Tuberculosis & Pregnancy

Building consensus on inclusion in research

February 2024

Contents

Key Terms

Definitions

Antenatal – the period of time from conception to before birth. Alternative terms are 'prenatal' and 'antepartum.' 'Antenatal' or 'prenatal' is preferred when referring strictly to maternal care from conception to birth, while 'antepartum' is preferred when referring to fetal care and/or events that happen during labor.

Breastfeeding – the process of feeding a mother's breast milk to her infant, either directly from the breast or by expressing (pumping out) the milk from the breast and bottle-feeding it to the infant.

Congenital – refers to the existence at or before birth.

Maternal tuberculosis – tuberculosis episodes which occur during pregnancy and the postpartum period.

Perinatal – the period from fetal viability (23 to 28 weeks) to one week post birth. An alternative term is 'peripartum.'

Pharmacokinetics – the study of what the body does to a drug, referring to the movement of drug into, through, and out of the body.

Postpartum – the period of time from immediately after birth up to six months after birth. An alternative term is 'postnatal.' 'Postpartum' is preferred when referring to issues pertaining to the mother and 'postnatal' (typically defined as up to six weeks post birth) is preferred when referring to issues concerning the infant.

Drug Regimens

6BPaL/M – six-month treatment regimens for drug-resistant TB disease comprised of bedaquiline (B), pretomanid (Pa), linezolid (L), with or without moxifloxacin (M)

4HPMZ – four-month treatment regimen for drug-susceptible TB disease comprised of isoniazid (H), rifapentine (P), moxifloxacin (M), and pyrazinamide (Z)

2HRZE/4HR – six-month treatment regimen for drug-susceptible TB disease comprised of two months of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E), followed by four months of isoniazid (H) and rifampicin (R)

3HP – three-month treatment for TB infection comprised of high dose isoniazid (H) and high dose rifapentine (P) given once weekly

1HP – one-month treatment for TB infection comprised of high dose isoniazid (H) and high dose rifapentine (P) given once daily

A note about language

It should be noted that in addition to pregnant and breastfeeding women, pregnant and lactating people of other gender identities are similarly excluded from research. While language such as "pregnant women," "breastfeeding (or lactating) women," and "mothers" or "maternal" is used throughout, we acknowledge and affirm that there are people who become pregnant that do not identify as women. While this report doesn't delve into the unique dimensions of trans and gender diverse people's experience with pregnancy, its general findings are intended to be inclusive of all people who have the potential to be affected by TB while pregnant and/or lactating/chestfeeding. We hope this report, and the associated consensus process, will advance inclusion of all pregnant and lactating people in TB research. We welcome feedback on our language and thinking throughout the consensus process.

Background

The impact of tuberculosis (TB) during pregnancy and the postpartum period can be physically and emotionally devastating, with mothers struggling to care for their newborn children and themselves, often in isolation.

Pregnant and postpartum women are up to two times more likely to develop TB disease compared to their nonpregnant counterparts, and the consequences can be grave for both mother and neonate.[1] TB remains an important cause of maternal morbidity and mortality in endemic countries and is associated with increased risk of preterm birth, low birth weight, and fetal death.[2,3] Despite these compelling statistics, pregnant and breastfeeding women are excluded from the majority of TB therapeutics and vaccine research.[4]

The exclusion of pregnant women from research is not unique to TB; pregnant women are excluded from most clinical research trials.[5-7] Their exclusion comes from a desire to avoid fetal risk. Instead of engaging in the complex risk-benefit calculus that considers the potential risks *and benefits* to both fetus *and mother*, the research community adopted the most expedient way to ensure no potential harm befalls fetuses: exclude pregnant, and often breastfeeding, women from research all together. Concerns over liability on the part of drug manufacturers, insurers, and institutional review boards, have reinforced this protectionist ethic.[8]

TB research has boomed over the last decade, resulting in a growing menu of newer, shorter, more effective TB treatment regimens.[9] Yet, pregnant and breastfeeding women remain unable to realize the full benefit of these scientific advancements owing to their exclusion from research.[10,11]

At the heart of this issue lies the question of risk and what degree of theoretical, perceived, and actual risk is tolerable, and for whom. Within the current research paradigm, the tolerable level of risk is often determined from the perspective of academics, regulators, and industry, with limited input from affected communities including pregnant women. However,

pregnant women develop TB, and women with TB become pregnant. Risk doesn't disappear when pregnant women are excluded from research; instead, the burden of risk is shifted from a controlled research setting onto the pregnant woman and her clinician at the time of care. The risks, both known and unknown, are well understood to be better mitigated and managed in the rigorous setting of research compared to under programmatic conditions.

In recent years, several institutions and expert committees have reinforced that we must shift our collective mindset from one of protecting pregnant women *from* research to protecting them *through* research.[12-14] Affected communities and civil society have long called for earlier inclusion of pregnant women in TB research.[15]

The Political Declaration of the High-Level Meeting on the Fight Against TB, formally adopted by the United Nations Generally Assembly in October 2023, newly included recognition of maternal and perinatal mortality caused by TB and a commitment to strengthen comprehensive TB care for women during pregnancy, breastfeeding, and the postpartum period. The World Health Organization (WHO) also recently amplified the call for increased inclusion of pregnant women in TB research in their 2023 Roadmap towards ending TB in children and adolescents.[16]

Despite growing advocacy and recommendations in support of inclusion, the widespread exclusion of pregnant and breastfeeding women from COVID-19 trials suggests that exclusion persists as the norm.[7] In order to fully realize global commitments and ensure pregnant women receive the benefits of scientific advances in TB, the field needs consensus on how to include pregnant women in research.

Why don't we know anything about what happens to pregnant women?

Kate's story of surviving TB in pregnancy

In 2015, Kate O'Brien was diagnosed with TB in the United States while five months pregnant, leading to her subsequent hospitalization and isolation from her family (including her young son) for nearly three months.

Kate experienced one challenge after another, starting with her difficulty getting diagnosed—some healthcare providers were reluctant to give her a chest x-ray while she was pregnant, others dismissed her symptoms as pregnancy-related. She only received her diagnosis once she landed in the intensive care unit.

Once Kate was finally diagnosed with TB, she had difficulties tolerating standard TB treatment and suffered from drug-induced hepatitis. She feared for her own health and that of her unborn baby, and for her young son at home without her. She felt frustrated at the lack of evidence to guide her care, as well as the lack of current research around pregnancy and breastfeeding. For example, there was no past research into whether the decades-old TB treatment she remained on postpartum

was safe while breastfeeding—requiring her to "pump and dump" breastmilk for three months to maintain her supply and eventually be able to breastfeed her newborn. Since no research was ongoing, her hope of at least being able to send her breastmilk samples for analysis to contribute to better care for others in the future was stymied. Kate explained, "there was this sense that my whole experience, everything I had been through, was for nothing. And that some other woman was going to go through the same thing and I couldn't help her."

Despite the challenges, Kate was also acutely aware of the relative privilege of even being diagnosed and eventually cured of TB, and that her baby was born healthy, which is tragically not the fate of many cases of TB in pregnancy, especially given the research gaps. As Kate puts it, "There's this disease that actually kills more than a million people every year and we've had a cure for this disease for a long time. Why don't we know anything about what happens to pregnant women?"

Her anger at the injustices around TB in pregnancy propelled her into TB advocacy geared towards changing the TB research landscape to include pregnant and breastfeeding women and answer the many remaining questions. Kate is a member of We Are TB, a supportive community of TB survivors, people in treatment, and family members committed to the common goal of eliminating TB.

Meeting Details

In October 2023, the SMART4TB Consortium, the IMPAACT Network, and the WHO Global Tuberculosis Programme co-convened a meeting to launch a consensus process on the optimal timing and design of studies to improve TB treatment and prevention options for pregnant and breastfeeding women.

The objectives of the meeting were to:

1. **Inform** key stakeholders of the latest evidence on TB in pregnancy and highlight the urgent imperative for evidence-based treatment and prevention strategies;
2. **Understand** the different challenges facing stakeholders in advancing TB research in pregnant women; and
3. **Develop** a roadmap towards consensus on earlier and optimal inclusion of pregnant women in TB treatment and vaccine research.

The meeting, held on 26-27 October 2023 in Washington, DC, United States of America, occurred alongside the 2023 IMPAACT Network Annual Meeting to facilitate the participation of leading experts on maternal research in the IMPAACT Network.

The meeting brought together more than 80 participants from across the world including people affected by TB and living with HIV (including during pregnancy), civil society representatives, academic researchers from multiple disciplines, clinical experts, regulators, industry leaders, funders and other key stakeholders involved in TB research, care, and prevention during pregnancy and postpartum.

In conjunction, SMART4TB convened, through its consortium member Treatment Action Group (TAG) and with support from consortium member the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), an additional two-day meeting for representatives of affected communities to develop their own consensus on the inclusion of pregnancy and breastfeeding women in TB research (see page four for details).

The list of meeting participants is included in Annex 1 and the meeting agenda is included in Annex 2. The scientific presentations can be found [here](#).

About the Conveners

Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination (**SMART4TB**) is a five-year cooperative agreement made possible by the United States Agency for International Development (USAID), with the assistance of the American people, that aims to transform TB prevention and care.

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (**IMPAACT**) is a National Institutes of Health-funded global collaboration of investigators, community representatives, and other partners organized for the purpose of evaluating prevention and treatment interventions for HIV and associated conditions in infants, children, and adolescents, and during pregnancy and postpartum.

The World Health Organization Global Tuberculosis Programme (**WHO GTB**) aims to guide the global response to the TB epidemic and facilitate partnerships; provide evidence-based norms, standards and policies; support Member States in adapting and adopting the End TB Strategy; measure global progress, monitor and assess national programme performance, financing and impact; and enable progress across the continuum of TB research.

This report captures the vital discussions, questions, and follow up points that came out of this convening.

First, the overarching takeaways are summarized. The following sections are organized by four critical research areas—preclinical, therapeutics, surveillance, and vaccines—and detail the opportunities and challenges for the inclusion of pregnant and breastfeeding women within each research area.

Community perspectives on inclusion

In October 2023, representatives of communities affected by TB and with experience related to TB in pregnancy from 15 countries across five continents convened to develop consensus on the inclusion of pregnant and breastfeeding women and persons in TB research.

The statement calls for the active engagement of pregnant and breastfeeding women and persons in research decisions, particularly decisions concerning their exclusion from trials. Key points from their statement are excerpted below. Read the full statement and calls to action here.

Treatment Research

- "We are discontented with the reality that pregnant and breastfeeding women and persons are burdened with making decisions regarding the health and safety of themselves and their child in the complete absence of data. Pregnant women and persons are denied their autonomy and the right to choose their own inclusion in clinical trials to generate data — infringing on their right to health and right to science."

- "We are in unanimous agreement that the potential benefits of including pregnant and breastfeeding women and persons in trials to identify better, safer treatment regimens often outweigh the potential risks."

Vaccine Research

- "We unanimously agree that the potential benefits of vaccination to prevent infection or disease demand the inclusion of pregnant women and persons in vaccine clinical trials. We also acknowledge that the risks of each vaccine candidate require individualized assessment to weigh the risks and benefits for pregnant women and persons."

- "We recognize that pregnant and breastfeeding women and persons share experiences. But we believe that there is little justification for excluding breastfeeding women and persons from TB vaccine studies, even those in which the exclusion of pregnant women and persons is supported by evidence-based rationale."

Key Takeaways

Over the course of this two-day meeting, several overarching themes emerged, including four stark evidence gaps affecting pregnant women with TB.

Urgent evidence gaps

1) The TB surveillance evidence gap: Given that most TB episodes among women occur during their reproductive years and the highest-risk period for women to develop TB is during pregnancy and the postpartum period, the incidence of maternal TB is thought to be high. Yet, no systematic global data are available on TB in pregnancy and the postpartum period. In 2014, a modelling study estimated that each year 216,500 women develop TB during pregnancy.[17]

In most countries, pregnancy/postpartum status (and associated indicators) are not routinely collected in TB registries and, likewise, TB status (and outcomes) is not routinely reported in pregnancy registries.[18]

2) The TB diagnosis evidence gap: When maternal TB data are collected, incidence is likely underreported due to underdiagnosis of TB. TB diagnosis in pregnancy is challenging for four primary reasons: 1) immune changes may reduce the sensitivity of diagnostic tools, 2) reluctance of health providers to offer chest x-ray to pregnant women, 3) common pregnancy symptoms may mask TB symptoms, and 4) pregnant women have a high rate of extrapulmonary TB, which is more challenging to diagnose.[19]

The WHO-recommended four-symptom screen for TB disease and the tuberculin skin test (TST) for TB infection have significantly reduced sensitivity in pregnant women.[20-24] Uniquely, the timing of TB infection testing matters in the context of pregnancy; studies in TB endemic regions show TST positivity decreases around labor and delivery and rebounds postpartum.[11] In short, the best approaches for TB screening and diagnosis in pregnancy are unclear due to lack of data.

3) The TB prevention evidence gap: Existing studies have produced inconsistent evidence on the association between isoniazid preventive therapy (IPT) and adverse pregnancy outcomes.[11] The WHO recommends that for women living with HIV, the risk-benefit analysis favors preventive treatment during any trimester, even in the absence of TB infection testing.[25] The safety of the new, shorter rifapentine-based TB prevention regimens has not yet been determined in pregnant women.

For the first time in 100 years, there are promising TB vaccine candiates in the pipeline. However, preclinical work to assess safety in pregnancy is not yet underway, and later stage clinical trials are currently not planning to enroll pregnant or breastfeeding women.[26]

4) The TB treatment evidence gap: The mean duration time between US Food and Drug Administration (FDA) approval and the first published pharmacokinetic (PK) data in pregnant women for first-line TB drugs was 53 years. Contributing to this delay is the lack of legislation and regulations that formally incentivize or mandate drug and vaccine studies in pregnant women.[27]

In 2022, WHO updated its guidelines to recommend HPMZ, the first-ever four-month regimen for the treatment of drug-susceptible TB (DS-TB).[28] This shortened regimen has not been studied in pregnancy, and therefore the WHO-recommended standard of care for pregnant women with DS-TB remains the six-month regimen.[25]

For pregnant and breastfeeding women with drug-resistant TB (DR-TB), the evidence gap is even larger.[29] In 2022, WHO updated its guidelines to recommend six-month all-oral regimens (6BPaL/M) for the treatment of DR-TB. Again, since these regimens have not yet been

studied in pregnancy, the WHO-recommended standard of care for pregnant women with DR-TB remains a nine-month (or longer) regimen.[30] Yet, even the data needed to determine appropriate dosing of older DR-TB drugs in pregnancy are limited.[31] Newer second-line TB medications (bedaquiline, pretomanid and delamanid) are not recommended by WHO for use during breastfeeding due to lack of data.[30]

Taken to together, these gaps highlight that TB research in pregnant women is an urgent priority.

Underrepresented in research does not mean "special" or "vulnerable"

Pregnant women are a scientifically and ethically complex population in TB research, but as several stakeholders at this meeting, including TB survivors, repeatedly noted, they should not be labeled a "vulnerable" or "special" population.

Historically, pregnant women were considered a vulnerable research population. In the research context, 'vulnerable populations' are those at risk of being exploited from research due to circumstances such as diminished autonomy, and difficulty providing voluntary, informed consent.[32] Pregnant women do not fit under such a definition of vulnerability, and while a fetus is unable to consent to participate in research, this must be considered in the context of the pregnant woman's right to autonomy as well as the potential benefits of research.

Notions around the "vulnerability" of pregnant women in research have evolved over the past decade. In 2010, the United States (US) National Institutes of Health (NIH) issued a recommendation to reclassify pregnant women from a 'vulnerable' population to a 'scientifically complex' population and change the presumption of exclusion to one of inclusion—i.e., there should be a specific rationale for excluding pregnant women from a given research study.[33] In 2015, the American College of Obstetrics and Gynecology published a similar opinion.[34] Lastly, a change to US federal research rules, which came into effect in 2019, removed pregnant women from the 'vulnerable population' category.[14]

In practice, the TB research community, and the scientific community more broadly, has been slow to adopt this new paradigm supporting presumed inclusion of pregnant women in research.

Pregnant women are no more "special" than they are "vulnerable." Pregnancy is an altered physiological state that a majority of women experience in their lifetime, and for some women, being either pregnant or breastfeeding accounts for a significant portion of their lifetime.

Labeling pregnant women as a "special" or "vulnerable" population only further enforces their exclusion from research that could better improve their and their fetuses' care.

Risk to women's mental health and human rights

Meeting participants who were treated for TB during pregnancy encouraged all stakeholders to remember that their exclusion from research has impacts which extend beyond physical health—stigma, fear, isolation, and guilt are all compounded when faced with difficult and complex decisions about taking TB medications while pregnant. Women's reproductive rights— to bodily autonomy, informed consent and choice—already tenuous in the context of pregnancy, may be further compromised after a TB diagnosis.[35]

Engaging stakeholders is paramount

The existing barriers to inclusion of pregnant women in TB research are numerous and vary depending on the perspective of the stakeholder. A foundational conclusion was the need to involve all stakeholders—especially pregnant women, civil society, academic, regulatory and industry—early in the consensus process to ensure all barriers to inclusion are adequately addressed. Community representatives at the meeting reinforced that engagement with affected communities along the entire research continuum is essential.

Preclinical Research

Preclinical research—research not conducted in humans—is a critical stage of drug and vaccine research where potential impacts on fetal health can be safely elucidated in the laboratory.

Preclinical studies are necessary to allow inclusion of pregnant and breastfeeding women in later phase efficacy trials.[36] However, a lack of funding and concerns about drug development timelines often prevent the timely execution of preclinical developmental and reproductive toxicity (DART) studies (see Box 1 for details).

DART studies, conducted in at least two animal models (one rodent and one non-rodent species), are used to predict whether therapeutics and vaccines are expected to be safe for use in pregnancy.

Currently, preclinical DART studies are generally conducted during Phase III or IV trials, leading to the exclusion of pregnant women from early enrollment in clinical trials, withdrawal of women from pre-licensure trials if they become pregnant, and strict use of contraceptives for participants of child-bearing age while on study.[37]

Physiology-based pharmacokinetic (PBPK) modelling is a non-clinical approach that can help predict human maternal and fetal exposure during pregnancy in an early stage of drug trials. Innovative study designs that allow different DART studies to be conducted simultaneously and using non-animal-based models (such as placenta-on-a-chip) may offer more efficient and cost-effective strategies for preclinical studies in the near future.[37]

BOX 1

Standard DART studies

- **Fertility and early embryonic development (FEED)** studies are designed to detect adverse effects on male and female fertility, and implantation and development of the embryo.

- **Embryo-fetal development (EFD)** studies are designed to detect adverse effects on the pregnant animal, development of the embryo and the fetus.

- **Pre- and post-natal (PPND)** studies are designed to detect adverse effects on the pregnant or lactating female and development of the offspring covering two generations.

What is "placenta-on-a-chip"?

Quantification of fetal drug exposure remains challenging since sampling from the placenta or fetus during pregnancy is invasive. "Placenta-on-a-chip" is a promising novel microfluidic device that mimics the nutrient exchange between the fetus and mother, thereby facilitating study of placental physiology and fetal exposure to maternally administered drugs.[38] Placenta-on-a-chip models are generally composed of three main parts: a maternal compartment, a fetal compartment, and a porous membrane in between. By pumping fluids through the model, researchers can test if, and to what degree, different substances cross the placental barrier. This technology has been used to study placental transfer of nutrients, such as glucose, as well as placental transfer of drugs, such as those used to treat opioid addiction, gestational diabetes, and high cholesterol.[39]

Beyond conducting the requisite preclinical studies, a parallel challenge is the interpretation of their results. This is particularly true for less severe signals of embryo-fetal development toxicity (i.e., signals other than anomalies/death at relevant exposures).[37]

The community delegation noted with concern the lack of community engagement at the preclinical research stage including when determining how safety data in animals are extrapolated for humans (in some cases to justify exclusion of pregnant women from further research studies).

With this context in mind, the preclinical breakout group discussed challenges and opportunities related to accelerating preclinical reproductive toxicity studies for TB therapeutics.

Challenges

- Imperfect animal and quantitative models to predict human toxicity during pregnancy and the postpartum period
- Unique challenges regarding the use of non-human primates for DART research
- Accurate evaluation/interpretation of safety signals in preclinical data, particularly for less severe signals, and when toxicity is seen in one animal species but not another

- Culture of risk aversion among some drug developers and regulators
- Low prioritization of funding for DART studies

Opportunities

- Performing preclinical studies/models earlier during drug development (e.g., early in Phase II) to support inclusion of pregnant women in Phase III trials
- Better understanding of the role of quantitative modeling and simulation for streamlining TB products development
- Developing a framework/algorithm to improve the interpretation of preclinical safety signals
- Explore the use of innovative non-animal models to complement toxicity studies (e.g., placenta-on-a-chip)
- Increasing transparency of existing DART data, as many early-stage preclinical results conducted by industry are protected by non-disclosure agreements
- Improving the linkage between preclinical, translation and clinical research, including the engagement and consultation of affected communities

Therapeutics Research

In the absence of research, pregnant women remain ineligible for newer treatments due to a lack of evidence on their use during pregnancy.

Pregnant women with TB continue to be treated with older, less effective or longer regimens associated with increased risk of adverse events—despite the fact that the safety of even the oldest TB medications are not well characterized in pregnancy.[40] In some cases, women may even be inappropriately counselled to choose between continuing their pregnancies and starting TB treatment.[41]

Expert recommendations and research policies exist to support the ethical inclusion of pregnant women in research, but have been slow to translate into action. The US Department of Health and Human Services has guidelines which permit research involving pregnant women and fetuses given that certain conditions, summarized in Box 2, are met. And, in 2015, the NIH convened an expert panel which endorsed the earlier inclusion of pregnant and postpartum women specifically in TB treatment clinical trials. A summary of their consensus statement can be found in Box 3.

BOX 3

NIH expert panel consensus statements[42]

- Pregnant and postpartum women should be eligible for Phase III multidrug-resistant TB trials unless there is a compelling reason for exclusion;

- Drug companies should be encouraged to complete reproductive toxicity studies before beginning Phase III trials;

- Trials of shortened treatment regimens for TB infection should be designed for pregnant women;

- Targeted PK studies should be nested in all studies when evidence is lacking; and

- Registries should be created to accumulate data on maternal-infant outcomes.

BOX 2

US regulations for research involving pregnant women

- Preclinical studies have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

- Risk to fetus is caused solely by interventions or procedures that hold prospect of direct benefit for the woman or the fetus or,

- If there is no such benefit, risk to the fetus is not greater than minimal and the research develops important biomedical knowledge not obtainable by any other means;

- Any risk assumed is the least possible for achieving the objectives of the research;

- Individuals engaged in the research will have no part in (1) any decisions as to the timing, method, or procedures used to terminate a pregnancy, and (2) determining the viability of the neonate; and

- No inducements, monetary or otherwise, will be offered to terminate the pregnancy.

Summarized from Subpart B of the US Department of Health and Human Services regulations for the protection of human subjects in research.[36]

While the field has advanced considerably in recent years (see Box 4), a lack of large, well-controlled studies has led to conflicting data and unanswered questions, such as:

- Can new shorter regimens for DS-TB (4HPMZ) and DR-TB (6BPaL/M) be used safely in pregnancy?
- Do certain TB drugs need to be dose-modified or not used?
- Is the rifamycin interaction with HIV antiretrovirals more of a concern during pregnancy?
- What is the optimal timing with regard to pregnancy to initiate TB preventive treatment?
- Can we safely use new shorter regimens for treatment of TB infection (1HP, 3HP) in pregnancy?
- How should pregnant contacts of DR-TB cases be managed?
- Which TB drugs are safe to use while breastfeeding?

Recognizing these critical data gaps, representatives from the FDA and the European Medicines Agency (EMA) shared their commitment to working with all stakeholders to advance the safe and effective use of medications and vaccines in pregnant and breastfeeding women.

BOX 4

Key clinical trials of TB treatment and prevention in pregnancy

- **2018: PREVENT TB (NCT00023452) and iADHERE (NCT01582711)** – Secondary analyses of two randomized, noninferiority trials comparing 3HP and 9 months of IPT found no unexpected fetal loss or congenital anomalies with either regimen.[43]

- **2019: TB-APPRISE (P1078)** – A Phase IV randomized placebo-controlled trial comparing the safety of IPT initiation during pregnancy with initiation postpartum among women living with HIV found no differences in maternal or live-born infant outcomes, TB incidence or death. However, the study found more adverse pregnancy outcomes in those who received IPT during pregnancy than the postpartum period.[44]

- **2021: IMPAACT P2001** – A Phase I/II trial evaluated the pharmacokinetics and safety of 3HP among pregnant women and found no dose adjustment was required. However, the study was not powered for safety.[45]

- **2023: BRIEF-TB (ACTG 5279)** – A secondary analysis of a randomized noninferiority trial comparing a standard 9 months of IPT with 1HP in people living with HIV found a nearly 2-fold increased risk of fetal demise with IPT exposure at conception and continuing into at least the first trimester of pregnancy,
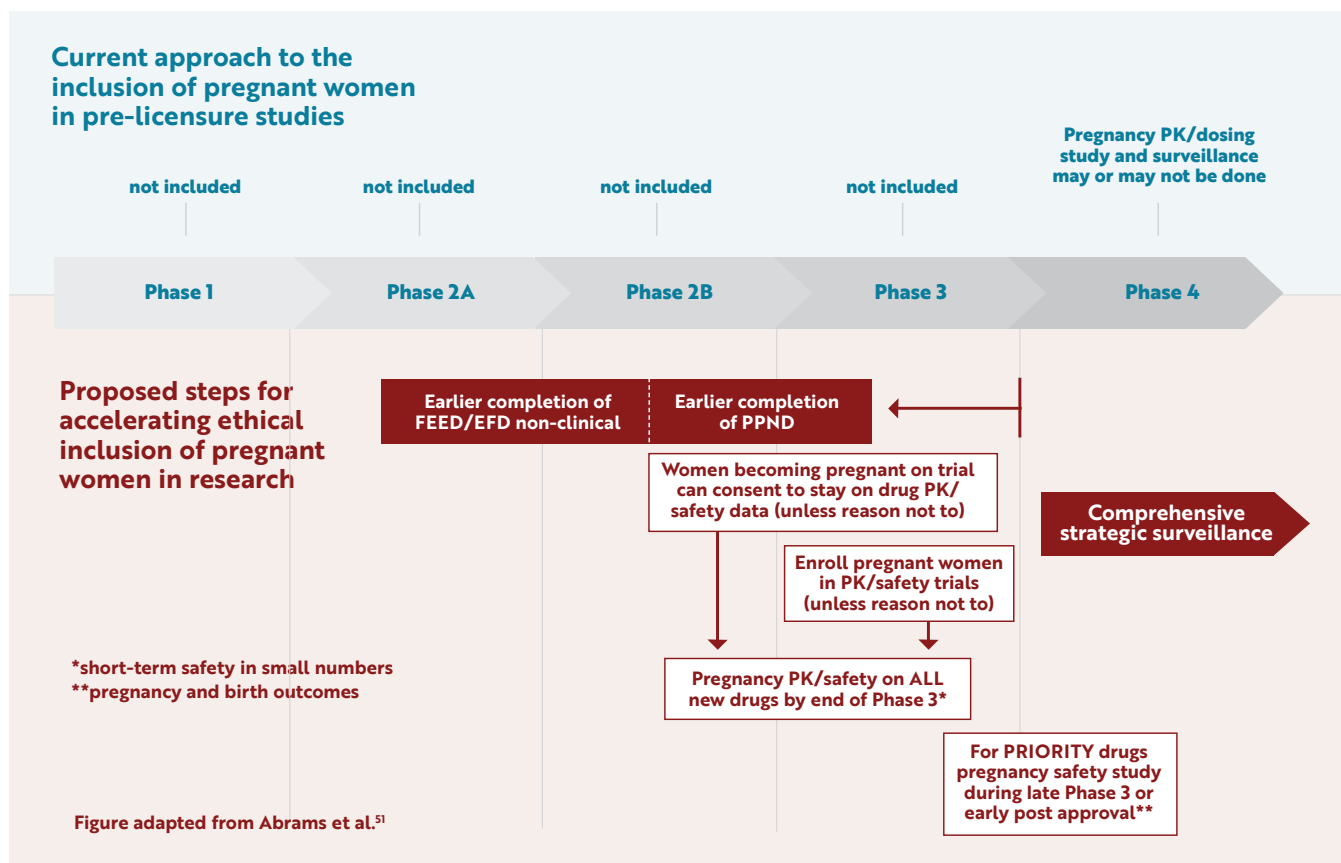
which was largely driven by spontaneous abortions. However, there was no significant association between exposure starting during the first trimester and preterm delivery or low birth weight.[40]

- **2023: IMPAACT P1026s** – A Phase IV, observational, prospective PK and safety study of first-line TB drugs during pregnancy and postpartum, which revealed lower concentrations of isoniazid and ethambutol during pregnancy. The clinical significance, if any, remains unknown.[46]

- **Ongoing: BEAT-TB** – A Phase III, randomized trial evaluating six months of bedaquiline, delamanid, and linezolid, with levofloxacin and clofazimine for treatment of rifampicin-resistant TB in pregnant and breastfeeding women in South Africa.

- **Ongoing: DOLPHIN Moms** – A Phase IV, randomized trial evaluating the safety, tolerability of 1HP and 3HP with PK of dolutegravir in pregnant women living with HIV.

- **Ongoing: IMPAACT P2026** – A Phase IV, prospective, PK study of second-line TB medicines when used in clinical care during pregnancy and postpartum.

FIGURE 1

Framework for accelerated inclusion of pregnant women in pre-licensure clinical trials

Current approach to the inclusion of pregnant women in pre-licensure studies

not included   not included   not included   not included   Pregnancy PK/dosing study and surveillance may or may not be done

| Phase 1 | Phase 2A | Phase 2B | Phase 3 | Phase 4 |

Proposed steps for accelerating ethical inclusion of pregnant women in research

Earlier completion of FEED/EFD non-clinical

Earlier completion of PPND

Women becoming pregnant on trial can consent to stay on drug PK/safety data (unless reason not to)

Enroll pregnant women in PK/safety trials (unless reason not to)

Comprehensive strategic surveillance

Pregnancy PK/safety on ALL new drugs by end of Phase 3*

*short-term safety in small numbers
**pregnancy and birth outcomes

For PRIORITY drugs pregnancy safety study during late Phase 3 or early post approval**

Figure adapted from Abrams et al.[51]

Several regulatory, legal and policy efforts are underway globally, including:

- The revision of several regulatory guidance documents related to pregnancy, breast-feeding, and TB, including four FDA industry guidelines;
- The establishment of an Implementation Working Group of Council to monitor and report on the implementation of the recommendations from the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC);[47]
- A 2020 meeting between the FDA, EMA and the Medicines and Healthcare products Regulatory Agency to discuss methods and strategies to improve knowledge for the rational use of medicines for pregnant and lactating populations;[48]
- The 2023 International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) E21 Guideline on the Inclusion of Pregnant and Breastfeeding Individuals in Clinical Trials;[49]

- Efforts to improve post-approval pregnancy safety data collection, including a 2023 commitment under the Prescription Drug User Fee Amendment VII (PDUFA VII) to "develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used"; and
- Ongoing work by the US National Academies of Sciences, Engineering and Medicine to examine the barriers and opportunities for including pregnant and breastfeeding women in clinical trials.[50]

Moving forward it will be crucial to engage regulatory agencies from high-burden TB countries in these efforts.

Previous work in the HIV field to advance the inclusion of pregnant women in research was referenced repeatedly during the meeting, reinforcing the idea that the TB community does not need to start from zero; the overarching framework developed during the HIV consensus process (Fig.1) can also apply to TB.

With this framework and the known challenges in mind, the therapeutics research breakout group discussed timely opportunities to advance the inclusion of pregnant women in new TB therapeutics trials and close the evidence gaps for pregnant women for existing TB regimens.

Challenges

- Statistical and study design considerations specific to conducting research in pregnant women
- Conflicting guidance from regulators
- Securing institutional review board (IRB) approvals
- Identifying and securing trial insurance that will cover pregnant participants
- Lack of a gold standard algorithm for TB diagnosis in pregnancy

Opportunities

- Building off the recommendations from previous consensus work and updated normative guidance
- Prioritizing existing TB drugs to be studied for dosing and safety in pregnancy and during breastfeeding
- Developing an ethical framework for the optimal inclusion of pregnant and breastfeeding women in TB drug trials
- Defining what preclinical data and clinical data among non-pregnant women are needed for inclusion of pregnant women in the second and third trimester and for reconsent of women who become pregnant while on study

- Defining and harmonizing maternal and neonatal outcomes
- Defining additional monitoring or assessments needed during pregnancy and breastfeeding
- Developing a set of optimal study designs for nested and standalone studies to accelerate the generation of dosing and safety data during pregnancy and breastfeeding
- Developing a free, open-source toolkit to facilitate the inclusion of pregnant women in TB drug trials (e.g., sample protocols, case report forms, informed consent forms, etc.)
- Developing resources to assist pregnant women in making informed risk-benefit decisions
- Ensuring routine inclusion of pregnant and breastfeeding women in TB diagnostics trials and conducting specific studies to determine the optimal type and timing of TB infection testing during pregnancy
- Training and capacitating IRBs to apply a principle of presumed inclusion for pregnant and breastfeeding women and to properly weigh the risks and benefits of participation for both women and their fetuses
- Increasing participation of affected communities on IRBs and protocol development teams
- Creating a public tracker to document which TB trials are planning to include pregnant and breastfeeding women and which would be good candidates for nested PK studies

Surveillance

There are two key surveillance needs related to maternal TB. The first, is improved surveillance of adverse outcomes for pregnant women treated for TB infection and disease, and the second, is improved surveillance of episodes of TB infection and disease diagnosed during pregnancy.

Surveillance of adverse events for mothers and infants

The presentations on surveillance highlighted that while trials address important questions such as efficacy and safety of TB drugs in pregnancy, the detection of rare adverse events require large numbers of exposed women, and this may only be achieved through post-marketing surveillance. The lack of post-marketing surveillance for TB drugs was identified as a gap which limits available evidence for updating policies, which in turn limits the ability of clinicians to safely recommend specific TB drugs during pregnancy. Isoniazid has been in use since 1953, yet the first systemic reporting of adverse outcomes among pregnant women who received isoniazid wasn't published until 2019, over 60 years later.[44]

The breakout group discussed that multiple forms of surveillance are possible. Birth outcome sentinel surveillance is best used to capture immediate outcomes (e.g., low birth weight, preterm delivery, small for gestational age, major congenital anomalies, and fetal loss), while noting that many exposures are necessary to accurately understand the risk of rare outcomes, such as congenital anomalies. For instance, 2,000 periconception exposures are needed to rule out a 3-fold increased risk of a neural tube defect with 0.1% prevalence in the population— something that can only be achieved through post-marketing surveillance.[52]

In contrast, outcomes related to rare exposures, such as treatment for MDR-TB during pregnancy, and long-term pediatric outcomes, will likely need to be captured through enrollment in prospective cohort studies and or specific research studies. Individual patient data meta-analyses have played an important role in understanding safety and treatment outcomes among children with DR-TB but are limited by voluntary reporting and the lack of a comparator group. Registries are similarly limited by underreporting and the lack of both a denominator of exposure and a comparator group.

A collaborative conceptual framework for the surveillance of safety of new antiretroviral HIV drugs in pregnancy was developed at a workshop convened by IMPAACT and the WHO's Global HIV, STI and Hepatitis Programmes in 2018. This framework provides a useful summary of the different types of surveillance that could be used for measuring maternal and infant outcomes related to TB drug exposure and includes reference to other forms of surveillance that were not discussed extensively during the breakout group, including existing national pharmacovigilance systems.[53]

While not specifically related to TB during pregnancy, active TB drug safety monitoring and management has also been promoted by WHO in order to detect, manage and report suspected or confirmed drug toxicities related to the introduction of new regimens or drugs for the treatment of DR-TB.[54]

Surveillance of TB episodes during pregnancy

Improved TB screening of pregnant women is necessary to understand the burden of maternal TB and maternal TB epidemiology. As noted in the introduction, pregnancy/postpartum status (and associated indicators) are not routinely collected in TB registries and, likewise, TB status (and outcomes) are not routinely reported in pregnancy registries.[18]

The lack of active data collection compounded by the challenges in diagnosing TB during pregnancy has meant that the burden of maternal TB is poorly quantified globally. Yet, as highlighted at this meeting, progress is possible. For example, in Uganda in 2022, approximately 85% of all antenatal patients were screened for TB because of the National TB and Leprosy Programme's recent efforts to improve the integration of TB services and antenatal care.

With this context in mind, the surveillance breakout group discussed the challenges and opportunities related to closing the surveillance gap in TB, including how to leverage the lessons learned from the HIV field.

Challenges

- National data sharing laws and privacy regulations which present barriers to pooling data across multiple countries
- Lack of integrated record keeping systems between programs
- Decentralized record-keeping (i.e., when pregnant women carry their own medical records)
- Absence of unique identifiers that link mother-infant pairs
- Overburdening of front-line health providers leading to missing, incomplete, or inaccurate data
- Lack of sustainable funding for sentinel surveillance sites
- Capturing delayed diagnosis in the postpartum period
- Differing definitions of adverse pregnancy, birth, and maternal outcomes/endpoints
- Obtaining the appropriate denominator
- Ascertaining timing of drug exposure
- Obtaining a large enough number of exposures to guard against misleading safety signals

Understanding congenital disorders: causes and risk factors

Congenital disorders, including congenital anomalies such as neural tube defects, are among the most worrisome adverse birth outcomes. An estimated 240,000 newborns die worldwide within 28 days of birth every year due to congenital disorders.[55] Most congenital disorders are caused by genetic or environmental factors, or a combination of the two.[56]

Environmental causes can include diseases and perinatal exposure to teratogens, defined as substances known to increase the risk of congenital anomalies. Exposure to teratogens during the first trimester (up to the 14th week of pregnancy) has the greatest chance of causing congenital anomalies due to the major structures of the body forming during this period (i.e., embryogenesis). For instance, the neural tube closes to form the brain and spinal cord within the first 28 days after conception.[57] As a result, the risk of congenital anomalies caused by in utero drug exposure is highest in the early weeks of pregnancy, often before a woman is even aware that she is pregnant.

The mechanisms that lead to congenital anomalies with respect to both genetic and environmental causes are poorly understood. However, it is crucial to understand that both untreated illness and infection (e.g., diabetes, rubella, Zika) and the pharmaceutical agents used to treat illness and infection (e.g., antiepileptic medications) can cause congenital anomalies.[55] As a result, risk-benefit calculations for expectant mothers affected by an illness can be extremely challenging in the absence of good data.

Opportunities

- Building on pre-established HIV sentinel surveillance sites for TB surveillance

- Providing support and training to improve facility-level TB data collection

- Analyzing existing surveillance data for associations with TB drugs

- Linking surveillance to orphan drug approval and clinical access programs

- Understanding what indicators are routinely collected as part of obstetric records in high-burden countries and exploring options to integrate TB screening and data collection into antenatal and postnatal care

- Exploring funding avenues to fund sentinel surveillance for TB including increasing local investment in routine data collection and sentinel surveillance

- Developing recommendations for the inclusion of pregnancy status (and potentially expanded data points such as gestational age, postpartum status, and infant outcomes) in TB treatment and prevention registries

- Developing normative guidance on the collection of TB data during pregnancy

- Improving sensitization, engagement, and cross-training between specialties

- Soliciting and pooling maternal TB data that are being collected by countries/sentinel sites

- Leveraging screening opportunities linked to childhood vaccination

- Early scoping and planning for maternal TB vaccination surveillance programs

Vaccine Research

There has been great progress in TB vaccine development over the past decade, with six vaccine candidates entering Phase III trials and 11 candidates earlier in the pipeline in 2023.[26] However, at the time of the meeting and to the participants' knowledge, none of these vaccine trials plan to enroll pregnant or breastfeeding women.[26] It is not known whether trial participants who become pregnant will be given the option to reconsent or whether vaccine immunogenicity and fetal outcome data from incidental pregnancies will be collected.

The ethical framing presented at this meeting emphasized that the decision to include or exclude pregnant and/or breastfeeding women from a given TB vaccine trial should be context-specific and evidence-based, and that the theoretical risk of the TB vaccine should be assessed in context of the documented increased risk of TB disease to both maternal and fetal health.

Presenters reviewed the platform, indication, and timing considerations related to maternal TB vaccination.

Vaccination during pregnancy

The precedent for maternal vaccination was emphasized by highlighting vaccines that are recommended by various agencies (e.g., FDA, EMA, WHO) for routine use in pregnancy (Fig.2).[58,59] The recommended vaccines are diverse in platform and include protein subunit, recombinant and, most recently, mRNA vaccines for COVID-19. Such platforms with existing safety evidence in pregnancy may be prioritized for study in the context of TB vaccine development. Potassium aluminum sulphate (e.g., Alum) is the most common adjuvant among vaccines recommended during pregnancy. One of the COVID-19 vaccines recommended in pregnancy, Novavax, is the first to use a saponin-based adjuvant (Matrix-M).[60] Future safety data emerging from the use of the Novavax vaccine in pregnancy may provide insight into the safety of the M72 TB vaccine in pregnancy as it also employs a saponin-based adjuvant, ASO1E.

Multiple indications for TB vaccines are being explored. There are prophylactic vaccines (which either prevent infection or disease), post exposure vaccines (which prevent disease), and therapeutic vaccines (which either shorten treatment or prevent recurrence).[26] This adds a layer of complexity when considering maternal vaccination and understanding which indications will be most appropriate for pregnant women and women of childbearing potential.

Another complexity is vaccine-related timing factors—time to immunogenicity, time to protection and duration of protection—and how they interplay with the gestation period. Knowledge of the clinical course of TB disease and data from the M72 Phase II trial suggests that time to vaccine efficacy may be longer for TB vaccines compared to vaccines for other diseases.[64] This has important implications for maternal vaccination, given that pregnancy has a finite duration. Depending on the time to protection, optimal protection during pregnancy may only be achieved by pre-pregnancy vaccination. Alternatively, vaccination during pregnancy may be needed to achieve optimal protection during the high-risk postpartum period. It is therefore critical to understand vaccine safety and efficacy throughout pregnancy and the postpartum period.

Similar to the administration of drugs during pregnancy, the safety, risks, and benefits of vaccination during pregnancy may differ for mother and infant depending on the period of gestational development during which the vaccine is administered. For example, the optimal timing of respiratory syncytial virus (RSV) vaccination is debated due the small (albeit nonsignificant) increase in premature birthrates observed in the vaccine-receiving cohort.[65] As a result, the FDA recommends RSV vaccination anywhere between 32 and 36 weeks of pregnancy to balance the potential risk of

FIGURE 2

Vaccines recommended for routine use in pregnancy

Disease	Vaccine platform	Number of doses	Types of adjuvants	Target for protection	Timing (weeks gestation)	WHO guidelines
Tetanus, diphtheria, pertussis	Subunit	1*	Alum	Infant	TT/Td: All Tdap: 27-36	WHO recommends vaccination with a tetanus-toxoid-containing vaccine during pregnancy with different dosing schedules depending on previous immunization history.[61]
Influenza	Subunit Recombinant	1	Alum or None	Mother & Infant	All	WHO recommends seasonal influenza vaccination at any stage of pregnancy, preferably prior to the start of the influenza season.[62]
COVID-19	mRNA Recombinant	1	Matrix M or None	Mother & Infant	All	WHO does not recommend delaying or terminating pregnancy because of COVID-19 vaccination, and no pregnancy testing is needed prior to vaccination.[63]
RSV	Subunit	1	None	Infant	32-36 (FDA) 24-26 (EMA)	Guidance from WHO for RSV vaccination is not yet available.

*Requires additional doses if not previously immunized.

Tetanus toxoid with tetanus and diphtheria (TT/Td); tetanus toxoid, diphtheria toxoid, and acellular pertussis (Tdap); Respiratory syncytial virus (RSV). Table adapted from Ruth Karron.

preterm birth with the time needed to develop the antibodies needed to confer protection to the infant.[66] The EMA, however, recommends RSV vaccination anywhere between 24 and 36 weeks of pregnancy, which is in line with the timing of administration during the registration trial.[67]

Vaccination while breastfeeding

In the clinical trial context, pregnant and breastfeeding women are often grouped together, and exclusion is jointly applied. However, the safety considerations for treatment during breastfeeding are different than for vaccination during breastfeeding.

Most existing vaccines are not known to adversely affect breastfeeding women or their infants.[68] Only live attenuated vaccines, specifically for smallpox and yellow fever, are contraindicated during breastfeeding due to the theoretical risk of transmission to the infant.[68] The theoretical risk of transmission of TB via breastmilk due to the administration of a live attenuated TB vaccines to a breastfeeding women is less relevant, as infants themselves

are vaccinated with Bacille Calmette-Guérin (BCG) vaccine, a live attenuated TB vaccine, at birth.

The de-facto exclusion of breastfeeding women from TB vaccine trials is particularly concerning given the lack of theoretical risk for vaccination during breastfeeding and known increased risk of TB disease in the postpartum period.

Practical considerations for vaccine roll-out

Determining a TB vaccine's safety during pregnancy and breastfeeding may have implications for the successful roll-out of a future TB vaccine. Pregnancy and the postpartum period are important periods of engagement with healthcare services: women attend regular antenatal visits, infant and child health checkups, and visits for maternal and infant immunizations. Linking vaccination to one (or more) of these time points is a known strategy for increasing vaccine uptake, such as in the case of postpartum measles, mumps and rubella (MMR) vaccination to protect future pregnancies against congenital rubella syndrome.[69]

In the context of the rollout of a future TB vaccine, it is impractical to consider that pregnancy testing will be required prior to vaccination, as will be the case during TB vaccine clinical trials. In pragmatic contexts, women will be vaccinated while unknowingly pregnant, most likely while in their first trimester—the most sensitive period of gestational development. Just as with drugs, the ability to effectively monitor and rigorously assess adverse events will be significantly reduced in this real-world, pragmatic context compared to during a clinical trial.

It is important to preemptively consider the data and evidence that will support WHO policy decision-making for new vaccines. As was highlighted at the meeting, a test-case for WHO's Evidence Considerations for Vaccine Policy (EVAP) initiative, focused on a future TB vaccine, reaffirmed that "efforts should be made to explore ways in which data can be generated for... pregnant women." [70]

With this context in mind, the vaccine breakout group discussed the challenges and opportunities related to studying TB vaccination in pregnant and breastfeeding women, including how to apply the lessons learned from the development, evaluation, and roll-out of COVID-19 vaccines in pregnancy.

Challenges

- Lack of understanding of ideal animal models for preclinical vaccine studies
- Unknowns about time to immunogenicity, time to efficacy and duration of protection for TB vaccine candidates
- Inadequate funding, including for upstream basic science and DART studies
- Delayed collection of DART data
- Lack of consensus between industry sponsors, regulatory agencies and researchers to define risk thresholds for inclusion of pregnant and breastfeeding participants in pre-licensure clinical trials, considering evidence based on vaccine platform from non-TB vaccines

- Perceived financial risk to industry sponsors to include pregnant and breastfeeding women in Phase II/III trials
- Lack of regulatory requirements to include pregnant and breastfeeding people in pre-licensure clinical trials for vaccines using platforms with lower risk profiles in the context of pregnancy and/or breastfeeding
- Approval from a stringent regulatory authority for a vaccine that won't routinely be used in the US or Europe

Opportunities

- Exploring the possibility for the M72 Phase III trial, and any future TB vaccine trials, to enroll breastfeeding women
- Developing a framework for monitoring individuals who become pregnant during vaccine trials, including the M72 Phase III trial
- Developing robust community engagement structures that allow vaccine developers and researchers to solicit feedback from affected communities before protocols are finalized
- Early completion of DART studies for vaccines in Phase I/II
- Increased understanding of different adjuvants' safety in pregnancy
- Increasing transparency of trial protocols and inclusion/exclusion criteria
- Early engagement with regulatory agencies, particularly in high-burden countries (e.g., the South African Health Products Regulatory Authority [SAHPRA])
- Engaging the expertise of obstetricians-gynecologists/perinatologists to better understand potential safety concerns of TB vaccine candidates on perinatal outcomes
- Developing a toolkit for the inclusion of pregnant women in TB vaccine trials (e.g., sample protocols and informed consents, mother-infant case report forms, endpoints, timing of vaccine administration according to gestational age)

Conclusion and Next Steps

This report summarizes the key challenges that must be addressed to facilitate the appropriate inclusion of pregnant and breastfeeding women in TB research.

The work of the impending scientific consensus process will be to develop recommendations to help address these challenges.

Following on from the October 2023 meeting, the next steps will be to:

- Establish the terms of reference and composition of five working groups that will advance aspects of this work. The five working groups will be: preclinical TB drug research, TB treatment clinical trials, TB vaccine research, maternal TB surveillance systems, and advocacy.

- Review and synthesize the available evidence on TB in pregnancy and during breastfeeding.

- Convene a consensus meeting in late 2024 which will culminate in a WHO consensus statement on the earlier inclusion of pregnant and breastfeeding women in TB research.

Through concerted and collaborative effort, this consensus process will generate connections, ideas, recommendations, and ultimately evidence, that will improve the lives of pregnant and breastfeeding women and their infants.

Get in touch

To receive updates from SMART4TB, including about the pregnancy consensus process, you can sign up at http://eepurl.com/ijq3G1.

If you have a personal story you would like to share, please contact smart4tbinfo@jh.edu.

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Annex 2. Meeting Agenda

Day 1 – Thursday, 26 October 2023

Opening Remarks from Paul Mahanna (USAID) and Sharon Nachman (IMPAACT)

The Lived Experience – Why This All Matters
Kate O'Brien (We Are TB)

Overview Presentation – Status Quo, Key Issues and Questions, Meeting Objectives
Dr Amita Gupta (Johns Hopkins University)

Current WHO Guidance on Treating and Preventing TB in Pregnant Women
Dr Sabine Verkuijl (World Health Organization)

Maternal TB Epidemiology and Risk
Dr Jyoti Mathad (Weill Cornell Medicine)

Maternal TB Treatment and Prevention – Landscape for DS-TB
Dr Nicole Salazar-Austin (Johns Hopkins University)

Maternal TB Treatment and Prevention – Landscape for DR-TB
Dr Ahizechukwu Eke (Johns Hopkins University)

Current Regulatory Framework - European Medicines Agency
Dr Marco Cavaleri (European Medicines Agency)

Current Regulatory Framework - US Food and Drug Administration
Dr Tamara Johnson (US Food and Drug Administration)

Paradigm Shift in Ethical Framework – Protecting Pregnant Persons through Research, Not from Research
Dr Ruth Faden (Johns Hopkins University)

Preclinical Drug Research Breakout Session
Moderated by Dr Ahizechukwu Eke (Johns Hopkins University) and Dr Christina Lancioni (Oregon Health & Sciences University)

Clinical Drug Research Breakout Session
Moderated by Dr Jyoti Mathad (Weill Cornell Medicine) and Dr Fuad Mirzayev (World Health Organization)

Day 2 – Friday, 27 October 2023

A Programmatic Perspective – Experience from Uganda
Dr Moorine Sekadde (Uganda National TB & Leprosy Program)

TB Vaccine Pipeline
Dr Lisa Marie Crammer (Emory University)

Maternal Immunization
Dr Ruth Karron (Johns Hopkins University)

Ethical Considerations for Maternal Vaccines
Dr Ruth Faden (Johns Hopkins University)

Q&A and Discussion
Moderated by Dr Rupali Limaye (Johns Hopkins University)

Approaches for Surveillance of Safety of Anti-TB Drugs in Pregnancy: Lessons from HIV
Dr Lynne Mofenson (Elizabeth Glaser Pediatric AIDS Foundation)

Prior Attempts at TB Drug Surveillance
Dr Adrie Bekker (Stellenbosch University)

WHO Collaborative Framework for Surveillance of ARV Safety in Pregnancy & Breastfeeding
Dr Françoise Renaud (World Health Organization)

Drug-Resistant TB IPD for Mother-Infant Pairs
Dr Anneke Hesseling (Stellenbosch University)

Innovative data Science to Impact the TB Epidemic - INSITE
Dr Emma Kalk (University of Cape Town)

Surveillance Breakout Session
Moderated by Lindsay McKenna (Treatment Action Group) and Dr Kerri Viney (World Health Organization)

Vaccine Breakout Session
Moderated by Dr Lisa Marie Cranmer (Emory University) and Mike Frick (Treatment Action Group)

Rapporteur Summaries and Discussion
All

Next Steps and Closing Remarks
*Dr Nicole Salazar-Austin (Johns Hopkins University)
Dr Fuad Mirzayev (World Health Organization)*

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