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Washington, D.C. Community Consensus on the Earlier Inclusion of Pregnant Women and Persons in TB Research

We, sixteen representatives of communities affected by tuberculosis (TB) and with experience related to TB in pregnancy, met in Washington, D.C., on October 25–28, 2023, to develop a consensus on the inclusion of pregnant and breastfeeding women and persons* in TB treatment and vaccines research. The community meeting was part of a larger convening hosted by the Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination (SMART4TB) Consortium, the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network, and the World Health Organization (WHO) Global TB Program (*Tuberculosis and pregnancy: Laying the groundwork for consensus on inclusion in research*).

* We have elected to use the phrase “pregnant women and persons” in acknowledgement that not all who become pregnant identify as women. We chose this approach as it underscores the experiences of women and the ongoing fight for gender equality and human rights, including those related to health and science, while being inclusive of other identities that share in these struggles. As we are all cisgendered women and men, we cannot speak for persons of childbearing potential that do not identify as women. But we hope this statement and our advocacy for the inclusion of pregnant women and persons in research benefits all individuals who can become pregnant, in all their diversity. We hope our statement catalyzes additional input from affected communities, especially community members that represent broader gender identities.

What follows is our consensus positions on how pregnant and breastfeeding women and persons should be included in TB research. These positions were informed by discussions held with scientists and clinicians and shaped by our lived experiences and the work we do in communities affected by TB. Our positions appear in bold with supporting rationale for each following. We end with a call to action and a commitment on our part to work together and with our communities to see these calls come to fruition.

It is our intention that these positions influence the discussions and recommendations that emerge from an ongoing scientific consensus process expected to inform a future WHO consensus statement on the earlier inclusion of pregnant women and persons in TB research.

1 ***TB remains a significant global health challenge, affecting hundreds of thousands of pregnant, postpartum, and breastfeeding women and persons. We demand nothing less than equitable health care that ensures the well-being of pregnant and breastfeeding women and persons affected by TB.***

Each year more than 200 million women and persons become pregnant. Estimates suggest that 216,500 of them are diagnosed with TB disease, increasing their risk of poor maternal and pregnancy outcomes, including mortality, miscarriage, pre-eclampsia/eclampsia, low birthweight, and premature birth.^{1,2} However, the true number of pregnant women and persons facing these risks is unknown because the WHO and other health agencies do not capture the data necessary to understand the magnitude of TB burden in pregnancy. Immune changes that occur during pregnancy make both pregnancy *and* the postpartum period a time when people — particularly those living in high TB burden settings — are at an increased risk of TB.^{3,4,5} Despite this known risk, pregnant women and persons have limited opportunities to participate in research or benefit from scientific advances.

2 Pregnant and breastfeeding women and persons have been historically excluded from clinical trials due to concerns about potential risks to the developing fetus or infant. We raise with concern that this exclusion has resulted in few evidence-based guidelines and treatment options available to pregnant and breastfeeding women and persons.

AND

3 We strongly believe that the exclusion of pregnant and breastfeeding women and persons from TB clinical research is not only a missed opportunity to improve the health outcomes of pregnant women and persons, the health outcomes of their infants, and public health as a whole, but it is also a violation of their basic human right to appropriate medical care and to enjoy the advancements of science. We argue this exclusion is rooted in misogyny and a form of sex-based discrimination.

The lack of data means pregnant and breastfeeding women and persons are often prescribed longer, more toxic, and less efficacious treatment regimens even as the standard of care for everyone else has improved. Or, in some cases, pregnant women and persons are counseled to abort their pregnancies. To be clear, we champion pregnant women and persons being counseled on *all* their options and having the autonomy to decide for themselves. However, when not otherwise medically indicated or acceptable to the individual, false dichotomies between receiving either an abortion or treatment may lead some pregnant women and persons to cease or refuse treatment entirely.

Studies to fill these critical data gaps are regularly deprioritized. Despite the higher risk of TB during pregnancy and the postpartum period, pregnant women and persons must wait decades between the introduction of a regimen and clinical trials on safety in pregnancy. An absence of data creates an absence of guidelines — forcing pregnant women and persons to make decisions using information from clinical trials in nonpregnant populations and expert opinion on how it translates to pregnant populations. In 2019, over 60 years from its initial introduction into TB programs, a randomized controlled trial revealed that prior assumptions about the safety of isoniazid preventive therapy (IPT) during pregnancy and the postpartum period were wrong. In fact, IPT *increased the risk* of adverse pregnancy outcomes, and postpartum women on IPT were more likely to experience liver toxicity.⁶

This existing status quo forces pregnant and postpartum women and persons to make decisions in the absence of data, unacceptably shifting the burden of risk onto individual women and persons who must decide what is best for themselves, their baby, and their families in the absence reliable information. All while simultaneously navigating guilt, shame, and stigma around their diagnosis.

It is critical that all those involved in TB research move toward the routine inclusion of pregnant and breastfeeding women and persons in research. Evidence-based guidelines and care practices depend on generating this data through research inclusion. Continued exclusion from research means that pregnant and postpartum women and persons will continue to be left behind by science, absorbing unknown risks to themselves and their children.

4 We acknowledge that respecting ethics and human rights is paramount when involving pregnant and breastfeeding women and persons in research, and we see pregnant and breastfeeding women and persons as key authorities in how ethics and human rights are maintained in the research setting. We agree that the following principles must be upheld:

- A commitment to **equity and reciprocity** in research is needed to overcome power imbalances between researchers, clinicians, and pregnant women and persons. Researchers must create equitable, mutually beneficial, and bidirectional relationships with pregnant and breastfeeding women and persons and their communities throughout research and beyond.
- **Participatory decision making** requires the direct and meaningful engagement of pregnant and breastfeeding women and persons in research decisions, especially those concerning their own exclusion from trials. Pregnant and breastfeeding women and persons are uniquely qualified to weigh the risks and benefits of research and enhance the relevance, acceptability, and impact of research through their contributions.
- **Intersectionality and cultural sensitivity** must inform all future research. Even between neighbors, experience, knowledge, and relationships with TB will differ. Researchers must build trials and programs that acknowledge, embrace, and address the unique needs, experiences, and realities of local communities and individuals.
- **Accessibility and flexibility** must be foundational to all research efforts to support pregnant and breastfeeding women and persons participation in their own care and in research. Researchers must consider the entire process of service delivery to communities participating in trials and integrate research with existing service delivery systems — meeting pregnant and breastfeeding women and persons where they are.
- The well-being, safety, privacy, and confidentiality of pregnant and breastfeeding women and persons and their choices must be prioritized and upheld through **integrity and robust informed consent** in research.
- The **autonomy** of individuals must be respected, with pregnant and breastfeeding women and persons centered as active collaborators in their own care and recognized as equal stakeholders in decision making.
- **Human rights** must be upheld and respected at each stage of the research process.

TREATMENT

5 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.

Pregnant and breastfeeding women and persons are currently left behind by science — relegated to older treatment regimens and excluded from trials of newer, shorter, and potentially safer or more efficacious regimens because of *potential* risks. Risks that would only be revealed through the research and surveillance from which they are currently excluded.

In the last two years, the standard of care for drug-resistant TB has been transformed by a shorter, all-oral regimen of new and repurposed drugs (BPaL/M: bedaquiline, pretomanid, linezolid, and moxifloxacin). BPaL/M represents a significant improvement over older, longer regimens featuring toxic medications, injectables, risk of permanent disability, and poor outcomes. Yet pregnant women and persons cannot benefit from access to BPaL/M because pretomanid remains unstudied during pregnancy.^{7,8}

6 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.

We acknowledge that the risks and benefits of each trial may differ significantly and should be considered individually. But researchers aim to conduct research in *ideal* scenarios while communities demand research that mirrors their *real* scenarios — including TB in pregnancy. And what researchers may consider risky based on imperfect animal models, pregnant women and persons may view as acceptable compared to the alternatives. The TB research field can only generate the data necessary to assess these risks by including pregnant and breastfeeding women and persons in research.

VACCINES

7 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 acknowledge that not all TB vaccine candidates, including some live or attenuated vaccines, will be appropriate for administering during pregnancy. However, TB research must move toward a model that assesses vaccine trial risks in pregnant women and persons on a candidate-by-candidate basis. There is little rationale to exclude pregnant women and persons from trials that leverage vaccine platforms (e.g., mRNA-based platforms) that have been successfully and safely administered during pregnancy in other disease areas. By excluding pregnant women and persons from *all* vaccine clinical trials due to fear of adverse events, we let fear dictate the research agenda. Pregnant and postpartum women and persons are at a higher risk of TB and deserve the chance of protection.

8 We recognize that vaccines are critical tools in TB prevention. The current failure to investigate vaccine safety in pregnancy during efficacy trials represents a missed opportunity to identify safe and effective vaccines to protect women and persons during pregnancy, the postpartum period, and/or beyond.

Pregnancy represents a period of regular and frequent engagement with the healthcare system, presenting multiple opportunities for preventative care. The inclusion of pregnant women and persons in vaccine clinical trials opens the door for vaccination during prenatal engagement with the health system, providing a critical opportunity to confer protection against TB. Depending on how long it takes for a vaccine to confer protection, some vaccines delivered during pregnancy will protect the pregnant women and persons and/or their child. Other vaccines given during pregnancy may protect women and persons during the postpartum period. And vaccines given postpartum may protect women and persons during their next pregnancy. Researchers should apply a holistic understanding of maternal immunization, encompassing distinct phases, when considering the inclusion of pregnant women and persons in vaccine clinical trials.

9 We believe that the risks to pregnant women and persons in vaccine clinical trials can be mitigated through earlier preclinical developmental and reproductive toxicology studies and clinical trial design that prioritize the safety of parent and child.

Earlier and more robust preclinical studies investigating vaccine safety during pregnancy in animal models are necessary to support the earlier inclusion of pregnant women and persons in vaccine trials. Collecting such data earlier may allow researchers and clinicians to build in additional protective mechanisms for pregnant clinical trial participants, enabling greater inclusion by minimizing unknowns. Further, potential trial participants that are pregnant will be better able to elect in or out of trials during the informed consent process when presented with data on potential risks from animal models and how researchers intend to monitor and mitigate against them during the clinical trial.

10 We strongly believe in each pregnant woman's and person's ability to gauge the risk of participating in clinical trials for vaccines when provided with necessary and complete information in an accessible and culturally appropriate form.

Current models of risk assessment for vaccines exclude the voices of pregnant and postpartum women and persons, neglecting to capture the real experiences that inform the health choices individuals make for themselves and their children. Further, failure to account for pregnant and postpartum women's and persons' concerns about vaccine candidates may undermine future vaccine acceptance and rollout. Vaccine developers and trialists must invest in supporting pregnant women's and persons' autonomy and ability to weigh context-specific risks of vaccines trials participation for themselves.

11 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.

Pregnant and breastfeeding women and persons are regularly grouped together because they represent specific biological experiences for women and persons who are childbearing and childrearing. While these states are related, breastfeeding women and persons should not be excluded from vaccine trials on the same grounds as pregnant women and persons.⁹ Breastfeeding women and persons and their children do not face the same risks as pregnant women and persons. By grouping them together in determining inclusion or exclusion in vaccine studies, researchers may be inadvertently denying parents, infants, and entire households potential protection from TB.

CALL TO ACTION

12 Continued failure to include pregnant and breastfeeding women and persons in the research agenda leaves pregnant and breastfeeding women and persons to shoulder the risks of older, untested treatments and without the prospect of protective immunity during pregnancy and the postpartum period through vaccination. We call on the following stakeholders to take immediate action:

- ➔ Policymakers, funding agencies, and regulatory bodies **must actively promote and support the inclusion of pregnant and breastfeeding women and persons in TB research.** This requires providing adequate resources, guidance, and training to researchers and product sponsors to address the specific needs and concerns of pregnant and breastfeeding women and persons.
- ➔ Researchers and product sponsors **must start with the assumed inclusion of pregnant and breastfeeding women and persons in clinical trials and justify any exclusions.** Exclusions should be based on clear rationale developed in consultation with pregnant women and persons and with their explicit support.
- ➔ Researchers and product sponsors **must protect pregnant and breastfeeding women and persons by normalizing their inclusion in phase III studies. Preclinical developmental and reproductive toxicology studies must be conducted earlier in the research process** (no later than Phase IIb) to achieve this.
- ➔ National programs **must collect and analyze data on TB in women and persons who are pregnant.** Multiple approaches, including sentinel sites, prospective cohorts, and birth outcomes surveillance studies are urgently needed to understand the safety of existing and future TB drugs in pregnancy.
- ➔ Researchers, product sponsors, and policymakers **must recognize that safety concerns differ for pregnant versus breastfeeding women and persons. Research inclusion, data, and policies should therefore be considered separately.**
- ➔ Research and product sponsors and other relevant stakeholders **must involve pregnant and breastfeeding women and persons and communities directly affected by TB in the entire research process, from preclinical to clinical studies, to design and distribution of innovations.** Pregnant and breastfeeding women and persons are uniquely situated to assess the risks and benefits of research that will affect them and can provide integral feedback to support the success of the trial and resulting policies.
- ➔ Research and product sponsors and national programs **must share information about treatments, vaccines, and the research process with the community before research begins and throughout the research process** in an accessible, simplified language so they can provide input into the research process and make informed decisions about their health and participation.
- ➔ **Acting on these recommendations will accelerate progress toward developing evidence-based interventions for and improved health outcomes among pregnant, postpartum, and breastfeeding women and persons that are affected by TB. We invite you to join us in rejecting the status quo and building a future in which pregnant women and persons have access to the full suite of scientific and health advancements.**

ENDNOTES

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