



CHANGING & IMPROVING
SOUTH AFRICA'S TRANSPLANT FUTURE

28th SATS & 5th SATiBA

CONGRESS

6 - 8 September 2019



Diagnosing TB

(in transplant donors and recipients)

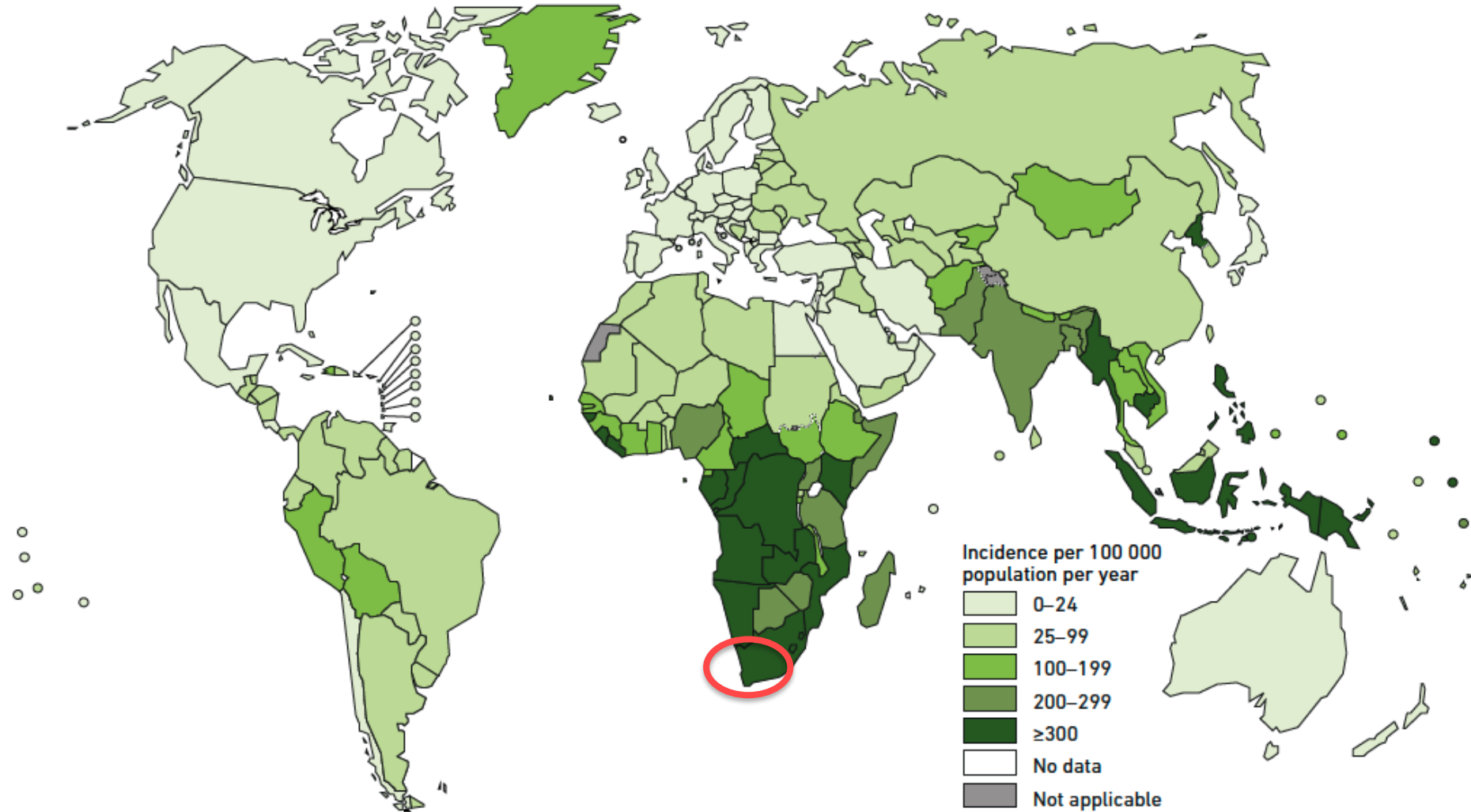
Greg Calligaro



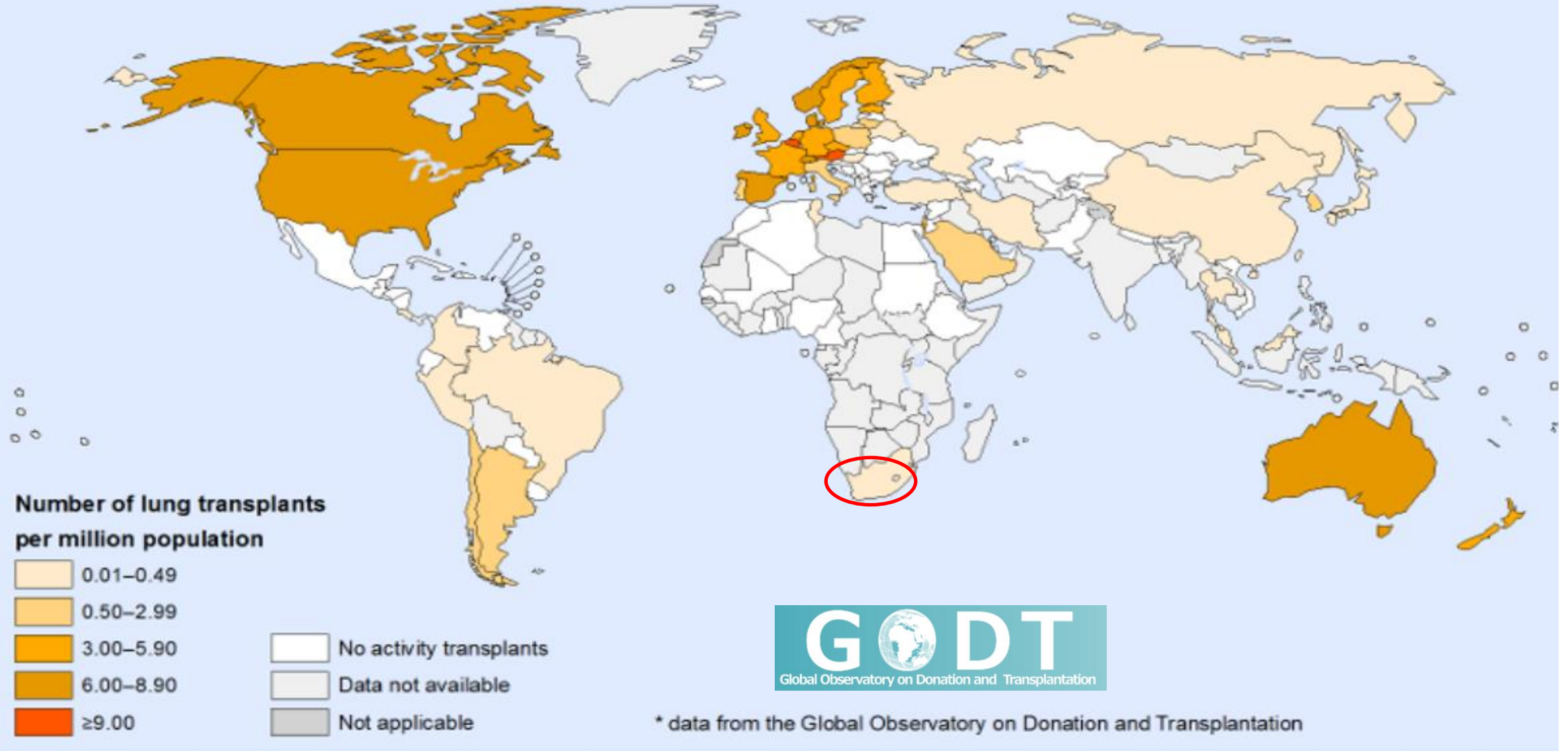
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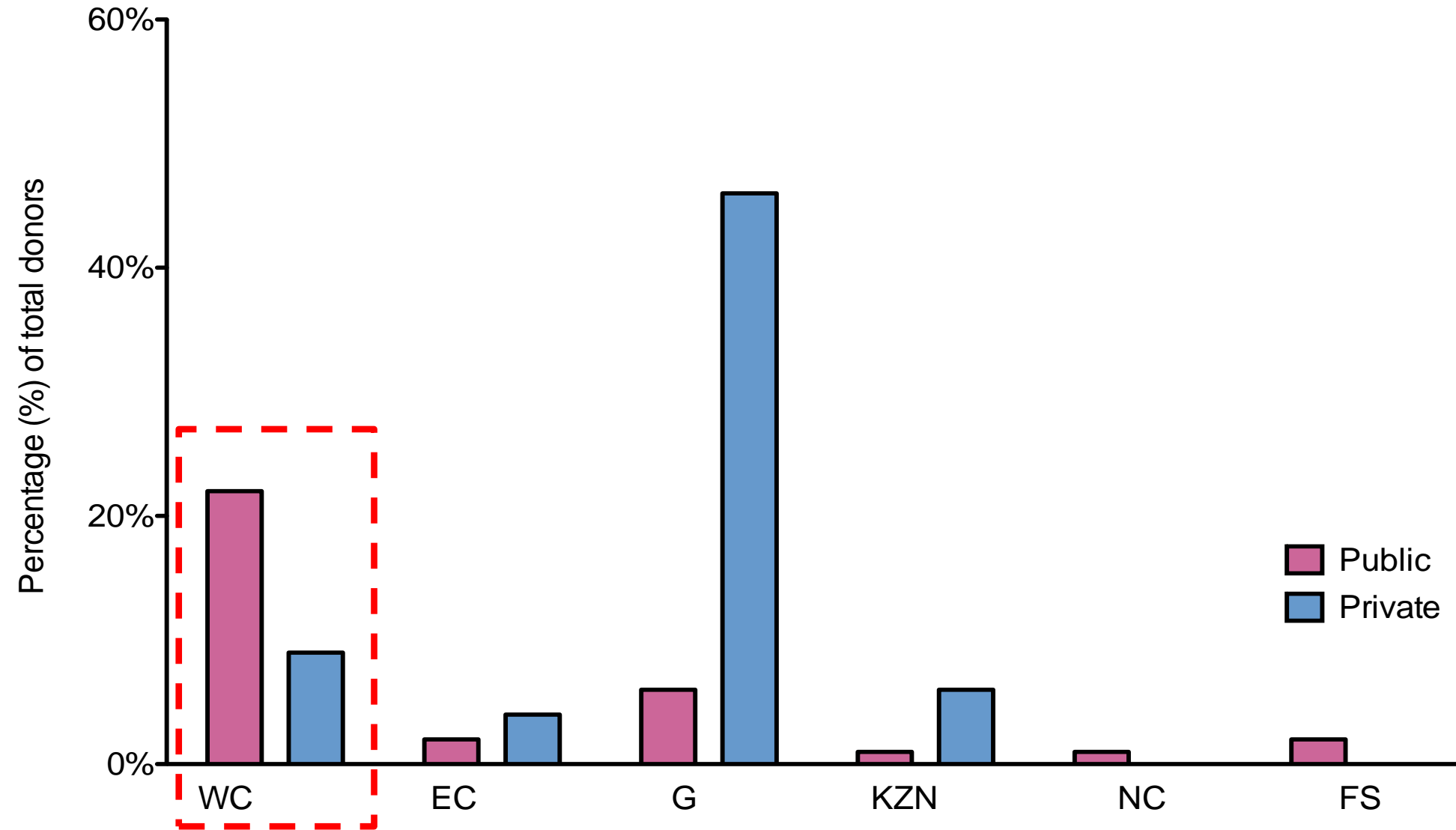
No relevant disclosures or conflicts of interest.

The scale of the problem



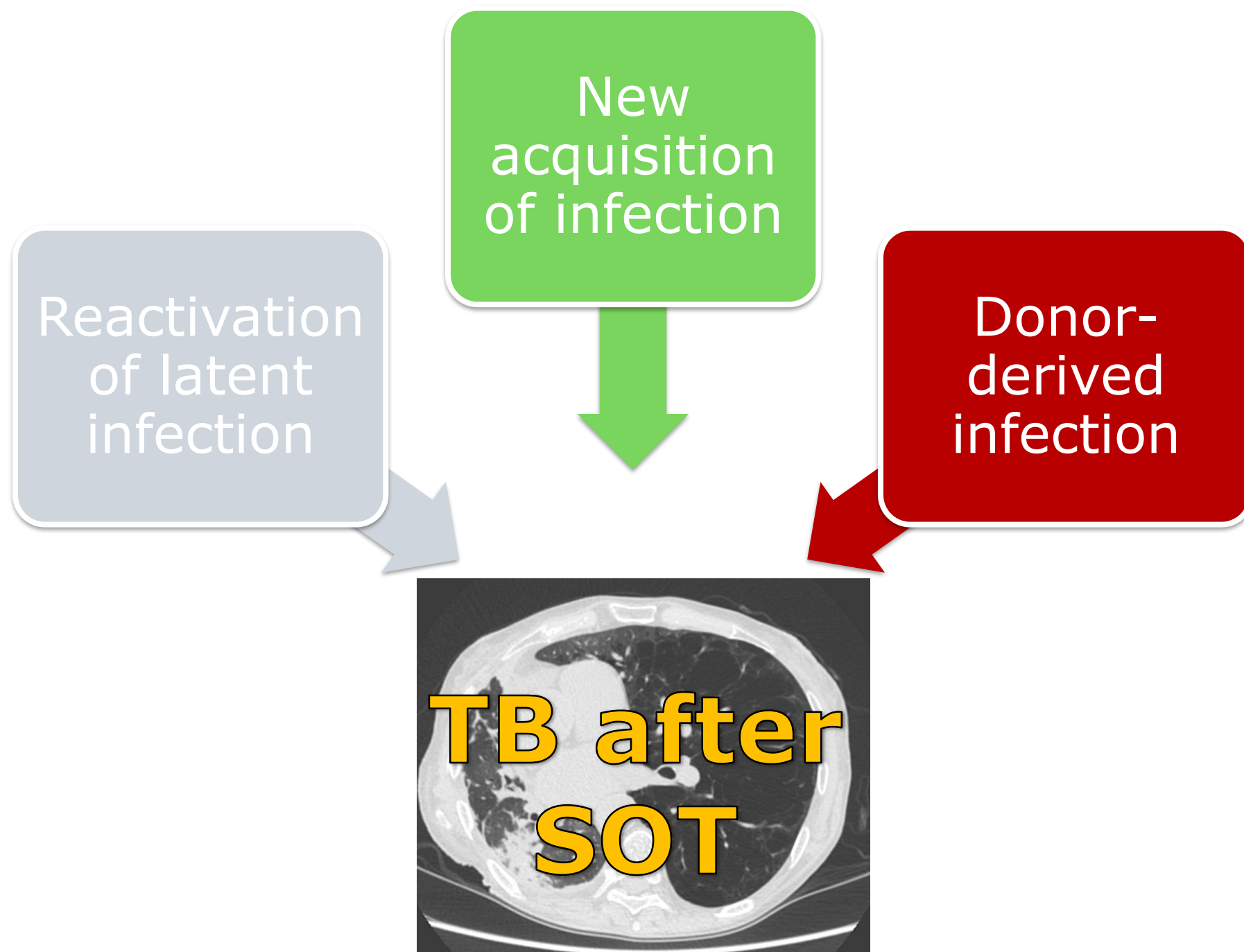
~4000 lung transplants globally annually



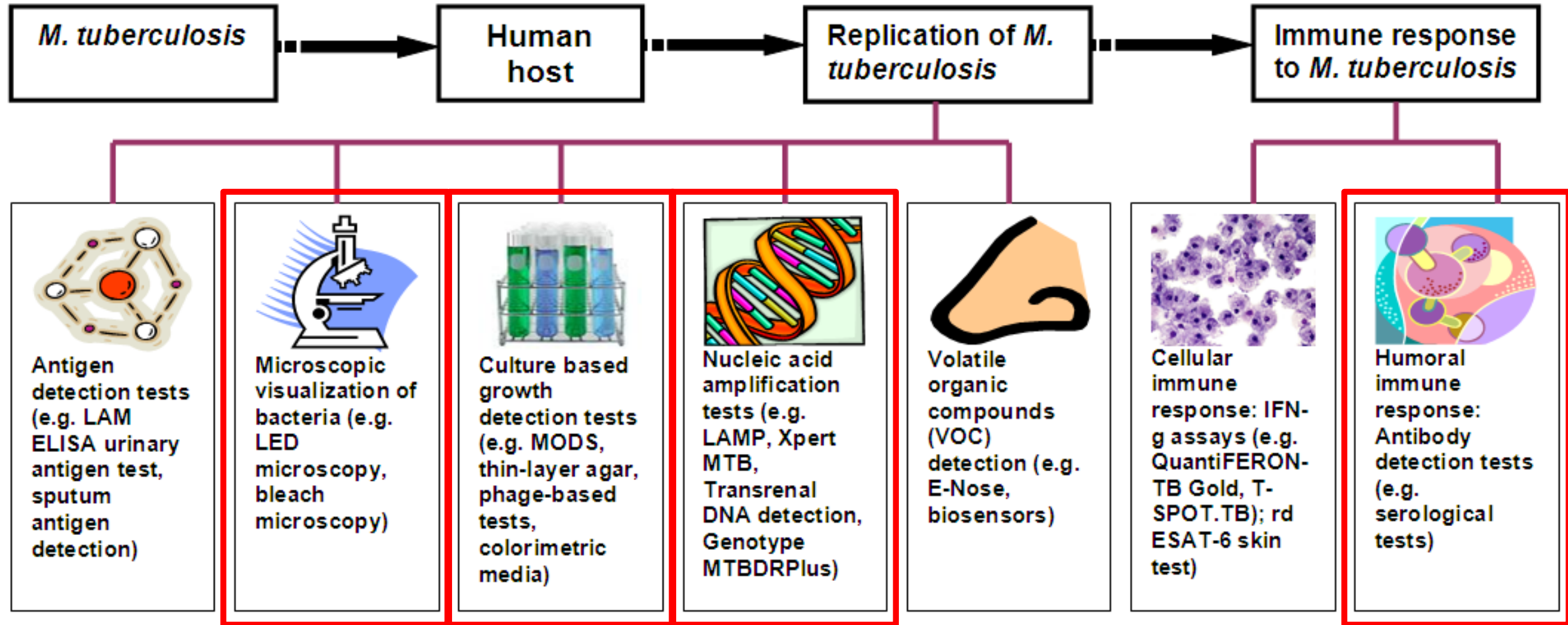


TB following lung transplantation

- Incidence of TB in LTX recipients:
 - 2072 per 100,000 transplant-years in Spain
 - 4750 per 100,000 transplant-years in Saudi Arabia
- Few studies from high-burden settings
- In the Saudi study, (and compared to general population), the incidence of TB was:
 - 8 times higher in renal recipients
 - 40 times higher in heart recipients
 - 42 times higher in liver recipients
 - 339 times higher in lung recipients



Available TB diagnostics



Conventional TB diagnostics

SMEAR

- Traditional cornerstone of TB diagnosis
- Sensitivity ~50%
- No information about drug resistance

CULTURE

- Liquid culture methods (MGIT): 2 – 6 weeks
- Indirect: Liquid media further 1-3 weeks
- Direct e.g. MODS, TLA: 1-3wks
- Problems: Delayed (1-3mths), expensive, technical issues (false +ve, contamination)

Nucleic acid amplification tests


1 Sputum liquefaction and inactivation
2:1 sample reagent

2 Transfer of 2 ml material into test cartridge

7 Seminested real-time amplification and detection in integrated reaction tube

8 Printable test result

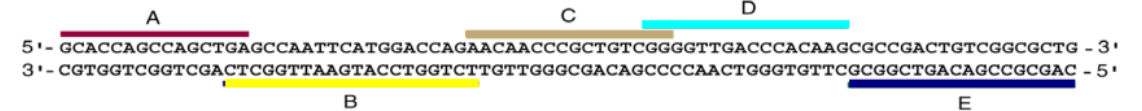
Xpert vs. Ultra
20CFU/ml vs. 130 CFU/ml



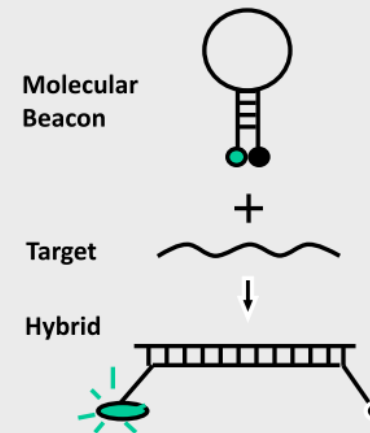
Time to result, 1 hour 45 minutes



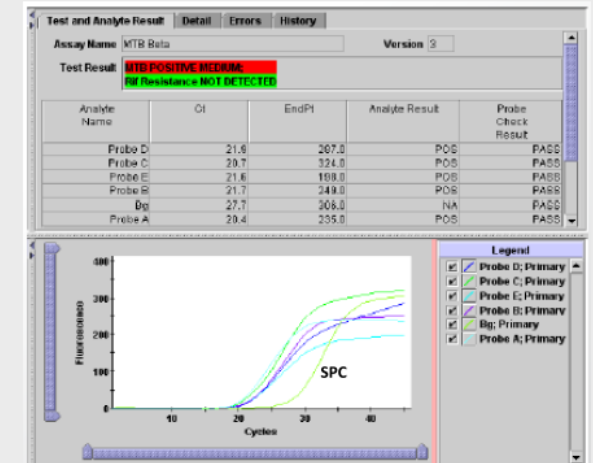
Xpert MTB/Rif molecular beacon assay



The PCR target is the 81 bp region of the *rpoB* gene: 5 probes bind to wildtype, but not mutant target



Each probe is labeled with a different fluorescent dye, permitting simultaneous detection



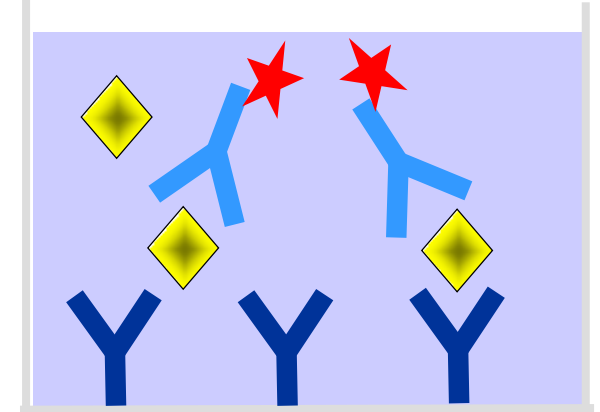
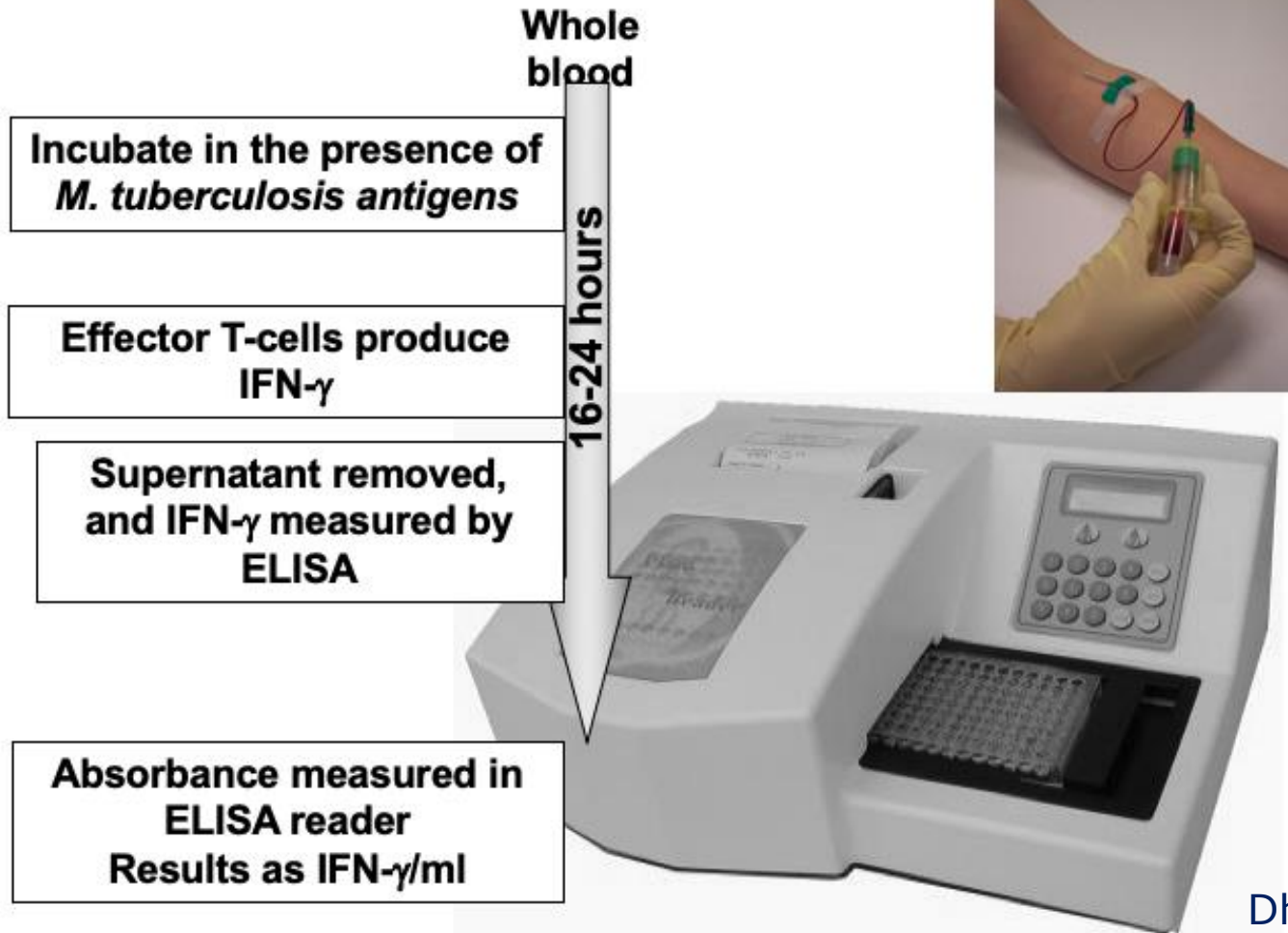
Example of Rif-Sensitive Profile – 5 probes & SPC show fluorescence

Problems: very sensitive - false-positives in patients with previous TB

Boehme C, NEJM, 2010.

Interferon- γ release assays

QuantiFERON®-TB Gold IT (Cellestis, Australia)

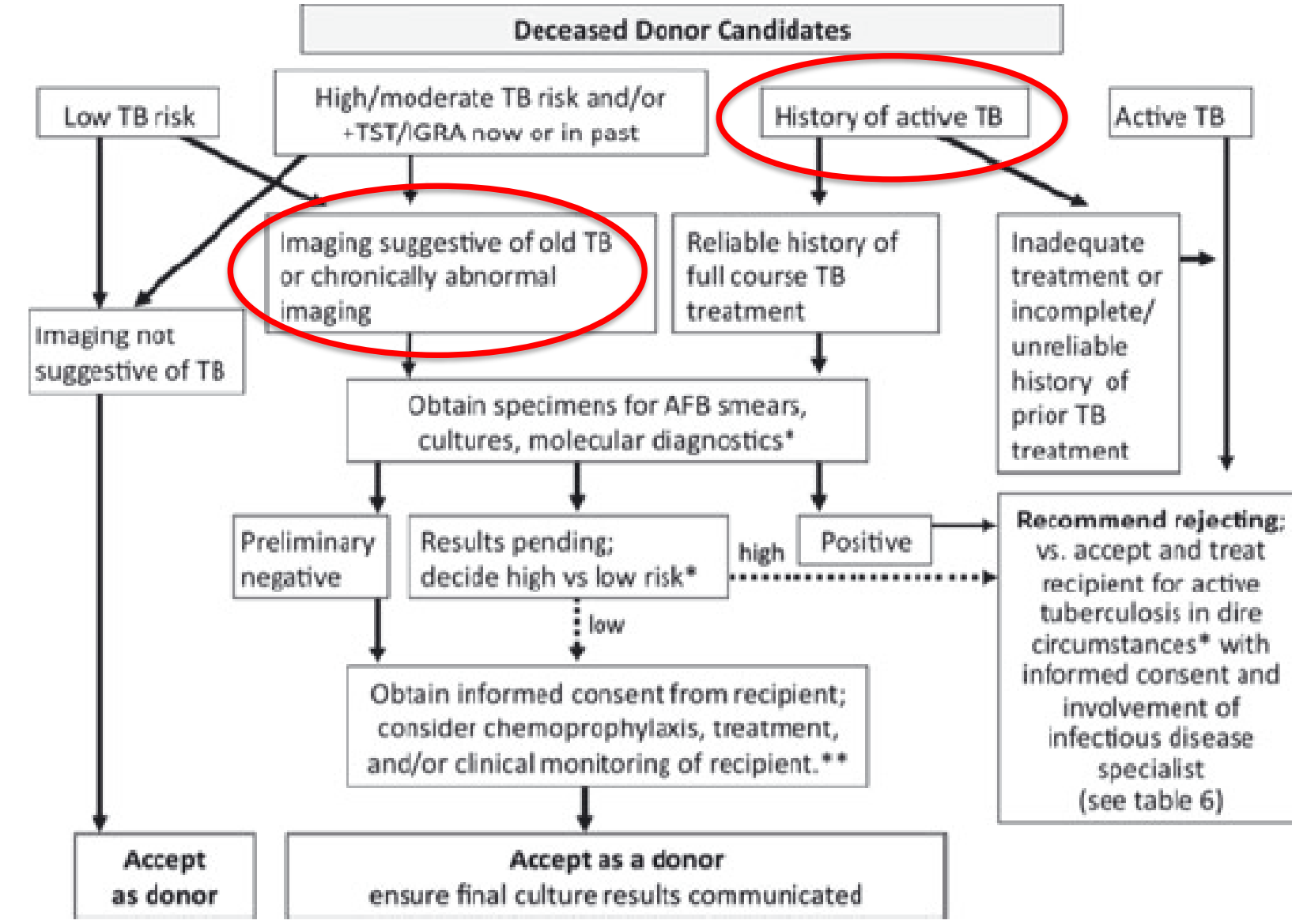


In high-burden setting like SA:
No role in diagnosing active TB
Indicate transient immune response to *M.tb* – significance unknown

Testing the deceased donor

- Active TB on radiology – **contraindication to Tx**
- **Must ask about history of treated TB**
- Presence of fibrotic or calcified lesions and no history of TB treatment – **contraindication to Tx**
- Presence of fibrotic or calcified lesions and positive history of TB treatment – **depends on extent of lung involvement, priority of the recipient (extended criteria)**
- LTBI does not have radiological changes
- TST is not practical
- IGRA – potential test, although result will be unavailable at the time of Tx (also some evidence that brain death is immunosuppressive and donors have higher indeterminate results, so possibly less reliable)

Screening donors for TB



Meeting Report

Diagnosis and Management of Tuberculosis in Transplant Donors: A Donor-Derived Infections Consensus Conference Report[†]

Table 2: Risk factors for tuberculosis (40)

Country of Origin	Incidence $\geq 100/100\ 000$
Social risk factors	Homeless Incarceration Alcohol Known TB contact
Medical risk factors	History of untreated TB Radiographic evidence prior TB BMI < 18.5 Diabetes mellitus Cigarette smoking
Organ transplanted	? Lung

Prevention of *de novo* infection

- Several studies from medium and high-burden countries show benefit of universal isoniazid prophylaxis post-transplant (Saudi Arabia, Pakistan) in renal transplantation
- Meta-analysis of 709 patients from 4 RCTS show reduction in risk of TB with INH prophylaxis (**RR 0.31**; 95% CI, 0.19–0.51) with no increase in hepatotoxicity.

Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis



- Universal prophylaxis at GSH in renal programme – however, in liver programme, only introduce INH at ~6 weeks (significantly increased hepatotoxicity – only ~40% of patients tolerate it)

Adamu B, Cochrane Database, 2014.
Naqvi R. Renal transplantation, 2006.
Al-Mukhaini SM, Annals of Saudi Medicine, 2017.

GSH protocol

DONORS

- Main emphasis on excluding **active TB**:
 - BAL/tracheal aspirate with sample for Xpert *Ultra* and culture on all donors
 - Low threshold for CT chest in potential donors with exclusion of donors with radiological changes suggestive of active TB
- Inclusion of donors with radiological changes of healed TB if known (completed) treatment history of drug-sensitive TB at clinician's discretion

RECIPIENTS

- No investigation or treatment for LTBI
- **Universal prophylaxis with INH post-transplant**

GSH protocol

Problems

- Drug-drug interactions
- Potential for hepatotoxicity (especially when on an azole)
- Potential for neuropsychiatric side-effects (especially in combination with tacrolimus, prednisone and azoles)
- Potential for INH resistance if active TB not diagnosed promptly
- Additional pill burden
- Neuropathy (routine supplementation with pyridoxine)



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