Exploring the impact of

subclinical TB on incidence estimates from prevalence surveys

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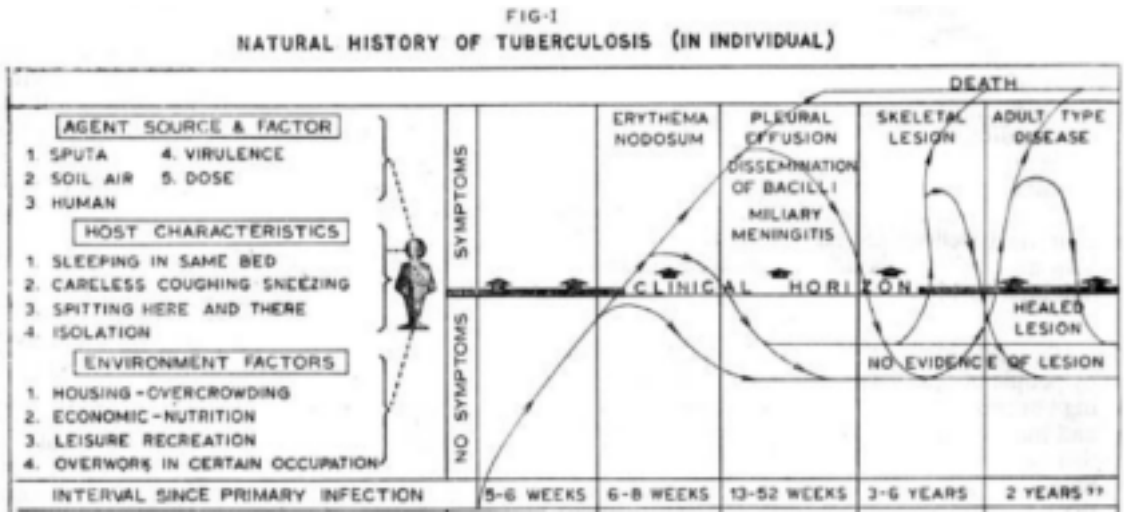
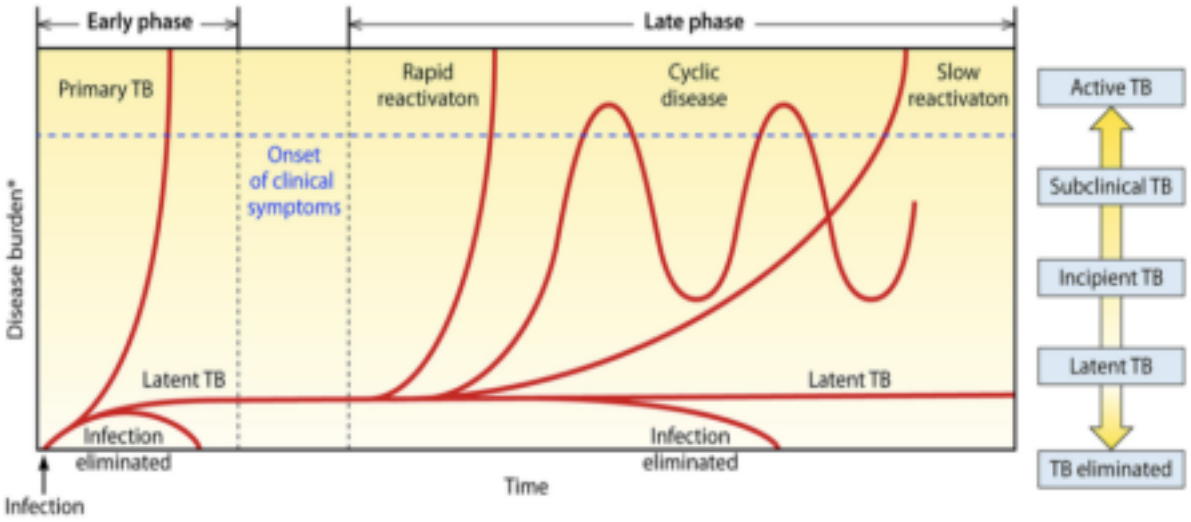
- I have **no**, real or perceived, direct or indirect conflicts of interest that relate to this presentation.

Esmail et al. 2014 Phil Trans

Barry III et al. 2009 Nat Rev



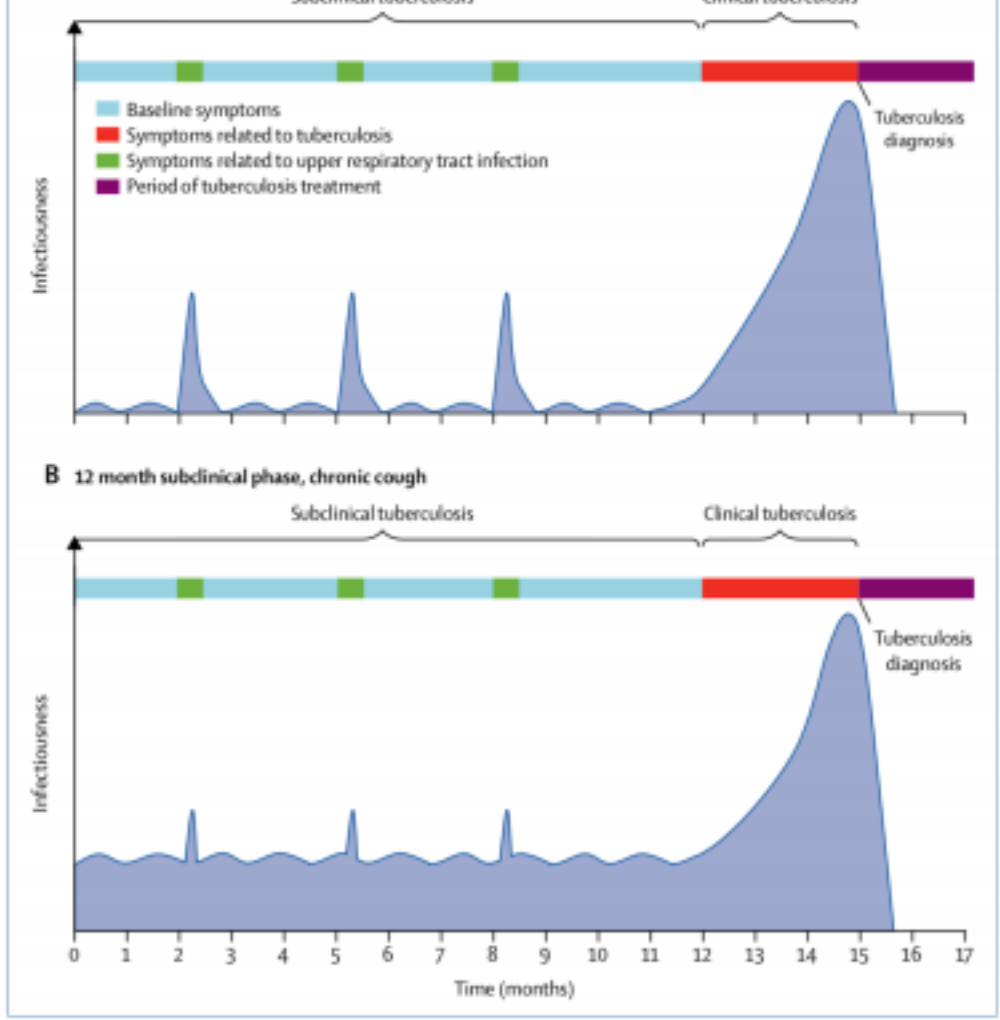


Drain et al. 2018 Clin Micr Rev Gothi. 1978 Ind J Tuber

- Culture positive, symptom screen negative

- Why is subclinical TB important?
  - can progress to symptomatic disease
  - can still be infectious
  - difficult to detect

- Potential to progress to active disease or regress to culture negative
  - Could have impact on incidence estimates



Esmail et al 2018 Lanc RM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- Prevalence surveys used to estimate incidence in 24 countries -

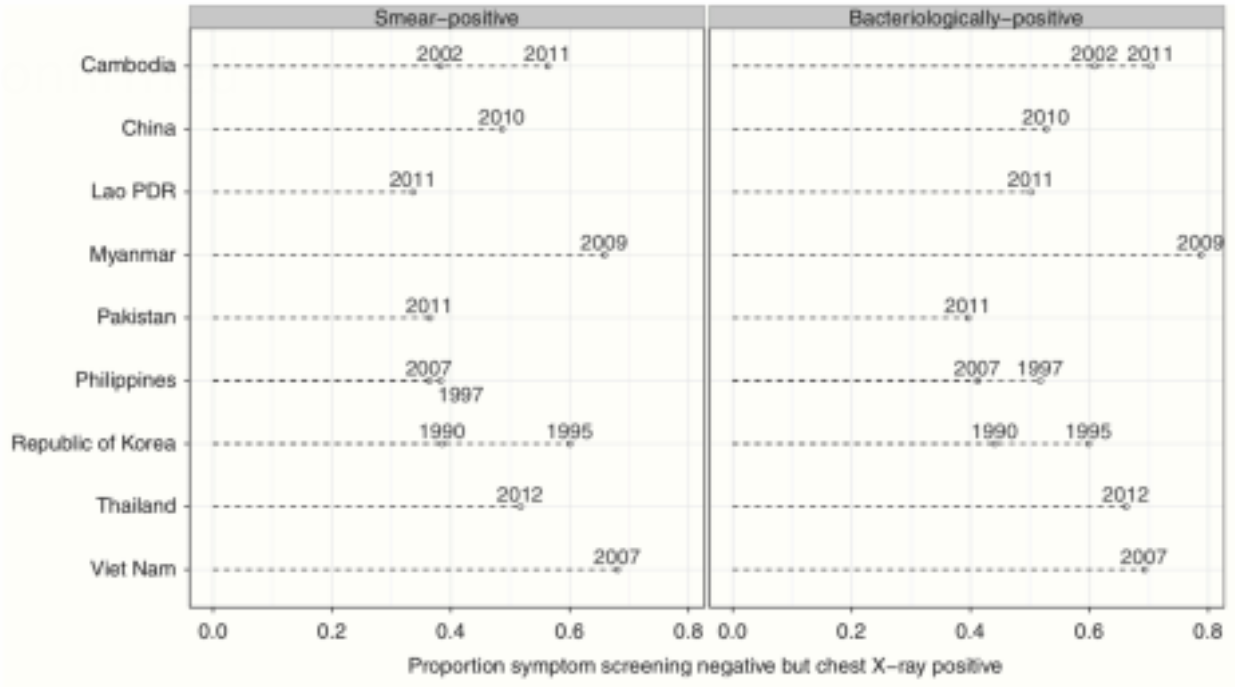
  Estimated 60% of global incident cases in these countries (2018)

- Disease defined as bacteriologically c

- High proportion of bacteriologically positive disease symptom negative -

  ~40% in Pakistan, 2011

  - ~ 80% in Myanmar, 2009



Onozaki Global tuberculosis report 2019 I, et al., 2015, Trop Med Int Health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- High proportion of bacteriologically confirmed disease screens symptom negative

- Currently assumed that all asymptomatic disease eventually progresses • What if it doesn't?

- In process of systematic review to find data on natural progression and regression
    - pre-chemotherapy, longitudinal studies
    - ~10,000 titles reviewed
    - data collected from 10 titles so far

Susceptible

• **Susceptible** = never been infected

• **Infected** = chance to progress without reinfection • **Minimal disease** = start of changes

but bacteriologically negative

- **Subclinical disease** = x-ray changes and bacteriologically positive, negative at symptom screening
- **Active disease** = x-ray changes, bacteriologically positive and symptomatic
- **Self-cure** = recovery without treatment, no progression without reinfection

Infected
(TST or IGRA +ve)

Minimal
(x-ray +ve,
culture –ve)

Subclinical
(culture +ve,
symptom –ve)

Active
(culture +ve,
symptom +ve)
Self cure


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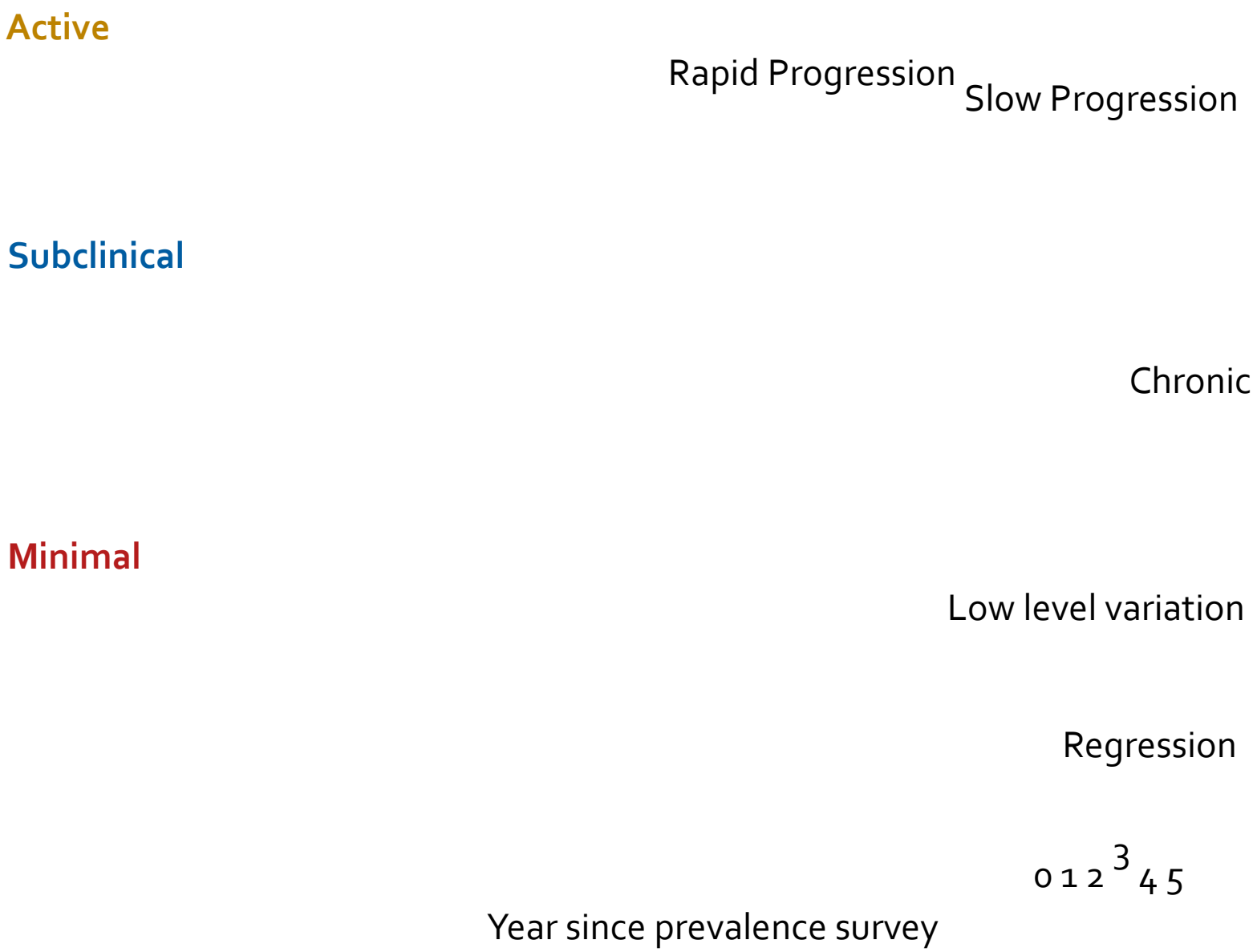
Active
Rapid Progression
Slow Progression
Subclinical
Chronic
Minimal
Low level variation
Regression
0 1 2 3 4 5
Year since prevalence survey


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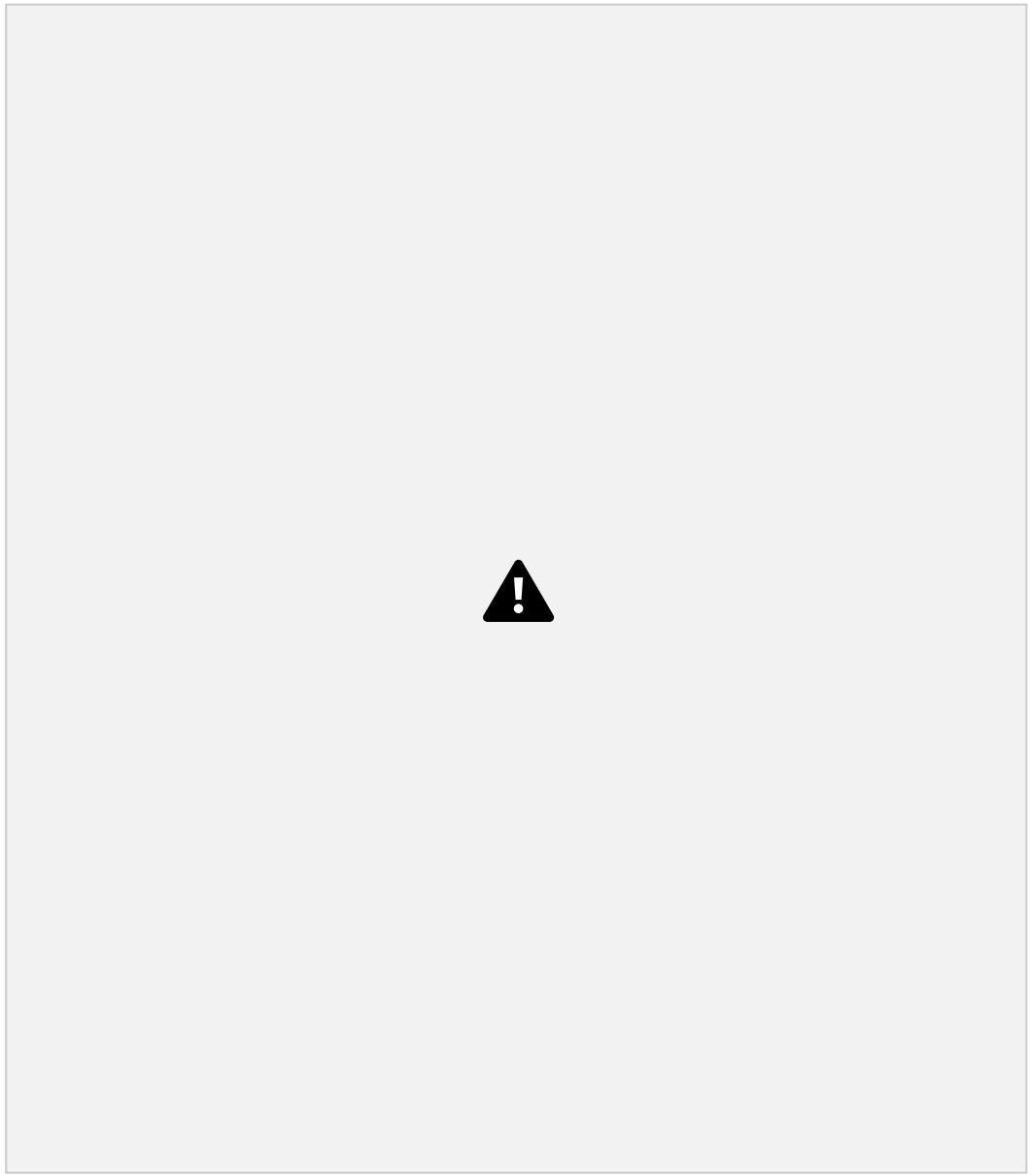
Want to understand the trajectory of bacteriologically confirmed disease (subclinical and clinical) that is found at prevalence surveys.

1. Population distribution: How does the overall distribution across disease states change over time?

2. Long-term trajectories: How do individuals move between disease states?

3. Proportion of trajectories: What is the relative importance of potential trajectories for subclinical disease?

Selection of example data



Minimal Subclinical 40 176 3 Minimal Subclinical 40 176 3 Subclinical

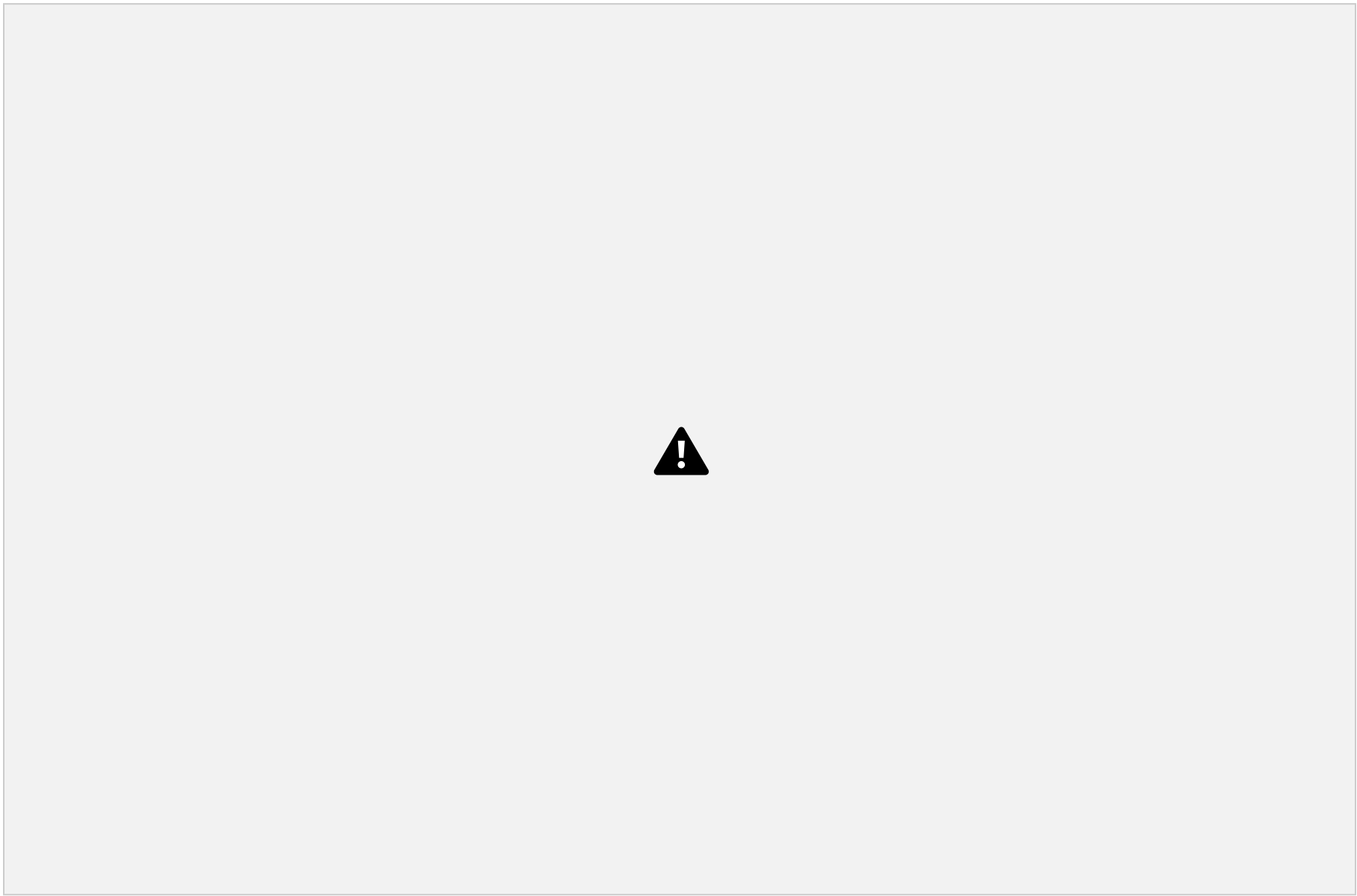
Active 11 34 12 Subclinical Active 11 34 12 Active Minimal 11 29 33 Active

Minimal 11 29 33

Subclinical (culture +ve)
Active (symptom +ve)

Minimal (x-ray +ve)

Borgdorff MW. 2004



0 Years since prevalence survey 5

Active

?%

?%

Subclinical Minimal

Rapid Progression Slow Progression

Chronic

Low level variation

Regression

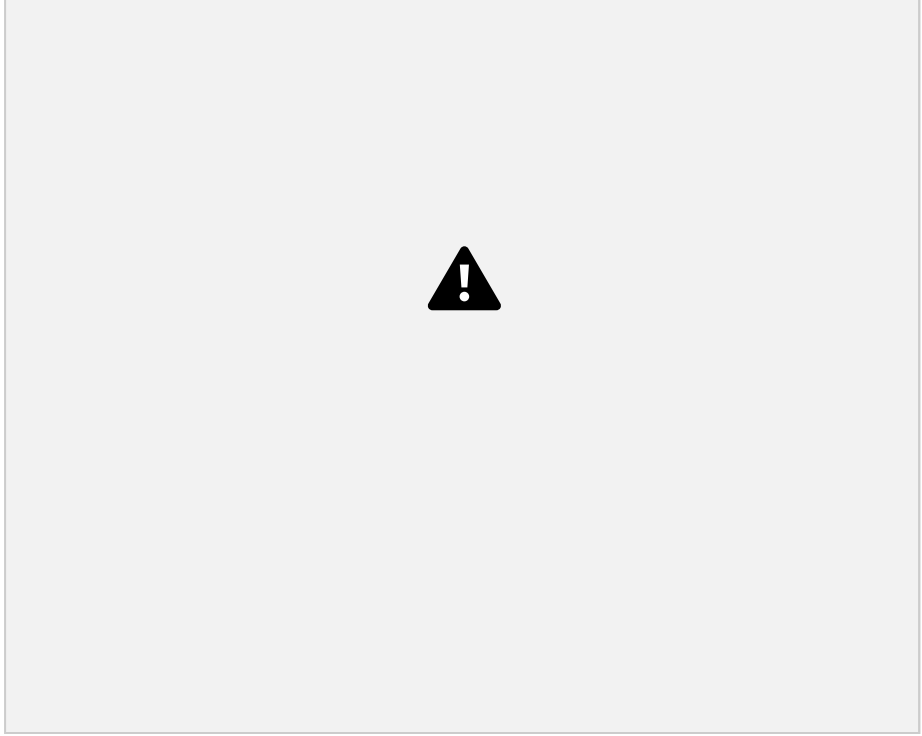
0 1 2 3 4 5 Years since prevalence survey

?% ?%

?%

Disease definitions:

- **Rapid Progressive** = Progress to active disease within 2 years of prevalence survey
- **Slow Progressive** = Progress to active disease after 2 years after prevalence survey
- **Permanent Regressor** = Regresses to bacteriologically negative disease immediately after survey
- **Chronic** = Stays bacteriologically positive but symptom negative
- **Low level variation** = not immediately and permanently regressed, not permanently subclinical



TB

death

Treatment

Active

Subclinical

Minimal

Time (months)

17%

34%

Active

Subclinical Minimal

Rapid Progression Slow Progression

Chronic

Low level variation

Regression

0 1 2 3 4 5 Years since prevalence survey

38% 3%

8%

- Work in progress, limited data at the moment but more coming through review

- Potentially overestimating progression
    - No recovery without treatment
        - Entire population assumed to be equally likely to progress to active disease

- Population assumed to be homogeneous
    - No age dependent risks
    - No consideration for previous TB infection/disease

- Data based analysis
    - Data from longitudinal studies, unaffected by treatment
    - Data will increase as more studies analysed
    - Maximising best opportunity of collating necessary data

- Bayesian modelling approach flexible to both absorb heterogeneity in results, and reflect uncertainty

- Example of fitting a model to data to quantify a mechanism.

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