Estimating contamination effects on measured trial results in TB active case finding cluster randomised trials

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Background

Cluster randomised trials have shown mixed results with many lacking population-level reductions in TB.

Participant **mobility** and interactions between study clusters or the general population can introduce **contamination**, which may contribute to these negative trial results. Contamination can **dilute the effects** of the intervention, resulting in an **underestimation** of its true impact. [1]

The influence of contamination is important for understanding trial results and can play a role in **optimising future study design and analysis**.

Contamination pathways

Systematic review of TB cluster RCTs[2]

Screening	Included trials	Contamination
• 1,039 titles/abstracts • 173 full text reports • 20 reports from 7 trials Interventions • Active and enhanced case finding • TB preventive treatment • HIV-TB test and treat	• ACT3 • DETECTB • Greenland • PopART/TREATS • SEARCH/SEARCH-TB • Thibela TB • ZAMSTAR	Facilitators • High mobility • Small cluster sizes • Workforce turnover • Social mixing Mitigators • Geographic isolation • Fried egg design

Social contact patterns

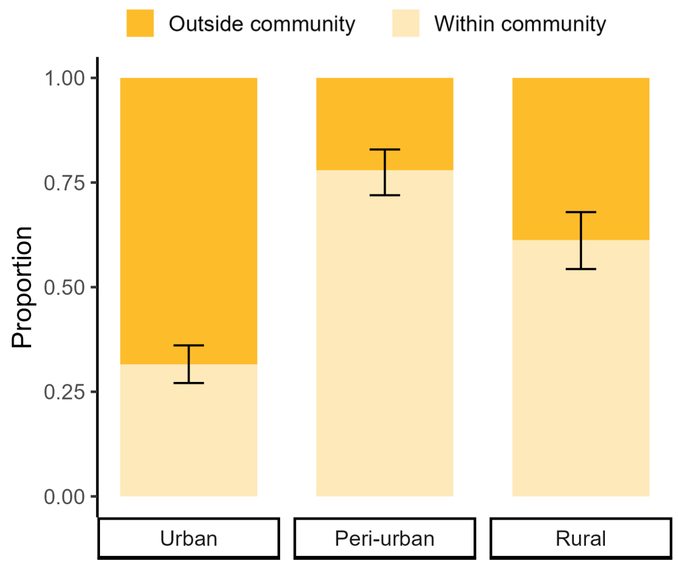
Identifying local contact patterns is crucial.

Recent molecular studies in high burden settings have shown that **over 80% of *Mtb* transmission occurs outside the home**.[3] To better understand transmission dynamics, we analyzed data from **a social contact survey** conducted in urban, peri-urban, and rural communities in South Africa.[4]

Contact hours were estimated in three settings: **within the home**, **outside the home**, and **outside the community**. Household contact was excluded in the second and third settings. The communities were considered intervention clusters in the third setting, and contact outside the community served as a measure of **mobility** to assess for potential contamination in a cluster RCT.

Our analysis showed **substantial heterogeneity** in the proportion of contact occurring outside the community.

Proportion of contact hours inside and outside the community



Urban participants spent 68% of contact hours outside the community

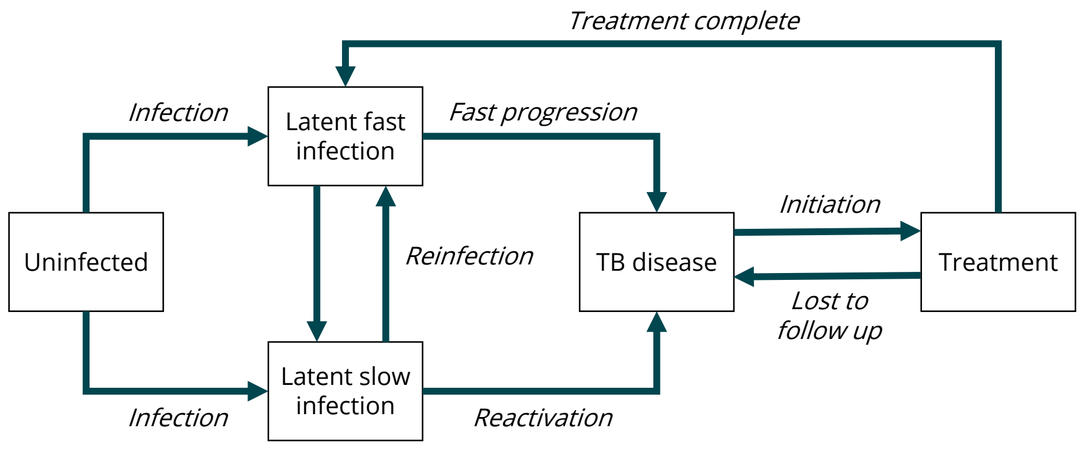
Peri-urban and rural mostly stayed in their communities

Transmission model structure

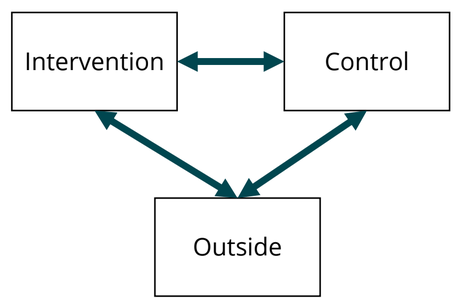
Mathematical models can be used to simulate transmission and intervention delivery scenarios.

To evaluate the **impact of contamination** in a simulated active case finding cluster randomised trial, we developed a **dynamic compartmental model** of TB natural history. Building upon established models,[5,6] this model incorporates HIV and ART status and our findings from the systematic review of TB cluster RCTs[2] and the social contact survey[4] to inform the ACF trial design and contamination parameters.

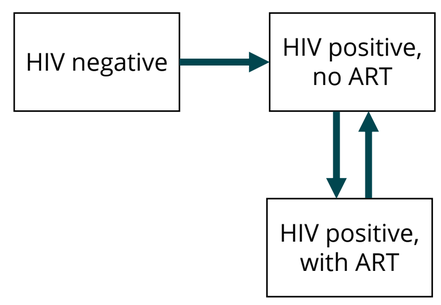
Natural history



Cluster migration

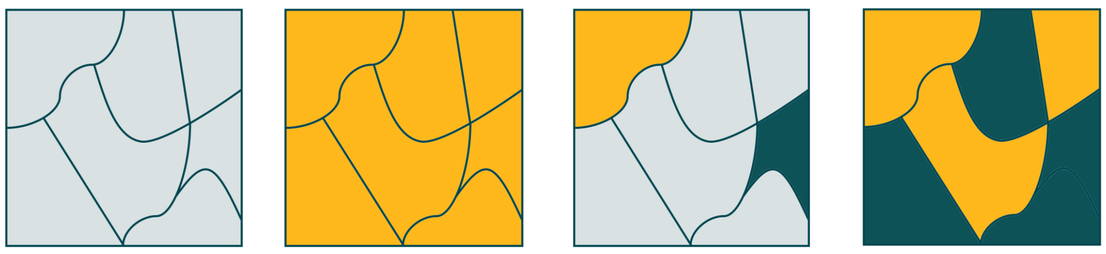


HIV status



Intervention scenarios

Three ACF delivery scenarios will be simulated: 1) Baseline, 2) Programme, and 3) a cluster RCT with varying levels of contamination. The results from the scenarios will be compared to determine the extent that contamination may bias the measured intervention effect.



Baseline *No ACF*

Programme *All receive ACF*

Cluster RCT *Low contamination*

Cluster RCT *High contamination*

Future applications

Improvements in trial design and reporting may reduce contamination and improve results.

By understanding local contact and movement patterns, policymakers and public health practitioners can develop more **effective and equitable** strategies to end TB, especially in high burden settings.

1. Hayes & Moulton, 2017
2. LeGrand et al. *IJTLD* 2025
3. Verver et al. Lancet 2004
4. LeGrand et al. *medRxiv* 2025
5. Clark et al. *Lancet Global Health* 2023
6. Sumner et al. *Vaccine* 2024

Learn more about this work!