The Union

Paris, November 15–18

WORLD CONFERENCE ON LUNG HEALTH 2023

TRANSFORMING EVIDENCE INTO PRACTICE

CONFLICT OF INTEREST DISCLOSURE FORM

X I have no Conflict of Interest to report.

☐ I have the following Conflict of Interest(s) to report:

Please tick the type of affiliation / financial interest and specify the name of the organisation:

☐ Receipt of grants/research supports: _____
☐ Receipt of honoraria or consultation fees: _____
☐ Participation in a company sponsored speaker's bureau: _____
☐ Tobacco-industry and tobacco corporate affiliate: _____
☐ Stock shareholder: _____
☐ Spouse/partner: _____
☐ Other: _____

RESEARCH ON TB DURING PREGNANCY AND THE POST-PARTUM PERIOD

Dr Jennifer Hughes, Desmond Tutu TB Centre, Stellenbosch University

Child and Adolescent TB Working Group Meeting, Paris, 14 Nov 2023

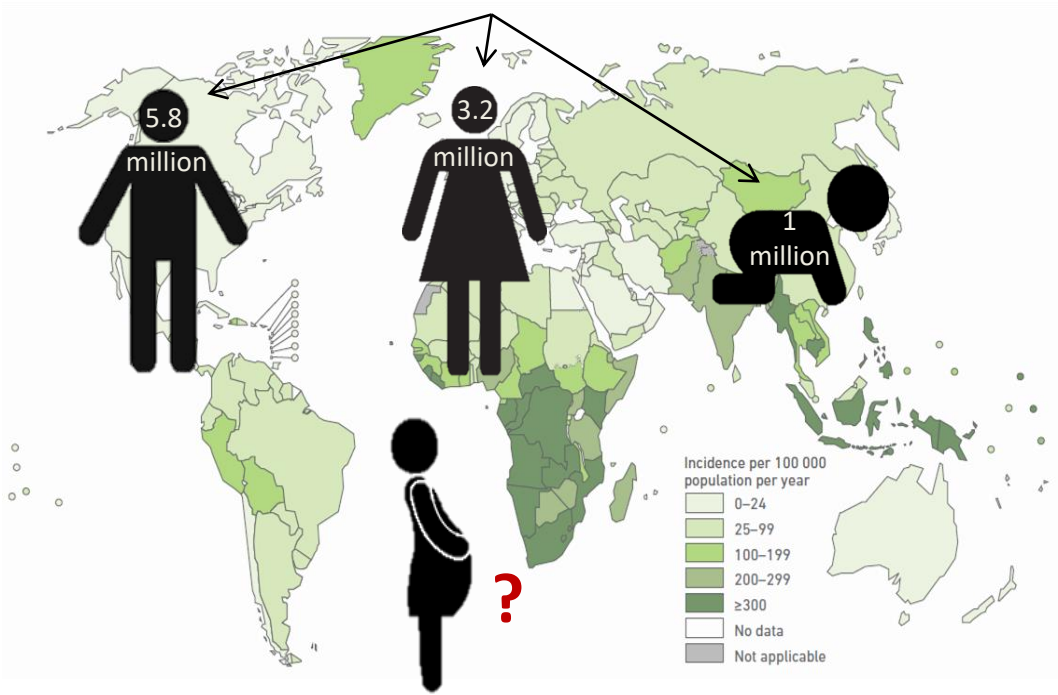
TB PREVALENCE

TB burden during pregnancy is likely high but not well quantified

RR/MDR-TB ????

Urgent need for better (or any!) surveillance and reporting of TB / RR-TB in pregnancy and vice versa

10.6 million new diagnoses of active TB



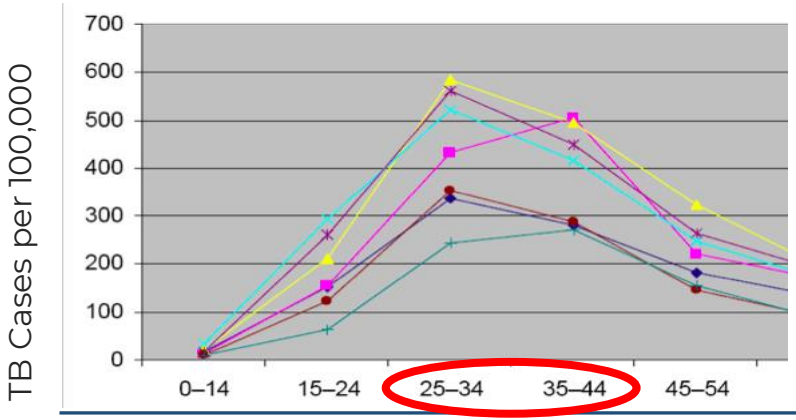
Est. 216,500 people had TB during pregnancy in 2014

Sugarman, et al. Tuberculosis in pregnancy: an estimate of the global burden of disease. Lancet Glob Health 2014;2(12): e710–6.

TB INCIDENCE PEAKS DURING REPRODUCTIVE AGES, IRRESPECTIVE OF HIV STATUS

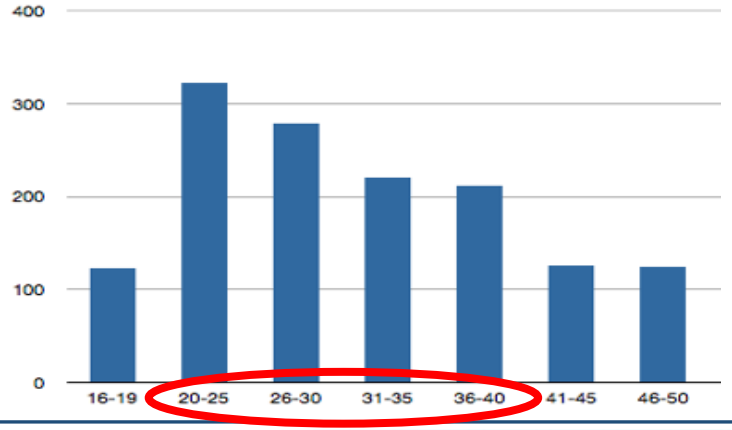
Women in sub-Saharan Africa

Deluca JAIDS 2009



Women in India

RNTCP Gender differentials in TB control 2004



Slide, courtesy, Amita Gupta

PREGNANCY OUTCOMES ASSOCIATED WITH TB

Mortality* **4-fold**

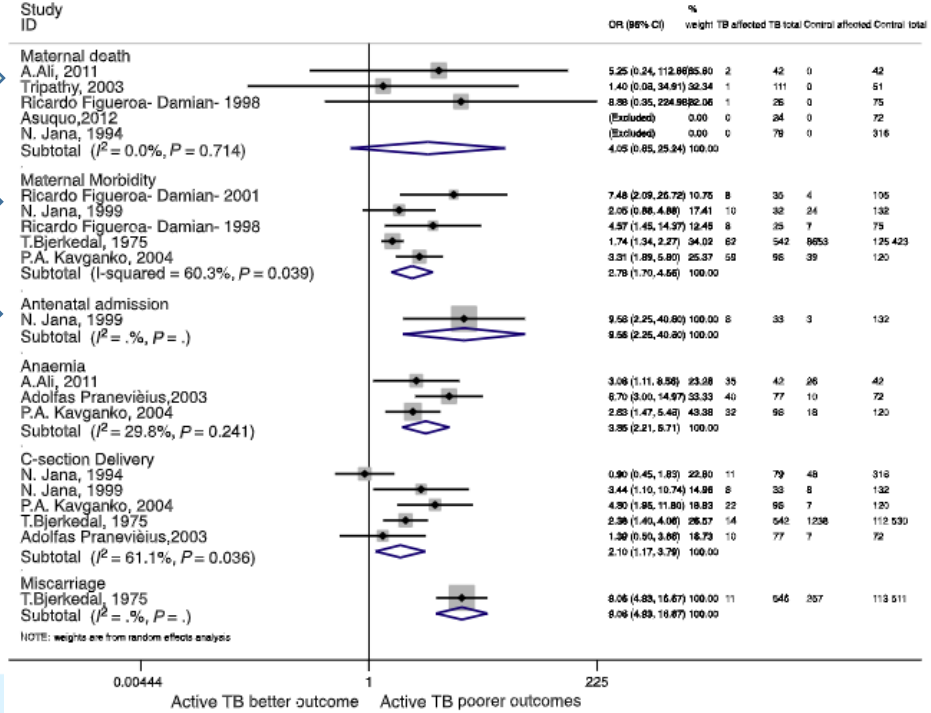
Morbidity **3-fold**

Hospitalization **10-fold**

Anemia **4-fold**

C-section **2-fold**

Miscarriage **9-fold**



Systematic review and meta-analysis:

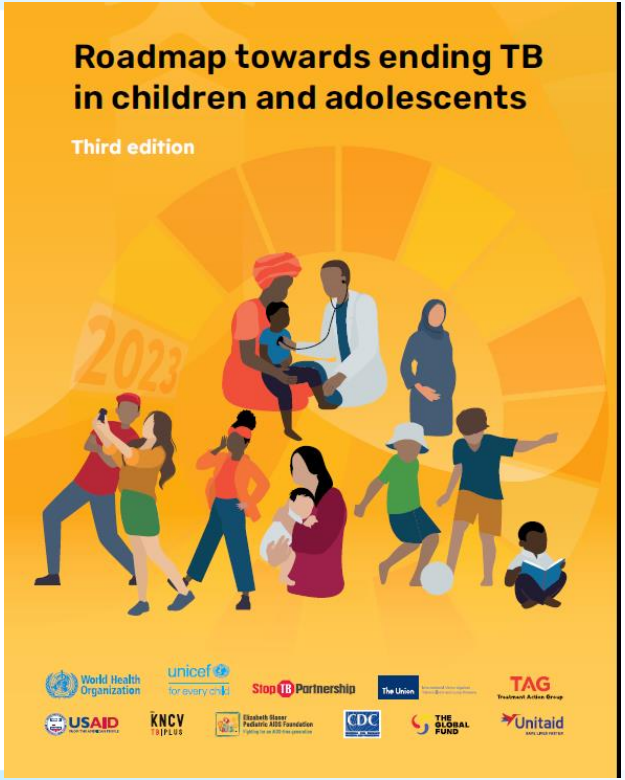
3,384 pregnancies **with active TB**

and

119,448 pregnancies **without TB**

Sobhy BJOG 2017

*not significant



KEY ACTION 10

Support TB R&D and innovation focused on children, adolescents, pregnant and post-partum women

Evidence gaps and required studies.

Gaps	Studies needed
Prevention	Randomised controlled trials to establish the safety and optimal timing of preventive therapy regimens in pregnancy and/or post-partum Pharmacokinetic and safety studies to establish appropriate dosing for pregnant women and neonates receiving preventive therapy Data on the efficacy of different contraceptive options, and programmatic data on contraceptive coverage among women of reproductive age receiving TB treatment
Detection	Operational research on the performance of different screening and diagnostic algorithms in diverse settings Evaluation of diagnostic tests for disease and infection in pregnancy Prevalence data from screening studies in antenatal care in diverse settings Routine TB surveillance data recording pregnancy status
Treatment	Pharmacokinetic studies to establish appropriate doses for treatment of disease in pregnant women and neonates Prospective cohort studies and randomised controlled trials of the safety of second-line TB drugs during pregnancy, including in the first trimester

Mini-Symposium: Tuberculosis

Tuberculosis in pregnant women and neonates: A meta-review of current evidence

K.J. Snow[a,b,c,*], A. Bekker[d], G.K. Huang[e], S.M. Graham[a,e,f]

Paediatric Respiratory Reviews 36 (2020) 27–32

Consequences of sub-optimal TB / RR-TB treatment during pregnancy

- parent – individual and community
- foetus / infant – safety and exposure

WHO RR-TB TREATMENT GUIDANCE, 2022

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB and pre-XDR-TB (a)

1.1 WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients.

(Conditional recommendation, very low certainty of evidence)

2. The 9-month all-oral regimen for MDR/RR-TB (a)

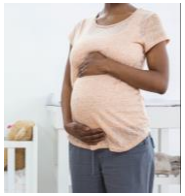
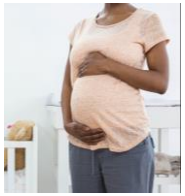
2.1 WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.

(Conditional recommendation, very low certainty of evidence)

3. Longer regimens for MDR/RR-TB (b)

3.1 In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.

(Conditional recommendation, very low certainty of evidence)

	Group A: BDQ / LZD / FLQ Other: **Pretomanid**
	Group A: BDQ / LZD / FLQ Group B: CFZ Group C: PZA / EMB Other: high dose INH
	Group A: BDQ / LZD / FLQ Group B: CFZ / CS Group C: *(if options are limited)*

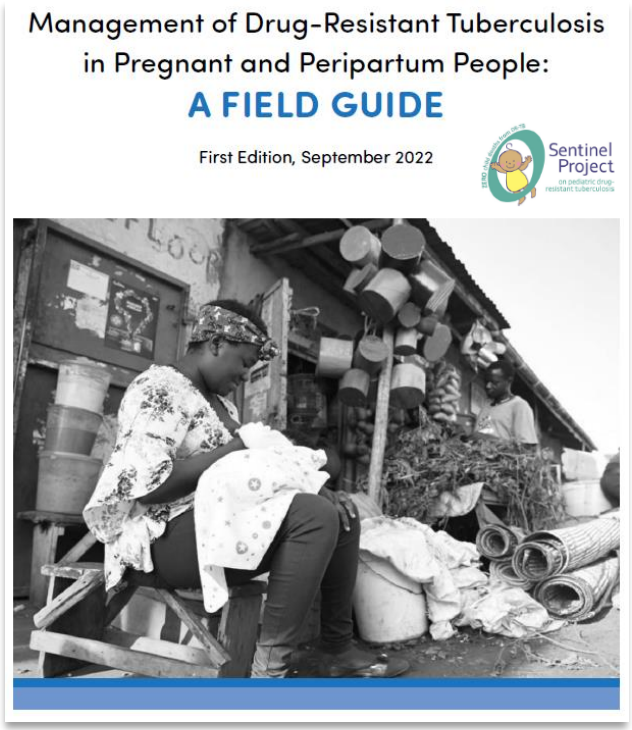


Table 2: Best Clinical Practices for Using Second-Line Medications in Pregnancy

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

EXISTING PERI-PARTUM PK DATA FOR WHO GROUPS A & B DRUGS

WHO Group Drug Name	Group **A** Fluoroquinolones	Group **A** Bedaquiline	Group **A** Linezolid	Group **B** Clofazimine	Group **B** Terizidone
During pregnancy	Moxi: ♀ (n=1) *PK at 2T and 3T* *Van Kampenhout 2017*	♀♀♀♀♀♀♀♀♀♀♀♀♀ (n=13) *PK at ≥ 28 wks* *Court 2022*	♀ (n=1) *PK at 2T and 3T* *Van Kampenhout 2017*		
Post-partum	Moxi: ♀ (n=1) *PK at 8 wks PP* *Van K'hout 2017*	♀♀♀♀♀ (n=6) *PK at 6 wks PP* *Court 2022*	♀ (n=1) *PK at 8 wks PP* *Van K'hout 2017*		
Breastmilk and foetal transfer		FT: ♂♂♂♂ (n=4) BM: ♂ (n=1) *Court 2022*			
Safety	?? risk to foetus Assoc. with LBW	Sig. BM transfer Assoc. w LBW	Incr. exposures 2T → 3T → PP		

CURRENT PK STUDIES: TB AND RR-TB IN PREGNANCY

RECRUITING

Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum

IMPAACT 2026 (preceded by P1026s)

ClinicalTrials.gov ID NCT04518228

Sponsor National Institute of Allergy and Infectious Diseases (NIAID)

Information provided by National Institute of Allergy and Infectious Diseases (NIAID) (Responsible Party)

Last Update Posted 2023-01-05

- Sub-study of BEAT Tuberculosis (South Africa) – NCT04062201
- Ongoing observational cohort study in KZN, South Africa
- Others? *(Not published or listed on clinicaltrials.gov)*

Loveday M, et al. Maternal and Infant Outcomes Among Pregnant Women Treated for Multidrug / Rifampicin-Resistant Tuberculosis in South Africa. Clin Infect Dis. 2021;72(7):1158-68.

WHO GROUP	TB MEDICINE
Group A *Associated with better outcomes and mortality benefit*	Levofloxacin or Moxifloxacin
	Bedaquiline
	Linezolid
Group B *Associated with better outcomes*	Clofazimine
	Cycloserine / Terizidone
Group C *Potentially effective*	Ethambutol, delamanid, pyrazinamide, carbapenems, amikacin, ethionamide, PAS

RR-TB is treated for 6-18 mths with 4-5 effective drugs

2T (20-26 weeks) | 3T (30-38 weeks) | Delivery | 2-8 weeks post-partum

Intensive PK sampling:

pre-dose and 0, 2, 4, 6, 8, 12 hours post-dose

LFX plasma concentrations measured with HPLC TMSA

Study P1026s

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

LFX IN PREGNANCY AND POST-PARTUM – NCA RESULTS

Pharmacokinetic parameters	**Second trimester (2T) (n = 6)** Median [Q1, Q3]	**Third trimester (3T) (n = 10)** Median [Q1, Q3]	**Post-partum (PP) (n = 8)** Median [Q1, Q3]	**2T vs PP (n = 4)** GMR [90% CI]	**3T vs PP (n = 7)** GMR [90% CI]
C_{max} (µg/mL)	**10.31** [9.33, 12.10]	**10.55** [7.71, 11.00]	**10.61** [8.20, 12.70]	**0.86** [0.59, 1.25]	**0.98** [0.85, 1.12]
C_{min} (µg/mL)	**0.94** [0.85, 1.03]	**1.45** [0.04, 1.59]	**1.41** [0.16, 1.72]	**0.72** [0.17, 3.00]	**1.23** [0.24, 6.23]
AUC_{0-12} (µg*h/mL)	**69.01** [60.12, 77.14]	**77.64** [70.51, 85.05]	**80.23** [71.80, 97.73]	**0.75** [0.60, 0.95]	**0.94** [0.81, 1.08]
$T_{1/2}$ (h)	**6.28** [5.71, 6.64]	**8.71** [5.95, 10.19]	**8.17** [6.42, 9.30]	**0.84** [0.73, 0.97]	**1.11** [0.83, 1.50]
CL/F (litres/hr)	**13.43** [12.03, 15.45]	**12.88** [11.76, 14.18]	**11.38** [9.96, 13.64]	**1.33** [1.05, 1.67]	**1.07** [0.93, 1.23]
Vd/F (litres)	**108.92** [97.39, 159.31]	**167.86** [114.44, 206.86]	**134.96** [107.44, 198.01]	**1.12** [0.86, 1.44]	**1.16** [0.79, 1.72]

Cmax = maximum concentration; Cmin = minimum concentration; AUC = area under the curve; $T_{1/2}$ = half life; CL/F = clearance; Vd/F = volume of distribution; 2T = second trimester; Q1 = first quartile; Q3 = third quartile; 3T = third trimester; PP = post-partum; GMR = geometric mean ratio

SOCIO-BEHAVIOURAL RESEARCH

"What concerns to you have about taking RR-TB drugs while pregnant?"

What are the perceptions, attitudes, beliefs, experiences and preferences of people receiving RR-TB treatment during pregnancy and post-partum?

"What advice would you give to other people diagnosed with RR-TB while pregnant?"

Diagnosis of TB **before** vs **after** pregnancy is identified

Stigma associated with TB – often highlighted during pregnancy, especially when there is a lack of knowledge and understanding of the disease

"What challenges do you encounter in accessing healthcare services while pregnant with RR-TB?"

TB AND PREGNANCY AT THE 2023 UNION CONFERENCE

OA28 Into the unknown: gender, TB and pregnancy

C3: Maternal and child TB

Thursday, 16 Nov 2023 17:45 - 19:15

OA28-418-16 Enrolment of pregnant women with rifampicin-resistant TB into the BEAT Tuberculosis Randomized Clinical Trial: Early outcomes

Thursday, 16 Nov 2023 17:50 - 17:59

MTE-07 TB and pregnancy: Drugs and vaccines

Other

Thursday, 16 Nov 2023 08:15 - 09:15

SP49 Into the unknown: Drug-resistant TB in pregnancy

C3: Maternal and child TB

Saturday, 18 Nov 2023 11:15 - 12:45