

# OVERDUE: Including pregnant & lactating participants in TB research

20 June 2024

Webinar presented by SMART4TB



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# A history of exclusion, a future of inclusion, and why it matters

20 June 2024

**Madlen Nash, MSc**  
**Assistant Director of Policy & Community**  
**Engagement**



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



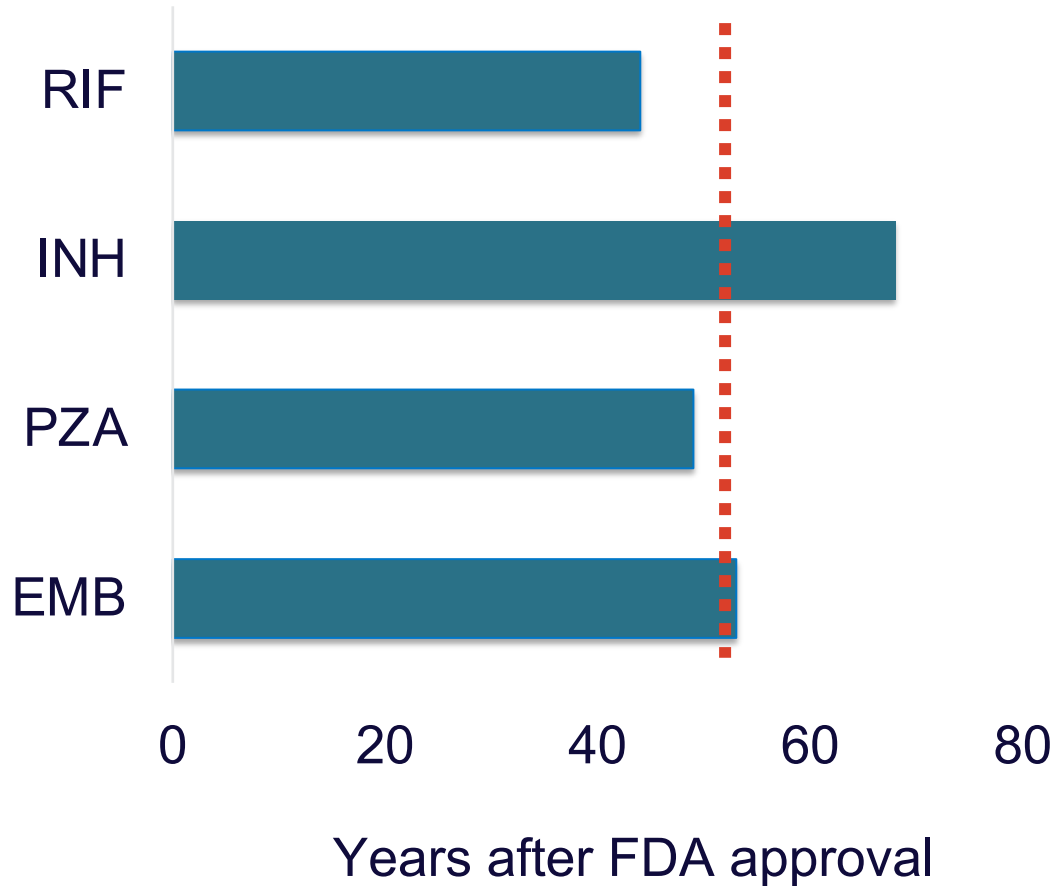
# slido



**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?**

ⓘ Start presenting to display the poll results on this slide.

# Lag time between FDA approval and PK data in pregnancy



**53**  
**years!**



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# 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**



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# 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**



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# Why have pregnant and breastfeeding women been excluded from research?



## 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



## REPUTATIONAL RISK

concerns for negative publicity



## COST AND COMPLEXITY

unwillingness to invest time and resources to properly conduct studies with pregnant and lactating women



## LACK OF FINANCIAL INCENTIVES

insufficient financial return on investment for additional research



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# A decade of progress, after 75 years of no

First TB drugs approved 1950-70s  
HIV vertical transmission trials Early 1990s

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

NIH expert panel consensus  
statement on earlier inclusion

**2013**

Launch of PHASES Project

**2017**

**2018-19**

Community perspective on  
inclusion published

Results of first trials looking  
at INH safety in pregnancy

**2022**

**2019**

Launch of first DR-TB trial enrolling  
pregnant women

**2021**

Launch of WHO/SMART4TB  
consensus process for TB

**2023**

Community consensus  
statement on inclusion

**2024**

National  
Academies  
Report



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



\* Kons Women's Health Issues 2022



# slido



**How many of the planned and ongoing TB vaccine trials are allowing enrollment of pregnant and breastfeeding women?**

ⓘ Start presenting to display the poll results on this slide.



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



slido



**True or False? The new 6-month BPaL[M] regimen is recommended for pregnant women with Drug-resistant TB**

① Start presenting to display the poll results on this slide.

# (Among the) last to benefit from scientific progress

## Treatment duration

# False!

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

	Non-pregnant adult	Pregnant adult
TB prevention	1-3 months	6-12 months
Drug-susceptible TB	4-6 months	6 months
Drug-resistant TB	6-9 months	9-20 months

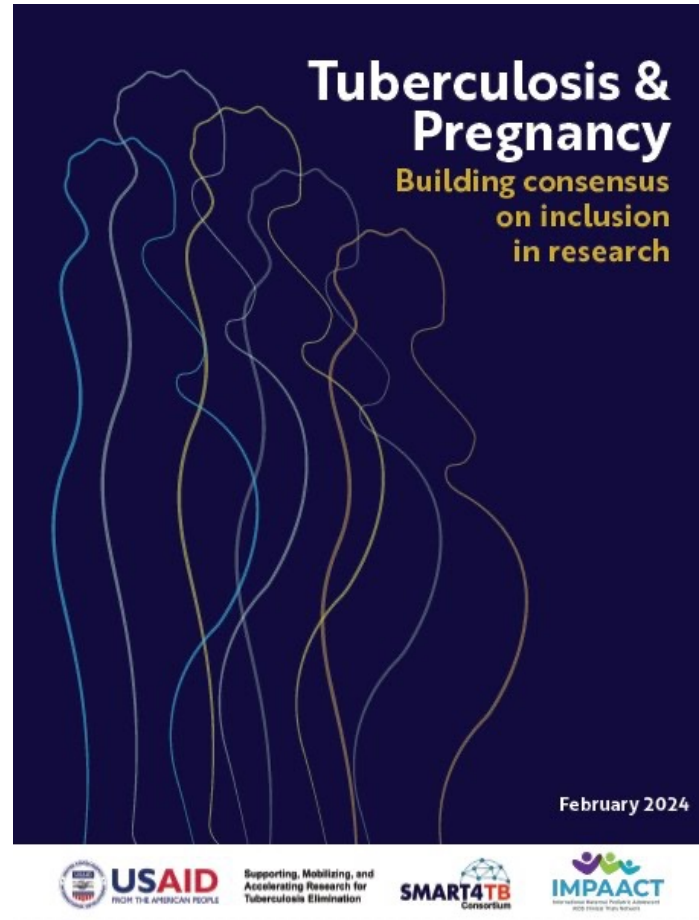
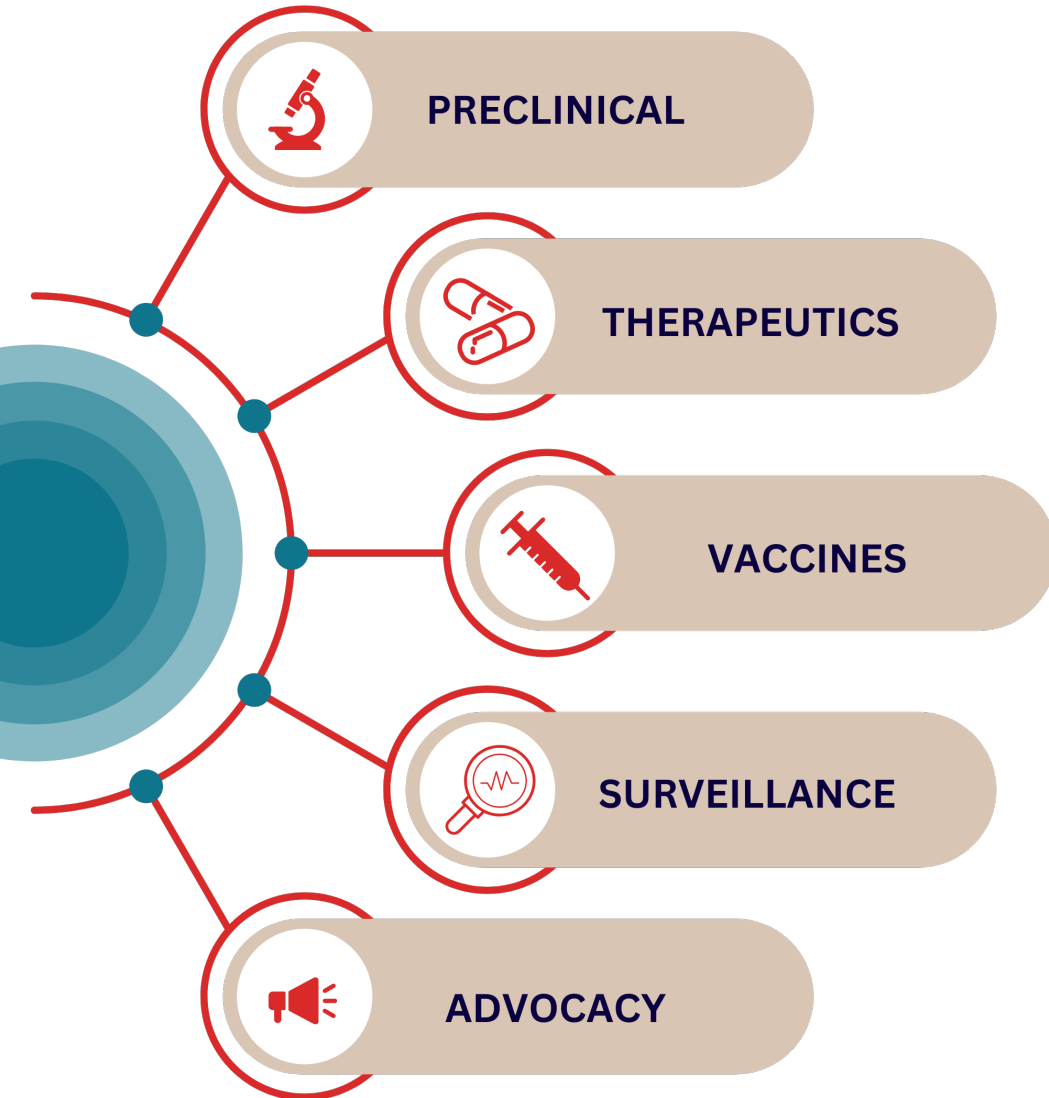


**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# WHO-led process to reach consensus on earlier inclusion



PREGNANCY CONSENSUS STATEMENT FEBRUARY 2024

USAID FROM THE AMERICAN PEOPLE  
Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination

SMART4TB Consortium

## 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 (IMPACT) 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.

1



Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination



# 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



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# Panel discussion

**Busisiwe Beko, TB Survivor & Advocate**

**Edna Tembo, Coalition of Women Living with HIV/AIDS**

**Oxana Rucsineanu, Global TB CAB**

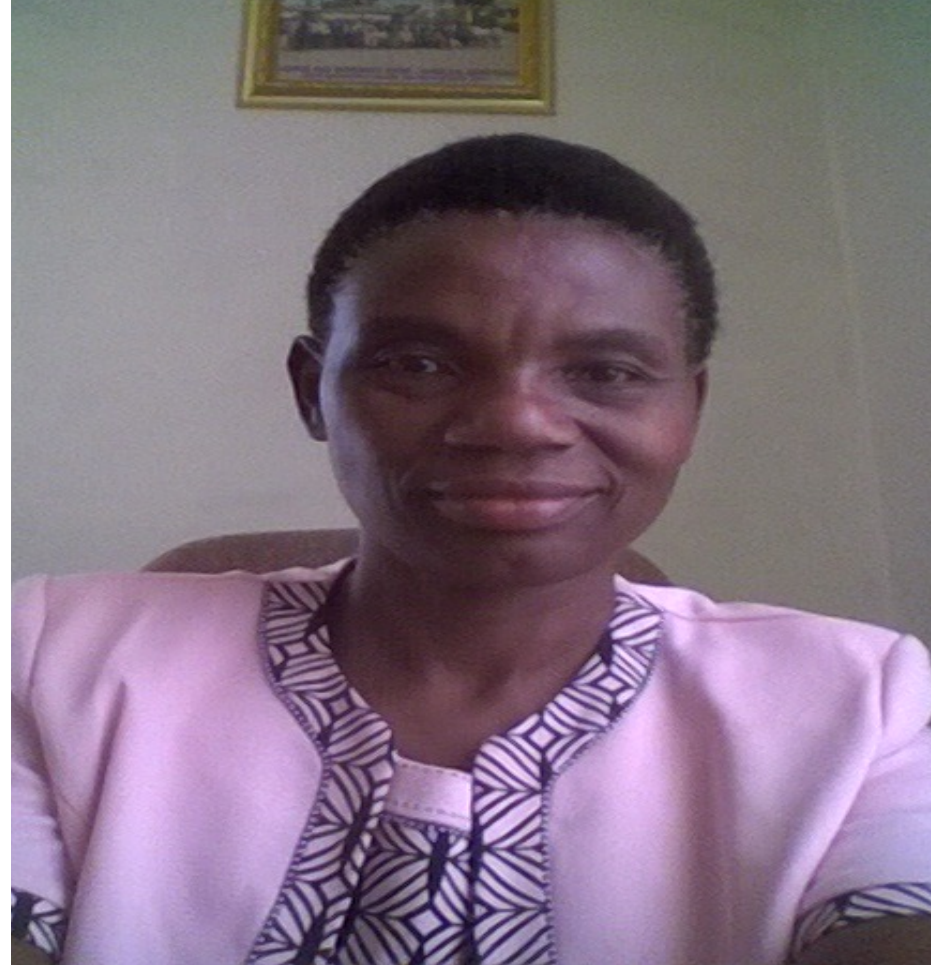


**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# Edna's story



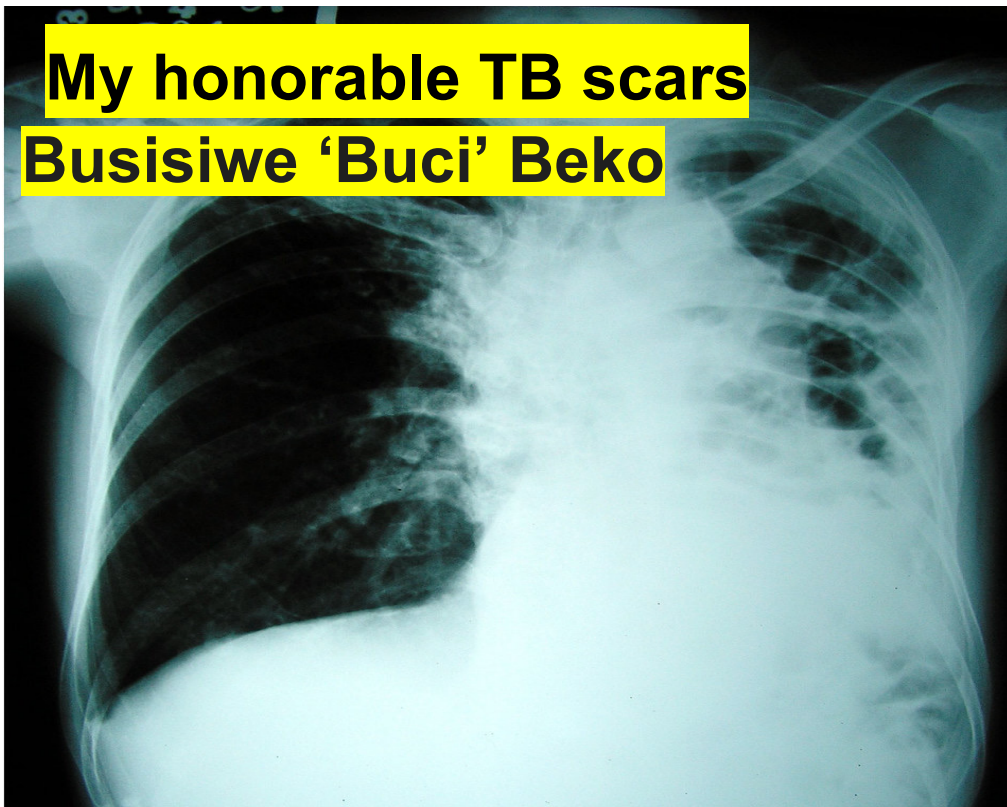
**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination





# Busisiwe's story



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# 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?



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# 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.



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# 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.



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# 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.



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# 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.



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# 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.



Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# Oxana's story



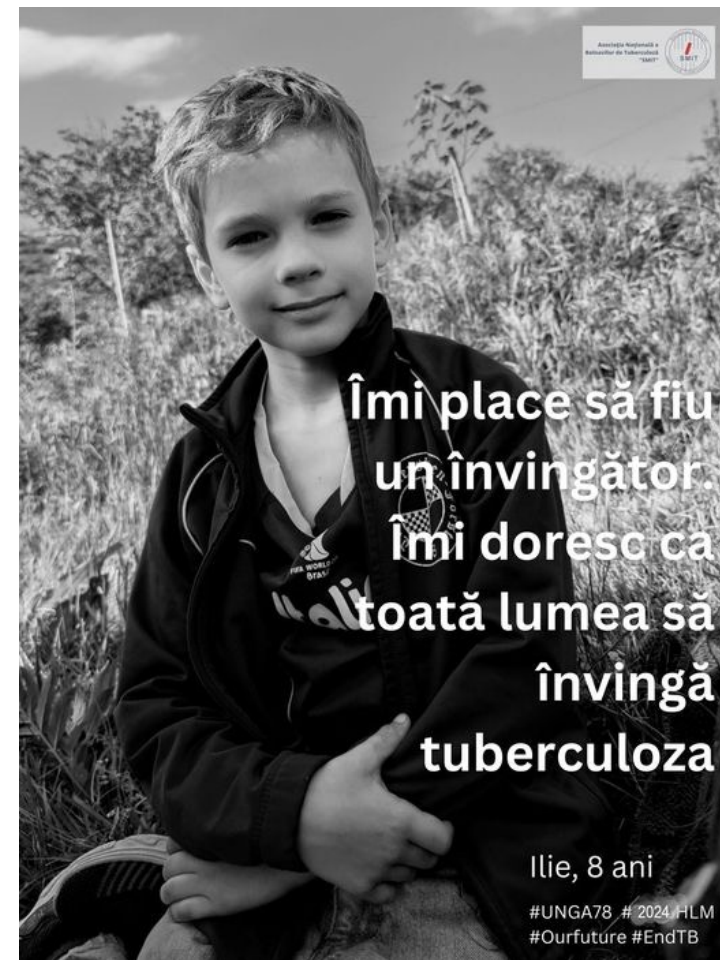
**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination





# Oxana's story



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# How we built consensus

## Community perspectives on inclusion



PREGNANCY CONSENSUS STATEMENT FEBRUARY 2024



Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination



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



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination



# 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 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.
- 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.



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# 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



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# Sharing knowledge about global efforts to change the practice at country levels



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# 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



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# SMART4TB's approach to inclusion of pregnant and lactating populations

**Nicole Salazar-Austin, MD**  
**Assistant Professor of Pediatrics**  
**Johns Hopkins School of Medicine**











**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# Do as we say and not as we've done in the past...

HISTORICAL APPROACH	SMART4TB'S APPROACH
 <p data-bbox="463 431 1039 525"><b>De facto exclude pregnant and breastfeeding women</b></p>	<p data-bbox="1286 402 1974 545"><b>Carefully weighed the risk/benefit for different contexts (e.g., between RR-TB treatment and prevention)</b></p> 
 <p data-bbox="438 631 1065 725"><b>Lump pregnant and breastfeeding women together</b></p>	<p data-bbox="1304 611 1956 759"><b>Considered pregnant and lactating populations separately, and each trimester of pregnancy individually</b></p> 
 <p data-bbox="463 825 1039 916"><b>No pregnancy/lactation experts consulted or involved</b></p>	<p data-bbox="1304 825 1956 916"><b>Included pregnancy, pediatric, and lactation experts on study teams</b></p> 
 <p data-bbox="438 1016 1039 1110"><b>Lack of experience of sites used as justification for exclusion</b></p>	<p data-bbox="1319 988 1941 1139"><b>Ability and experience enrolling pregnant women was considered when selecting sites</b></p> 



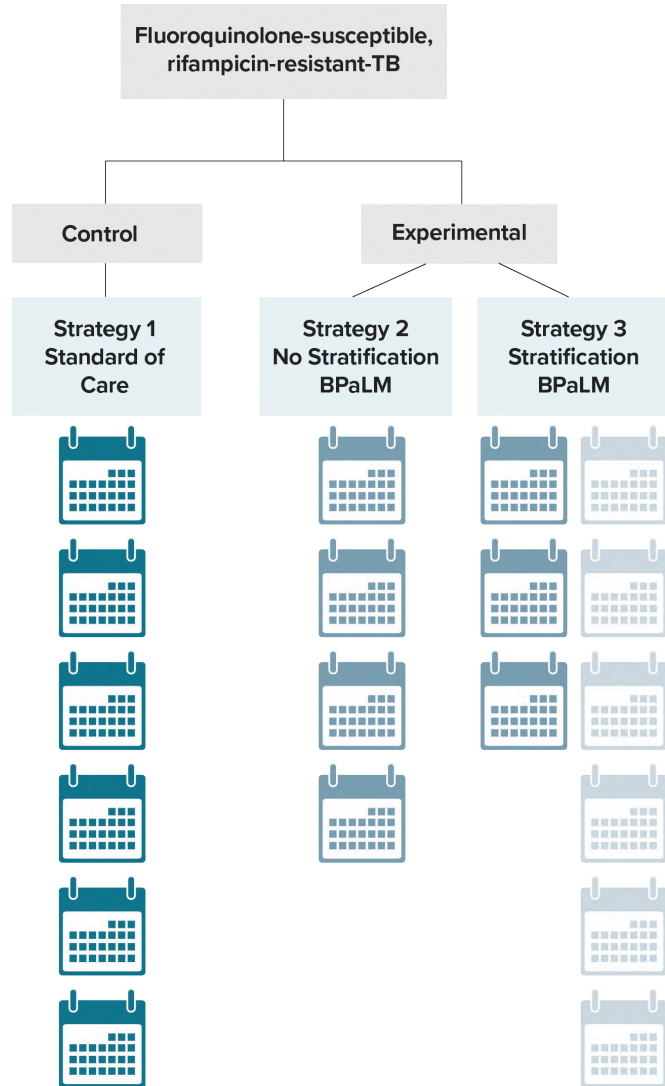
**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination





# PRISM: stratified medicine for adolescents and adults with RR-TB



B=bedaquiline, Pa=pretomanid, L=linezolid, M= moxifloxacin

## 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)

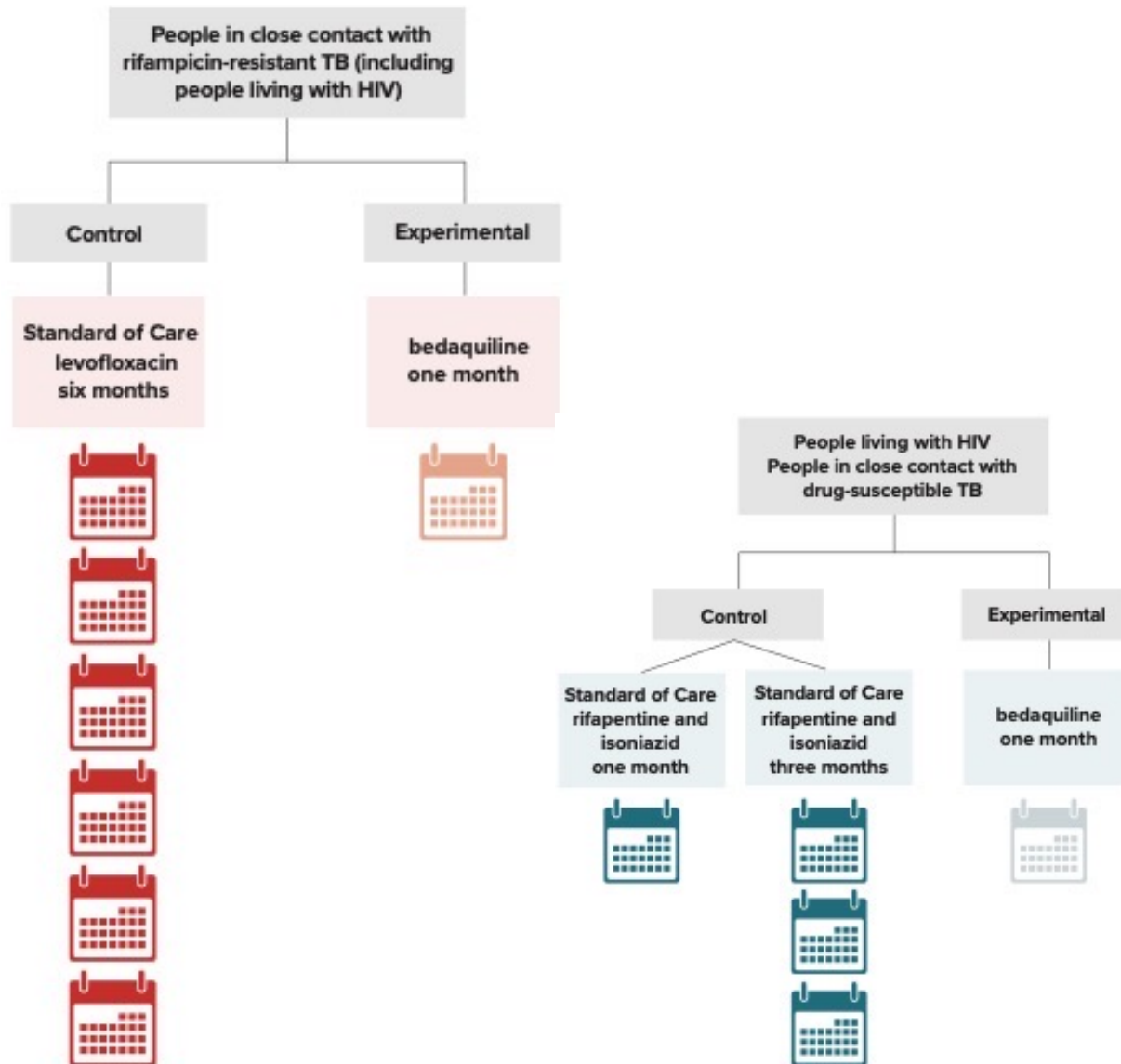


**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# BREACH: a one-month BDQ for pan-TB prevention



## 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

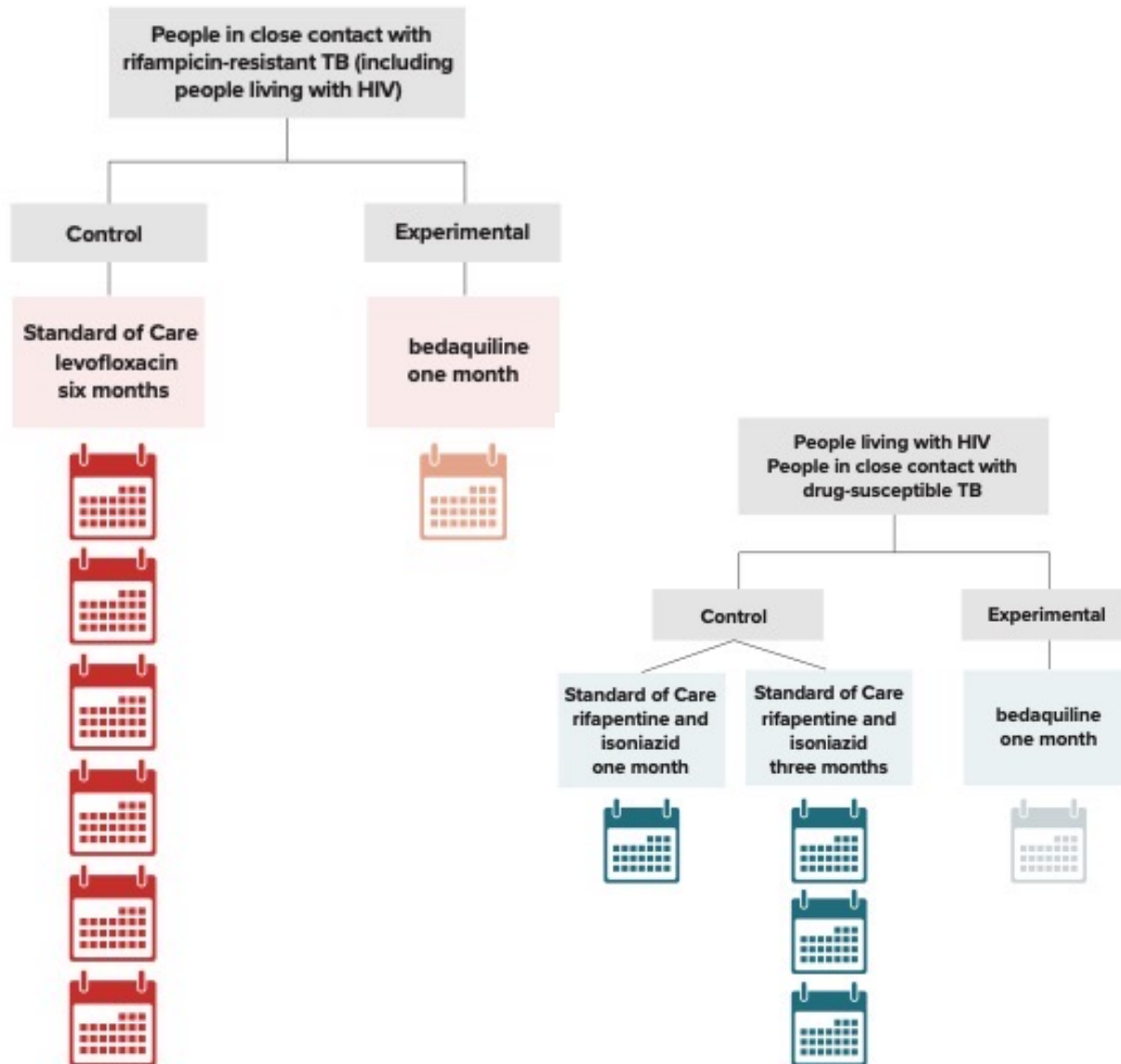


**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# 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



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# Q&A

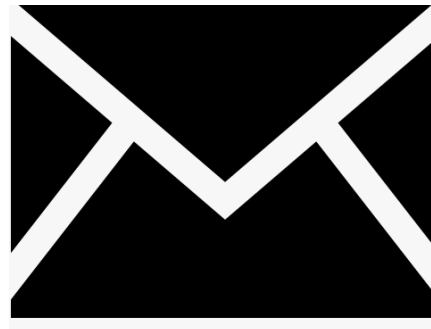
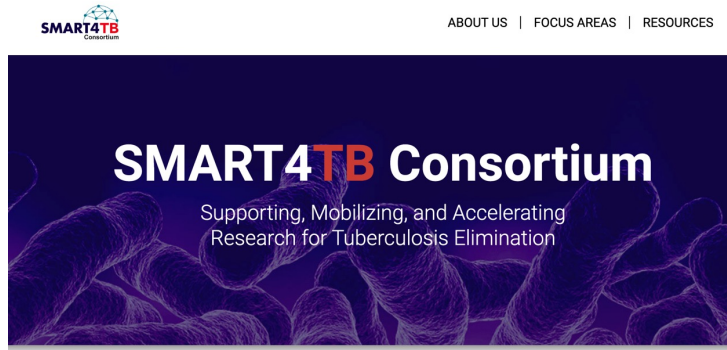


**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



# To get the latest updates, keep up with SMART4TB



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination



*SMART4TB is made possible by the generous support of the American people through the United States Agency for International Development (USAID) and is implemented under cooperative agreement number 7200AA20CA00005. The consortium is managed by prime recipient, Johns Hopkins University.*

# Thank you!



**USAID**  
FROM THE AMERICAN PEOPLE

Supporting, Mobilizing, and  
Accelerating Research for  
Tuberculosis Elimination

