What new insights from immunology and natural history should be investigated or incorporated into models of TB prevention?

Thinking of TB from the perspective of the infectious host

Hanif Esmail

Clinical Lecturer – University of Oxford

Hon. Consultant in Infectious Disease – Oxford University Hospitals

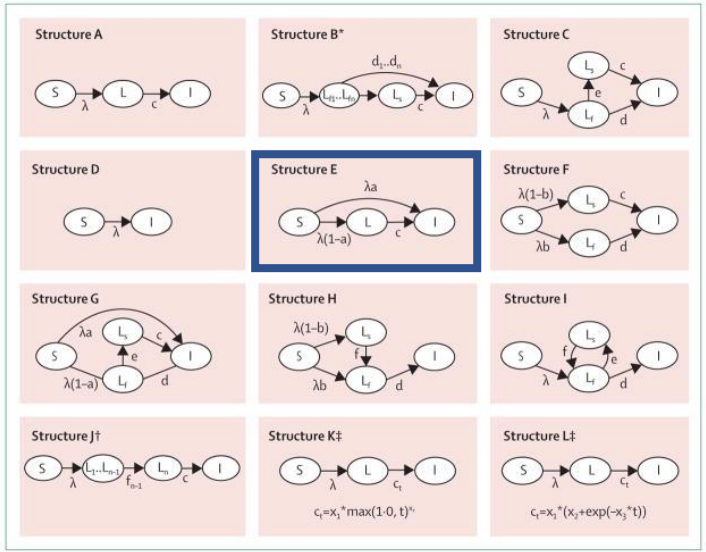
Hon. Research Associate – University of Cape Town

JMGP Fellow – Royal College of Physicians

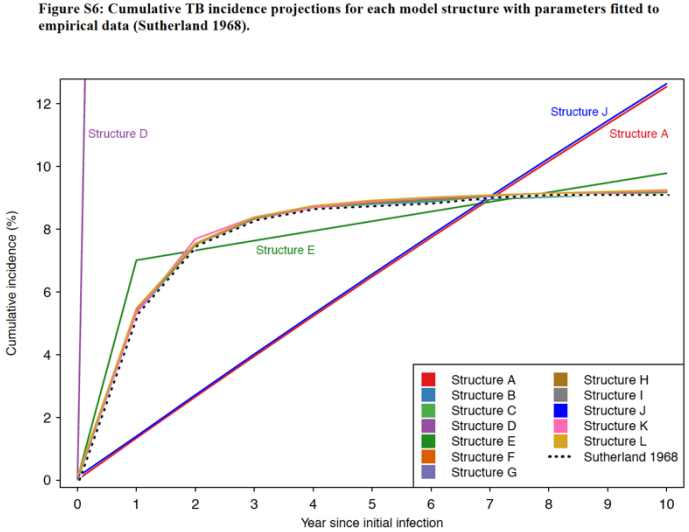
Overview

- Overview of TB pathogenesis as relevant to this presentation
- Kinetics of disease progression – historical data
- Implication for infectiousness/models

Current mathematical models

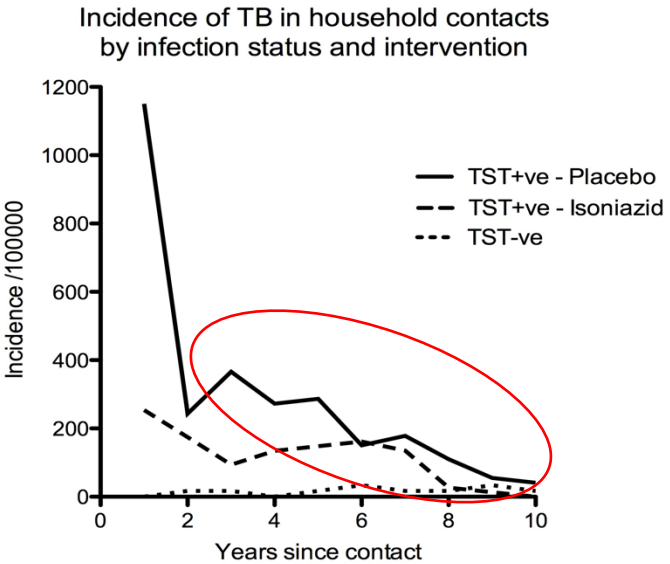


Menzies LID 2018

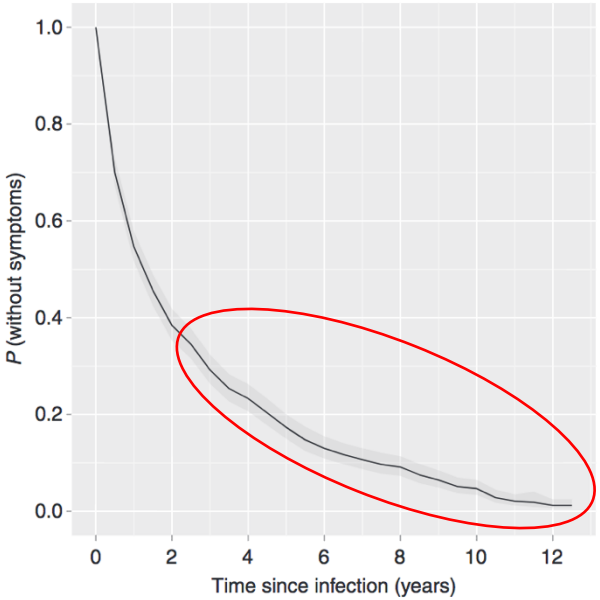


- Highlights importance of fitting to epi data
- 2 latent compartment models fit data best
- In latent stage, assumption no adverse health effects and will not transmit

Epidemiological data being fit to



Ferebee Adv. Tuberc Res 1970

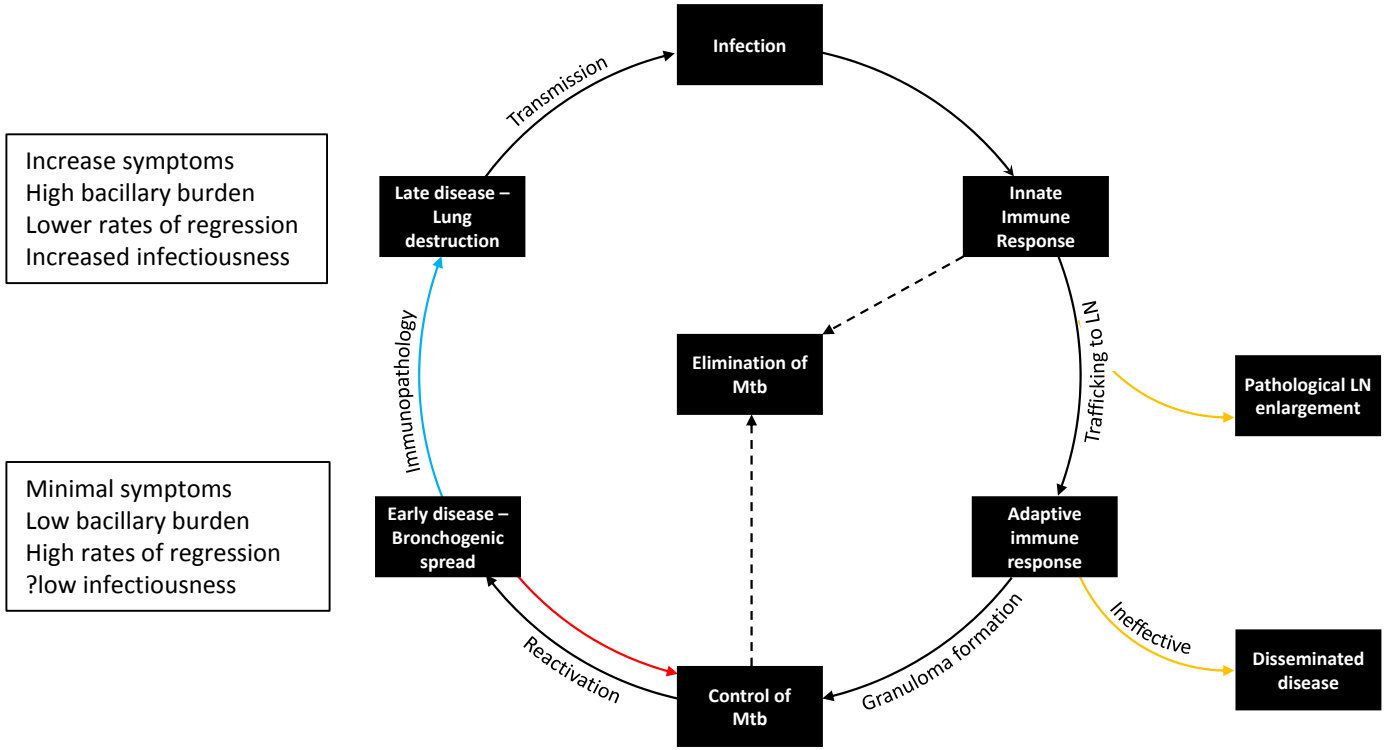


Borgdorff et al Int journ epi 2011

Passive case finding

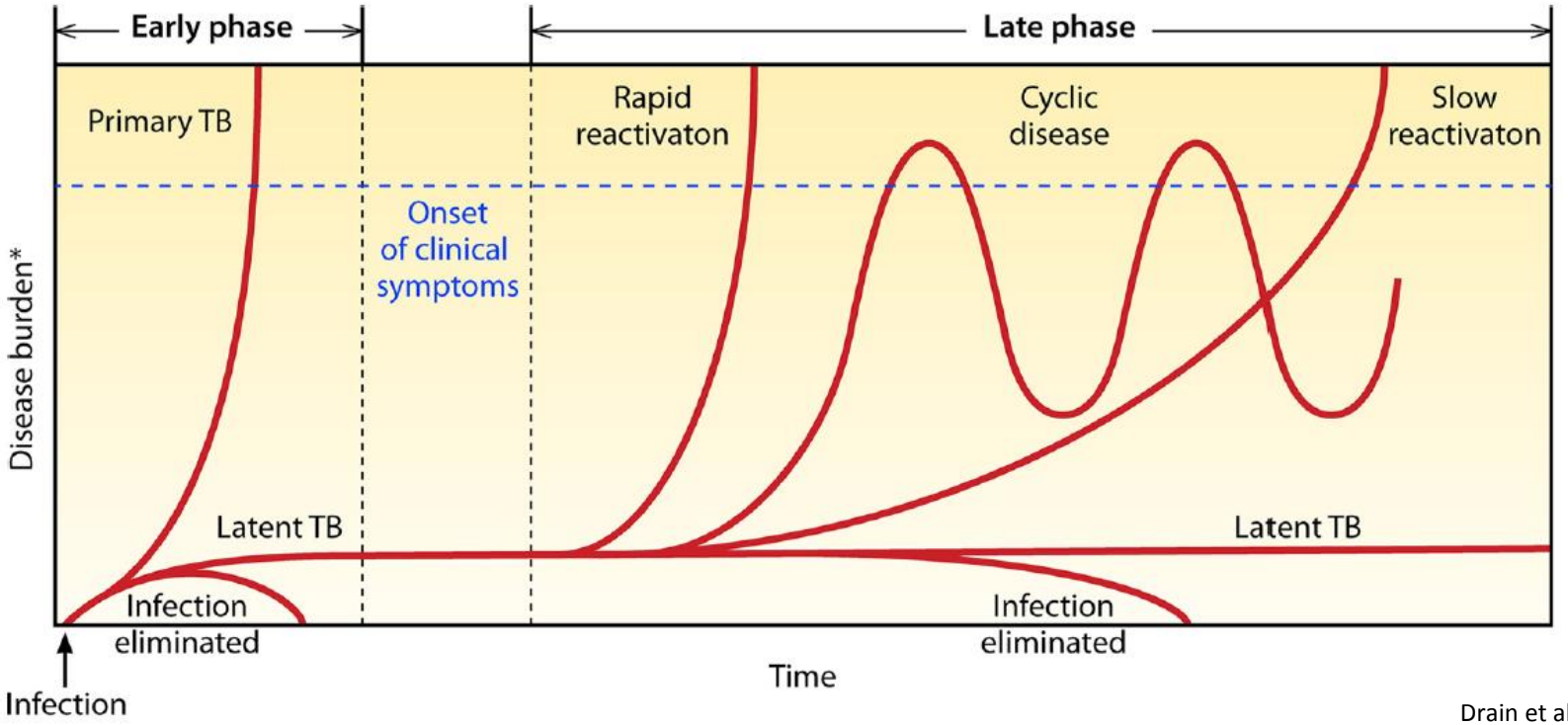
When does disease/infectiousness begin

TB pathogenesis



Seddon, Chiang, Esmail, Coussens – submitted

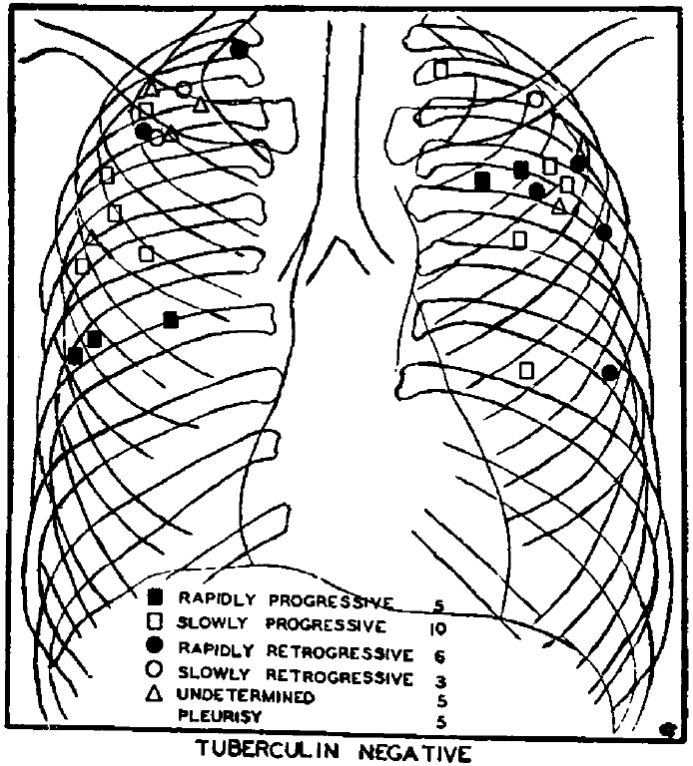
What is occurring in late reactivation?



Drain et al CMR 2018

Modern imaging studies may be helpful to investigate but may lead to early treatment

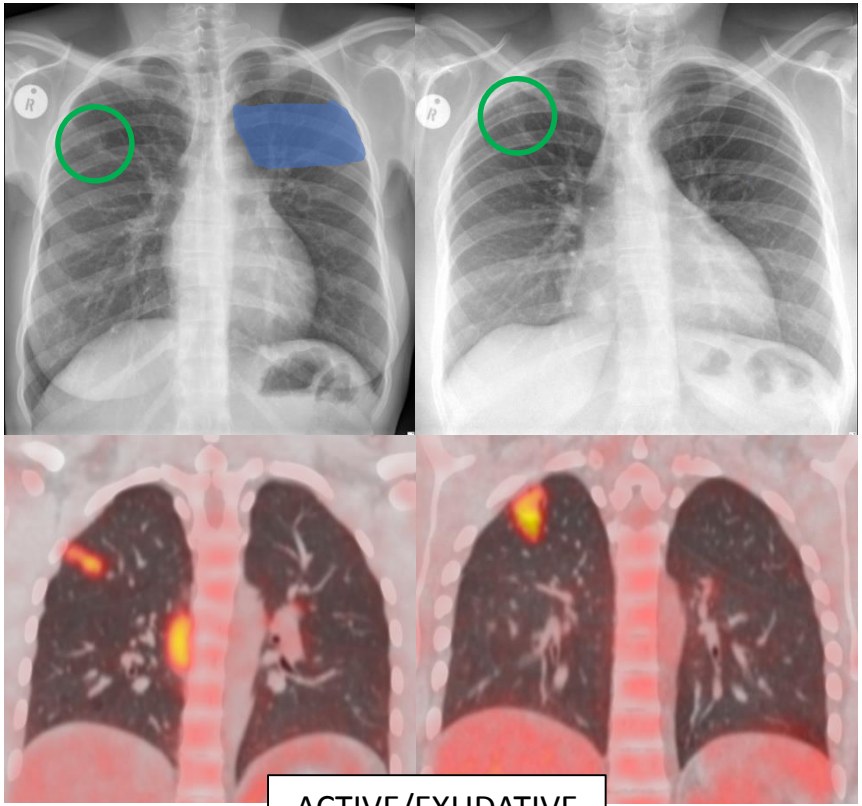
Kinetics of initial lesions



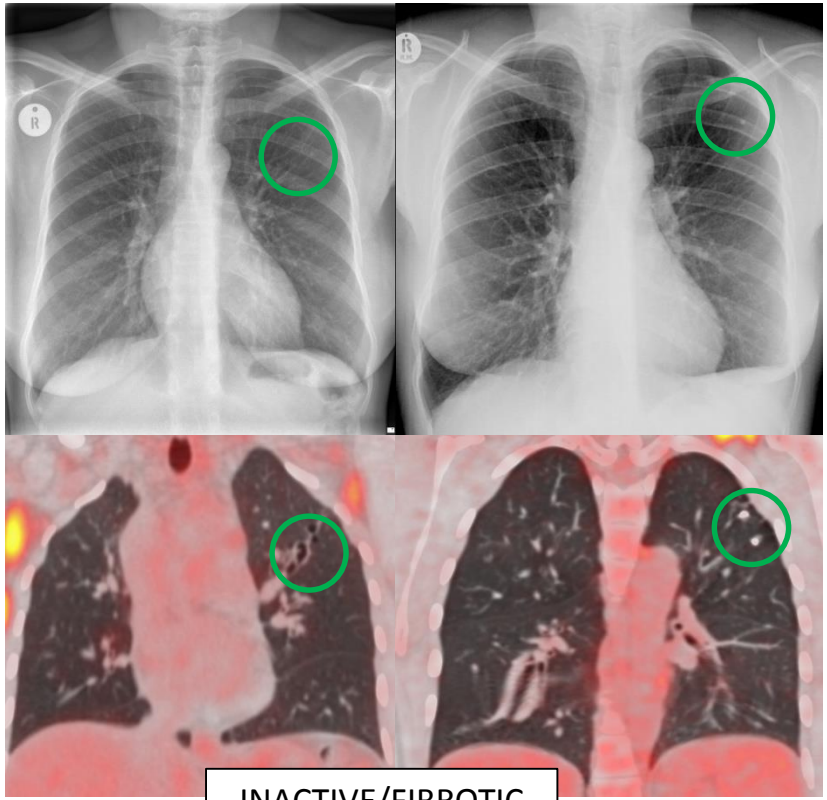
Israel et al JAMA 1941

- 277 TST-ve Nursing students USA 1935-9
- All became TST positive (tested 4mthly)
  - 85.9% (1 year), 95.3% (2 years), 100% (3 years)
- CXR (4mthly)
  - 29 (10.4%)- Pulmonary lesions
    - Rapid progression 5/29 (17%)
    - Slow progression 10/29 (34%)
    - Rapid Regression 6/29 (21%)
    - Slow Regression 3/29 (10%)
    - Undetermined 5/29 (17%)

Minimal lesions from mass screening



ACTIVE/EXUDATIVE



INACTIVE/FIBROTIC

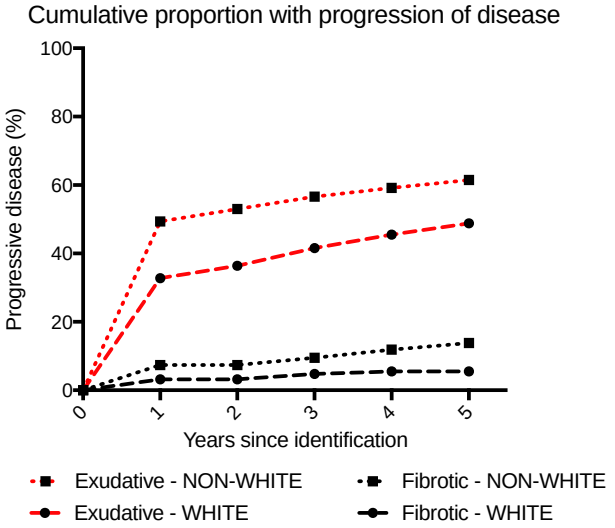
Minimal lesions

- Typically identified by mass CXR screening or employment/HHC screening
- Likely missed the rapid progressors
- Patients “well” –but may have symptom on direct questioning
- 5 year mortality typically low 0.7-3%
- Microbiology
  - Decker et al - 269 admitted to sanatoria with 1930-41
    - 5.9% smear positive
    - 14% positive – sputum Guinea Pig inoculation (58% unable to produce sputum)
    - 69% positive if at least 3x Gastric lavage and 72 hour cough specimen – Culture + GP inoculation
  - HKCS/BMRC studies 1979-1984
    - Minimal TB all culture –ve x 5
    - 18.5% culture positive at 2 months/35% at 1 year

RCP Prophit TB survey 1956
Decker et al Am Rev Tuberc 1943
HKCS/BMRC Am Rev Resp Dis 1984

Follow-up of minimal lesions

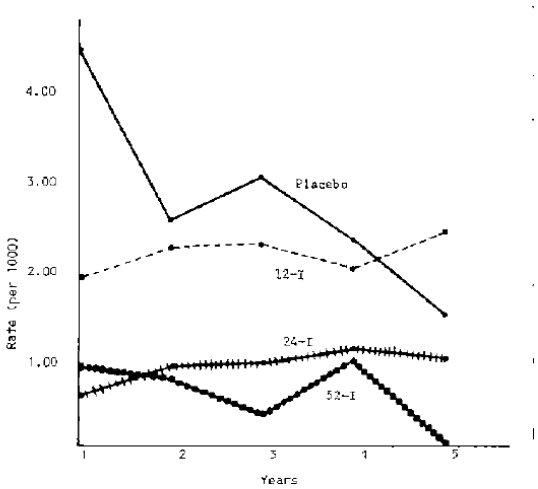
- 469 cases of minimal TB (standard def)
  - New York 1940s
  - 76% no symptoms
  - 4 categories of CXR
    - Exudative/Exudative productive – 46.9%
    - Productive-fibrotic – fibrocalcific – 53.1%
  - Observed over 5 years+
    - Progression more frequent in
      - Exudative lesions
      - Young adults
      - Non-white



	EXUDATIVE	FIBROTIC
Progressive	45%	6%
Unstable	6%	2%
Regressed	44%	1%
Stable	5%	91%

Reisner and Downes Am Rev Tuberc 1945

Fibrotic lesions



- Stead NEJM 1967
  - 178 1st episode of TB > 50yrs
  - 128 had CXR available at least 1 year prior to presentation
    - 108 (84%) upper zone fibrotic scars

- IUAT Bull WHO 1982
  - 28,000 Fibrotic lesion - no prev TB tx
  - Randomized Placebo/12/24/52wk INH
  - Placebo – 1.4% 5 yr incidence (cult +)

Conclusions/Thoughts

- Caveats
  - CXR imperfect tool (but consistent findings) – PET/CT studies ongoing
  - Historical data from pre chemotherapy era(but may reflect current resource poor settings)
  - Length time bias
  - Subclinical? (Oligosymptomatic period - may be a more accurate concept)
- Should this be investigated or incorporated into models of TB prevention?
  - Implications
    - Late presenters may have been infectious earlier in disease course
    - Investing resource in detecting early disease may have a greater impact than predicted
    - Recognition of chronic spreaders

Acknowledgements

UCT

Robert Wilkinson

Friedrich Thienemann

Anna Coussens

Bianca Sossen

LSHTM

Rein Houben

Support

Oxford University OUCAGS Clinical Academic Graduate School

NRF National Research Foundation

Royal College of Physicians

saMRC advancinglife

NIH