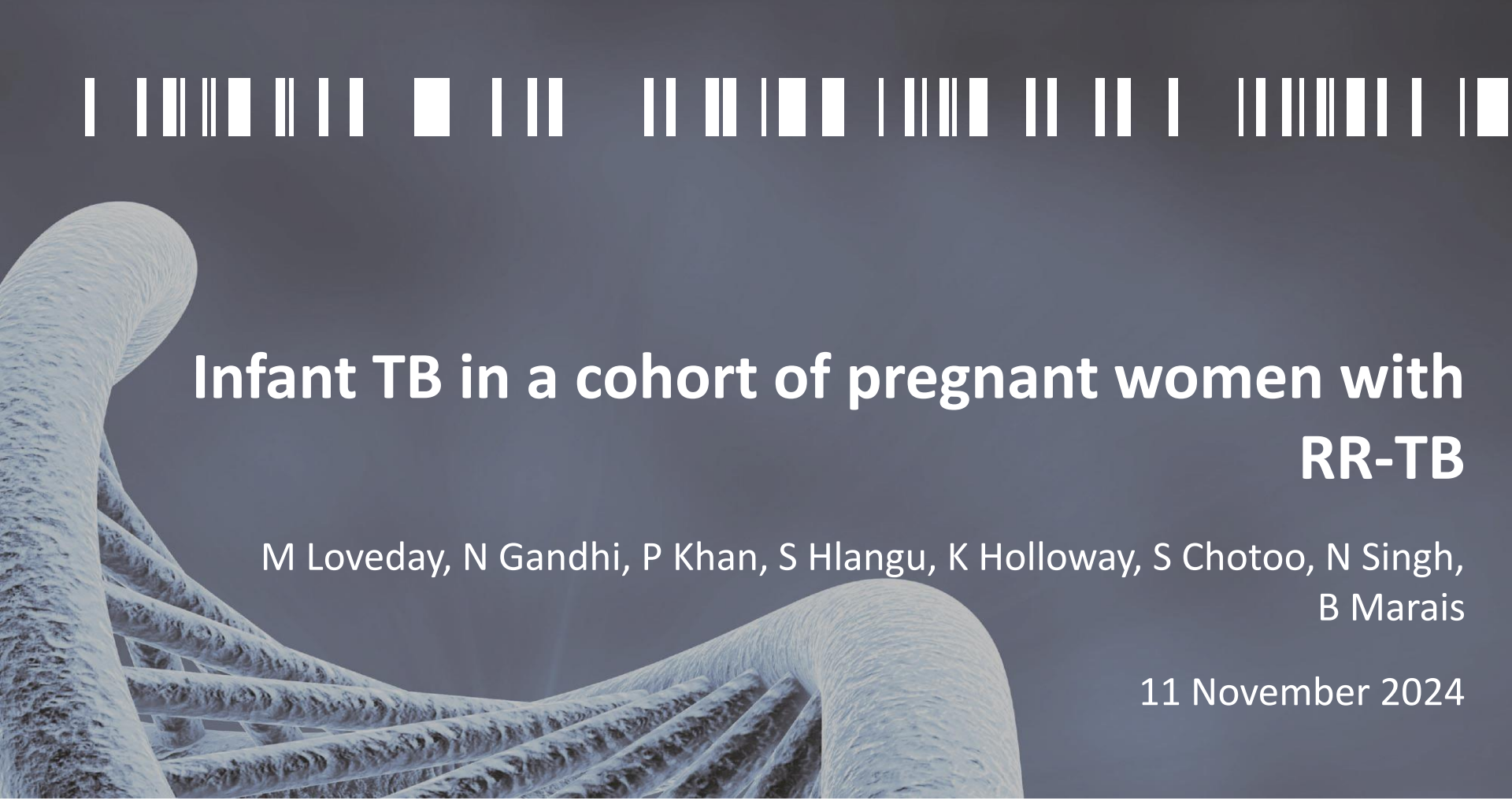

Infant TB in a cohort of pregnant women with RR-TB

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Background

Ongoing cohort of pregnant women with RR-TB (2013 – 2024)

Observational study documenting maternal treatment, pregnancy and infant outcomes amongst women treated for RR-TB in pregnancy:

- Enrol women during pregnancy when first diagnosed with RR-TB;
- Follow them until they have completed treatment and delivered their infant.

We follow-up the mother-infant pair until the infant is 1-year old.

- Clinically assess the infant at 6 weeks, 6 months and 12 months:
  Monitoring growth, development and signs and symptoms of TB disease

In our cohort of >200 pregnant women with RR-TB, we followed 101 mother-infant pairs for 12 months and 23 (23%) of the infants developed TB.

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Background

- Progress towards TB control is hampered by our limited understanding *Mtb* **infectiousness** and **transmission**, especially in settings with a high burden of HIV and high TB incidence rates.
- Historically, households were considered the major locus of *Mtb* transmission, but studies from high TB incidence countries in sub-Saharan Africa have demonstrated that most transmission occurs in the community where the source of infection is known, including in young children.
- Effective treatment of pregnant women is critical to prevent adverse maternal and neonatal outcomes, but optimal management of the mother-infant pair is complex and rarely discussed.
- A better understanding of likely transmission dynamics is needed to inform strategies that reduce the infection risk in babies born to mothers with TB. The unique biological link and close social nature of the bonds in the mother-infant pair provides an opportunity to critically explore likely transmission pathways.

Aim and Methods

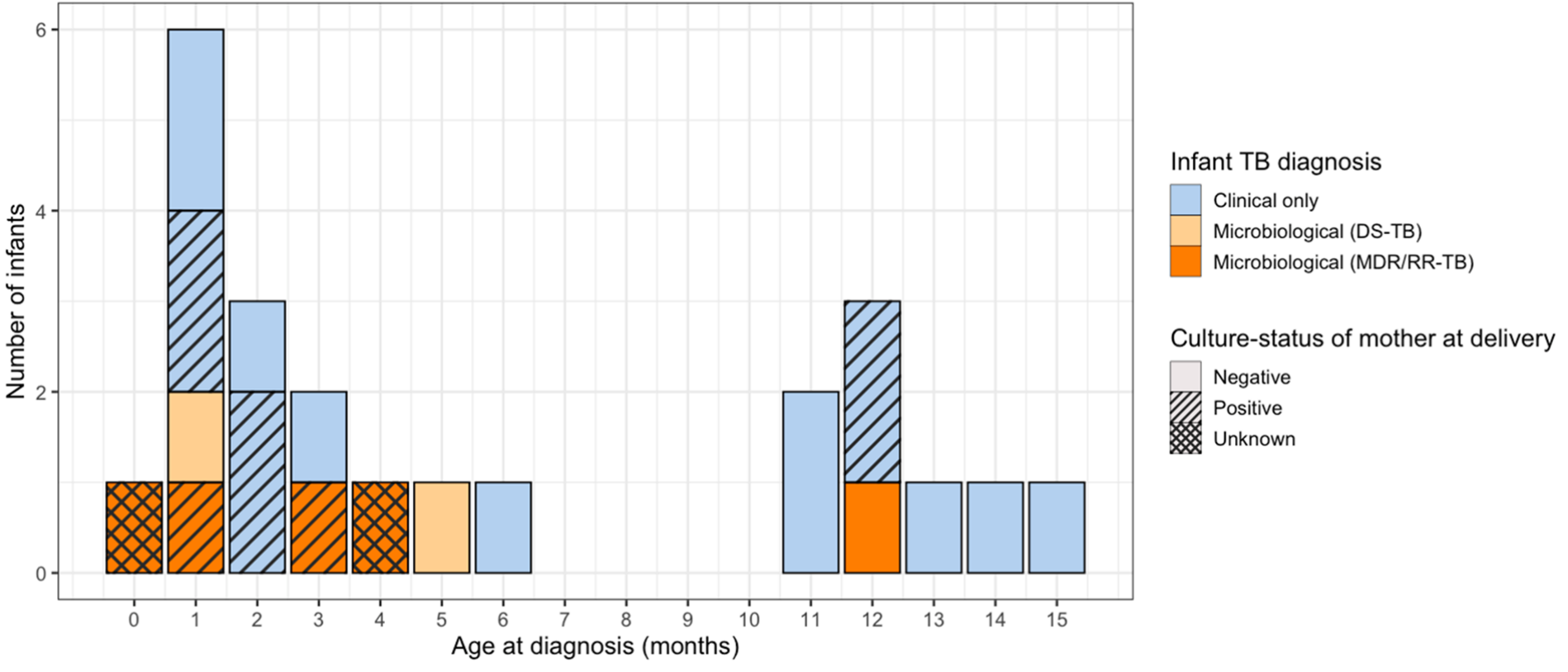
Aim:

To explore possible *Mtb* transmission routes and provide detailed descriptions of the infants' clinical presentation and disease trajectories, according to the most likely *Mtb* transmission route.

Method:

- The infant was clinically assessed at 6 weeks, 6 and 12 months of age.
- Data collected from the Road to Health card on TB screening at birth, HIV prophylaxis for HIV exposed infants.
- Identified all infants started on TB treatment following either a laboratory or clinical diagnosis.
- We interrogated potential risk factors and health system failures by comparing the infants' date of birth and development of TB with the treatment history of the mother to determine:
  - How long the mother had been on treatment before the infant was born;
  - How long she had been on treatment before the infant developed TB;
  - The mother's sputum culture status at delivery and when her infant developed TB;
  - The mother's adherence to RR-TB treatment and ART.

Timeline reflecting month, diagnostic method and maternal sputum culture status at the time of delivery in infants diagnosed with TB disease.



* Some children attended the 12-month visit late, up to 15 months of age

Abbreviations: TB, tuberculosis; DS-TB, drug-susceptible TB; RR-TB, rifampicin-resistant TB

Clinical and birth characteristics in mothers with RR-TB whose infants were diagnosed with TB disease compared with those whose infants did not develop TB.

Baseline characteristics	Mother-infant pairs with infant TB (N=23)	Mother-infant pairs without infant TB (N=78)
Age: years, median; [IQR]	28 [23-32·5]	28 [23-32·25]
HIV-positive: no (%)	18 (78%)	66 (85%)
Baseline CD4 count, median cells/mm3 [IQR]	410 [220-808]	410 [208-803]
TB characteristics		
Culture positive at TB treatment initiation	16 (70%)	(n=76) 55 (72%)
Previous TB or MDR/RR-TB	(n=19) 10 (53%)	(n=66) 33 (50%)
Chest radiograph	(n=22)	(n=68)
Extensive disease pattern on chest radiograph[†]	9 (41%)	28 (41%)
Resistance pattern: no (%)		
RR-/Rif-mono/MDR-TB	19 (83%)	66 (85%)
Pre-XDR-/XDR-TB	4 (17%)	12 (15%)
Culture positive at delivery	**(n=20)** **8 (40%)**	**(n=70)** **10 (14%)**
Time from treatment initiation to delivery, median; [IQR]	116 [75-202]	114 [79-202]
Birth characteristics		
Gestational age at the time of maternal TB diagnosis: weeks, median [IQR]	24 [15·86-31·86]	24 [15·89-31·39]
Gestational age at delivery: weeks, mean; SD	36·78; 5·01	39·96; 4·44
Birth weight, grams, median [IQR]	2900 [2046-3400]	2900 [2455-3390]

Categorisation by likely route of *Mtb* transmission

1. *in utero* transplacental infection
2. intra-partum aspiration
3. postpartum inhalation
    - maternal source of infection
        - mothers with sub-optimal treatment;
        - mothers with sub-optimal treatment adherence;
        - infants not screened for TB or provided with appropriate TPT
    - non-maternal source of infection
        - within the household
        - outside the household

Case histories categorized according to likely route of *Mtb* transmission

Likely *In utero* transplacental infection

An HIV negative woman had a much awaited and longed for infant following in vitro fertilisation (IVF). The mother was diagnosed with miliary RR-TB at 5 weeks of gestation and started an all-oral 20-month regimen 5 days later. The baby was born 161 days after maternal treatment initiation at 28 weeks GA, weighing 1.8kg. At birth there were placental granulomas suggestive of congenital TB (the results could not be located) and the mother was sputum culture positive. The baby was hospitalised for a month with signs and symptoms of TB, as well as chest x-ray changes suggestive of TB disease. This infant was likely infected *in utero* and born with congenital RR-TB. Despite strong advice, the mother declined treatment of her infant, who continues to be monitored.

Case histories categorized according to likely route of *Mtb* transmission

Possible Intra-partum aspiration

During her pregnancy, this mother lived in the same house as her mother (the infant's grandmother) who had RR-TB. Living with HIV, the pregnant woman disengaged from care and did not take ART during the third trimester of her pregnancy. She developed RR-TB at 35 weeks gestation when her CD4 count was 9 cells/mm3. She was initiated on the all-oral 20-month regimen 34 days before her infant was born at 39 weeks GA, weighing 3,1kg. At the time of delivery, the mother was not virally suppressed, (viral load 71577copies/ml), and was sputum smear and culture positive. A week later the infant was admitted to the local hospital where, despite the gastric aspirate being negative for *Mtb*, there were changes on chest x-ray. As the infant failed to respond to antibiotics, RR-TB was considered the most likely diagnosis, possibly due to intra-partum aspiration. The infant was started on the 9-month RR-TB regimen 12 days after birth. Both the mother and infant responded to treatment which they successfully completed.

Case histories categorized according to likely route of *Mtb* transmission

Likely post-partum inhalation: (maternal source)

This mother living with HIV first attended antenatal care at 29 weeks gestation. In line with country guidelines, she was tested for TB and started on DS-TB treatment. However, the health facility failed to pick up that she had RR-TB. Her baby was born two months later at 37 weeks gestational age, weighing 2.8kg. The baby was screened for TB at birth. Given that the TB diagnosis was made soon after birth, with perihilar changes on chest x-ray, no sign of a Ghon focus in the liver and a gastric aspirate positive for RR-TB on Xpert MTB/RIF, this was considered likely intra-partum aspiration. Both the mother and infant were started on a 9-month treatment regimen based on the mother's resistance pattern within the first few days of the infant's life, responding well to treatment and were cured and completed treatment respectively.

Infectious mother not provided with appropriate treatment

Case histories categorized according to likely route of *Mtb* transmission

Likely post-partum inhalation: (maternal source)

This mother was diagnosed with RR-TB and started an all-oral 9 – 11 months regimen at 18 weeks gestation. At the same time, she was diagnosed as HIV-positive and started ART two weeks later. She took treatment for 66 days and then stopped both TB treatment and ART. Three months later, when she was still sputum culture positive, her baby was born at 40 weeks gestation weighing 3.08kg. The mother started taking treatment (TB treatment and ART) again when her infant was 2 months old, but only for a short time. She disengaged from care and at 5 months left her infant in the care of his father. The infant was not brought for his scheduled 6-month visit, but after repeated calls was brought in at 9 months. He was very unwell, with a fever, cough, losing weight, and a chest x-ray showing extensive changes suggestive of TB. He was referred for a gastric aspirate, but this was never taken. We were informed he died 2 months later. It is likely this infant was infected postnatally due to sub-optimal maternal adherence to both RR-TB treatment and ART. We lost all contact with the mother and cannot report her outcome.

Infectious mother with poor treatment adherence

Case histories categorized according to likely route of *Mtb* transmission

Likely post-partum inhalation: (non-maternal source)

The father of this infant was diagnosed with RR-TB early in the mother's pregnancy (12 weeks gestation). He was initially started on an all-oral 9-month regimen, but as he failed to respond to treatment, was changed to a long regimen all-oral regimen a month before the infant was born. The mother, who was HIV negative, was not screened for TB during antenatal care and neither she nor the infant were screened for TB when the infant was born at 39 weeks GA weighing 2.92kgs. At 4 months old the infant developed signs and symptoms suggestive of TB (cough, fever and loss of weight). His gastric aspirate was cultured with a similar phenotypic resistance pattern to that of his father and he was started on a 9-month treatment regimen. When he was 6 months old his mother also developed RR-TB with the same resistance pattern as the father and started on an appropriate 9-month regimen. It is likely this infant and his mother were infected by his father. Both the mother and infant are responded well to treatment which is now complete.

Non-maternal source within the household.

At-birth management of infants born to mothers with RR-TB. (N=101)

(based on 2019 South African guidelines used during study period)

Management component	Yes	Not done	Not recorded
Chest radiograph done	43 (42%)	25 (25%)	33 (33%)
Gastric aspirate done	45 (44%)	20 (20%)	36 (36%)
TPT given at birth*	47 (46%)	22 (22%)	32 (32%)
BCG given at birth	36 (36%)	43 (42%)	22 (22%)
BCG given after TPT (N=47)	22 (47%)	20 (43%)	5 (10%)

Identified health service challenges and suggested recommendations to minimise *Mtb* transmission from mothers with TB to their infants.

Health service challenge	Recommendations
Absence of routine screening for TB in the ante- and post-partum periods	Pregnant women should be routinely screened for TB at every ante- and post-partum visit. If TB disease is ruled out, they should be considered for TPT. Women of reproductive age who develop TB should be advised to avoid falling pregnant and provided with contraceptives, while on TB treatment.
Poor integration of TB into primary maternal and child health services.	TB services must be fully integrated into maternal and child health services. Pregnant/post-partum women and their vulnerable infants should not sit in overcrowded and poorly ventilated clinic waiting rooms. HCWs in delivery wards must be trained to routinely screen infants for TB as is locally feasible if their mother has TB, provide TPT or BCG and encourage maternal treatment adherence.
Infant TPT	The updated WHO TPT guidelines for RR-TB are available. The availability of child-friendly dispersible levofloxacin should facilitate infant administration.
Suboptimal maternal TB and anti-retroviral treatment adherence.	Additional counselling, information and adherence support for women on TB, or RR-TB treatment and ART should be provided during pregnancy and the postpartum period.

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