying out a basic physical examination;
- Reviewing the additional testing or assessments that might be done at a clinic for some members of the family, including collection of samples (blood, urine, stool) and/or chest X-ray;
- Planning for days, times, and transportation pathways for the household members who need to go to the clinic;
- Discussing plans for following up on any results, including the initiation of treatment of infection to prevent RR/MDR-TB disease in persons who are not sick and the initiation of treatment for RR/MDR-TB disease in people who are sick.

For additional supplemental health education materials on this topic, see: https://www.treatmentactiongroup.org/wp-content/uploads/2024/02/TB_after_disclosure_exposure_final.pdf.

ACTION 3: EVALUATION FOR RR/MDR-TB DISEASE

From the start of the PEP process, household members will be interacting with doctors, nurses, and other clinic personnel. It is best to go into these interactions prepared for the most productive discussions possible. Box G includes some tips for talking with health care providers during treatment of infection.

BOX 3C: STRATEGIES FOR TALKING WITH HEALTH CARE PROVIDERS

- Consider making a list or diary of any problems the child/adolescent might have—ask someone to help you make a list or diary if you need to;
- Notice how long the problem or symptoms lasted and if there was anything that made the problem better or worse;
- Talk about anything you might have done to help the child/adolescent—sometimes families know best how to help each other;
- Ask the health care provider what they think might be causing the symptom or side effect;
- Ask the health care provider if they have any advice on how to help the child/adolescent with the problem;
- Ask the health care provider if there are any things you should NOT do when the child/adolescent is having the problems;
- Make sure you know how to get in touch with the person's care provider if you have any questions or worries;
- Tell the health care providers if you are using any traditional medicines or herbs to help the person on treatment of infection;
- Write down (or ask the health care provider to write down) the names of any new diagnoses, treatments or tests that are recommended as well as why;
- Write down or ask the health care provider to write down the date and place of any follow up appointments;
- Always be honest with the health care providers about things—remember that you are a team;
- Expect to be treated with kindness and respect: asking questions means you are doing your part to take care of the person on treatment of infection and this is a wonderful thing.

In addition to talking with health care providers, families receiving PEP may choose to speak with other members of the community about what the family is going through. This can be an important way to gain support during a difficult time. While not all institutions or groups in the community may be supportive, most families will be able to identify a group that can help them, including a religious organization, a social group, or other families living in the neighborhood. Box H includes tips for talking with other members of the community about what the family/household is experiencing.

BOX 3D: TIPS FOR TALKING WITH OTHERS ABOUT RR/MDR-TB

- Knowing the facts can help—RR/MDR-TB is spread through the air and anybody who breathes can get RR/MDR-TB (and we all breathe). RR/MDR-TB infection and disease are not caused by bad behavior or being dirty or witchcraft or curses, and it can happen to anyone. When someone is taking treatment, there is almost no chance that others can catch TB from them. People with RR/MDR-TB did not do anything wrong, and they need the love and support of people around them.
- Make a plan for how to respond if/when people ask questions. Some questions people might ask include "Why were you out of school/church?" "Why do you look different?" "Why do you have to take tablets now?" "Why do you have to go to the clinic so much?" You may want to provide more a detailed or honest answer to close and trusted people than to more casual or superficial acquaintances.
- Remind people that you/the child/adolescent are still the same person as before, with the same hopes and interests and dreams.
- If other children/adolescents are teasing or mean about the RR/MDR-TB, know who you can turn to for help/support: it may be another child/adolescent or adult who can help diffuse the situation.
- Remember people have a right to be back at school, a job, church or other activities that matter after they have been exposed to RR/MDR-TB.
- Ask your doctor, nurse or counselor if they have any advice for how to talk to others about RR/MDR-TB—they might even be willing to talk to people at your school or church or in other places.
- Stick with the people who are kind and supportive and surround yourself with them—you deserve this.

ACTION 4: STARTING ON TREATMENT OF INFECTION

People from a household who are found to have RR/MDR-TB disease will be referred to the clinic to start and maintain treatment for RR/MDR-TB disease. If TB disease is ruled out in a person, that person should be offered treatment of infection (i.e. tuberculosis preventive therapy or "TPT"). Prior to starting treatment of infection, it is important to review the therapy with the person receiving it and his/her supporters. With the family-centered approach advocated here, it is likely there will be several members of the household being started on treatment of infection together. They can support one another in taking treatment and, if they agree, participate in joint counseling sessions together.
Activities that should be done in the "starting in treatment of infection" session include:

- Review the goal of preventive therapy (to eliminate the TB germ from the lungs so a person does not get sick) as well as the medications that will be used.
- Plan for how to remember to take the treatment daily, including during periods of travel, holidays, and during important events at school/work or in the community (see topic area 4 below).

- Discuss the possible side effects of the medication and how to manage them (see topic area 5 below).
- Describe the types of follow up visits that are needed and how to communicate with the health care team if there are questions, challenges or concerns (see topic area 6 below).

The decisions about whether or not to start on treatment of infection should be made jointly by providers and the household members being offered this therapy through *shared decision making*. Shared decision making recognizes that each person in the care session brings expertise that must be considered in the ultimate decision on whether or not to start medication. People being offered therapy know themselves and their households best and should be offered the opportunity to share their core values, their future hopes, and what their lives were like before DR-TB affected the family. The medical providers understand the potential risks and benefits of treating DR-TB infection. They are there to help the household members navigate this landscape, but ultimately the decision—and successful completion—rests in the hands of the person being offered therapy. When approached in this way, a true therapeutic partnership can form and lead to a more successful and satisfying experience for all involved.

People taking treatment of infection may face unique challenges with their medications. Often, they feel completely well and, therefore, it can be difficult to be motivated to take a daily medication. The medication may be a painful daily reminder of how much the family is suffering because of RR/MDR-TB, and this could discourage people from taking the medication.

In general, the following tips can help with medication administration during treatment of infection:

- Remind the person that the treatment is temporary and could prevent a notable amount of suffering in the future.
- Review motivations for the person on treatment of infection to stay healthy and engaged in activities that are important in his/her life.
- Discuss the specific medication that should be taken, how it should be taken, when it should be taken, and what should be done if any doses are missed. This information can be provided by the clinic provider.

Helping children/adolescents to take medications can be challenging, with different issues coming up depending on the age of the child/adolescent. For very young children, the tablets may be difficult to swallow, while older children may refuse to take medications in order to exert control. Children/adolescents on treatment for DR-TB infection may not feel sick and thus may not understand why they need to take the medications. Some tips for helping support children/adolescents to take their treatment every day are included in Boxes A-D.

BOX 3E: TIPS FOR REMEMBERING HOW TO TAKE MEDICATIONS

- Ask the health care providers to give a picture chart of each medicine and the number of tablets of each that should be taken in the morning or at night.
- Ask for a pill box to be provided and for help filling the pill box—remember to bring the pill box to each clinic visit.
- Work with the person on treatment of infection to make a "wall chart" or a tick sheet to mark after each medicine dose is swallowed. Stickers can also be used to indicate that a dose was taken.
- Use a calendar with images that are appealing to the person on treatment of infection and mark off each day when the medicine is taken.
- Set an alarm on a phone or clock to remind the person on treatment of infection to take the medication—consider using a happy or special ring tone or song as the reminder.
- Ask a trusted family member or friend to help remember to take the medicine.
- Plan the medication taking around something that happens every day—such as brushing teeth or putting on shoes/underwear.
- If the person on treatment of infection misses a dose of medicine, let their health care providers know. If the medicine is usually taken in the morning, it can be taken at night if the missed dose is noticed before then.
- If the person on treatment of infection misses multiple doses of medicine, try and figure out why and make a plan for having additional reminders.

BOX 3F: TIPS FOR SUPPORTING PEOPLE TO TAKE TREATMENT EVERY DAY

- Every person on treatment of infection is different and there is no one-size-fits-all strategy.
- Different strategies may be needed for children as the child grows and their development progresses.
- People who have to take medications often feel that they have no control, so allowing them some choices can be helpful.
- While there cannot be a choice between taking medication or not taking medication, people can be given some choices in the process, such as where they want to take the medications, what time of day they want to take the medications, or the order in which they want to take the medications.
- Positive reinforcement always helps, especially for children—consider singing a special song for the child/adolescent, having the family clap and cheer for the child/adolescent, or doing a "high five" or some type of other celebratory signal when the child/adolescent takes the treatment.
- For small children, having the child sit on the lap of a loved sibling or family member while taking the medication may help.
- For older children, involving play in the medication administration may help—allow them to "give medicine" to a favorite toy or doll, or consider making a game to play around the taking of the medication.
- For adolescents, allowing them to assume some responsibility for their own medications may help—and they also need encouragement, such as listening to a song they love while taking treatment.
- Mixing the medications with foods or drinks may help with the bitterness or difficult taste.
- Some of the medications may have a smell that the person finds upsetting or unpleasant—taking the medicine outside or by an open window might help with this.
- Set short-term goals with the person around medication taking—for example, if you take all your tablets this week, we can go play together in the park.
- Consider rewards for meeting short-term goals, including sweets, air time, or another small gift the person on treatment of infection will appreciate.
- Punishing or fighting with children/adolescents—including holding them down or forcing them to swallow by holding their noses or blowing on their faces—may seem like a short-term answer, but it usually backfires in the longer term since children have to take RR/MDR-TB medications for several months.
- Ask the person if there is anything s/he would like to try that would make it easier to take the medications, and listen to what they have to say—sometimes the best advice comes from the children/adolescents themselves.
- Ask the person what his or her motivation for taking treatment is and then remind him/her of this motivation on days when treatment may be difficult. For example, a child may say "I want to take my treatment so I feel strong enough to play football with my friends." Remind him or her of this goal on days when s/he may not want to take the medicine by saying "Remember how much fun you had playing football with your friends after being sick for so long? If you keep taking your medicines, you will be able to keep playing football and run faster and harder."

BOX 3G: TIPS FOR TAKING MEDICATIONS DURING SPECIAL TIMES OR CIRCUMSTANCES

- If the family is traveling for a holiday or event, remember to let the clinic know and make sure there is enough medicine to last during the time the person on treatment of infection will be away.
- If traveling, normal routines can be interrupted and thus additional reminders should be considered.
- If someone else will be looking after a child during the travel, then it is important that that person also understand why and how to give the medications.
- Some children/adolescents may not want to take their medications during examinations or sporting events—it is important to stress that medications should be taken each day, so it might help to allow the child/adolescent to take the medication at night or after the exams/events are finished for the day.

BOX 3H: TIPS FOR HELPING PEOPLE SWALLOW TABLETS

- Practice "swallowing" with pieces of fruit or candy that are about the size of the tablets the person needs to take—or start smaller and build up to the tablet size.
- Give the tablet with yogurt, jam or a peanut spread—something that is thicker or easier to swallow than just a liquid.
- Ask if there are any dissolvable or "dispersible" tablets that can be used to help make it easier for the person to swallow.
- If the person is on dissolvable medications, mix and administer them with a small amount of liquid or food (a spoonful of something is usually enough)—using too much liquid can make it difficult for the child to finish the medicine and may cause nausea or vomiting afterward.
- Place the tablet under the tongue—instead of on top of the tongue—as some people find this both less bitter and easier to swallow.
- Have the person practice swallowing with her/her head in different positions—with head tipped back, head tipped forward, head turned left and head turned right—ask him or her to pick which position was easiest to swallow and encourage them to use that position when taking the tablet.
- Try practicing taking the tablet while drinking through a straw—if this helps the person then have a straw available when they take their medications.
- Play a game with children where you watch a bird swallow some water—note how the bird tips his head back and shakes his throat and imitate doing this with the child.
- Have the child clap his/her hands or wiggle his/her toes while trying to swallow the tablets, and this can help distract them and make the tablets easier to go down.
- If there is an adult or older child/adolescent in the family taking tablets, have him/her show the child how to swallow tablets and practice taking their medications together.

ACTION 5: MONITORING AND SUPPORT FOR HOUSEHOLD MEMBERS

People on treatment for RR/MDR-TB infection generally feel well. Therefore, even the most minimal experience of side effects may not only be distressing for the person on treatment of infection but may also lead to early discontinuation of therapy. For this reason, it is essential that household members be counseled about adverse events and how they can be managed. Below are some tips for talking about how to manage adverse events during treatment of infection:

BOX 3I: TIPS FOR TALKING WITH PEOPLE ABOUT SIDE EFFECTS

- Asking the person how s/he feels each day is a good start.
- Sometimes people may be overwhelmed by asking a general question, so it may be good instead to ask: "Do you have any pain in your tummy?" "Do you hurt anywhere?" "Did you have any funny dreams?" or "Do your hands or feet hurt"?
- Always give the person plenty of time to answer the question.
- Sometimes, observing how the person is doing can give more information than asking about it—look to see how the person is eating, notice if they are playing less, see if they are limping or rubbing a certain body part.
- For children, adolescents, or people who are less likely to talk, use drawing or pictures if possible or dolls/other toys—ask the child/adolescent to show you "where it hurts."
- Reassure the person that you are there to help with the side effects and that the problems they may be experiencing are temporary and will go away.

BOX 3J: STRATEGIES FOR HELPING PEOPLE WITH COMMON SIDE EFFECTS

- If the person has nausea or vomiting, make sure s/he is able to take in some liquids; consider using rehydration salts; avoid strong smells which can make these symptoms work; try sitting by a window or in the fresh air; eat soft or bland foods such as grain meal, banana, apples, or rice; avoid rich foods such as meats, things that are deep fried, or dairy products; try eating small amounts multiple times a day.
- If the person vomits after taking treatment, ask the health care provider if s/he should take another dose--usually, if more than 30 minutes have passed between taking the tablet and the vomiting, it is not necessary to take another dose.
- If the person has diarrhea, make sure s/he is able to take in some liquids; consider using rehydration salts; avoid fatty foods and dairy foods.
- If the person has pain try massaging the area that is painful; place a warm or cool compress on the area, whichever feels better; try rubbing the area with menthol or camphor cream.
- If the person has a rash, try washing the area with mild soap; consider rubbing it with aqueous cream.
- If the person has a fever, consider using Panadol or rubbing the child/adolescent with a cool cloth.
- If a child has trouble sleeping or develops nightmares, consider identifying a "comfort object" such as a doll/blanket/toy s/he can use to sleep; sing a soothing song; rub his/her back or feet until they are sleeping.
- **DANGER SIGNS** that mean you should contact a health care provider right away are: the inability to take liquids; rapid or shallow breathing; coughing or vomiting blood; a rash all over the body; inability to walk; sleep from which the child cannot be woken up; bumping into walls or other objects; excessive tripping; skin or eyes turning yellow; violent or threatening behaviors towards themselves or others. Any side effects should be reported to the health care team.

RR/MDR-TB can be especially stressful for households and families, many of whom were facing difficult times before RR/MDR-TB became part of their lives. Some of these stresses include: 1) food insecurity; 2) lack of adequate housing; 3) unemployment or under-employment; 4) displacement from communities of origin; 5) substance use disorder; and/or 6) interpersonal violence. These problems may seem overwhelming both to the household and to the health care providers.

Because there are no simple solutions to any of the challenges noted above, it is tempting to leave them out of discussions on RR/MDR-TB PEP. Doing so, however, might have multiple negative consequences. Families could feel ashamed or isolated when trying to manage these other issues and fail to seek the help they need to address them. As they try to address them without support, it will likely become more challenging for them to participate in important PEP activities. Health care providers may become frustrated and feel that they are working at cross purposes with the family, unable to build bridges that will lead to healthy outcomes for the patient and his/her household. Thus it is essential that all households be asked if they are managing other challenges and, if so, to describe them to providers.

While not all of the psychosocial challenges being faced by families with RR/MDR-TB can be easily addressed, the following counseling activities can be carried out:

- Listening with empathy to the household members and what they are going through.
- Seeking out other potential resources or service providers in the community who might be able to address some of these issues.
- Partnering with food pantries, dignity kitchens, and/or religious institutions to help meet the basic needs of the families.
- Reporting on these issues to programs and policy makers so that additional support can be garnered.

BOX 3K: TIPS FOR MANAGING STRESS AND ANXIETY

- Talk about the feelings with a trusted person, as stress/worry can grow when it is kept inside.
- Set aside time to do something enjoyable each day—even taking five or ten minutes to relax or do something pleasing can help.
- Ask for support when you need it—DR-TB treatment is a long journey and it is normal to need support and ask for support along the way.
- Plan a special day when certain key milestones have been reached: for example, after completing one month of treatment, consider taking a walk to the park or the beach or cooking a special meal.
- Cry if you need to cry: tears can be a relief and are not a sign of weakness.
- Avoid alcohol and drugs: they may seem to help ease or forget things in the short-term but they often lead to more problems in the future.
- Embrace spirituality—either through a church, a religious leader, or meditation—find the comfort when you can.
- Talk with others who have been through a similar journey as they will understand what you are going through and may be able to help.
- Remember this situation is temporary and it will pass.
- Remember there may be good days and bad days during treatment—take time to be grateful for something each day.

Part 4: DATA TOOLS FOR PEP PROGRAMS

General approach to data collection, monitoring, and evaluation

In our experience implementing the Khayelitsha PEP, we developed a number of monitoring and evaluation tools. We share those here as a starting point for other programs wishing to start implementing the RR/MDR-TB PEP. These tools can be adapted as needed to fit local contexts and needs.

Program Indicators

Program monitoring and evaluation is a fundamental component of implementing any health assessment. Doing this could mean governmental and program change when implemented. Almost all health departments around the world have guidelines stipulating the provision of preventive treatment for close contacts of TB patients. With this in place, one might expect that preventive treatment would be implemented widely. Unfortunately, this is not the case.

One of the biggest obstacles is the availability of guidance on how to implement and what to look at when monitoring and evaluating these programs. With this in mind basic indicators are provided, along with forms for data collection for use during implementation of the program.
To assess if your program is working, it is recommended that some baseline measures be recorded from the year prior to the program being launched. Collecting baseline measures of TB disease, TB infection, and treatment initiation rates will allow for a comparison to be made to rates after the implementation of your program. This comparison will inform your understanding of the program's performance and what needs to be improved.

Baseline data that would be helpful to collect include, but are not limited to, the following:

- Number of patients diagnosed with RR/MDR-TB disease in the last year;
- Number of patients diagnosed with RR/MDR-TB disease through contact investigations in the last year;
- Number of patients with RR/MDR-TB disease who initiated TB disease treatment in the last year; and
- Number of close contacts of patients with RR/MDR-TB disease who initiated DR-TB infection treatment in the last year.

We have proposed a basic framework of four process indicators that will allow you to evaluate your program's performance. These process indicators will provide important information about areas in which the program is successful and areas in which the program can be improved. Identifying areas for improvement may trigger some corrective action measures to be taken, such as reallocating resources where necessary, changing approaches to the tracing of contacts, triage or support phases, providing further training to your team members, or adapting forms and/or processes to better reflect the workflow of your program.

Process indicators can be assessed at different time points depending on the length of treatment for infection. Suggested time frames are three and six months during preventive TB treatment and six months' post completion of treatment for infection.

Useful program indicators include:

- Number of index case with contacts identified through the PEP program
- Number of contacts starting and completing each activity in the PEP program
- Number of contacts given nutritional supplementation
- Number of contacts started on medication treatment for infection
- Number of contacts who completed medication treatment for infection
- Number of contacts given psychosocial support

RR/MDR-TB PEP register and forms

These three sample forms are available in Annex B.

Form 4.1: Contact registration form/register
Form for capturing individual-level information about each of the contacts found for each index case. Contact-tracing staff would complete this data collection with health facility as well as during home visit. Form can be used for patient management, following up to ensure completion of scheduled visits, and compiling monthly reports.

Form 4.2: Contact initial assessment form
Form for capturing all data during initial assessment of each contact, collecting individual medical history, symptoms, and medical investigations done.

Form 4.3: Close contact follow-up form
Form for capturing follow-up investigations done as required.

Data management tips

Data collection

- Make sure all forms are completed.
- Always verify information with health staff if unclear.
- Collect all data available.
- Do not leave empty spaces where data should be captured.
- Collect data at time point that it is required. Collecting data at a later time point will be more difficult and time consuming.

Data capturing

- Capture all data on form and always double check captured information.
- Capture data at time point required.

Program monitoring

Assess program according to the goals set out at start.

Treatment for infection Data Collection Codebook and Databases

Codebooks can be used to create databases required to capture contact information from forms. Data variables are from Form 2 and Form 3. Setting up database will depend on what each project wants to collect and capture to assess their program.

Formulated codebooks and databases are available upon request. Please contact the Sentinel Project (tbsentinelproject@gmail.com) to access these sample codebooks. A link to a sample codebook can be found at: https://sentinel-project.org/. Excel data base: A link to an excel database can be found at: https://sentinel-project.org/. Redcap online database (Can be imported into redcap): A link to an excel database can be found at: https://sentinel-project.org/.

PART 5: OVERCOMING CHALLENGES IMPLEMENTING PEP

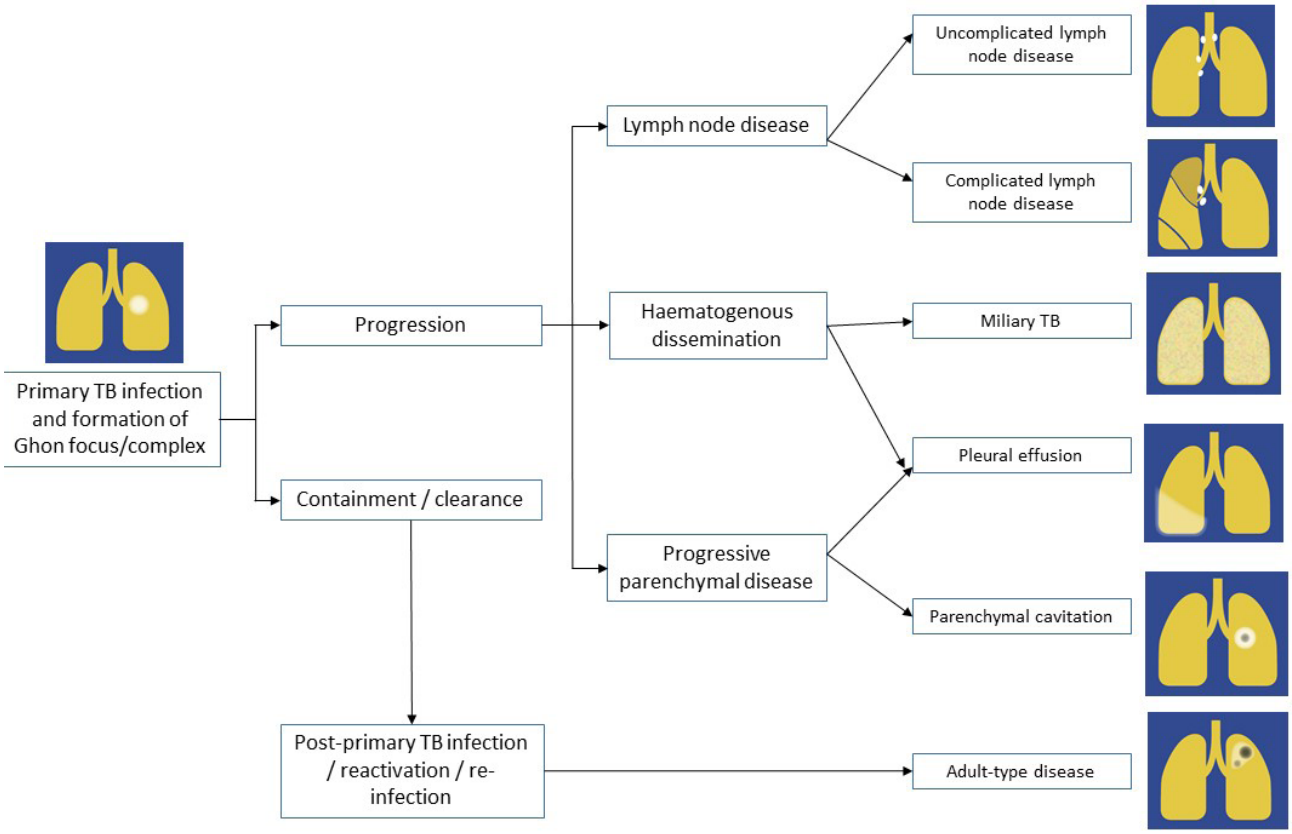
Common challenges encountered when implementing PEP and possible solutions are summarized in the table below.

Challenge	Possible strategies to overcome the challenge
Lack of buy-in and resistance from TB staff (health care workers may be overworked and prioritize acute care)	• Foster open discussions between staff and management. Listen to concerns and reasons for hesitation. Brainstorm solutions with staff (have them make suggestions and come up with solutions and what is possible). Advocate for sufficient resources for PEP implementation. • Present evidence based, human rights perspective and benefits of PEP. Work towards an understanding that PEP ultimately can decrease workload and decrease costs. • Task shift: identify cadres of staff that have capacity to take on PEP activities. • Consider community-based PEP models to decrease burden on health facilities
Lack of buy-in from community, as well as families diagnosed with RR/MDR-TB	• Involve civil society groups, community forums and leaders to build awareness and knowledge around PEP (demand generation) • Provide high quality disclosure counselling and health education (aim to empower persons) • Implement a brief survey or interviews to ascertain reasons for lack of buy-in and address these reasons • Ensure PEP model is delivering accessible and acceptable post-exposure activities to community and patients (this includes ensuring activities do not cause stigma in the community). • Engage communities in helping to create PEP models of delivery that are acceptable and appropriate to them
Lack of capacity and resources for PEP within health facilities	• Build buy-in and commitment to PEP at higher levels of TB program and health system • Advocate for resources for PEP activities • Start somewhere! Start with what is possible (e.g., start with children and adolescents) and then grow activity once systems have been established • Task shift to cadres of staff that have capacity within health systems (e.g., community health workers, nurses) • Apply for grant or private funding to support PEP rollout
Loss from care during initial PEP evaluation stage	• Identify where along the care cascade losses are happening and address these (use of a contact register can be helpful in identifying where persons are lost from care) • Identify and where possible remove barriers to initiation of treatment of infection (this may include things like CXR or tests of infection). • Aim for same day initiation of treatment of infection for most household contacts • Ensure TB evaluation is accessible and acceptable to persons in community (i.e., screen at household level or at school, consider after-hours screening)
Poor retention in care for persons on treatment of infection (high loss to follow up)	• Identify reasons for poor retention (through tools like audit, survey, interviews) and address these reasons • Ensure that PEP model is acceptable and easily accessible to persons (i.e., consider drops of medications, giving medication to a family member for home delivery, telephonic follow up) • Strengthen patient support package of PEP and implement enablers to counter any barriers to follow up care (i.e., provide transport allowance, compensation for loss of time from work). • Implement milestone incentives (small gifts for children) or use enablers as incentives (i.e., transport allowance, air time) • Strengthen counselling and health education component of PEP • Strengthen relationships between PEP providers and persons on PEP • Ensure nutritional support is part of PEP package

Challenge	Possible strategies to overcome the challenge
Lack of access to paediatric formulations for children on treatment of infection	Levofloxacin: dispersible tablet is available through Global Drug Facility. If not available, adult tablets can be crushed and mixed with juice or milk or water, or taken with yoghurt. Isoniazid: dispersible tablet is available. If not available, adult tablets can be crushed and mixed with juice or milk or water, or taken with yoghurt. Delamanid: dispersible tablet is available. If not available, adult tablets can be crushed and mixed with juice or milk or water, or taken with yoghurt. If such formulations are not available, advocacy in partnership with civil society organizations should be done to obtain them. In settings where the dispersible tablets cannot be obtained, mixing devices should be used (such as the soft plastic X-Temp R device which is available from the Global Drug Facility).
Concerns about generating additional drug resistance	Studies do not show any higher rates of drug-resistant TB in people who have received medication treatment of infection, thus this concern is not based on data. Supporting people to complete the steps in assessing for RR/MDR-TB disease will further minimize this risk. Supporting people to complete medical treatment of infection and provision of nutritional support are also important ways to guard against this concern.

ANNEX A: Pathophysiology and natural history of TB infection

When evaluating persons exposed to RR/MDR-TB it is helpful to have a basic understanding of the pathophysiology of RR/MDR-TB. An individual becomes exposed to *Mycobacterium tuberculosis* by inhaling the TB germ that is in the air (i.e. if they share the same air with someone who has TB). Following this exposure one of two things may happen: 1) the person's immune system may either eradicate the bacillus or try to control it by walling it off; or 2) the TB germ may overpower the immune system and result in TB disease. Disease can sometimes develop immediately after exposure, especially in young children. Or the TB germ is initially controlled (sometimes for years) but later overpowers the immune system. This may happen if the immune system is weakened (i.e. malnutrition, HIV, cancer). Most PEP interventions focus on completely eliminating the TB germ from the body after a person has been infected but before he or she becomes sick with the disease. *Figure taken from the Union's Diagnostic CXR Atlas for TB in Children.*



ANNEX B: Data management tools

- Form 4.1 (p 47)
- Form 4.2 (p 48)
- Form 4.3 (p 49-50)

FORM 1 **PEP CONTACT REGISTER**

Index Patient Name	Address	Contact Number/s	DR-TB treatment start date	DR-TB TYPE	Date of Home visit

Contacts (DEPENDED ON DEFINITION USED)

Household Ccontact Name	DOB	AGE	Weight at first contact	TB Symptoms at first contact	Medical Facility Assessment Yes/No Date	PEP or TB Rx or None	Date PEP / TB Rx started date	PEP Regimen started	Follow-up date 1 Date seen	Follow-up date 2 Date seen	Follow-up date 3 Date Seen	Follow-up date 4 Date seen	Follow-up date 5 Date seen	Follow-up date 6 Date seen	Outcome 1. Completed 2. Lost to follow-up (LTFU) 3. Stopped (AE) 4. Stopped (Active TB) 5. Stopped (other than active TB) 6. Transfer out 7. Death Add number below	Notes/ Comments

FORM 2

DR-TB CLOSE CONTACT SCREENING FORM

Name			**MEDICAL Record number**		**Assessment date:**	**Medical Facility:**
Gender M ☐ F ☐	**Date of birth/ Age**	**Home Address:**	**Name of Index patient**		**Type of DR-TB**	
					Index Patient Med Record no	

MEDICAL ISTORY	TB Ever diagnosed ☐ Yes ☐ No ☐ Does not know				Previous Received TB treatment ☐ Yes ☐ No ☐ Does not know			
	Medical condition	HIV status	☐ Positive ☐ Negative ☐ Does not know	On ART ☐ Yes ☐ No	Taking Regular medication:	☐ Yes	☐ No	
					If Yes (List meds)			
	Other Medical conditions							

SCREENING	**A, Signs and Symptoms**			**B. Physical Examination**		
	Cough/wheeze > 2 weeks	☐ Yes	☐ No	Temperature _____	Weight _____	Height _____
	Weight loss*, Poor weight gain or failure to thrive	☐ Yes	☐ No			
	Persistent fever > 2 weeks	☐ Yes	☐ No	**Physical Exam findings**		
	Drenching night sweat	☐ Yes	☐ No			
	Reduced playful /Fatigue	☐ Yes	☐ No			

INVESTIGQTIONS	**HCT** ☐ Yes ☐ No ☐ Already known	**Date done**	Result ☐ Negative ☐ Positive ☐ Refused	**BACTERIOLOGIC ASSESSMENT**	**GXP done** ☐ Yes ☐ No	**Result:** ☐ Negative ☐ Positive, RS ☐ Positive, RR	
	Chest X-Ray ☐ **Yes** ☐ **No**	**Date done**	**Findings** NAD / Abnormal		**Date specimen for GXP:**		
	Currently pregnant: ☐ Yes ☐ No ☐ Does not know	**Pregnancy Test done** ☐ Yes ☐ No	**Result:** ☐ Negative ☐ Positive	**IGRA TESTING**	**Igra test done** ☐ Yes ☐ No	**Igra test Result**	
					Test date	☐ Neg ☐ Pos ☐ Indeterminate	

OVERALL ASSESSMENT	Assessment Outcome	☐ Possible or Likely TB disease: requires additional evaluation for TB Disease ☐ DS-TB	☐ DR-TB ☐ No TB disease: Treatment for infection
	Date treatment for infection initiated_____		Treatment regimen: ☐ LEVOFLOXACIN ☐ OTHER (specify)
	Follow-up Visit Date:		Treatment Dose: Duration of Supply:
	Was Nutritional supply provided: ☐ Yes ☐ Yes		Date nutritional supply provided: _____

FORM 3 **DR-TB CLOSE CONTACT FOLLOW-UP SCREENING**

Name		**MEDICAL No**												

	Screening date			Patient on continued nutritional support	☐ Yes ☐ No		
FU SCREENING	**Signs and Symptoms**			Psychosocial or adherence challenges identified: ☐ Yes☐ No	Action Taken if identified: _____ _____		
	Cough/wheeze > 2 weeks	☐ Yes	☐ No	Patient referred for further testing	☐ Yes ☐ No		
	Weight loss*, Poor weight gain or failure to thrive	☐ Yes	☐ No	Patient continued on preventive treatment without changes	☐ Yes ☐ No		
	Persistent fever > 2 weeks	☐ Yes	☐ No	If yes for medication change, indicate reasons:			
	Drenching night sweat	☐ Yes	☐ No	Physical FU Exam Findings:			
	Reduced playful /Fatigue	☐ Yes	☐ No	**Adverse event type**	Adverse event Grade (add number)	**Adverse outcome**	
	Temperature_____ Weight_____			Comments:			
	Screening date			Patient on continued nutritional support	☐ Yes ☐ No		
FU SCREENING	**Signs and Symptoms**			Psychosocial or adherence challenges identified: ☐ Yes☐ No	Action Taken if identified: _____ _____		
	Cough/wheeze > 2 weeks	☐ Yes	☐ No	Patient referred for further testing	☐ Yes ☐ No		
	Weight loss*, Poor weight gain or failure to thrive	☐ Yes	☐ No	Patient continued on preventive treatment without changes	☐ Yes ☐ No		
	Persistent fever > 2 weeks	☐ Yes	☐ No	If yes for medication change, indicate reasons:			
	Drenching night sweat	☐ Yes	☐ No	Physical FU Exam Findings:			
	Reduced playful /Fatigue	☐ Yes	☐ No	**Adverse event type**	Adverse event Grade (add number)	**Adverse outcome**	
	Temperature_____ Weight_____			Comments:			

Outcome at 6 months: ☐ Completed ☐ Lost to follow-up (LTFU) ☐ Stopped (AE) ☐ Stopped (Active TB) ☐ Stopped (other than active TB) ☐ Transfer out ☐ Death	**Outcome date**	**6 Months Post Preventative Treatment outcome** ☐ No TB Diagnosed ☐ Diagnosed with TB ☐ Death	**Outcome date**

Adverse events grading: Grade 1 (MILD), Grade 2(Moderate), Grade 3 (Severe), Grade 4 (Potentially life-threatening), 9 Unknown

Annex C: Selected References

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