OVERDUE: Including pregnant & lactating participants in TB research

20 June 2024

Webinar presented by SMART4TB
A history of exclusion, a future of inclusion, and why it matters

20 June 2024

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Assistant Director of Policy & Community Engagement
For first-line TB drugs, what was the average lag time between when the drugs were approved by the U.S. Food and Drug Administration and when the first pharmacokinetic data were available in pregnant women?
Lag time between FDA approval and PK data in pregnancy

Years after FDA approval

- RIF
- INH
- PZA
- EMB

53 years!
The unjust reality for pregnant and breastfeeding women

Considered as one homogenous group

De facto excluded from clinical trials

And when they get sick…

Must make medical decisions in the absence of data
Risk of TB during pregnancy

Bad for mom...
- 4-fold increased **maternal mortality**
- 3-fold increase **morbidity**
- 10-fold increased **hospitalization**
- 4-fold increase **anemia**
- 2-fold increase **cesarean**
- 9-fold increase **miscarriage**

Bad for baby...
- 4-fold increased **perinatal death**
- 2-fold increase **low birth weight**
- 2-fold increased **preterm birth**
- 2-fold increase **acute fetal distress**
- 5-fold increase **birth asphyxia**

Source: Sobhy BJOG 2017
Why have pregnant and breastfeeding women been excluded from research?

Factors That Dissuade Sponsors and Investigators from Including Pregnant and Lactating Women in Research

The exclusion of pregnant and lactating women from clinical research is often attributed to legal liability. However, available evidence demonstrates that such liability is limited, suggesting that perceptions of liability may be more influential than real liability. Six additional dissuasive factors face individuals and organizations involved in the development, testing, oversight, approval, and marketing of medications and vaccines. These factors are sometimes termed liabilities even though they involve no legal risk because they are considered in the aggregate along with real and perceived liability. Many of the factors overlap, interact with, and affect one another; thus, mitigation strategies must take the relationships into account.

- **A Culture of Exclusion**: Systematic underfunding of women’s health research
- **Challenges with Recruitment and Enrollment**: Inadequate resources for investigators and research participants to recruit or enroll in studies
- **Lack of Research Expertise**: Limited number of trained investigators with expertise conducting research with pregnant and lactating women
- **Cost and Complexity**: Unwillingness to invest time and resources to properly conduct studies with pregnant and lactating women
- **Reputational Risk**: Concerns for negative publicity
- **Lack of Financial Incentives**: Insufficient financial return on investment for additional research

Learn more and read the full report at nationalacademies.org/liability-study.
A decade of progress, after 75 years of none…

First TB drugs approved 1950-70s
HIV vertical transmission trials Early 1990s
NIH expert panel consensus statement on earlier inclusion 2013
Launch of WHO/SMART4TB consensus process for TB 2018-19
Results of first trials looking at INH safety in pregnancy 2017
Launch of PHASES Project 2018-19
Community perspective on inclusion published 2017
Launch of first DR-TB trial enrolling pregnant women 2022
Community consensus statement on inclusion 2023
National Academies Report 2024

Pandemic interruption: 98% of COVID-19 vaccine trials and 71% of treatment trials excluded pregnant women* 

* Kons Women’s Health Issues 2022
How many of the planned and ongoing TB vaccine trials are allowing enrollment of pregnant and breastfeeding women?
True or False? The new 6-month BPaL[M] regimen is recommended for pregnant women with Drug-resistant TB.
(Among the) last to benefit from scientific progress

**False!**

BPaL[M] is **NOT** recommended for pregnant and lactating women

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<tr>
<th></th>
<th>Non-pregnant adult</th>
<th>Pregnant adult</th>
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<tr>
<td><strong>TB prevention</strong></td>
<td>1-3 months</td>
<td>6-12 months</td>
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<tr>
<td><strong>Drug-susceptible TB</strong></td>
<td>4-6 months</td>
<td>6 months</td>
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<tr>
<td><strong>Drug-resistant TB</strong></td>
<td>6-9 months</td>
<td>9-20 months</td>
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Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination
WHO-led process to reach consensus on earlier inclusion


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 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.
Take home messages

- TB disease during pregnancy and postpartum is HIGH RISK. NOT being treated is not an option.
- In the absence of research, healthcare decisions must be made with LITTLE TO NO data on dosage, safety, and efficacy.
- Ethical inclusion in research demands careful consideration of the risks AND BENEFITS to fetus and mother.
- Pregnant and lactating women have a HUMAN RIGHT to benefit from scientific progress—including shorter, safer regimens.
Panel discussion

Busisiwe Beko, TB Survivor & Advocate
Edna Tembo, Coalition of Women Living with HIV/AIDS
Oxana Rucsineanu, Global TB CAB
Edna’s story
Busisiwe’s story

My honorable TB scars
Busisiwe ‘Buci’ Beko
Busisiwe’s story

Scars of one disease in two bodies

• I went for pregnancy test
• Tested for HIV positive
• Became sick, tested TB and diagnosed with drug-sensitive TB and after 5 months found that it was drug-resistant TB. I was terrified, especially when they told me in the clinic that my “close contacts” were also at risk. It does not get any closer than sharing the same body, after all, and although I was coughing and losing weight, I was afraid for what might happen to my child that preoccupied me most of all. How will the TB/HIV affect her? Will she get it too? Will the tablets that I was taking to try save my life end up hurting hers?
Busisiwe’s story

Planning for me, not with me

Terminate

Termination of pregnancy is still a taboo in some cultures and in most instances not communicated well but decided as only option.

Not exploring of emotions, values and norms.

In some instances, the day that a person feels pregnant, there is excitement and feeling proud as I also felt that my body was designed to nourish, protect and grow baby in my belly.
Busisiwe’s story

Is it a crime to be diagnosed with TB while you’re pregnant?

• Although there are more than 10 million people sick with TB every year, and thus I certainly was not the first or only woman trying to figure out how to manage the two very different “passengers” whom one badly wanted the other most, with whom I was sharing my physical form. I found out nobody in the clinic could answer any questions for me. Fragmented into “adult” and “paediatric” world as TB services are, there was nowhere I could turn.

• I felt guilty, and the things they were telling me in the clinic made me feel that way even more—since people with TB are often treated like nothing more than the vehicle of infection.
Busisiwe’s story

Family matters

• My daughter was unfortunately diagnosed with Drug-resistant TB when she was five months old and things became more difficult.
• Not only did I have my own health needs, but I also had to look after her needs. Although we both did our best, she did not cope well with treatment as sometimes she became like a zombie and struggled so much.
Busisiwe’s story

Our treatment journey

- To get care for her and me was a struggle, queues, sent from post to pillar, even when we finally saw the health staff, they were not equipped to deal with her as a child, me as a mother, and us as a family.

- The tablets she had to take did not come in child-friendly version: they were so painful to swallow. I found them nearly impossible to prepare (how to measure out $\frac{3}{4}$ of a tablet?) and give her, and feared I was likely under-dosing or overdosing her. I felt like I was set up to fail.

- We fought hard and both we survived.
What can the research community do?

• There is room for improvement through lessons learned;
• Recognise, appreciate, and embrace that communities are experts of their own care;
• Include pregnant people in TB research;
• Involve TB survivors in design, implementation, and execution of research and public health activities through community engagements with other multi-sectoral action teams; and
• Nothing about us without us.
Oxana’s story

Îmi doresc un viitor fără TB

David, 11 ani

Îmi place să fiu un învingător. Îmi doresc ca toată lumea să învingă tuberculoza

Ilie, 8 ani

#UNGATB #STOPTB #Ourfuture #EndTB
How we built consensus

Community perspectives on inclusion

Community call to action

• Policymakers, funding agencies, and regulatory bodies must actively promote and support the inclusion of pregnant and breastfeeding women and persons in TB research.
• Researchers and product sponsors must start with the assumed inclusion of pregnant and breastfeeding women and persons in clinical trials and justify any exclusions.
• 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.
• National programs must collect and analyze data on TB in women and persons who are pregnant.
• Researchers, product sponsors, and policymakers must recognize that safety concerns differ for pregnant versus breastfeeding women and persons. Research inclusion, data, and polices 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.
• 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.
World Health Organization Pregnancy Consensus Advocacy Group

The Advocacy group is one of the five groups convening at the WHO level on a regular basis (Preclinical, Vaccine, Treatment, Surveillance and Advocacy TWGs).

Goal - build consensus amongst stakeholders on finding ways to include pregnant women in research.

Monthly meetings between March and October 2024 with shared key takeaways among the members.

Several cross-cutting questions appear throughout the group’s discussions calling for collaboration across the groups.
Sharing knowledge about global efforts to change the practice at country levels
Key Lessons

Voice the impact in lives of women who get TB in pregnancy and lactation and how lack of research impacts the care.

Make stakeholders aware that there is an unrecognized issue and keep the issue high on the agenda.

Share clear messages to mobilize stakeholders, communities and advocates to be on our side.

Call for CHANGE IN PRACTICE (earlier inclusion of pregnant women and persons in TB research).

Advocate on the ground and share the news and knowledge.
SMART4TB’s approach to inclusion of pregnant and lactating populations

Nicole Salazar-Austin, MD
Assistant Professor of Pediatrics
Johns Hopkins School of Medicine
Do as we say and not as we’ve done in the past…

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<th>HISTORICAL APPROACH</th>
<th>SMART4TB’S APPROACH</th>
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<td>De facto exclude pregnant and breastfeeding women</td>
<td>Carefully weighed the risk/benefit for different contexts (e.g., between RR-TB treatment and prevention)</td>
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<td>Lump pregnant and breastfeeding women together</td>
<td>Considered pregnant and lactating populations separately, and each trimester of pregnancy individually</td>
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<td>No pregnancy/lactation experts consulted or involved</td>
<td>Included pregnancy, pediatric, and lactation experts on study teams</td>
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<td>Lack of experience of sites used as justification for exclusion</td>
<td>Ability and experience enrolling pregnant women was considered when selecting sites</td>
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Weighing Risk and Benefit

- Weigh risk/benefit for both mother and fetus/infant
  - Preclinical data without significant signal
  - Clinical data from trials and observational cohorts
- Absent standard of care necessitates value judgements
- Informed consent is critical
  - Acknowledge risk, benefit and the unknown
  - Separate forms for consenting and reconsenting incident pregnancy (embrace complexity)
Selection of Control Regimen

- Differing/non-existent guidelines for pregnant women may require a different control or the exclusion of that group
  - Lack of evidence for the 3HP/1HP control
  - Planned inclusion pending data from DOLPHIN Moms (NCT05122026)
- Historic exclusion being used as a reason to impede their inclusion in future research—this cycle needs to be broken
BREACH: a one-month BDQ for pan-TB prevention

Consider Pregnancy & Lactation Separately

- BDQ’s has a long half life and is concentrated in breast milk
- Limited data suggest breastfeeding infants may have therapeutic BDQ levels (n=1)
- Breastfeeding infants cannot safely receive BDQ for TB prevention without further understanding BDQ levels in breast milk and infants
Inclusion raises (surmountable) trial design challenges

Randomization
• Can you randomize a mother and follow their infant for outcomes?
• Randomize a “mother-infant pair” (e.g., PMTCT Trials)

Schedule of Events
• The inclusion of pregnant and lactating women will add complexity
• Pharmacokinetic sampling must consider steady state, but also trimester of pregnancy
• Added visit around delivery for pregnancy outcomes
• Added evaluations – baseline ultrasound to exclude fetal anomalies

Pregnancy Experts
• Clear communication of roles and responsibilities on the protocol team
Q&A
To get the latest updates, keep up with SMART4TB