# “Closing the loop” – routine pooling of data linking TB reactivation episodes in contacts to quantify risk of disease following infection

# Proposal for a research collaboration/protocol

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## Background

### General

TB is now the world’s leading infectious cause of death by a considerable margin1 and latent infection (LTBI) with the causative organism (*Mycobacterium tuberculosis*, or *Mtb*) affects around one quarter of the world’s population.2 The lifetime risk of TB reactivation after disease is often stated to be 5 to 10%, with half of this risk accruing in the years following infection. However, this broad estimate was derived from studies undertaken many decades ago when rates of reinfection were considerably higher, the diagnosis of both recent infection and of active TB were inconsistently defined and disaggregation of rates by age was not reported.3–5

For example, two of the most commonly estimates of the rate of reactivation from LTBI are derived from follow up of the placebo arms of randomised controlled trials of intervention studies, including the MRC study of TB vaccines6 and the USPHS study of isoniazid preventive therapy.5,7 However, there are several limitations of these earlier studies, including increased rates of unrecognised reinfection and the difficulty in now accessing appropriately disaggregated data for reanalysis. For these reasons and others, we consider that the prospective collation of data from contacts of TB patients could be of great value in defining risk of future disease.

### Specific past studies

More recently, a number of studies have emerged to estimate the risk of active TB following infection using formal survival analysis techniques applied to surveillance data. The first such study was undertaken in Amsterdam and considered tuberculin skin test (TST)-positive contacts of active cases and the rate at which they developed subsequent disease.8 A subsequent study in Victoria imputed censorship due to preventive treatment, migration and death, allowing the absolute risk of reactivation disease following infection to be directly appraised.9 Other studies with similar methods have also recently emerged from centres in the USA,10 Spain,11 and from the Netherlands,12 where LTBI has been a notifiable condition in certain circumstances since 2003.

### Rationale

Estimates of reactivation risk are crucial for:

* Counselling patients individual patients as to their risk of disease
* Quantifying the benefits of preventive therapy at the individual or group level, including economic analyses
* Planning the public health response to LTBI in high and low-burden settings, including for the construction of mathematical models of TB transmission

In relation to the first bullet above, we aim to “close the loop”, using data from reactivation rates from LTBI to active TB to quantify the risk of disease for future contacts diagnosed with LTBI.

## Project status

### Engagement

We are currently in the engagement stage of this project, seeking in-principle support for the activity from stakeholders (particularly data custodians).

### Approvals

In principle support from ACTnet, approved by vote of membership. Approved at the ACTnet annual meeting on 31st May 2018 (at the TB-CRE Symposium, Sydney).

### Approaches to research groups

The following research groups have been approached, including:

* KNCV (Connie Erkens, Rosa Sloot, Frank Cobelens)
* Centers for Disease Control and Prevention (Mary Reichler)
* University College London (Rishi Gupta)

Further authors of individual eligible studies will also be approached.

### Current research completed or underway

Preceding stages to this research undertaken by our group have included the following studies:

* Approach of data linkage from contacts to cases in Victoria described
  + Moyo et al.13
* Survival analysis to quantify rates of progression from LTBI to active disease overall and by age group reported
  + Establishes the paradigm of imputing censorship for the anticipated depletion in the cohort over time from infection
  + Trauer et al.14
* Systematic review of modelling latency structures and mathematical analysis of the relationship between observed reactivation profiles and epidemiological rates
  + Establishes mathematical equations and approaches for estimating progression parameters from survival data – for use in simulation of latency (e.g. compartmental modelling
  + Ragonnet et al.15
* Defining profiles of reactivation project
  + Aiming to distinguish characteristic reactivation profiles by risk group
  + Using similar methodologies to those established in Moyo et al and Trauer et al above
  + Melsew et al. – approaching completion
* Correspondence highlighting the need for studies such as those described above in section 2.2 published in response to review16 of current approaches to modelling latency structures
  + Trauer et al.17
* Systematic review of studies estimating rates of late reactivation
  + Dale et al. – approaching completion

## Proposed methodology

### General approach

We propose to collate individual-level data on rates of reactivation from infection with *Mtb* (i.e. new LTBI) to active TB from multiple jurisdictions. The exact approach remains to be defined and this document is intended to stimulate discussion as to the optimal approach to achieving this.

### Involvement of multiple jurisdictions

Contributing data from multiple jurisdictions is anticipated to improve the accuracy of our estimates, enabling progressively more precise estimates to be obtained. Further, this will enable sufficiently precise estimates to be provided for progressively more specific risk groups.

### Embedding the approach in routine public health response

For jurisdictions for which LTBI is a notifiable condition in contacts (e.g. the Netherlands) or for jurisdictions for which this is the case *de facto* (e.g. Victoria), we propose regular data extractions from surveillance systems to update estimates. Ultimately, this could even be done as part of routine public health practice, creating a living tool for quantifying TB reactivation risk in contacts. We are currently working towards this in Victoria.

### Standardising data collection

We propose a standardised set of individual-level data be centrally collated, consisting of the minimum data required for survival analysis. Required minimum data fields would likely include:

* Age in whole years
* Serial interval from index case diagnosis to reactivation (or dates of each)
* TST result in millimetres

*or*

* IGRA response value (QuantiFERON or T-SPOT)

Desirable data fields may also include

* BCG vaccination status
* Index case smear status and index case age
* Duration of contact with index (where available)
* Contact comorbidities associated with TB reactivation (where available, e.g. diabetes, HIV)
* Preventive therapy started (categorical with levels likely including: did not commence, commenced and completed, commenced but did not complete, uncertain)
* Genomic linkage between index case and contact reactivation

### Data curation and ethics

This is one of the key issues for future discussion. Ethics committee approval for centralised data management will likely be sought. However, we are first seeking to engage with collaborators, including those listed above. Moreover, for this to become an ongoing process, the data collection could rather be seen as a public good registry. Monash University’s School of Public Health and Preventive Medicine is a world-leader in registry science and could support this process. The University of Melbourne’s Peter Doherty Institute has the advantage of already storing local surveillance data, as does KNCV.

## References

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