Lymph nodes as niches for *Mtb* infection in humans and profiling of associated host immune responses

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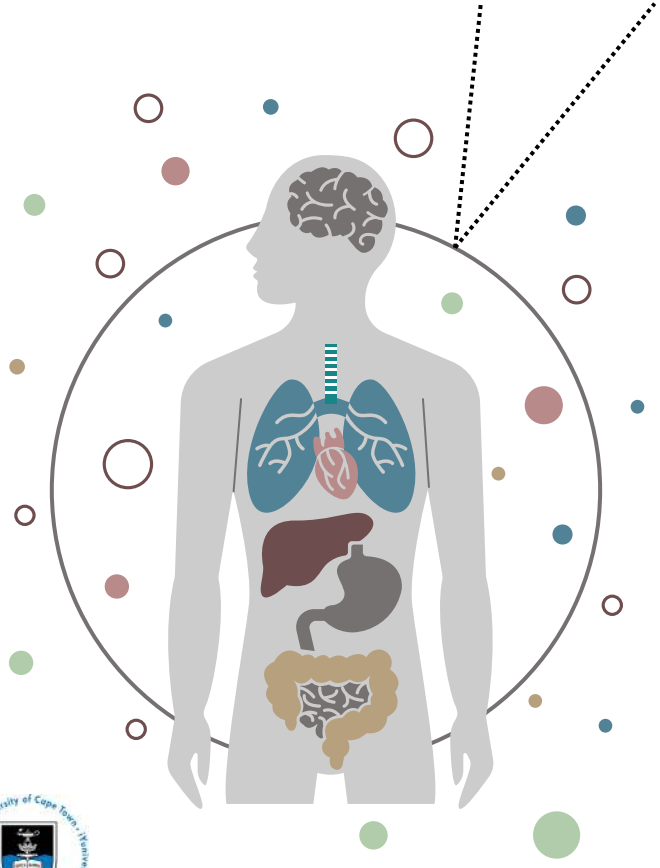
7TH GLOBAL FORUM ON TB VACCINES | 8-10 October 2024 Rio de Janeiro, Brazil

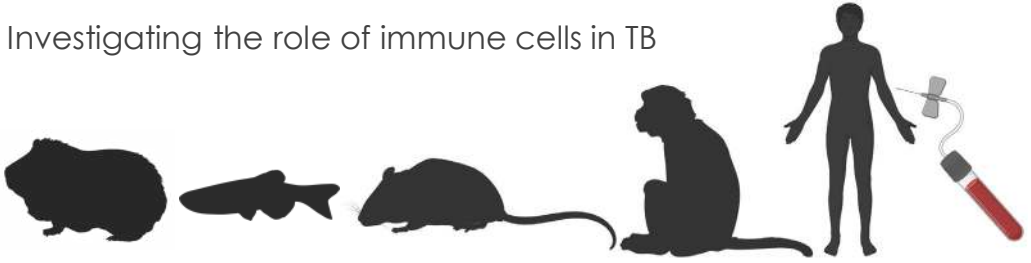
Driving innovation from discovery to access

20 YEARS OF TB RESEARCH | satvi TOWARDS A WORLD WITHOUT TB

Investigating tissue immunology



Investigating the role of immune cells in TB



But in humans….

- Focus on peripheral blood (accessible)
- Circulating cells → only a subset of the immune cell landscape
- Understanding human immunity requires assessing features of immune cells within and across tissues

A potential solution:

Sampling post-mortem human tissues during autopsies

Postmortem cohorts

Observatory Forensic Pathology Institute (OFPI)

Trauma & unnatural deaths

Massive caseload (4522 cases in 2023)

Western Cape Government

FORENSIC PATHOLOGY SERVICE

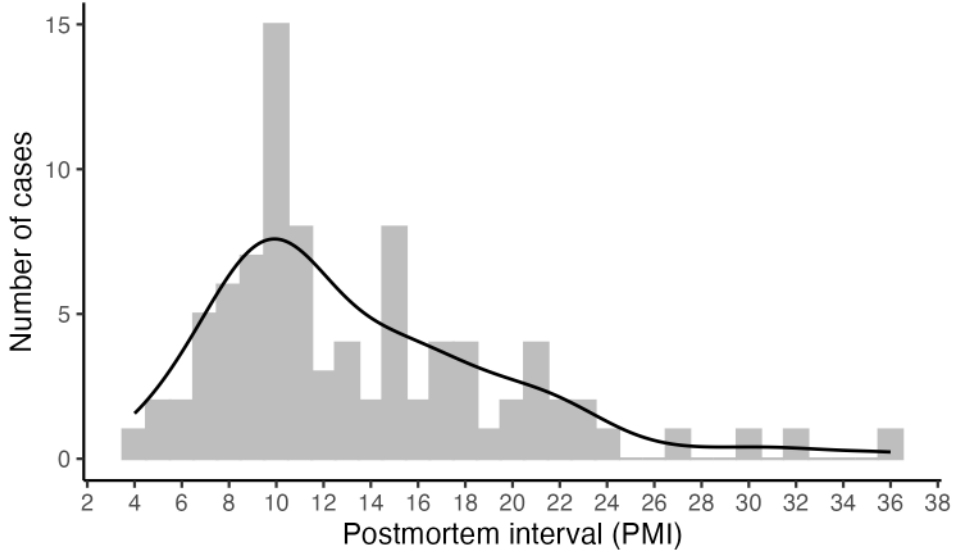
Forensic Pathologists

Dr Laura Taylor

Dr Celeste de Vaal

Short postmortem interval (PMI)

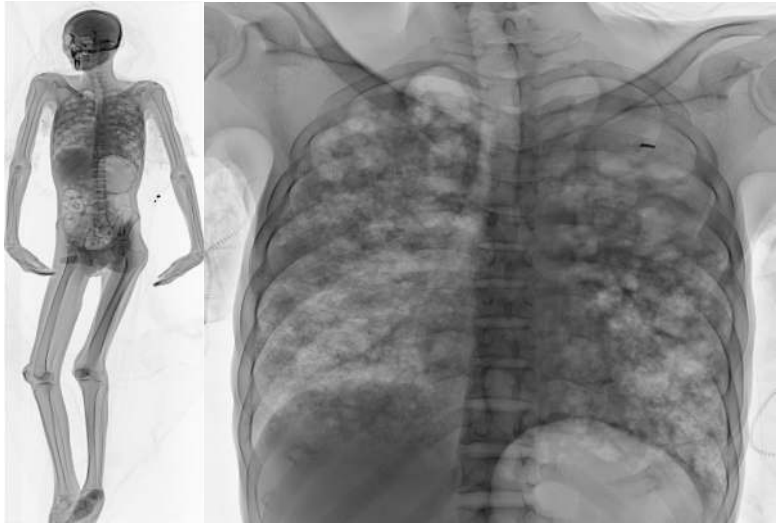
Median 11 hours from death to autopsy



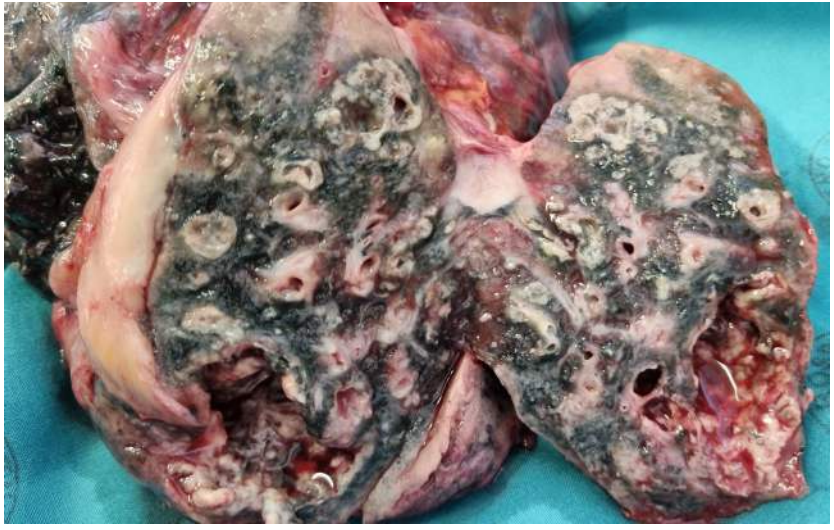
Maintain cell functionality

Evidence of TB at autopsy

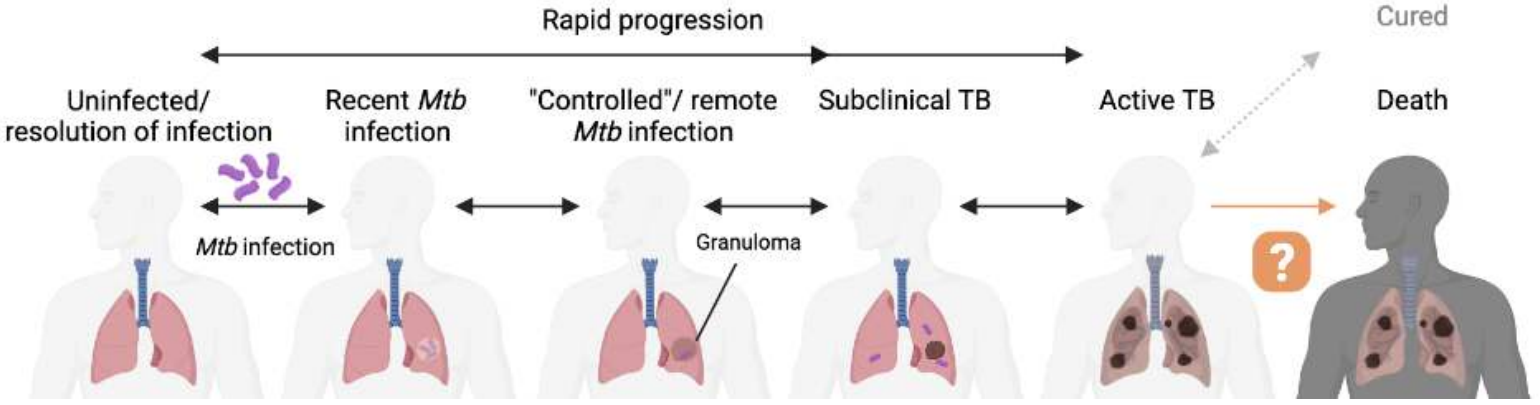
Imaging: LODOX scan



Macroscopic evidence



Postmortem cohorts capturing the TB spectrum

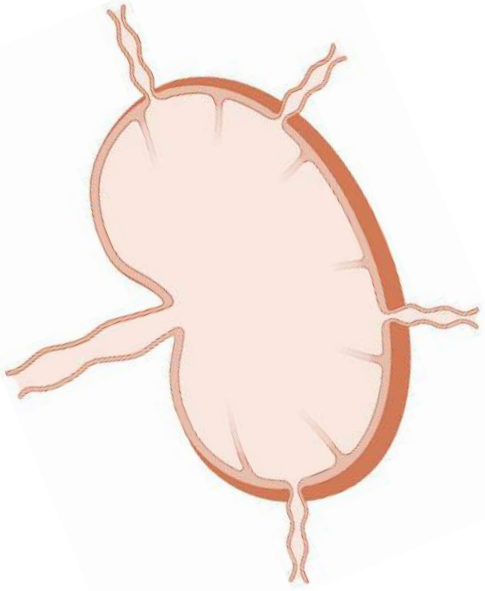


Adapted from: Pai *et al.* Nature Reviews Disease Primers, 2016

Lymph nodes as battlefields in TB

Why lymph nodes?

- Sites for initiating adaptive immune response.
- Niches for *Mtb* growth and persistence (in NHPs).
- We are studying lymph node as the immune organs draining the lung.



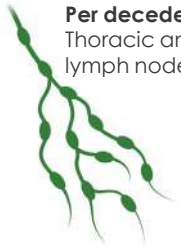
Personal View

Lancet Infect Dis 2014;
14: 250–55

Is tuberculosis a lymphatic disease with a pulmonary portal?

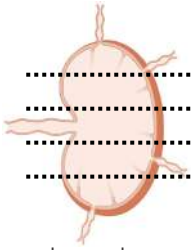
Marcel A Behr, W Ray Waters

Sampling lymph nodes



Per decedent:
Thoracic and non-thoracic lymph nodes

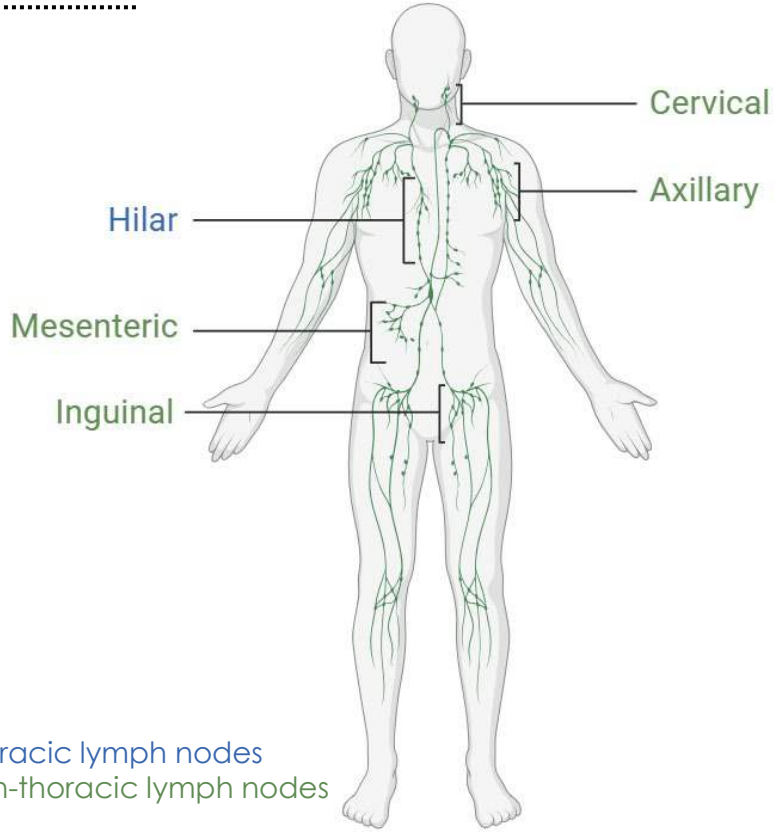
3-5 lymph nodes collected from same cluster or general draining area



Each lymph node sectioned into 3-5 slices

*

2-3 slices: ddPCR *Mtb* DNA detection RD9 (specificity), IS*6110* (sensitivity)



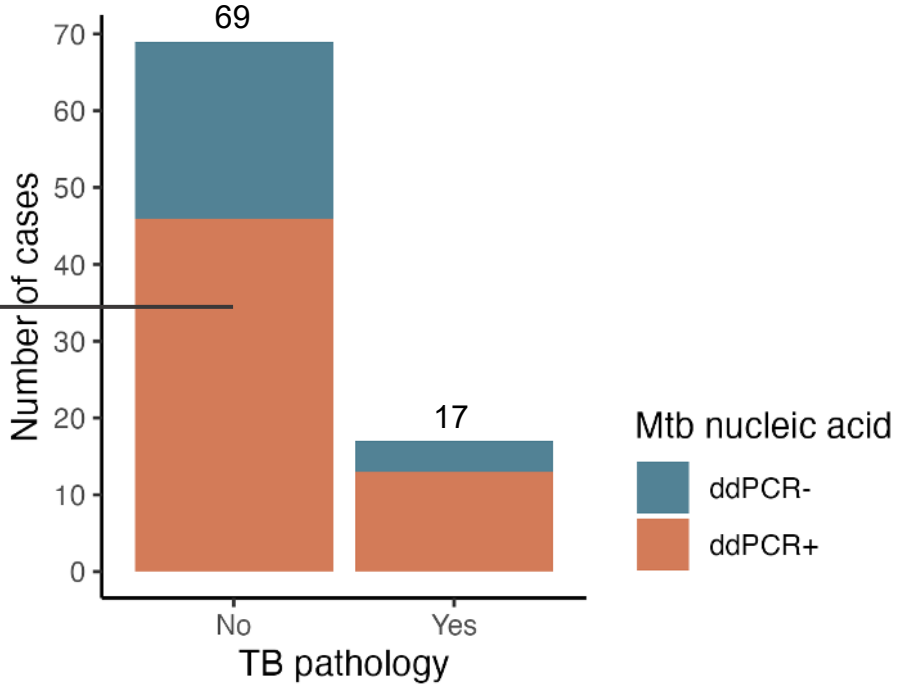
Thoracic lymph nodes
Non-thoracic lymph nodes

***Dr Dharanidharan Ramamurthy**
Molecular Mycobacteriology Research Unit (MMRU), UCT

Lymph nodes as niches for *Mtb* infection

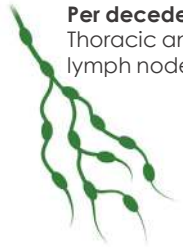
Total Decedents: 86

***Mtb* detected in ~67%**
of "healthy" cohort,
in at least one lymph node



Dr Dharanidharan Ramamurthy
Molecular Mycobacteriology Research Unit (MMRU), UCT

Sampling lymph nodes



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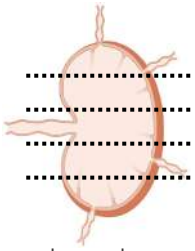
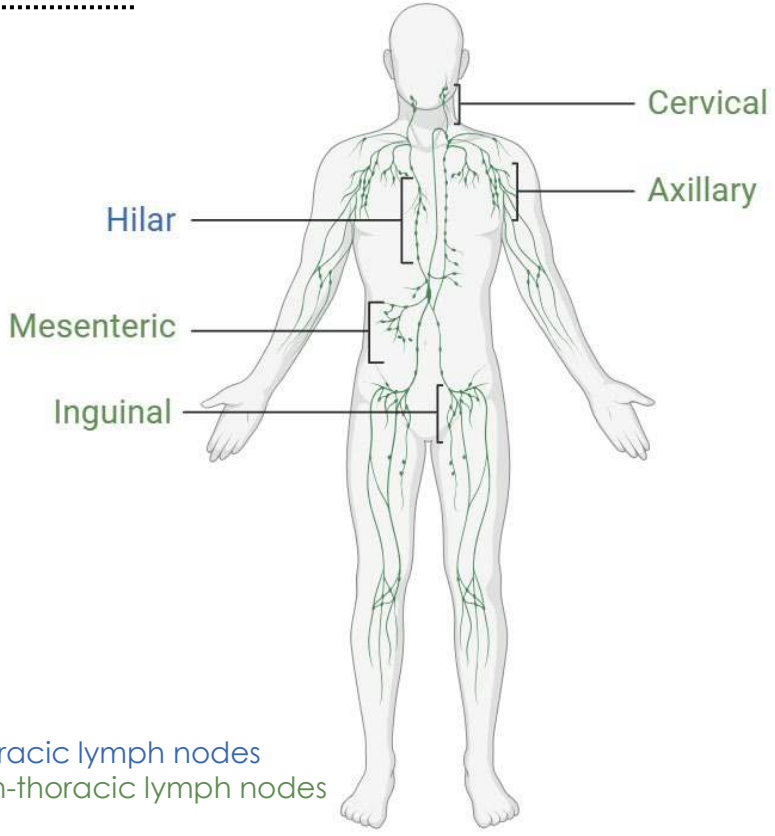


Each lymph node sectioned into 3-5 slices

Remaining slices from all lymph nodes pooled for scRNA-seq & mass cytometry

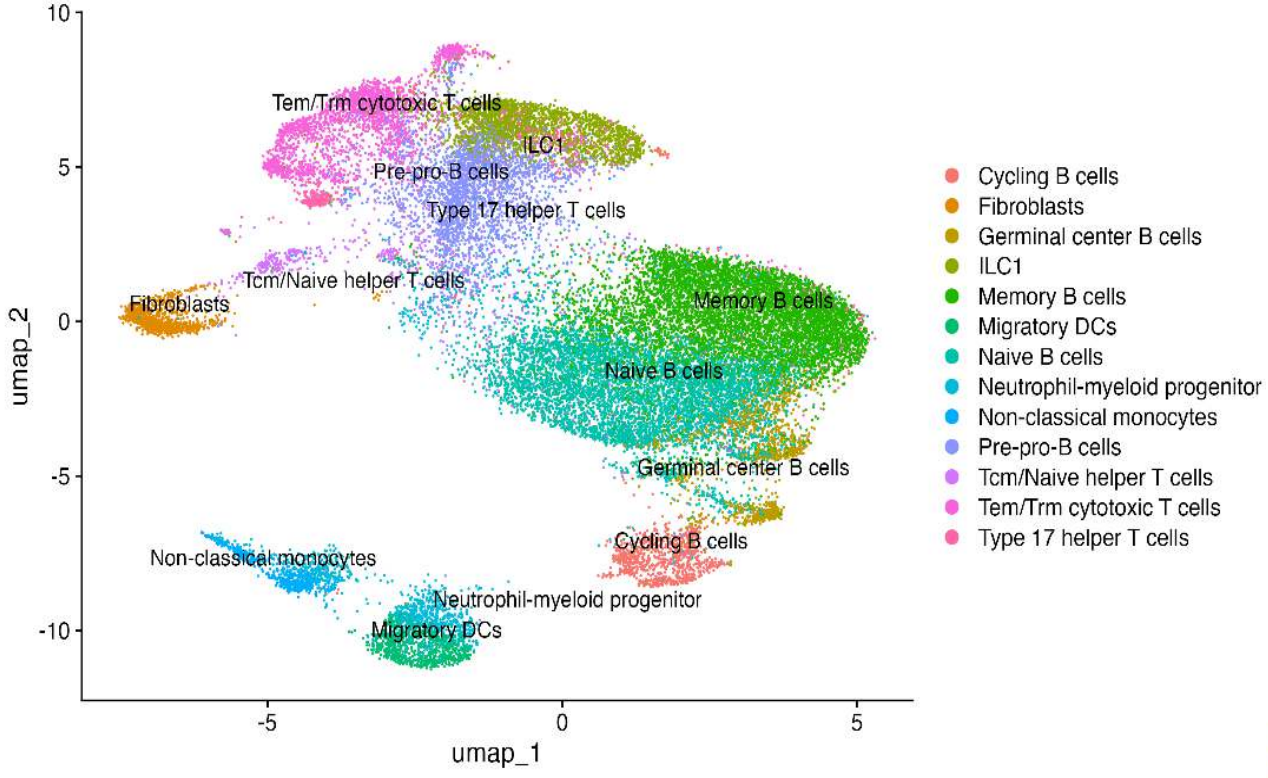
2-3 slices: ddPCR *Mtb* DNA detection
RD9 (specificity), IS*6110* (sensitivity)



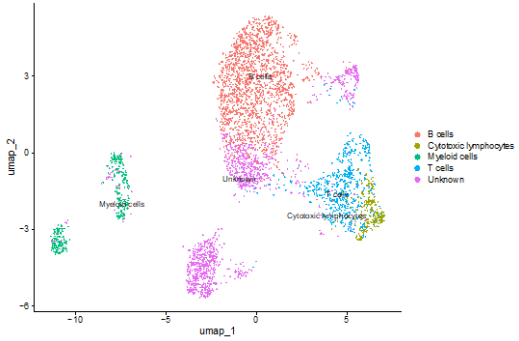
Thoracic lymph nodes
Non-thoracic lymph nodes

Immune response profiles in lymph nodes

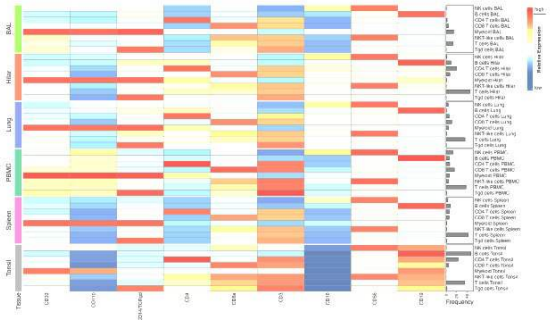
scRNA-seq data



Next steps



scRNA-seq



Mass cytometry

PBMC

Thoracic lymph nodes

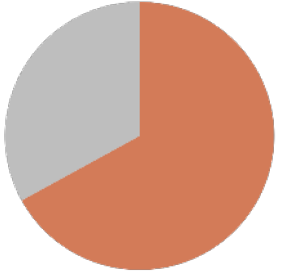
Non-thoracic lymph nodes

Association of functional immune outcomes with pathology and bacterial burden in tissues

Conclusions and Takeaway

Lymph nodes as niches for *Mtb* infection

- Detected *Mtb* nucleic acid in ~69% of our cohort, in at least one lymph node.
- And 67% of the healthy cohort (without TB pathology).
- ***Mtb* is highly prevalent in the population served by the Western Cape Forensic Pathology Services.**



Feasibility

- Our postmortem platform is feasible for studying the TB spectrum in human tissues.
- **Significance:** identifying immune responses associated with pathology or control of *Mtb* in human tissues.
- **Potential:** identify correlates of outcome of *Mtb* infection.

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Next-of-kin and families