Management of Drug-Resistant Tuberculosis in Pregnant and Peripartum Women/People: A FIELD GUIDE

Second Edition, September 2024

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Disclaimer

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SUMMARY AND KEY POINTS

Pregnant women/people are an under-served and complex population when it comes to drug-resistant tuberculosis (DR-TB). The complexity of pregnancy and DR-TB extends far beyond their physical susceptibility to DR-TB and includes risks for: receiving sub-standard care; experiencing stigma and discrimination; being separated from their children; and facing tremendous suffering due to a lack of compassionate counseling. The goal of this field handbook is to develop communities of service and promote best practices in the care of pregnant women/people with DR-TB throughout all phases of their pregnancies and in the peripartum period. Although there are limited data on the care of such individuals, those that do exist show that most pregnant women/people with DR-TB and their infants can be safely treated and go on to lead healthy, productive and normal lives. These data are supplemented by the experiences of the providers who have come together to develop this guide and to cultivate a series of best practices. This field guide provides more detailed information that can be followed not only for the care of pregnant women/people with DR-TB but which can be adapted to improve services for women/people with all forms of TB who are pregnant. The most important practices for care in these individuals include access to:

- Free family planning services at all stages of DR-TB diagnosis and treatment so that women/people can be in control of their reproductive lives while working to regain their health from their DR-TB;

- WHO recommended diagnostic tests, including rapid molecular tests and chest radiography as well as to routine screening for DR-TB given the heightened risk of developing TB during pregnancy;

- Compassionate counseling and support for either continuing or terminating a pregnancy when the person is also living with DR-TB, depending on the preferences and needs of the pregnant person;

- Effective treatment (including with newer drugs such as bedaquiline, delamanid, linezolid and the third-generation fluoroquinolines), even if specific data on pregnant women/people are lacking due to their limited inclusion in studies (although drugs that are known to cause reproductive toxicity such as pretomanid or clear damage to the developing fetus such as the injectables should be avoided if possible);

- Routine monitoring to ensure treatment is progressing well and that side effects are being assessed, managed, and minimized;

- Skilled medical care and support during all phases of pregnancy—including delivery—without unnecessary and discriminatory infection control practices being enforced beyond what is provided to other pregnant women/people (with some rare exceptions for women/people who are only recently started on DR-TB treatment);

- Their newborn child and the right to feed that child in a way that promotes the health of the newborn and the postpartum mother/parent and aligns with the mother/parent's values, preferences and needs around feeding;

- Support to remain on therapy for DR-TB with practical information about the risks and benefits of all aspects of treatment provided by informed and compassionate staff.

INTRODUCTION

Pregnant and peripartum women/people are an under-studied and under-reached group with respect to all forms of tuberculosis disease (TB), including drug-resistant TB (DR-TB). Because they are a complex population however, their care may fall outside the usual routines and practices of DR-TB service providers. This can lead to challenges in management (e.g., delayed treatment or sub-standard regimens), as pregnant individuals with DR-TB are either referred for services a great distance from their homes (a proven barrier to quality treatment) or managed by providers who are unaware of the best practices for treating DR-TB in pregnancy. This situation is exacerbated by the unpredictable nature of labor and birth, so that peri-partum individuals and their infants maybe subjected to further sub-optimal care at a time when they most need dedicated compassion and support. Furthermore, pregnant women/people and neonates are often excluded from clinical trials. Uncertainty about the safety in pregnancy of new and repurposed medications for the treatment of DR-TB has meant that pregnant women/people do not benefit from the major advances that have characterized the diagnosis, treatment, and support of women/people living with DR-TB in the past decade. The scientific literature on optimized management of DR-TB in pregnant and peripartum individuals is sparse, but there is worrisome documentation of discriminatory practices being a normal part of the care, and they often describe feeling isolated and alone during this vulnerable period.

To counter this, a group of providers and researchers with decades of experience caring for women/people with DR-TB who are pregnant or in the peripartum period joined forces to develop this "Field Guide". It constitutes a set of current best practices to improve the quality of care provided to individuals during this exciting but complex period in their DR-TB care. It is meant to supplement existing guidelines—which describe pregnant and peripartum individuals as well as their neonates as a "special population"—but often state that no formal recommendations can be made regarding their care. There is an urgent need to conduct formal studies on the ideal management of women/people with DR-TB during pregnancy and the peripartum period and strong advocacy efforts must be undertaken to address this unacceptable evidence gap. Until that time, however, this Field Guide can be seen as constituting a set of tools derived by clinical consensus and based on real-world practice with women/people who are pregnant and their neonates.

Whenever possible, management of pregnant and peri-partum women/people with DR-TB should take place within the activities of a National TB Program (NTP). There are multiple advantages to doing this, including a contextual approach, integration with other health initiatives, and health systems strengthening. If activities occur outside of an NTP, all efforts should be made to report standardized outcomes and to collaborate with the NTP whenever possible.

Definition of Terms

It is important to introduce the terms that are used throughout this Field Guide. A person is defined as being **pregnant** if s/he has had a medical test/examination documenting pregnancy. **Peripartum** is defined as being within six weeks of having given birth. A **neonate** is defined as an infant between the ages of 0 days and four weeks, and an infant as between the ages of four and 52 weeks. We use the term **DR-TB** throughout this guide to refer to strains of *M. tuberculosis* that are resistant to at least one antituberculous medication (rifampicin). Most of the practices we discuss can apply to pregnant and peripartum individuals with drug-sensitive TB as well. However, the clinical best practices described around diagnosis and regimen design refer to DR-TB that is resistant to at least rifampicin, the most powerful first-line antituberculous medication in use at the time of writing. This is because resistance to rifampicin requires major changes in the treatment and prevention strategies. Some sections also refer to isoniazid mono-resistant (INH-R) TB, but when this is the case, it will be specified. Of note, there may be individuals with allergic reactions or intolerance to rifampicin, isoniazid, and other antituberculous medications who cannot receive them and thus require the same treatment as women/people who have strains that are resistant to these medications. Finally, we use the term "**rapid molecular test**" throughout this document to refer to a WHO-recommended molecular diagnostic test (or what is often abbreviated as a "mWRD"). We stress that only WHO-recommended diagnostic tests should be used but wanted to avoid too many abbreviations and jargon in the Guide.

We have tried to use inclusive language in this document (although we may have failed in some instances). Not all women/people who are pregnant or give birth identify as "women" and thus we have used the term "person" (and we use the gender-neutral pronouns of "they/their" as well in these instances). We acknowledge, however, the important and often-overlooked place of women and mothers in many settings. We did not want to marginalize or "erase" these women, and so we also use the term "woman" and "women" as well. While the use of both of these terms may be awkward in the text, we have found the selection of one term over another has led to distraction from the key messages of this field guide. We hope women/people will be able to move beyond the language and focus instead on the care practices described herein, and so we use both terms. In the patient scenarios, we use the term preferred by the person whose story is shared, if that is known (otherwise we use the term "woman/person"). We have used the term "breast feeding" and "breast milk" since they are inclusive and gender-neutral terms, although we note that some might prefer the terms "chest feeding" or "human milk". We will continue to strive to include all individuals living with DR-TB who are pregnant, give birth, and use their bodies to feed the babies in efforts to improve care and apologize to any if this document has fallen short of this goal. We welcome feedback along these lines!

Table 1: Definition of terms

Term	Definition of terms
Drug-resistant TB (DR-TB)	Strains of *M. tuberculosis* that are resistant to rifampicin. Multidrug-resistant TB (MDR-TB) with additional resistance to isoniazid. Pre-XDR TB is MDR-TB with additional resistance to a fluoroquinolone. XDR-TB is MDR-tuberculosis with additional resistance to a fluoroquinolone and another Group A medication (bedaquiline or linezolid).
Isoniazid mono-resistant (INH-R) TB	A strain of *M. tuberculosis* that is resistant to isoniazid only.
Pregnant person	A person is defined as being pregnant if they have had a medical test/examination documenting pregnancy. While many pregnant women/people identify as women, some do not, and thus we use the term "person" or "individual" throughout this field guide.
Peripartum period	The period from birth until 6 weeks after childbirth
Antepartum period	During pregnancy
Postpartum period	The period immediately after birth to 6 weeks after childbirth
Neonate	An infant age 0 – 4 weeks
Infant	A child age 5 – 52 weeks

Structure of the Field Guide

This Field Guide is meant to provide "best practices" for the care of pregnant women/people and their infants who are living with DR-TB. In each section, a series of best clinical practices are presented, based primarily on the experiences of the women/people who contributed to this guide. Published studies and guidelines—where they exist—were also used. Summary points are provided at the end of each section. These are followed by a "patient scenario" based on lived experiences of pregnant women/people with DR-TB. The scenarios have been edited (and in some instances combined) to protect confidentiality and to emphasize some of the key issues being discussed. Unfortunately, because they represent real-world examples, they often highlight damaging or ill-advised practices. Thus, at the end of each scenario, a review of suggested alternative practices is provided.

SCREENING, DIAGNOSIS AND PATHWAYS TO CARE

Women/people who are pregnant and have DR-TB tend to come to the attention of health services through one of two pathways. Either they are pregnant and receiving antenatal care when they are found to have DR-TB or they are receiving care for DR-TB when they are found to be pregnant. Clinical best practices for screening and diagnosis are slightly different for each of these groups, so they will be considered separately. In general, however, the same samples and tests that are carried out in women/people who are not pregnant should be carried out in pregnant individuals and in the postpartum period. Chest radiographs may be indicated and safely used in women/people who are pregnant and in the peripartum period, with abdominal lead shielding if it is available (however if not

available, it is still reasonable to proceed with the radiograph since there is minimal radiation exposure to the developing fetus).

Women/people who are pregnant are at a higher risk of developing active TB than are women/people who are not pregnant. For this reason, it is a best clinical practice that individuals who are pregnant be screened for TB routinely at every antenatal visit. TB screening should be part of all postpartum visits, and the offer of TB preventive therapy can be linked to postpartum TB screening where active disease is ruled out. Although historically symptom screening has been used with the WHO-recommended four-symptom screening assessment (cough of any duration, fever, night sweats, and/or weight loss), hormonal changes and the weight gains that occur during pregnancy mean this tool is even less sensitive in pregnancy than other populations, where it is known to under-preform. For this reason, other strategies for screening pregnant individuals for active TB must be considered. The best option is routine sputum sample collection and testing with a rapid molecular test (i.e., Xpert MTB/RIF or Truenat) that can also detect rifampicin resistance, but if this is not possible then it should be strongly considered at the first and final pre-natal visits. Although chest radiographs (CXR) with abdominal shielding can be considered during pregnancy, repeated radiation exposures should be avoided. All pregnant individuals should be tested for HIV, and those found to be living with HIV who are seriously ill and/or have low CD4 counts can also be screened for TB using urine lipoarabinomannan (LAM) testing. If these tests are positive, TB diagnosis is confirmed and treatment should be started immediately. It is important to remember for any bacteriologic test, that a negative result does not completely rule out TB. Any pregnant person who is not gaining weight after the first trimester or who is losing weight during pregnancy should be tested for TB either with a sputum specimen assessment or chest X-ray.

Women (and other individuals of child-bearing potential who may not identify as women) who are on treatment for DR-TB should be tested for pregnancy at the time of treatment initiation. They should also be offered contraception (i.e., family planning) at no cost as part of their DR-TB care. Women of reproductive age should be asked at each follow-up visit for DR-TB care when they last had their menstrual period and what types of family planning they are using. Women with DR-TB may report amenorrhea or changes in their menstrual cycles as a result of DR-TB or as a side effect of their treatment. Quarterly urine B-HCG testing (i.e., a urine pregnancy test) should be considered.

If a pregnant person is found to have DR-TB or if an individual with DR-TB is found to be pregnant, intensive counseling should be made available to them (see section on "Counseling and Support"). They should be treated with compassion and made to feel sufficiently comfortable to enable a frank discussion about their pregnancy choices. Counselling should be unbiased manner using an active listening approach so that they can make an informed decision about the continuation of their pregnancy in alignment with their values, hopes, and family goals. DR-TB treatment is NOT contraindicated in pregnancy and being on DR-TB therapy does not mean a person should not be pregnant (although most providers would advise deferring pregnancy until the completion of DR-TB treatment, when possible). If a pregnant person with DR-TB would like to terminate their pregnancy, these services should be provided in a safe, confidential, and non-judgmental manner at no additional cost.

Key points on diagnosis and pathways to care are summarized below:

- Pregnant women/people with DR-TB usually come to services in one of two ways: they are either pregnant and found to have DR-TB during antenatal care or they are on DR-TB treatment and found to be pregnant;
- Pregnant individuals should be screened for TB at all antenatal care visits, and because symptom screening lacks sensitivity, obtaining sputum samples for testing with rapid molecular diagnostics should be considered. Chest radiography and/or urine LAM (for certain people living with HIV) are alternatives;
- Pregnant women/people who are not gaining weight or who are losing weight should be thoroughly investigated for TB (sputum, chest X-ray);
- All women (and other individuals of child-bearing potential who may not identify as women) with DR-TB should undergo baseline pregnancy testing and be offered family planning as part of their DR-TB care;
- All women on DR-TB treatment should be asked about their menstrual cycles and family planning methods at each visit, but because DR-TB and treatment can cause menstrual cycle irregularities, routine urine B-HCG testing for pregnancy can be considered;
- Chest radiographs (and other imaging) are not contraindicated in pregnancy, but abdominal shielding should be used if possible;
- If a person is found to be pregnant while living with DR-TB, intensive and supportive counseling should be offered so that it can be decided whether to continue with their pregnancy or not. Should they choose to terminate the pregnancy, termination services should be offered without judgement and free of charge.

Patient Scenario

Bangladesh

MM is a 34 year-old woman who is in her second trimester of pregnancy and being followed at local health center for her pregnancy. She is also living with HIV. She has been tired since her pregnancy (her third) and noted that she has not really gained weight since she found out she was pregnant. This has been different when compared with her other pregnancies, but her mother-in-law tells her this is because she is probably pregnant with a boy (her first two children were girls). For the last month, she has felt short of breath. Her partner (and the father of her baby) is coughing at home too. She tells her nurse in the antenatal clinic who asks her to provide a sputum sample, but MM cannot cough and says she is “dry”. The nurse refers her to a physician who is worried about her, but says there are not any other tests they can do at this point, since a chest X-ray “might expose the baby to radiation”. The physician says if the cough continues after she delivers the baby, they can obtain an X-ray then. They also adviser her to try and cough sputum in the morning if she can and to bring in a sample anytime.

Recommendations to improve practices in this scenario would include the use of a urine LAM test (the woman is living with HIV and has symptoms of TB) and also of a chest radiograph since she has symptoms of pleuritic involvement. TB is high on the differential given her HIV status, her symptoms, her lack of weight gain, and the fact that her partner is also coughing. Thus, an extensive assessment is indicated given that her pregnancy may have increased her risk for developing active TB and that untreated TB is a risk to her health and the health of her baby that would far outweigh any risks associated with a chest radiograph. Her partner should be referred for TB work-up as soon as possible.

TREATMENT REGIMEN DESIGN AND INITIATION

Pregnant women/people who are also living with DR-TB are at higher risk of poor outcomes compared with adults who are not pregnant. The best way to ensure the health of the fetus and neonate and to support the health of the pregnant person is to start treatment immediately using medications that have been associated with improved outcomes and lower mortality among people who are treated for DR-TB. Although safety data on the use of most of the second-line antituberculous agents in pregnancy come from animal studies or small cohorts of pregnant individuals, the only category of medications where there are data documenting damage to the developing fetus are the injectable agents. These agents should not be routinely given to anyone living with DR-TB, and they should be avoided except in situations where amikacin might be the only option the save the person's life. The only other medication that may be concerning among pregnant women is pretomanid, since it has been associated with reproductive toxicity in animal studies. There are other agents in the nitroimidazole class that can be given—specifically delamanid. Bedaquiline can also be used.

Treatment should be initiated immediately after a diagnosis of DR-TB is made, as untreated DR-TB is life-threatening to pregnant women/people and a public health risk. The overarching goal of management is for pregnant women/people to access timely and high-quality treatment regimens for DR-TB to maximize the chances of treatment success. If possible, treatment should be started in the outpatient setting, but if a referral is needed for specialized care, treatment should not be delayed while the referral is set up. Free/subsidized transportation and other support should be provided to those who have to travel far to receive specialized care.

Amikacin and pretomanid are the only medications that should be avoided during pregnancy (unless there are no other options available to save the individual's life), but there are some medications that should be used with close monitoring. Linezolid is a Group A medication that is associated with improved outcomes and lower mortality and it can be used in pregnancy. Because linezolid can cause anemia, and pregnant women/people are at high-risk for anemia, they should have a complete blood count checked monthly while on linezolid and offered iron supplementation if anemic. Ethionamide is only advised for pregnant women/people with limited treatment options and has been associated with neural tube defects, and should be given with prenatal vitamin supplementation. Ethionamide can cause nausea and vomiting and may exacerbate the nausea and vomiting of pregnancy. In addition, ethionamide-related hepatotoxicity may be an added deterrent given higher rates of hepatitis in pregnant women/people, especially in the third trimester. If possible, ethionamide should be avoided in pregnant women/people. The same is true of PAS, which is also associated with

nausea and vomiting. Clofazimine may cause hyperpigmentation not only of the mother/parent's skin but also of the neonate's skin and counseling should be provided about this. The hyperpigmentation is completely reversible but can take several weeks to months to resolve. Fluoroquinolones have been safely used in pregnant women as have bedaquiline, clofazimine, and cycloserine/terizidone. In observational studies of fluoroquinolones and bedaquiline, their use may be associated with lower birth weight babies and thus pregnant women/people on these medications require nutritional supplementation and support. Delamanid appears to be safe based on animal studies and there is some experience safety in small cohorts of pregnant women/people. Table 2 summarizes the best practices advice on the second-line medications and their use in pregnancy (medications are listed by WHO groupings from the 2019 Guidelines on the Management of Drug-Resistant TB).

Table 2: Best Clinical Practices for Using Second-Line Medications in Pregnancy

Medication	Pregnancy Best Practice	Comments
WHO Group A Medications		
Bedaquiline	Safe in small cohorts. Can be used but may be associated with lower birth weight babies	Consider nutritional supplementation
Levofloxacin/moxifloxacin	Safe in small cohorts and can be used but may be associated with lower birth weight babies	Consider nutritional supplementation
Linezolid	Safe in small cohorts and can be used but associated with bone marrow suppression and anaemia. Monitor hemoglobin and full blood count regularly (i.e., at baseline, week two, and then monthly while on linezolid)	Give with iron and vitamin B6 supplementation
WHO Group B Medications		
Clofazimine	Safe in small cohorts and can be used. However, the mother/parent must be counselled about skin discolouration.	May lead to reversible hyperpigmentation in pregnant person and neonate which may take weeks to resolve.
Cycloserine/terizidone	Safe in small cohorts and can be used,	Give with vitamin B6 supplementation
WHO Group C Medications		
Delamanid	Safe in very small cohorts and can be used	Nitroimidazole of choice owing to the potential reproductive toxicity of pretomanid
Amikacin	Associated with damage to fetal ear and to the hearing of the pregnant person and should be avoided during pregnancy	Can be considered if there is no other option and the life of the pregnant person is at risk

Medication	Pregnancy Best Practice	Comments
Ethionamide	Associated with neural tube defects and must be given with prenatal multivitamin Can exacerbate nausea and vomiting during pregnancy Can be associated with increased risk of hepatotoxicity, especially in the third trimester Can be associated with hypothyroidism. If used TSH should be monitored monthly.	Can be considered if there are limited treatment options. Give with folate, thiamine and vitamin B6 supplementation (i.e. a prenatal vitamin)
PAS	Can exacerbate nausea and vomiting during pregnancy Can be associated with hypothyroidism and TSH should be monitored monthly if used	Can be considered if there are limited treatment options
Imipenem (or meropenem) in combination with amoxicillin/clavulanic acid	Safe in small cohorts and can be used	Requires placement of intravenous line for administration over prolonged periods of time, although they can be administered through a normal IV cannula for shorter periods of time. Amoxicillin/clavulanic acid must be given orally 30 minutes prior or the carbapenem will not be active against M. tuberculosis
Pretomanid	Should not be used in pregnancy as it has been associated with reproductive toxicity in animals	Delamanid should be used as the nitroimidazole of choice if a medication from this category is needed

Many pregnant women/people with DR-TB are also living with HIV. It is essential that they continue to take their antiretroviral therapy (ART) while on treatment for DR-TB. There are some medication-medication interactions to consider with ART and DR-TB: specifically, efavirenz cannot be used with bedaquiline as efavirenz lowers bedaquiline concentrations. Integrase inhibitors are thus preferred (e.g., dolutegravir). Some medications may have overlapping toxicities that require close monitoring: most notable among these is the anemia that can be caused by linezolid and AZT and which may be a problem during pregnancy in general.

The WHO has recently recommended several new, all-oral shorter regimens for the treatment of RR/MDR-TB. These recommendations were based on randomized controlled trials that included a small number of pregnant women/people. The drugs in these regimens have also been shown to be relatively safe in the small numbers of pregnant women/people who received them.

The first study was called the “BEAT Tuberculosis” trial, and it was done in South

Africa. The study compared a treatment strategy in which a six-month regimen of bedaquiline, delamanid, linezolid (600mg), levofloxacin, and clofazimine was given at treatment initiation. This regimen was then tailored when the results of fluoroquinolone susceptibility testing became available. In patients whose strains of TB showed no evidence of fluoroquinolone resistance, the clofazimine was stopped and the other four drugs (bedaquiline, delamanid, linezolid, and levofloxacin) were continued for a total of six months of treatment. In patients whose strains of TB showed evidence of fluoroquinolone resistance, the levofloxacin was stopped and other four drugs (bedaquiline, delamanid, linezolid, and clofazimine) were continued. Of note, few people who had strains of MDR-TB that were also resistant to the fluoroquinolones were included in the study. In patients who did not have fluoroquinolone susceptibility results, all five drugs were continued. The regimen was shown to be non-inferior to the 9-month standard of care regimen being used in South Africa at the time, with comparable safety.

The second study that utilized drugs that have been shown to be relatively safe in the small number of pregnant women who received them was the endTB trial. This study was done in multiple countries, allowed women/people who became pregnant during the trial to remain in the study, and assessed five different, nine-month regimens containing different combinations of bedaquiline, delamanid, linezolid (600mg with dose reductions allowed), levofloxacin/moxifloxacin, clofazimine, and/or pyrazinamide. The study only included people whose strains of TB had no evidence of resistance to the fluoroquinolones. The regimens were compared to the locally accepted standard of care. Three of the regimens were found to be non-inferior to the standard of care both in terms of efficacy and saefty and are recommended by the WHO. They are:

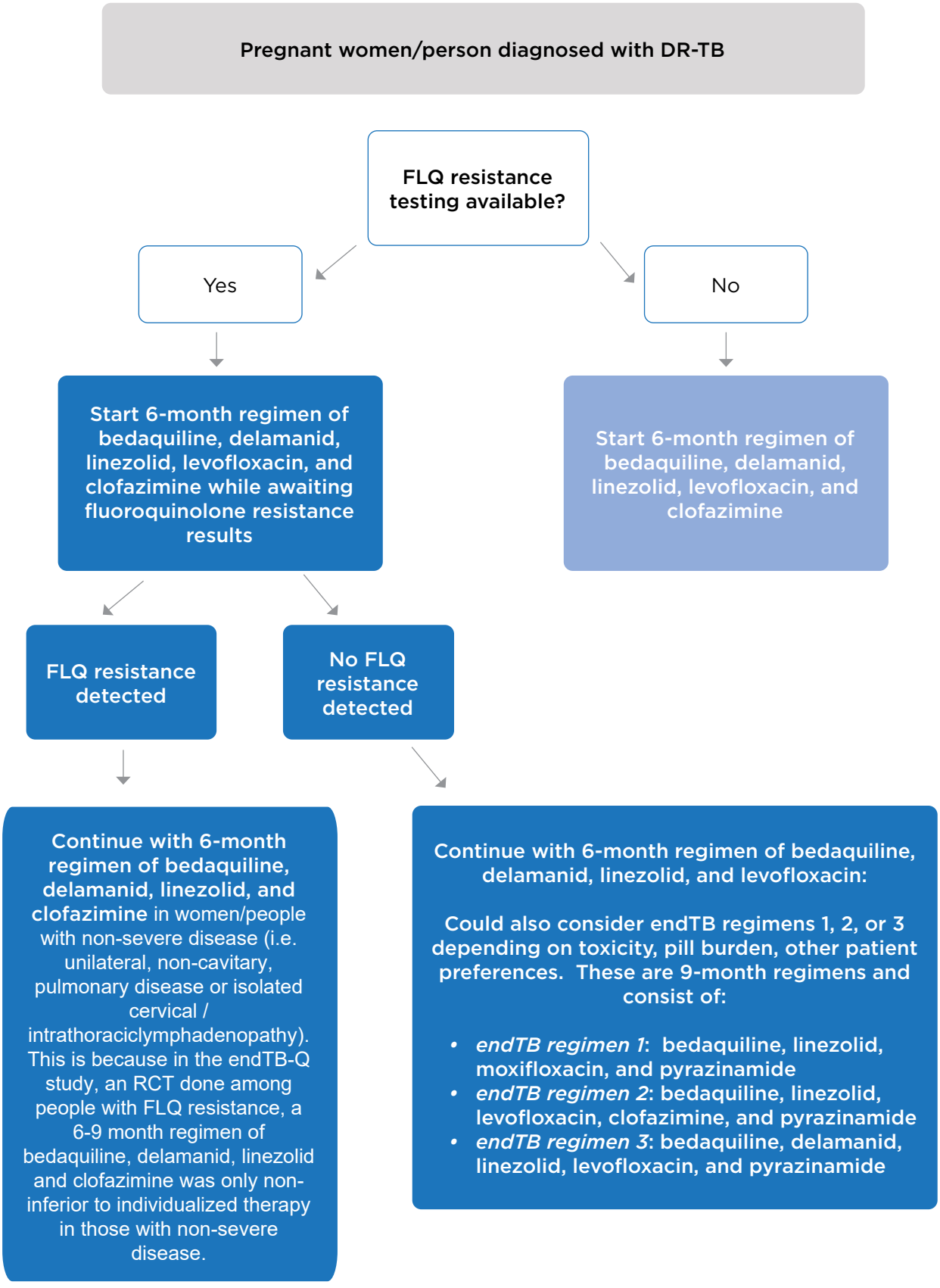
- *endTB regimen 1*: 9 months of bedaquiline, linezolid, moxifloxacin, and pyrazinamide
- *endTB regimen 2*: 9 months of bedaquiline, linezolid, levofloxacin, clofazimine, and pyrazinamide
- *endTB regimen 3*: 9 months of bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide

Each of these regimens represent potential options for pregnant women/people who are diagnosed with RR/MDR-TB.

The endTB-Q study was a multi-center, randomized controlled trial done to assess an all-oral, shorter regimen for people with strains of RR/MDR-TB that also have additional resistance to the fluoroquinolones (https://endtb.org/endtb-q-clinical-trial-results). This is the only randomized trial to specifically assess regimens in this population. The study compared a 6-9 month regimen of bedaquiline, delamanid, linezolid, and clofazimine to an individualized longer regimen. The 9-month duration was used if the participant had a delayed clinical or bacteriologic response to therapy. Although the study found excellent outcomes in people who had non-severe forms of disease (treatment success rates of 93%), the study overall found the regimen was NOT non-inferior to a longer individualized regimen. It is therefore recommended that the BEAT Tuberculosis regimen in the setting of known or likely fluoroquniolone resistance only be used in pregnant women/people with non-severe form of disease (unilateral or non-cavitary pulmonary TB or isolated cervical/intrathoracic lymphadenopathy). Pregnant women/people with severe forms of disease (i.e. bilateral disease, cavitary disease, or extra-pulmonary disease other than cervical or intrathoracic lymphadenopathy) who have known or likely fluoroquinolone resistance should receive a longer, individualized regimen.

When deciding which regimens to offer pregnant women/people with RR/MDR-TB, providers should work with patients to understand their needs around duration of therapy (six months compared with nine months), pill burden, and possible side effects. These regimens should not be used in pregnant women/people who have received bedaquiline, linezolid, delamanid, or clofazimine for one month or more, unless documented susceptibility to these agents can be confirmed. It is noteworthy that all the regimens contain linezolid, a drug which may be problematic in pregnant women/people who are at increased risk for anemia. Dose reduction strategies (either to 300mg daily or 600mg every other day) for linezolid either when side effects develop or after 4 months of treatment were built into the endTB trial and could be used in pregnant women/people who develop or are at high risk of anemia. BEAT Tuberculosis also allowed linezolid to be interrupted and reintroduced (after normalization of lab abnormalities) in participants. With persistent myelosuppresions, linezolid could be dose reduced from 600mg daily to 300mg daily, provided that the participant received 8 weeks at the full 600mg dose. If regimens containing pyrazinamide are used, then close monitoring of liver function should be done, especially in patients who have any gastrointestinal symptoms. A possible approach to treatment is summarized in Figure 1.

Figure 1: Sample Regimens for Pregnant Women/People with DR-TB



All pregnant women/people started on treatment for DR-TB should be notified and registered with the national system. They should also be reported to the agencies responsible for pharmacovigilance in the country so that additional safety data on the second-line medications can be collected. An example of core reporting form can be found in the Annex. :

Key points on treatment regimen design and initiation are summarized below:

- Pregnant women/people with DR-TB should be started on treatment immediately with fully active regimens because untreated and under-treated DR-TB poses a serious risk to the pregnant individual and the fetus;
- The only medication that is contra-indicated in pregnancy is amikacin (and other injectable agents), which should only be used if there are no other options to save the person's life. Pretomanid may have reproductive toxicity and should be avoided until additional data are available.
- Pregnant women/people with DR-TB can receive linezolid with monitoring of the complete blood count and iron supplementation;
- Pregnant women/people with DR-TB can receive fluoroquinolones and bedaquiline safely but nutritional support should be considered to ensure adequate growth of the fetus;
- Ethionamide and PAS may be used in pregnant women/people who have limited treatment options but could worsen nausea and vomiting associated with pregnancy and thus anti-emetic therapy should be considered if they must be administered. They may also be associated with an increased risk of hepatotoxicity. Ethionamide must be given with a prenatal vitamin given its association with neural tube defects;
- Clofazimine may cause reversible hyperpigmentation in pregnant women/people and neonates but this resolves over weeks/months;
- Pregnant women/people should receive one of the four all-oral, shorter regimens, now recommended by the WHO for treatment during pregnancy, provided they meet other criteria for receiving these regimens.
- Pregnant women/people with DR-TB should be reported to national programs and bodies responsible for pharmacovigilance.

Patient Scenario

FG is a 32 year-old woman who is pregnant and in the first trimester when she finds out she is living with DR-TB. She has a rapid molecular test that is positive for M. tuberculosis as well as rifampicin-resistance and fluoroquinolone resistance. She has bilateral cavitary disease on chest radiograph and is started on a regimen of bedaquiline, clofazimine, cycloserine and ethionamide. Linezolid is omitted after a baseline hemoglobin is 7.7 g/dL and delamanid is not given because the providers are worried about safety owing to "limited information" on its use in pregnancy. She continues to cough, does not put on weight and in her second month of treatment, she still has a positive smear and culture. She also reports daily vomiting after taking DR-TB treatment.

Recommendations to improve practices in this scenario would include the use of an individualized regimen containing linezolid and delamanid. Given her FLQ resistance and her severe disease, she should not receive the endTB-Q/BEAT Tuberculosis regimen. She could have been started on an initial regimen of 12-15 months of bedaquiline, delamanid, linezolid, levofloxacin, clofazimine, and cycloserine. Thes drugs can all be safely used in pregnant women/people. If she had only unilateral or non-cavitary pulmonary disease, then the 6-9 month endTB-Q/BEAT tuberculosis regimen (bedaquiline, delamanid, linezolid, and clofazimine) could have been used. The BEAT Tuberculosis regimen is recommended by the WHO for pregnant women/people.

MONITORING

Pregnant individuals who are living with DR-TB should be seen monthly by a clinician with expertise in the management of DR-TB. They should undergo the routine baseline testing that is recommended for all pregnant women/people (including HIV testing, Hepatitis B (HBV) testing, screening for STIs, blood pressure screening, and testing for gestational diabetes). They should receive the standard monitoring that is part of DR-TB care, which varies depending on the medications they receive. In addition, they should have their weight, blood pressure, and urine (proteinuria) assessed monthly. They should have the tetanus vaccine and other relevant vaccinations indicated in pregnancy (e.g., influenza, COVID-19).

Most people with DR-TB who are pregnant can be managed safely in the community and do not need specialized obstetric care. If such care is needed, pregnant women/people with DR-TB should be provided with transport and other support to attend referral visits since the services are often located far from their homes.

Pregnant individuals with DR-TB should receive nutritional counseling and support to ensure a good TB outcome and support the growth of their baby. They should receive a prenatal vitamin with folate and may need additional iron supplementation, especially if taking linezolid.

A suggested programme for routine monitoring is included in Table 3. Of note, additional testing and monitoring may be needed depending on the clinical situation. The table is based on the month of DR-TB treatment and not on the month of the pregnancy.

Table 3: Suggested Monitoring Schedule for Pregnant women/people with DR-TB

Test	Baseline	Wk2	M1	M2	M3	M4	M5	M6	M7	M8	M9	Tx Comp	Commnt
Weight	X	X	X	X	X	X	X	X	X	X	X	X	Monthly until treatment complete
Height	X												
BP	X	X	X	X	X	X	X	X	X	X	X	X	Monthly until treatment complete
Urine dipstick for protein	X	X	X	X	X	X	X	X	X	X	X	X	Monthly until delivery
Blood glucose screening	X												
Sputum for culture, AFB	X		X	X	X	X	X	X	X	X	X	X	Monthly until treatment complete
Symptom screen	X	X	X	X	X	X	X	X	X	X	X	X	Monthly until treatment complete
Nutrition screen	X	X	X	X	X	X	X	X	X	X	X	X	Monthly until treatment complete
Adherence support and screen	X	X	X	X	X	X	X	X	X	X	X	X	Monthly until treatment complete
Side effect screen		X	X	X	X	X	X	X	X	X	X	X	Monthly until treatment complete
HBV testing	X												
HIV testing	X			X	X	X	X	X	X	X	X	X	Routine testing practices for HIV during pregnancy should be followed if HIV
CD4 testing	X							X					Only if living with HIV
HIV viral load	X							X					Only if living with HIV
STI screen	X												
Full blood count	X	X	X	X	X	X	X	X	X	X	X	X	Week 2 then monthly while on linezolid
ECG for QTcF	X	X	X	X	X	X	X	X					Week two then monthly while on bedaquiline, clofazimine, delamanid or moxifloxacin
Visual acuity	X	X	X	X	X	X	X	X	X	X	X	X	Week 2 then monthly while on linezolid
Liver function	X				X			X			X	X	
TSH	X				X			X			X	X	Baseline and every three months if on Ethionamide or PAS
Chest Xray	X											X	
Peripheral neuropathy screen	X	X	X	X	X	X	X	X	X	X	X	X	Week 2 then monthly while on linezolid
Renal function	X												

Of note, if a pregnant person has to be treated with amikacin, they should have a baseline audiometry screen and formal audiometry monthly and monthly renal function testing. Assessment of electrolytes (including potassium and magnesium) should be done if they have any vomiting or diarrhea.

Key points on routine monitoring of pregnant women/people with DR-TB during treatment are summarized below:

- Most pregnant women/people with DR-TB can be cared for in the community by DR-TB providers, but if referral is needed transport and other socioeconomic support should be provided;
- Routine monitoring should follow the usual standards for DR-TB and prenatal care, with additional baseline testing for HIV, HBV, STIs, gestational diabetes and hypertension. Regular (i.e., monthly) screening of blood pressure and proteinuria should also be done;
- Symptom-guided monitoring is also important, with vomiting prompting review of electrolytes, liver function tests for hepatitis, nutritional status, and hydration;
- Nutritional support is essential for pregnant women/people with DR-TB to ensure they have good TB treatment outcomes and to support the pregnancy.

Patient Scenario

RP is a 24 year-old woman who is pregnant with her first child. She was found to have DR-TB in the second trimester of pregnancy and started on a regimen of levofloxacin, linezolid, clofazimine, and cycloserine with a plan to add bedaquiline after delivery. She is seen in the clinic each month and a complete blood count is checked given that she is on linezolid. At the 8 week visit (now in the third trimester of pregnancy), she is complaining of fatigue and found to have a hemoglobin of 6.7g/dL and iron tablets are prescribed. She is unable to take the iron due to gastrointestinal intolerance, and the hemoglobin at the next monthly visit is now 5.9 g/dL, and she is short of breath. The linezolid is stopped and she is given a blood transfusion and told to continue on iron tablets. Bedaquiline is started since the linezolid is stopped.

Recommendations to improve practices in this scenario would include the use bedaquiline from the start of treatment (it is not contraindicated in pregnancy and is associated with improved outcomes and lower mortality), which might allow for a shorter period of linezolid use. Both pregnancy and linezolid are associated with anaemia and in this scenario, when the hemoglobin was low, the patient should have been given a transfusion immediately and the linezolid withheld or dose reduced. At the very least, the patient should have been recalled sooner than the usual 4 week follow up for repeat hemoglobin assessment. Although pregnant women with DR-TB can receive linezolid and usually tolerate it well, closer monitoring should be considered, especially in people with anemia.

MANAGEMENT DURING LABOR AND DELIVERY

Many pregnant women/people living with DR-TB face discrimination in their interactions with the health care system. These often manifest as fear-based infection control practices, where pregnant and peri-partum people are isolated, avoided, or forced to mask/face restrictive measures because of their DR-TB status. It is more likely that pregnant women/people will face this discrimination when they are encountering providers who are not familiar with DR-TB, and thus labor and delivery are especially risky times for these individuals.

Because labor cannot be predicted, pregnant women/people may end up seeking care at health care facilities where there is limited experience managing people with DR-TB. This not only puts them at risk for discrimination but also for potential medical mismanagement. Most often, this takes the form of not administering DR-TB medications as prescribed. This may be because providers fear giving the medications during labor and delivery or simply because they do not have the medicines. Missing dosages increases the risk of having a problem with their DR-TB status—including returning to a smear-positive status (and once again having infectious DR-TB). Thus, all health care workers caring for pregnant women/people with DR-TB should provide them with a one-page summary letter detailing their treatment and the monitoring required. The pregnant individual should also be provided with a one- to two-week emergency supply of DR-TB medications as the time for delivery gets closer, in case they cannot return timeously for their DR-TB monitoring appointment.

In terms of infection control, most pregnant individuals on treatment for DR-TB are unlikely to transmit living bacilli provided their medication is appropriate. Table 4 provides some issues to consider in best practices for infection control in this context. In general, most pregnant or peri-partum people do not need be isolated or required to wear a mask for a prolonged period (unless there is another indication e.g., COVID-19), especially if this is not standard practice for people in labor in the facility. Individuals on DR-TB treatment who are in labor, should be treated as any other person in labor would be treated, with routine monitoring and assessment. They should not be left alone or isolated. There is no need to perform a Caesarian section (unless there are other indications) or to undertake any special labor and delivery precautions simply because a person has DR-TB.

Table 4: Infection Control Considerations for Pregnant and Postpartum People Living with DR-TB and their Infants

TB Status of the pregnant or postpartum person	Health status of the infant/ newborn	Infection control best practice
If <u>any</u> of the following is present: • Treatment for RR-TB was started less than 2 weeks ago; • Treatment is possibly ineffective (i.e. there is known or likely resistance to the WHO Group A or B medications); • The person being treated remains smear-positive after baseline; • The person being treated has current extensive, cavitary disease; • The person being treated is clinically deteriorating; • The person being treated has experienced challenges with adherence and may be incompletely treated	*If <u>any</u> of the following is present* • The infant is immunocompromised; • The infant is premature (born before 37 weeks gestational age); • The infant is very underweight (weighs less than 1,500 grams at birth)	Pregnant/postpartum person should wear a surgical mask whenever possible when around others, including when in close contact with infant (i.e., during holding or feeding)
If <u>all</u> of the following are present: • Treatment for RR-TB was started 2 or more weeks ago; • Treatment is likely to be effective; • The most recent smear of the person being treated is negative, if available; • The person being treated is likely to be adherent	*If <u>all</u> of the following are present:* • The infant is gaining weight; • The infant is on effective treatment for their immunocompromising condition (if such conditions are present); • The infant is on effective RR-TB preventive therapy, if indicated	Pregnant/post-partum person does not need to wear a mask, as long as they are able to adhere to treatment

Key points on management during labor and delivery are summarized below:

- Pregnant women/people with DR-TB often face discrimination from health care providers, and the risk is especially high during labor and delivery;
- Pregnant women/people who are on treatment for DR-TB for more than 72 hours have a very low likelihood of transmitting DR-TB (provided they are able to take their medications and are on appropriate therapy) and should not be isolated or made to follow restrictive infection control measures during labor and delivery;
- Pregnant women/people with DR-TB should be given a summary letter with the details of their treatment and an emergency supply of their medications around the anticipated time of their delivery so that they can continue to receive treatment.

Patient Scenario

JF is a 32 year-old woman with no co-morbidites who is pregnant with her fifth child when she is diagnosed with DR-TB during her first trimester. She is started on a regimen of bedaquiline, linezolid (for 8 weeks while awaiting the results of her strain's fluoroquinolone resistance testing), levofloxacin, clofazimine, with a plan for 9 months of treatment. She does well on the regimen and converts her culture after 1 month on treatment. She is excited about the baby who is coming and that she will be almost done with treatment by the time the baby arrives. Her strain comes back with susceptibility to the fluoroquinolones, and she is continued on a regimen of bedaquiline, levofloxacin, clofazimine, and cycloserine. Her pregnancy proceeds normally and she does well at a special clinic for people with DR-TB who are pregnant. At week 38, while visiting her sister, she unexpectedly goes into labor and because she sees some blood when her water breaks, her sister takes her to the nearest hospital for delivery. The doctors there ask about her medications and she explains to them she is on treatment for DR-TB and she is doing well. The doctor leaves the room immediately, and the nurses do not come and check on her. Her sister attends the birth of a healthy baby boy, and demands the nurses come in to clean up the infant and deliver the afterbirth. They do so only after repeated shouting. Nobody comes to check on the baby or the woman who just delivered again. They all leave the hospital the next day since she does not have her DR-TB treatment. The family is happy with the new baby but distressed and depressed about the treatment she received and file a complaint with the ministry of health services.

Recommendations to improve practices in this scenario would include providing the pregnant woman with a note explaining her treatment as well as an "emergency packet" of medication she can take should she need to deliver suddenly. While the letter should protect her privacy, it should also note that she is not a risk for transmission of her DR-TB and that staff only need to follow the infection control practices they normally would for any pregnant person. The ministry of health should have a representative meet with the family to hear and address their concerns. Staff at the hospital where the incident occurred should also receive additional training on infection control and how to reduce discrimination.

POSTPARTUM MANAGEMENT OF INDIVIDUALS WHO HAVE GIVEN BIRTH

An infant who is born to a person who is living with DR-TB is likely to be a normal, healthy child who needs to bond with his or her mother/parent. This infant, however, requires clinical attention beyond that routinely provided to a neonate; and s/he will need additional support since it is likely his or her family is under stress from the DR-TB diagnosis. Most children born to people living with DR-TB do not suffer acute health consequences from either DR-TB exposure—which can be limited if the pregnant individual is timeously and appropriately treated —or from in utero/breast milk exposure to second-line DR-TB medications. However, there are three important issues to consider in the management of these neonates.

1. Assess for congenital DR-TB

It is important to exclude congenital DR-TB in these babies. The most important way to prevent congenital DR-TB is to ensure the mother/parent is treated with an effective regimen. Some neonates, however, still develop congenital DR-TB. The mechanism of transmission is usually hematogenous and the risk is elevated in people with tuberculous endometritis or disseminated disease. There are reports implicating ingesting or aspirating amniotic or genitourinary fluid containing DR-TB bacilli as an additional mechanism of acquiring true congenital DR-TB, although this is exceedingly rare.

All babies born to individuals with DR-TB should be examined clinically upon delivery with a focus on possible signs of TB infection. These include respiratory distress, poor feeding, fever, lethargy, irritability, low birthweight, or hepatosplenomegaly. If a newborn has any of these, congenital DR-TB should be considered and the child should have a chest radiograph (posterior-anterior and lateral), an abdominal ultrasound, and a lumbar puncture. A stool specimen should be obtained and sent for TB testing using a rapid molecular test. All other specimens should be tested using a rapid molecular test and TB culture. Placental examination with histology, smear, culture, and testing with a rapid molecular test should be considered a routine part of the care of people who were recently (i.e., less than 4 weeks) started on DR-TB treatment. If the infant has findings consistent with TB, s/he should be treated for DR-TB based on the drug susceptibility testing results or treatment regimen of the mother/parent. For more on the care of children with DR-TB, please see the Sentinel Field Guide on the Management of DR-TB in Children (http://sentinel-project.org/wp-content/uploads/2022/04/DRTB-Field-Guide-2021_v5.1.pdf). Most neonates with congenital TB present in the first 6-8 weeks of life, and thus close follow up of an infant born to a person with DR-TB should be conducted during this period. Neonatal TB may have a similar appearance to other common causes of neonatal sepsis and thus it is important to support the family to disclose the DR-TB history to any providers who might be assessing the child.

2. Assess for Neonatal DR-TB

Neonatal DR-TB differs from congenital TB in that infection occurs via the respiratory route after birth. It is challenging to differentiate congenital from neonatal DR-TB (and not relevant to clinical management) in a child born outside of the health care setting, but it is important to emphasize that the risk of DR-TB transmission to a neonate is low if the mother/parent—and other adults in the household—is on effective therapy for DR-TB. Families may fear stigma and discrimination from health providers if they seek care

for DR-TB and they may also fear their infant will be separated from them if the diagnosis is disclosed. These fears and anxieties can result in delays in seeking treatment. Thus, it is important for health care providers to be compassionate with families where there is a pregnant person who is living with DR-TB and to avoid fear-based infection control practices (i.e., separating mother/parent and newborn). Neonatal DR-TB should be assessed in the same way as congenital TB and the diagnosis and treatment approaches are the same (although the placenta may not be available for examination for older neonates and children born outside of the health care system). The child should also be assessed for other common causes of neonatal sepsis. Post-partum individuals and their families should also be counseled about possible signs of DR-TB in a newborn and to come to the health facility urgently if they note any of them in the baby. Infants born to people living with DR-TB should also have more routine follow-up during the first 6-8 weeks of life to assess the child, and families should be supported to attend these additional visits if needed (i.e., transportation support, flexible scheduling, etc.).

3. Consider DR-TB preventive treatment

Infants born to people with DR-TB should be considered for DR-TB preventive treatment (i.e. "treatment of infection") if there is no TB disease. For more on DR-TB preventive treatment, see the associated sections of the Sentinel Field Guide on the Management of DR-TB in Children (http://sentinel-project.org/wp-content/uploads/2022/04/DRTB-Field-Guide-2021_v5.1.pdf). If the neonate is given DR-TB preventive treatment, the BCG vaccination should be delayed until two weeks after the completion of this treatment, as it can render the BCG vaccine ineffective.

Infants with in utero exposure to second-line medications usually do not have any permanent congenital abnormalities (although current cohorts documenting this are relatively small). The exception to this is the permanent damage to cranial nerve VIII—and resulting damage to the fetal ear—from the use of aminoglycosides (amikacin) and polypeptides that may be used for treating DR-TB, despite the long-standing recommendations against their routine use. For this reason, pregnant women/people with DR-TB should be prioritized for all-oral regimens, and injectables must be avoided unless they are necessary to save the life of the pregnant person. If an infant is born to a person who received an injectable agent, then a hearing assessment should be done around the time of birth and again after a few months, with support to the family if hearing loss has occurred. Infants born to people taking clofazimine may present with skin hyperpigmentation, which usually resolves within weeks after delivery or after the mother/parent has completed treatment in the case of breastfeeding. Some medications may be associated with lower birth weight (i.e., fluoroquinolones, bedaquiline) and thus the pregnant individual should be provided with nutritional support and encouraged to bond with their child. Neonates born to women who are receiving ethionamide or PAS should have their thyroid function assessed at the time of birth and at three months of age.

Table 5 below lists best clinical practices regarding assessments for neonates born to women with DR-TB

Assessment	For whom advised	Comments
Screening for TB symptoms such as fever, lethargy, irritability, poor feeding, respiratory distress	All neonates	Be sure to counsel families about these symptoms in the neonate and what they should do if the neonate develops them
Physical examination with a focus on birthweight, lung findings, hepatosplenomegaly, and lymphadenopathy	All neonates	All neonates
Chest radiograph (PA and lateral)	Neonates with any TB symptoms or physical exam findings	
Abdominal ultrasound	Neonates with any TB symptoms or physical exam findings	If ultrasound is available, this could be considered in all infants born to people being treated for DR-TB.
Stool, CSF or other specimens for molecular testing, culture	Neonates with any TB symptoms or physical exam findings	Because Xpert testing of stool has similar results to gastric aspirate and is a more humane sample to collect, best practice supports stool (as opposed to or in addition to gastric aspirate or nasopharyngeal aspirate) as the preferred sample from infants being tested for TB, unless they have findings of extra-pulmonary sites of TB to guide sampling.
Placental examination for histology, cartridge-based nucleic acid amplification testing, culture	Neonates with any TB symptoms or physical exam findings	May be difficult to obtain placenta or have it tested
Audiometry to assess for hearing loss	Any neonate exposed to streptomycin, amikacin, capreomycin or kanamycin	Formal testing for high frequency hearing loss: if detected family should receive support for interventions free of charge from the TB program
TSH	Any neonate exposed to ethionamide or PAS	

As discussed, there is no indication to routinely separate people with DR-TB from their newborns if the individual is on effective treatment (see Table 4 for infection control considerations). Separation of mother/parents and newborns can have serious consequences for the neonate and should be discouraged. If there are concerns about the possible respiratory transmission of DR-TB, the mother/parent should be supported to wear a surgical mask while with the infant and to be started and maintained on effective DR-TB therapy.

Key points on management of the neonate are summarized below:

- There is no need to separate newborns from people on treatment for DR-TB provided the individual is on effective therapy; this is a damaging practice and should be avoided wherever possible;
- Most infants born to people living with DR-TB are healthy and do well, especially if the individual is diagnosed early and supported on effective therapy;
- Infants born to people with DR-TB are at risk of acquiring congenital or neonatal TB and should be assessed for respiratory distress, fever, poor feeding, lethargy, irritability, low birthweight, and hepatosplenomegaly. Infants are at highest risk if the mother/parent is being treated for disseminated, miliary, or genitourinary DR-TB;
- If any of these findings are present, then investigations for DR-TB are required, including obtaining specimens for rapid molecular testing, chest radiographs (PA and lateral) and abdominal ultrasound;
- If the neonate has findings consistent with TB, then empiric DR-TB treatment should be started unless fully susceptible TB is confirmed. If drug-susceptible TB is diagnosed first-line TB treatment should be started;
- Neonates exposed to second-line DR-TB medications usually do well but injectables should be avoided as they can damage the fetal ear: any infant exposed to injectables needs hearing tested routinely with support provided to those with hearing loss;
- DR-TB preventive treatment should be considered for neonates and infants with possible DR-TB exposure during pregnancy once congenital/neonatal TB disease has been excluded.

Patient Scenario

SS and TS are twins born to a woman who is HIV-negative and who is being treated for DR-TB. She has a history of social challenges—including substance use—and is on treatment with endTB regimen 1, which consists of 9 months of bedaquiline, linezolid, moxifloxacin, and pyrazinamide. She was referred to a "high-risk" obstetrician but the appointment was not scheduled until after her due date. She delivered unexpected twins, one of whom did well. However, the second had low birth weight (2000gm) and APGAR scores of 6 and then 8. The mother was not allowed to see either baby, and both were started on ciprofloxacin preventive therapy, although it is not clear if they ever received it. The babies were given BCG vaccine and discharged when they weighed more than 3kg.

Recommendations to improve practices in this scenario would include the provision of substance use treatment as well as rapid referral (and support for this referral) to the obstetrician prior to her due date. The babies should have had a placental examination, X-rays at birth, and an abdominal ultrasound to assess for active TB and stool could have been sent for a rapid molecular test. Levofloxacin is available in a pediatric formulation and would have been a good choice for preventive

therapy, and BCG should only have been administered after the preventive therapy was completed. The mother/parent should have been provided with a mask and allowed to visit and be with her infants.

INFANT FEEDING CONSIDERATIONS

Breast feeding is not only an important source of nutrition for a neonate but also promotes bonding between mother/parent and child. Unfortunately, fear-based infection control practices often dominate the advice given to people living with DR-TB about infant feeding options. Every attempt should be made by health care providers to understand a mother/parent's goals and hopes for how they would like to feed their child. See Table 4 for infection control considerations.

Multiple studies document clear health benefits for a newborn who is breastfed, and breastfeeding should be supported in individuals who are living with DR-TB. It is common for health care providers to advise that people who are living with DR-TB to avoid breastfeeding; this is misguided at best and dangerous at worst. Avoiding breast feeding, especially in settings where there may be limited access to clean water or infant formula, can place a neonate at high risk of diarrhea, malnutrition, and other infectious diseases since the infant will be lacking in the antibodies that are passed through breastmilk.

Often, individuals living with DR-TB are counseled not to breastfeed owing to concerns that the newborn will be exposed to second-line medications. There are limited studies documenting the safety of breastfeeding for people on DR-TB treatment and few examining concentrations of second-line medication in breast milk. Generally, these studies report that breastfeeding is safe and should be supported among women with DR-TB. Some medications that concentrate in the mother/parent's adipose tissue, such as bedaquiline and clofazimine, could lead to higher exposures in the infant. These higher concentrations of second-line medications may also be present in breastmilk and could, theoretically, protect the infant from DR-TB. Exposure to clofazimine in breastmilk may result in temporary skin hyperpigmentation in the infant and mother/parents should be counseled about this possibility. People living with DR-TB who are breastfeeding should be given nutritional support as a routine part of their DR-TB treatment.

Table 6 below lists what is known about breastmilk concentrations and second-line antituberculous medications.

Medication	Breastmilk considerations
Bedaquiline	Concentrates in the mother/parent's adipose tissue and has been shown to be present in breastmilk in higher concentrations that in maternal plasma. Theoretically this could offer protection to the infant from DR-TB infection. Infants should be assessed regularly for signs of bedaquiline toxicity, which include liver toxicity and QtcF prolongation.
Levofloxacin/moxifloxacin	Likely present in the breastmilk, but in concentrations that do not exceed the recommended doses in infants.
Linezolid	Likely present in the breastmilk but in concentrations that do not exceed the recommended doses in infants.

Medication	Breastmilk considerations
Clofazimine	Concentrates in the mother/parent's adipose tissue and is likely present in breastmilk. This may lead to discoloration of the breastmilk (ranging from pink to red). This could lead to temporary skin hyperpigmentation in the infant and families should be counseled about this.
Cycloserine/terizidone	Likely present in the breastmilk, but in concentrations that do not exceed the recommended doses in infants.
Delamanid	Likely present in the breastmilk, but in concentrations that do not exceed the recommended doses in infants.
Amikacin	Associated with hearing loss in mother/parent and should be avoided unless necessary to save the mother/parent's life. Likely present in the breastmilk only in low concentrations
Ethionamide	Likely present in the breastmilk and may be associated with adverse effects in the child. This agent is not advised for routine use in the treatment of DR-TB and if possible an alternative agent should be considered for breastfeeding mother/parent. If this is not possible, breastfeeding can be supported, but the infant should be monitored for symptoms of toxicity.
PAS	Likely present in the breastmilk, but only in low concentrations that do not exceed the recommended doses in infants.
Imipenem (or meropenem) and amoxicillin/clavulanic acid	Likely present in the breastmilk. May be used during breastfeeding but the infant should be monitored for symptoms of toxicity such as liver toxicity, rash and seizures.
Pretomanid	Should not be used in breastfeeding mother/parent as it may be associated with reproductive toxicity. If a nitroimidazole is needed, delamanid should be given instead.

Adherence to DR-TB treatment is often difficult for the mother/parent as they have so much to attend to with their new baby. They must be supported and encouraged to take their treatment daily, for the health and well-being of both them and baby. People who are co-infected with HIV must also take their ART daily and infants born to women living with HIV should be provided with HIV preventive treatment.

Although breastfeeding among people on treatment for DR-TB should be supported, there may be some individuals who are too ill to be able to breastfeed or who choose not to. This should also be supported, as there may be stigma around the practice of bottle feeding. If people choose to bottle feed, they should be provided with infant formula and bottles. The individual and their social support networks should be counseled about the importance of preparing the formula using clean water and taught how to do this so that the risk of diarrhea and malnutrition in the infant is reduced.

Key points on infant feeding considerations are summarized below:

- Pregnant women/people living with DR-TB should be asked about their feeding preferences and beliefs as part of DR-TB counseling;
- People living with DR-TB should be supported to breastfeed their infants; being on treatment for DR-TB is not a contraindication to breastfeeding;
- People living with DR-TB who are breastfeeding should be given nutritional support as part of their DR-TB treatment;
- Most studies assessing infants exposed to breastmilk while their mother/parents were treated for DR-TB do not show any evidence of harm;
- Some people living with DR-TB may be unable to breastfeed or prefer to use infant formula and should be supported to do this with provision of formula and supplies and counseling about formula preparation and bottle hygiene.

Patient Scenario

KG is a 27 year-old woman who is on treatment for DR-TB without results resistance to the fluoroquinolones (treatment is the BEAT Tuberculosis regimen of bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine). She has been on treatment for 4 months when she delivers a healthy, term, male infant, her second child. Although he is doing well, he is slightly underweight at 2375gm. A nurse notes that KG is seen breastfeeding the child and reports this to a physician. The physician is very concerned about the possibility that the child "might be exposed to medications" through breastfeeding and tells KG to "stop it immediately". She is advised to give him formula and is provided with one can of powdered formula to use in the hospital and at home. KG is worried that her family will see she is not breastfeeding the baby (like she did with her first son) and think she is not taking good care of him. She is also very concerned that she cannot afford to pay for additional formula and that she has to fetch her water from a pump located 2km away. The nurses counsel her about the importance of clean water and the formula preparation, but with the additional costs of the new baby, her family can only afford a small amount of the formula so she doubles the amount of water she mixes it with. The baby keeps crying and develops diarrhea and when a community health worker comes to visit them at home, there is noted concern that the baby now weighs only 2027gm.

Recommendations to improve practices in this scenario would include the continued breastfeeding for this mother/parent-infant pair. There is limited risk to the infant from breastfeeding, and if this is the practice preferred by the mother/parent-infant pair, then it is appropriate. If breastfeeding is not preferred or cannot be done for other reasons, then the family should be provided with support to procure formula as well as the supplies for preparing and using the formula (including clean water). They should also be counseled about messages to share with people who ask why the mother/parent-infant pair is not breastfeeding. The mother/parent and family should also be counseled about signs and symptoms that should prompt urgent referral to the health center.

FAMILY PLANNING/CONTRACEPTION

People with DR-TB who are pregnant, who have recently given birth, or who have lost/terminated a pregnancy may wish to have access to family planning/contraception, which should be offered in a non-judgmental way, free of charge. Many people believe they cannot become pregnant shortly after giving birth. This belief is false and all individuals should be advised of this and offered contraception. While receiving second-line medications, the contraception of choice is intramuscular medroxyprogesterone as there is less risk of medication-medication interaction. Intrauterine devices, the etonorgestrel implant, and tubal ligations are also effective.

COUNSELING AND SUPPORT

The diagnosis of DR-TB is challenging at any point in a person's life. Living with DR-TB during pregnancy can increase anxiety. This should be acknowledged and individuals may require additional counseling support and resources to optimize their health and well-being if they proceed with the pregnancy. There may be a risk of peripartum depression which could be exacerbated by the additional burdens of DR-TB. People living with DR-TB presenting with clinical signs of depression or anxiety need timely referral to appropriate mental health services including a detailed medication history, for appropriate treatment and specialized follow-up.

Unfortunately, there is limited experience in caring for pregnant women/people with DR-TB, which includes counseling and social support requirements. This may lead to fear-driven practices such as scolding/shaming, coercive discussions about pregnancy termination, or threats of separating the mother/parent from their child/children. Even when compassionate counseling is offered, providers may feel that they lack the information or tools to provide support and answer questions. Although well intentioned, such advice may leave the pregnant person feeling isolated, uncertain, and anxious.

Despite the limited global experience in the care of pregnant women/people living with DR-TB compared to that in the non-pregnant population, the data that do exist are reassuring. Most people with DR-TB who are pregnant have healthy, normal babies provided the individual is started on effective treatment as quickly as possible. There is no need to separate the pregnant person from their infant on account of their living with DR-TB. Although there is not a large amount of published data, what is available shows that these babies can be breastfed and usually grow into robust and developmentally healthy children and adolescents. This is all information that should be shared with a pregnant person who is living with DR-TB, and they should be reassured that they are not the first or only person to have gone through this experience.

Each pregnant person is unique, and during discussions their preferences about whether or not to continue with the pregnancy should be solicited and supported. Support should be non-judgmental and unbiased so people do not feel pressured into any decision. If the individual decides to terminate the pregnancy, they should be referred to a provider who can perform the procedure safely and free of charge. If they decide to continue with the pregnancy they should be reassured that the likelihood they will have a normal, healthy infant is high. In either circumstance, additional counseling may be needed as the individual may be especially vulnerable at this time.

The time of delivery has been shown to be a difficult one for a pregnant person who is living with DR-TB as the health facility where they present for delivery may not be familiar with DR-TB risks and management. Health care providers are often fearful of the infectious risk of DR-TB and their behavior may be discriminatory with sub-standard medical care. The pregnant person should be counseled about this potential scenario, including strategies for disclosing to health providers at the time of their delivery, and provided with a brief referral letter with information about DR-TB (see sample in Annex 1).

Often, pregnancy is a joyful time for the pregnant individual, their family and the community, but this may be dampened in the context of DR-TB. In addition to counseling and support, the individual should be asked about other supportive people in their social network who may be able to help and should be supported to disclose their DR-TB status to these individuals. Often their own mother/parents or partner are key individuals who can provide emotional or other support, but this will vary. The privacy and dignity of the pregnant individual who is living with DR-TB should always be respected, and disclosure of their DR-TB status should only be with their permission. If individuals from the social network are identified they can be counseled about how to support the pregnant person throughout treatment and to be present at times when they may face additional challenges (e.g., labor and delivery).

In addition to counseling and social support, pregnancy can be a time of financial stresses for individuals and their families. They have increased nutritional needs owing to pregnancy and DR-TB infection and treatment. The need to attend multiple medical appointments may compromise employment and the ability to optimally provide for the baby's material needs (nappies, clothing etc.) Thus, a pregnant person who is living with DR-TB should be provided with nutritional, transport, and other material support, if possible. They should be referred to community, non-governmental, or faith-based organizations who can assist with supporting these needs.

Key points on counseling and support are summarized below:

- Being pregnant and living with DR-TB is an especially complex time for people, and they will need additional compassionate counseling and support;
- Fear-based or shame-based counseling practices should be replaced with compassionate strategies designed to reassure a pregnant individual that they are not alone;
- Preferences around pregnancy termination should be sought and supported;
- People who choose to proceed with pregnancy should be reassured that most pregnant women/people living with DR-TB do well and have normal, healthy babies, provided they are able to adhere to treatment;
- In addition to health care providers, social network support can be important and should be sought, if pregnant person agrees;
- Labor and delivery may be difficult times and the individual may need additional emotional support during this period;

- In addition to social and emotional support, pregnant women/people with DR-TB face financial challenges and should be provided with nutritional, transportation and other material support.

Patient Scenario

RT is a 22 year-old woman who is on treatment for DR-TB with a regimen of bedaquiline, delamanid, linezolid, and levofloxacin. She had a positive rapid molecular test that showed rifampicin resistance but her baseline culture was contaminated and subsequent sputum specimens were negative on smear and culture. During her second month on treatment, she reports missing her menstrual period and a pregnancy test shows she is pregnant. This news makes her distraught and she asks her doctors what might happen to her or to the baby. She is told that DR-TB may be dangerous and that they "don't really know" how the medications will affect the baby. She is referred to see an obstetrician in the capital city but has no transportation funding to go to the consult. She is deemed "non-compliant" with her medical plan, a view that is only reinforced when she stops taking her treatment and begins skipping her DR-TB appointments. She is ultimately given an outcome of "lost to follow up".

Recommendations to improve practices in this scenario would include offering her family planning free of charge as part of her DR-TB treatment. When she is found to be pregnant, she should be compassionately counseled about possible options, including pregnancy termination if she chooses. If she decides to continue the pregnancy, she should be given transportation support for any referrals. She should be reassured that although data are limited, the information that does exist shows most people who are pregnant and being treated for DR-TB have normal healthy infants and do well themselves. She should be offered increased support for mental health and other social stressors that may occur and close, compassionate follow up with a counseling team, including peer support if available and agreed to.

Patient Scenario:

MR is a 33 year-old woman who is undergoing treatment for DR-TB when she becomes pregnant. She describes being frightened to disclose her pregnancy to her health care providers because they will "shout at" her, noting that one provider told her that she and her baby could "die at any time". This is especially difficult for her because she had another pregnancy end with a stillborn child. She was not given contraception and say becoming pregnant again was a "mistake" but she is confused as to why the providers treat her in an antagonistic way. She describes her interactions at the clinic as a source of great "suffering". She also describes the health care providers as being afraid to touch her or have her personal things near them because they say she will make them sick. These interactions lead her to avoiding the clinic and health care personnel whenever possible.

Recommendations to improve practices in this scenario would include the provision of an acceptable form of contraception during DR-TB treatment available free of charge. The health care environment should also be welcoming to pregnant women/people with DR-TB: even when providers do not necessarily agree with the

choices made by the individuals in their care, they have an obligation to behave in a professional and compassionate manner. Discriminatory and fear-based practices around infection control should be eliminated. This can be supported by through education, training for people working in the DR-TB clinics and the antenatal services as well as the practice of universal precautions. Coercive or anxiety-based counseling should be replaced with fact-based and relationship-building approaches that emphasize the return to health for people with DR-TB and the likelihood of a normal, healthy child, should they choose to proceed with the pregnancy. Fear and avoidance are natural responses when people feel judged or criticized, and this can lead to poor health outcomes for the pregnant person and the child.

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ANNEX 1: REFERRAL LATTER PREGNANT AND PERIPARTUM PEOPLE WITH DR-TB

Referral letter for a pregnant person with DR-TB

Dear.....,

Thank you for being prepared to take over the management of this patient who is currently pregnant with DR-TB. The details of the patient and their pregnancy are documented below, together with their TB and HIV history and the details of their current DR-TB regimen.

Please continue the treatment and management of this patient. Monthly monitoring is advised in the case of pregnant individuals with DR-TB.

During delivery standard infection control measures as would be followed for any other woman delivering should be adhered to.

Included in this envelope is a summary of the key points regarding the management of a patient with DR-TB and their infant at this time. Additional information on labor, delivery, postpartum management of the individual and infant, including breastfeeding are available and can be sent to you if you require them.

Regards

.....

Details of the patient:

Patient name: .....Date of Birth: .....

Address: .....

Phone number: .....

Next of Kin and phone number: .....

Details of the DR-TB and treatment:

Date DR-TB diagnosed: ..... Drugs resistant to: .....

Treatment regimen: .....

Treatment state date: ..... Length of treatment: .....

Previous history of TB: ..... Chest X-ray: .....

HIV status: ..... If positive ART treatment start date: .....

If positive current ART regimen: .....

Latest CD4 count and date: ..... Latest viral load and date: .....

Details of pregnancy:

Gestational age at the start of DR-TB treatment: .....

Obstetric history: .....

.....

ANNEX 2: SUMMARY INFORMATION FOR HEALTH CARE PROVIDERS ON DR-TB AND PREGNANCY

Information regarding DR-TB in people who are pregnant

Treatment regimen design for pregnant women/people

Below are summarized some key points on treatment regimen design for pregnant women/people which we used in deciding on the treatment regimen for this person:

- The only medication that is contra-indicated in pregnancy is amikacin (and other injectable agents). These should only be used if there are no other options to save the woman's life.
- Pretomanid may have reproductive toxicity and should be avoided until additional data are available.
- Pregnant women/people with DR-TB can receive linezolid, but need regular monthly monitoring of the complete blood count and iron supplementation.
- Pregnant women/people with DR-TB can receive fluoroquinolones and bedaquiline safely but nutritional support should be considered to ensure adequate growth of the fetus.
- Ethionamide and PAS may be used in pregnant women/people who have limited treatment options but could worsen the nausea and vomiting often associated with pregnancy and thus anti-emetic therapy should be considered if they must be administered. They may also be associated with an increased risk of hepatotoxicity. Ethionamide must be given with a prenatal vitamin given its association with neural tube defects.
- Clofazimine may cause reversible hyperpigmentation in pregnant women/people and their infants but this resolves over weeks/months.
- Pregnant women/people should receive one of the all-oral shorter regimens recommended in 2024 by the WHO, provided they meet all other criteria for receiving the regimens. These include the "BEAT Tuberculosis" regimen consisting of 6 months of bedaquiline, delamanid, linezolid, levofloxacin and clofazimine or one of the 3 recommended endTB regimens, which are nine-month regimens consisting of the

following combinations:

- *endTB regimen 1*: bedaquiline, linezolid, moxifloxacin and pyrazinamide
- *endTB regimen 2*: bedaquiline, linezolid, levofloxacin, cloazimine, and pyrazinamide
- *endTB regimen 3*: bedaquiline, delamanid, linezolid, levofloxacin, and pyrazinamide.

Ongoing management

- Adherence to both DR-TB treatment and ART (if the person is co-infected with HIV) is of the utmost importance for both the pregnant individual and their infant during pregnancy and after delivery.
- Given that this is a period of extreme vulnerability, additional emotional and material support maybe needed at this time, in addition to routine clinical monitoring.
- Routine monitoring should follow the usual standards for DR-TB and prenatal care, with additional monthly testing for HIV, STIs, gestational diabetes and hypertension. Regular (i.e., monthly) screening of blood pressure and proteinuria should also be done.
- Symptom-guided monitoring is also important, with vomiting prompting review of electrolytes, liver function tests for hepatitis, nutritional status, and hydration.
- Nutritional support is essential for pregnant women/people with DR-TB to ensure they have good TB treatment outcomes and to support the growth of their baby.
- Pregnant women/people with DR-TB should be reported to national programs and bodies responsible for pharmacovigilance.
- Most pregnant women/people with DR-TB can be cared for in the community by DR-TB providers, but if referral is needed the person should be provided with transportation and other socioeconomic support.

Further information on the management of drug-resistant TB in pregnant and peripartum people is available in a handbook entitled 'Management of Drug-Resistant Tuberculosis in Pregnant and Peripartum People: A Field Guide' which has been published by The Sentinel Project for Pediatric Drug-Resistant Tuberculosis. It is available at this link: https://sentinel-project.org/.

Important information regarding labor, delivery, postpartum management of an individual with DR-TB and their infant

Below, the key points regarding the management of a person with DR-TB during labor and delivery and the immediate postpartum management of the individual and infant are summarized. This guidance will optimize the health and wellbeing of both the pregnant person and the infant.

Below, the key points regarding the management of a person with DR-TB during labor and delivery and the immediate postpartum management of the individual and infant are summarized. This guidance will optimize the health and wellbeing of both the pregnant person and the infant.

Management of a person with DR-TB during labor and delivery:

- Pregnant women/people with DR-TB often face discrimination from health care providers at the time of labor and delivery. As this may be a difficult time, they need extra compassionate emotional support.
- Pregnant women/people who are on treatment for DR-TB for more than 72 hours have a very low likelihood of transmitting DR-TB. They must continue to take their treatment daily at this time.
- They should not be isolated or made to follow restrictive infection control measures.
- Please ensure this information is shared all relevant people in the labor ward.

Postpartum management of the individual who has just given birth are summarized below:

- There is no reason to separate the mother/parent from their newborn infant. Doing so may be harmful to both the mother/parent and their infant.
- Close monitoring of the person who has just given birth is required. They should not be isolated or left alone.
- Daily DR-TB treatment after birth should continue as prescribed, as this will minimize the risk of transmission to the infant. If the mother/parent has a postpartum complication exacerbated by a specific DR-TB medication, it may be necessary to consider stopping the particular offending drug/s.
- If treatment started less than 72 hours before delivery or there is concern about the effectiveness of the regimen (i.e. XDR-TB), the mother/parent can wear a surgical mask around the infant.
- Compassionate support must be provided to ensure postpartum adherence to both DR-TB and ART.

Postpartum management of the newborn infant:

- The newborn should not be separated from their mother/parent if their mother/parent is on effective DR-TB treatment. This is a damaging practice and should be avoided.
- Most infants born to people living with DR-TB are healthy and do well. However, they are at risk of acquiring congenital or neonatal TB and should be assessed for respiratory distress, fever, poor feeding, lethargy, irritability, low birthweight, and hepatosplenomegaly. Infants are at highest risk if the mother/parent is being treated for disseminated, miliary, or genitourinary DR-TB.
- If any of these findings are present investigations for DR-TB are required, including obtaining specimens for rapid molecular testing, chest radiographs (PA and lateral) and abdominal ultrasound.
- If the infant has findings consistent with TB, then empiric DR-TB treatment should be started unless fully susceptible TB is confirmed. If drug-susceptible TB is diagnosed first-line TB treatment should be started;

- Infants treated with second-line DR-TB medications usually do well. However, the injectables should be avoided as they can damage the fetal ear: any infant exposed to injectables needs hearing tested routinely with support provided to those with hearing loss;
- DR-TB preventive treatment should be considered for the infant once congenital/neonatal TB disease has been excluded.

Breastfeeding:

- Transmission of DR-TB to the infant is unlikely if treatment started more than 72 hours before delivery and the prescribed treatment is taken daily. In addition, most studies assessing infants exposed to breastmilk while their mother/parents were treated for DR-TB show no evidence of harm. Therefore, it is safe for the mother/parent on DR-TB treatment to breastfeed and they should be supported in this choice.
- Some women/people living with DR-TB may be unable to breastfeed or prefer to use infant formula and should be supported to do this with provision of formula and supplies and counseling about formula preparation and bottle hygiene.

Further information on the management of drug-resistant TB in pregnant and peripartum women/people is available in a handbook entitled 'Management of Drug-Resistant Tuberculosis in Pregnant and Peripartum People: A Field Guide' which has been published by The Sentinel Project for Pediatric Drug-Resistant Tuberculosis. It is available at this link: https://sentinel-project.org/.

ANNEX 3: SAMPLE PHARMACOVIGILANCE REPORTING FORM

Full forms can be found at: https://endtb.org/sites/default/files/2016-06/PVTB-D02%20-%20Pregnancy%20report%20form%20completion%20guidelines.pdf

https://www.who.int/docs/default-source/documents/tuberculosis/a-practical-handbook-on-the-pharmacovigilance-of-medicines-used-in-the-treatment-of-tuberculosis.pdf?sfvrsn=6e5fc0cf_5

or

https://who-umc.org/media/1481/creating-adr-report.pdf

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

PREGNANCY REPORT FORM
Guidelines for completion

1. Introduction

Pregnancies occurring in clinical trials (CTs) or programs sponsored by MSF are collected and reported using a dedicated form. Unless described otherwise in the CT protocol or the program's PV guideline, pregnancies with or without serious outcomes are **reportable within 24 hours of awareness** to MSF Pharmacovigilance (PV) Unit using a Pregnancy Report Form:

Email: PVunit.GVA@geneva.msf.org

Additional information on already transmitted pregnancies, called follow-up information, should be reported similarly within 24 hours of awareness of the new information.

When applicable, Serious Adverse Event (SAE) Report Forms are additionally required to capture information on SAEs occurring in the course of the pregnancy in the mother and/or the foetus/child.

2 General instructions

The Pregnancy Report Form is designed to specifically follow mothers and foetuses/children exposed to drugs in the frame of CTs or programs. The available fields must be completed as much as possible with the relevant information available at the time of reporting.

The minimal information to be reported includes:

1. Name or any identifier of a **reporter** (e.g. a function such as 'nurse' is acceptable),
2. Any identifier of the **pregnant patient** (e.g. patient number, initials, date of birth),
3. **Exposure during/before pregnancy to at least one drug** (study drug in a CT/ delivered drug in a program).

The following general points aim at helping the completion of the Pregnancy Report Form:

- Dates should be provided in the "Day/Month/Year" format: dd/Mmm/yyyy (e.g. 06/Apr/2015). If the exact date is not known, a partial date can be provided and the full date completed later upon follow-up (e.g. UNK/Apr/2015).
- In case you need to add more information than a field allows you to enter, please reprint the page, add manually the mention 'Supplemental page', and capture the additional information.
- Upon receipt of follow-up information on a pregnancy already notified (e.g. pregnancy outcome is known), the initial information does not need to be fully repeated on the Pregnancy Report Form, only the new information with identifiers allowing to retrieve the initial information (site number, patient's identifiers, case number, etc.).
- In case corrections are needed, the correct vs. the incorrect information should be clearly identifiable and the correction should include the initials of the person who performed the modification and the date of such modification.
- All information about the patient must be anonymized in all documents before transmission to the MSF PV Unit.
- One Pregnancy Report Form should be populated for each separated pregnancy of a same patient. Multiple pregnancies should generally be captured within a same Pregnancy Report Form.

The MSF PV Unit is available for questions and further guidance on the Pregnancy Report Form completion.

3 Detailed instructions

3.1. Administrative information

		Case number:
PREGNANCY REPORT FORM		
Sponsor: Médecins Sans Frontières	**Protocol/Program n°:**	**Site n° (for studies) or country:**
Initial report: ☐	**Follow-up report:** ☐	**Date of report:** ___ / ____ / _____ (dd/Mmm/yyyy)

For CTs, protocol and site numbers should be informed. For other programs, the program number or name as well as the country of occurrence of the event should be entered.

When transmitting information on a pregnancy for the first time, the box 'initial report' should be ticked, when reporting supplementary information on a pregnancy previously transmitted, 'follow-up report' should be selected.

'Date of report' field's title is self-explanatory.

The field 'Case number' is available to capture the number of the case attributed by MSF PV unit; at time of initial reporting this field should be left blank.

3.2. Patient information (mother)

Patient information (mother)				
Patient n°: [**Father** ☐ **Mother** ☐]	**Mother initials:**	**Mother date of birth:** ___ / ____ / _____ (dd/Mmm/yyyy)	**Mother height:** ..... cm	**Mother weight:** ..... kg

In Pregnancy Report Forms, the patient is always the mother. For CTs and programs where patients are allocated an alpha-numeric identifier, the appropriate field ('Patient n°') should be populated with this information. In the cases, where the patient is the female partner of an enrolled male patient (drug exposure via father), the father's patient n° should be entered for reference. By using the tick boxes 'father' / 'mother', there is no ambiguity on who is referred to via the patient number.

All information about the parents must be anonymized. Other fields' titles are self-explanatory.

3.3. Relevant drug(s) exposure before/during pregnancy

	Relevant drug(s) exposure before/during pregnancy						
1	**Drug name (INN)**	.....	.....	.....	.....	.....	.....	.....
	Daily dose & route							
	Batch number							
	Treatment start date (dd/Mmm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
	Treatment stop date (dd/Mmm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
	Drug taken by	**Father** ☐ / **Mother** ☐	**Father** ☐ / **Mother** ☐	**Father** ☐ / **Mother** ☐	**Father** ☐ / **Mother** ☐	**Father** ☐ / **Mother** ☐	**Father** ☐ / **Mother** ☐	**Father** ☐ / **Mother** ☐
2	**Action taken in response to the pregnancy**							
	Dosage maintained	☐	☐	☐	☐	☐	☐	☐
	Dose reduced	☐	☐	☐	☐	☐	☐	☐
	New daily dose							
	On (dd/Mmm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
	Drug permanently withdrawn	☐	☐	☐	☐	☐	☐	☐
	On (dd/Mmm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
	Drug interrupted	☐	☐	☐	☐	☐	☐	☐
	From (dd/Mmm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
	To (dd/Mmm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
	Not applicable	☐	☐	☐	☐	☐	☐	☐

1. Up to 7 drugs can be entered, if more drugs have to be reported, the page can be re-printed with the mention 'Supplemental page' added manually. Information on each drug including the International Non-proprietary Name (INN - preferred) (or trade name/active substance), daily

- As a convention, in a CT, all study drugs (including Standard of Care drugs) are to be considered relevant drug exposures. In the post-marketing setting, medical judgment should apply when selecting relevant drug exposure. As a general rule, in a tuberculosis (TB) program, at least all ongoing TB treatments administered at time of event should be considered relevant drug exposures. Other drugs can be recorded as relevant drug exposure as per best medical judgment (e.g. highly active antiretroviral therapy).
    - In the cases, where the patient is the female partner of an enrolled male patient (drug exposure via father), the father's relevant drugs should be entered. Any relevant pregnancy exposure to a drug taken by the mother should be additionally entered (see also section 4.2). Tick boxes allow identification of whether the mother or the father was taking the drug(s).
- In the special situation where the pregnancy itself is considered a drug adverse reaction, e.g. if one of the drug is considered to have interacted in any way with the contraception method used, this information should be specifically highlighted and all drugs including contraceptives should be listed.

2. Action taken following pregnancy knowledge should be documented for each drug using the possibilities presented in the table. Action taken is considered not applicable, if the drug was already stopped before pregnancy or taken by the father (drug exposure via father).

3.4. Pregnancy information

Pregnancy information			
Date of 1st day of last menstrual period *(dd/Mmm/yyyy)*	____ / _____ / _____	**Estimated date of delivery** *(dd/Mmm/yyyy)*	____ / _____ / _____
Pregnancy test	☐ **Positive urine test** Date: ____ / ____ / _____	☐ **Positive blood test** Date: ____ / ____ / _____	☐ **Positive ultrasound** Date: ____ / ____ / _____
Pregnancy outcome			
1. Did the patient experience any complication during pregnancy?	☐ **Yes. Specify:**		
	☐ **No**		
2. Did the patient give birth to (a) live infant(s)?	☐ **Yes. Date of delivery** *(dd/Mmm/yyyy)*: ____ / _____ / _____		
	☐ **No. Specify reason:**		
3. Was the infant normal at birth?	☐ **Yes**		
	☐ **No. Specify abnormality and reason:**		
Additional comment on pregnancy/delivery			

General information on the pregnancy should be collected including the last menstrual period date and the estimated date of delivery (for ongoing pregnancies). The positive pregnancy tests undertaken to confirm pregnancy as well as the corresponding dates should be entered.

Pregnancy outcome information should be captured as follows:

1. Pregnancy complications should be described as free text,
2. Pregnancy outcome should be detailed:
    - Live birth should be captured as well as date of delivery.
    - In case of detrimental pregnancy outcomes, details on the type of outcome (e.g. miscarriage, foetal death in utero) and underlying causes (when known) should be provided as free text. Elective abortion should also be captured in this field, highlighting the reason for such procedure (e.g. patient's choice, foetal defects).

- In case of foetal defects/congenital anomalies, the reporter is expected to create an SAE Report Form to capture detailed information on the foetal abnormality (see also section 4.1).

- For ongoing pregnancies, when last menstrual period and/or estimated delivery date is unknown, it is advised to mention the pregnancy is ongoing in the field Additional comment on the course of pregnancy.

3. Any abnormality in the infant should be briefly described; in parallel the reporter is expected to create an SAE Report Form to capture detailed information on the infant's abnormality (see also section 4.1).

Additional comments on the course of the pregnancy and/or delivery can be entered as free text.

3.5. Infant(s) information

Infant(s) information						
Infant number	Sex	Length *(cm)*	Weight *(g)*	APGAR score	Exposure during breastfeeding	Comment
1	F ☐ M ☐				Yes ☐ No ☐	
2	F ☐ M ☐				Yes ☐ No ☐	
3	F ☐ M ☐				Yes ☐ No ☐	

This section aims at capturing detailed information on the live infant(s). For multiple pregnancies, the order of the babies at birth should be followed when filling in the table. Fields' titles are self-explanatory; a free text field is available for any additional comment on the infant's health.

3.6. Relevant medical history

Relevant medical history *(with focus on relevant prior gynaecological/obstetric history)*	

Relevant medical history of the mother should be included, especially gravidity, parity and abortus, as well as relevant gynaecological diseases.

3.7. Reporter information

Reporter				
Name of reporter:	Role in trial/program:	Date of awareness: ____/_____/_____	Address: Email: Phone:	Date and signature: ____/_____/_____

Titles in this section are self-explanatory. For CTs, the Investigator or co-Investigator is responsible to approve and sign the Pregnancy Report Form. In post-marketing programs, the relevant function (physician, nurse, etc.) should sign the form as per program's PV guideline.

4 Focuses

4.1 When to create foetus/child cases?

In the situations where a female patient exposed in the frame of CT or a program is found to be pregnant, a Pregnancy Report Form should be populated and transmitted to MSF PV Unit. This is also the process for a pregnancy in the female partner of a male patient exposed in the frame of a CT/program.

In addition, any SAE occurring in the mother or the foetus/child has to be recorded and transmitted to MSF PV Unit using an SAE Report Form.

- In the event of an SAE in the mother (e.g. late miscarriage), an SAE Report Form should record the serious mother's event with the patient being the mother. In addition, the Pregnancy Report Form should capture all pregnancy information.

- If both the mother and the foetus/child experienced SAEs (e.g. vaginal haemorrhage and foetal distress), 2 SAE Report Forms should be completed (1 for vaginal haemorrhage in the mother and 1 for foetal distress in the baby), as well as 1 Pregnancy Report Form that captures all pregnancy information.

4.2 What should be done for drug exposure via father?

In the cases, where a pregnancy occurs in the female partner of an enrolled male patient (i.e. the father is treated in the frame of the MSF-sponsored CT or MSF program and not the mother):

- All patient information (age, date of birth, height and weight) should be entered for the mother. Only the father's patient n° should be entered for reference (ticking the box "father").
    - *Example, the wife of the male patient n°002 enrolled in the TEST program is found pregnant. Her name is MM, she is born in 1976 and her height is 165 cm / weight 50 kg.*
- Relevant drugs taken by the father should be entered and identified using the tick box "father". Any relevant exposure to a drug taken by the mother should be entered and identified using the tick box "mother".
    - *Example, the male patient n°002 was treated with interferon in the frame of the TEST Program, this drug is entered as relevant pregnancy exposure. In addition, his wife (MM) was receiving efavirenz during pregnancy.*

All other fields should be completed as guided in sections 3.4 to 3.7. The mother's information must be treated in a confidential way with the same precautions as the father's information. Signature of an Informed Consent should be considered for the mother, as applicable.

							Case number:
PREGNANCY REPORT FORM							
Sponsor: Médecins Sans Frontières			**Protocol/Program n°:** TEST program			**Site n° (for studies) or country:** Chile	
Initial report: ☒			**Follow-up report:** ☒			**Date of report:** 15 / DEC / 2015 (dd/Mmm/yyyy)	
Patient information (mother)							
Patient n°: 002 [**Father** ☑ **Mother** ☐]	**Mother initials:** MM		**Mother date of birth:** 05 / OCT / 1976 (dd/Mmm/yyyy)		**Mother height:** 165 cm	**Mother weight:** 50 kg	
Relevant drug(s) exposure before/during pregnancy							
Drug name (INN)	Interferon alpha	Efavirenz					
Daily dose & route	3miU 3 times a week SC	600 mg/day PO					
Batch number	K 002	Unknown					
Treatment start date (dd/Mmm/yyyy)	04 / JAN / 2015	___/___/2010	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
Treatment stop date (dd/Mmm/yyyy)	___/___/_____	___/APR/2015	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
Drug taken by	**Father** ☑ / **Mother** ☐	**Father** ☐ / **Mother** ☑	**Father** ☐ / **Mother** ☐	**Father** ☐ / **Mother** ☐	**Father** ☐ / **Mother** ☐	**Father** ☐ / **Mother** ☐	**Father** ☐ / **Mother** ☐
Action taken in response to the pregnancy							
Dosage maintained	☐	☐	☐	☐	☐	☐	☐
Dose reduced	☐	☐	☐	☐	☐	☐	☐
New daily dose							
On (dd/Mmm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
Drug permanently withdrawn	☐	☐	☐	☐	☐	☐	☐
On (dd/Mmm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
Drug interrupted	☐	☑	☐	☐	☐	☐	☐
From (dd/Mmm/yyyy)	___/___/_____	___/APR/2015	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
To (dd/Mmm/yyyy)	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____	___/___/_____
Not applicable	☑	☐	☐	☐	☐	☐	☐

5 References

ICH E2A - Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. 27 October 1994.

ICH E2B(R2) - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports. 5 February 2001.

The Sentinel Project on Pediatric Drug-Resistant Tuberculosis c/o the
Department of Global Health and Social Medicine Harvard Medical School

641 Huntington Avenue
Boston, MA 02115 USA

www.sentinel-project.org