Subclinical TB: implications for TB vaccine trial designs and development

Plenary 3. Advancing TB vaccine clinical development

Global TB vaccine Forum

Rio de Janeiro

9th October 2024

Gavin Churchyard

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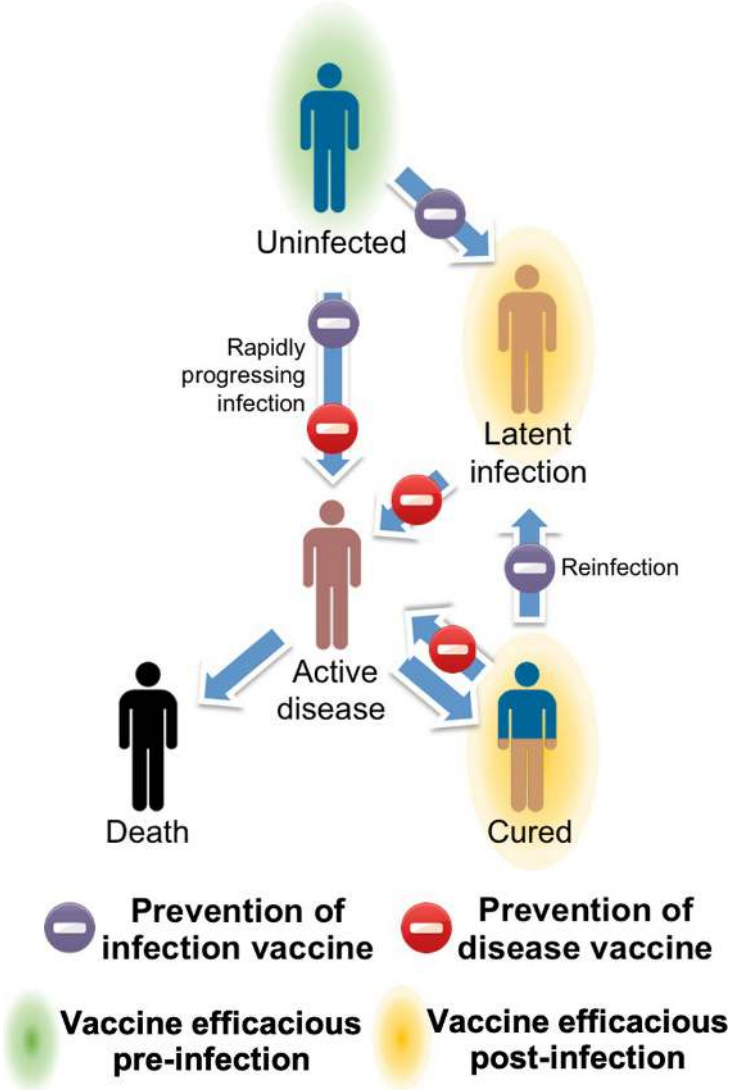
Overview

- Background
- Subclinical TB
  - Clinical characteristics
  - Implications of infectious scTB for POD TB vaccine trials
  - Trial design options
- Evolving landscape
- Conclusion



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Background

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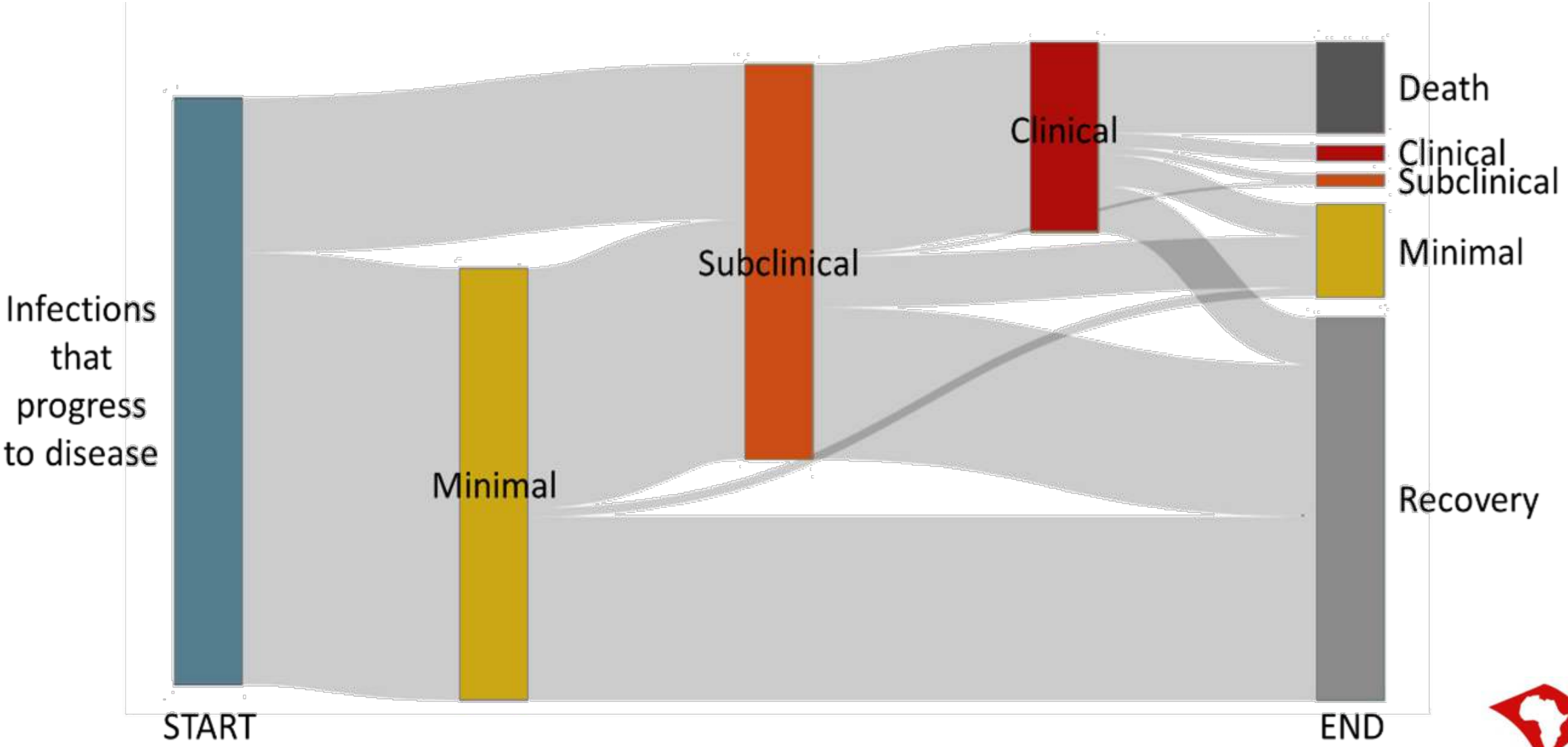
Background

- Definition: un-infectious or infectious, but are without, not aware, or not reporting symptoms/signs related to TB
- scTB accounts for half of prevalent TB globally
- Data on transmissibility of scTB and its post-TB sequelae are limited
- The WHO Preferred Product Characteristics for POD TB vaccines do not consider the implications of subclinical TB
- The TB vaccine Roadmap identifies subclinical TB as a research gap
- Regulators typically require efficacy endpoints to be specific, it is therefore likely that only microbiologically confirmed scTB would be counted as an efficacy endpoint

Pathways over 10 years following *Mtb* infection



Horton KC. Proc Natl Acad Sci USA. 2023

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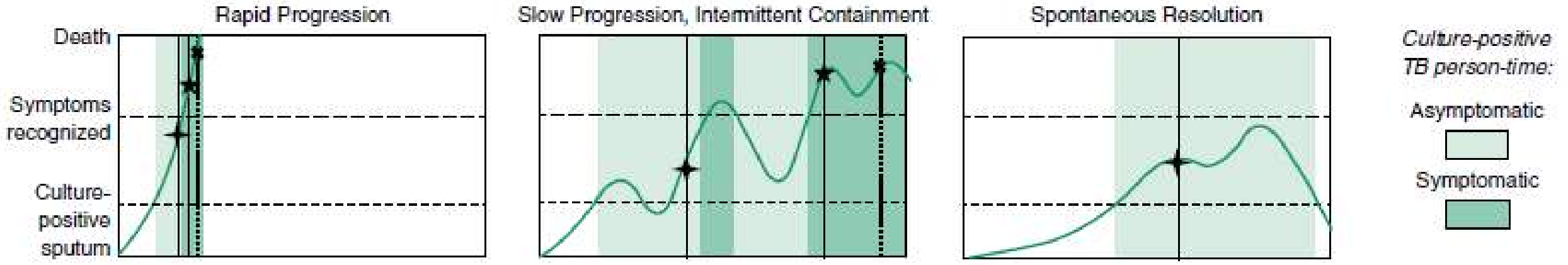
Natural history



Kendall. Am J Respir Crit Care Med, 2021

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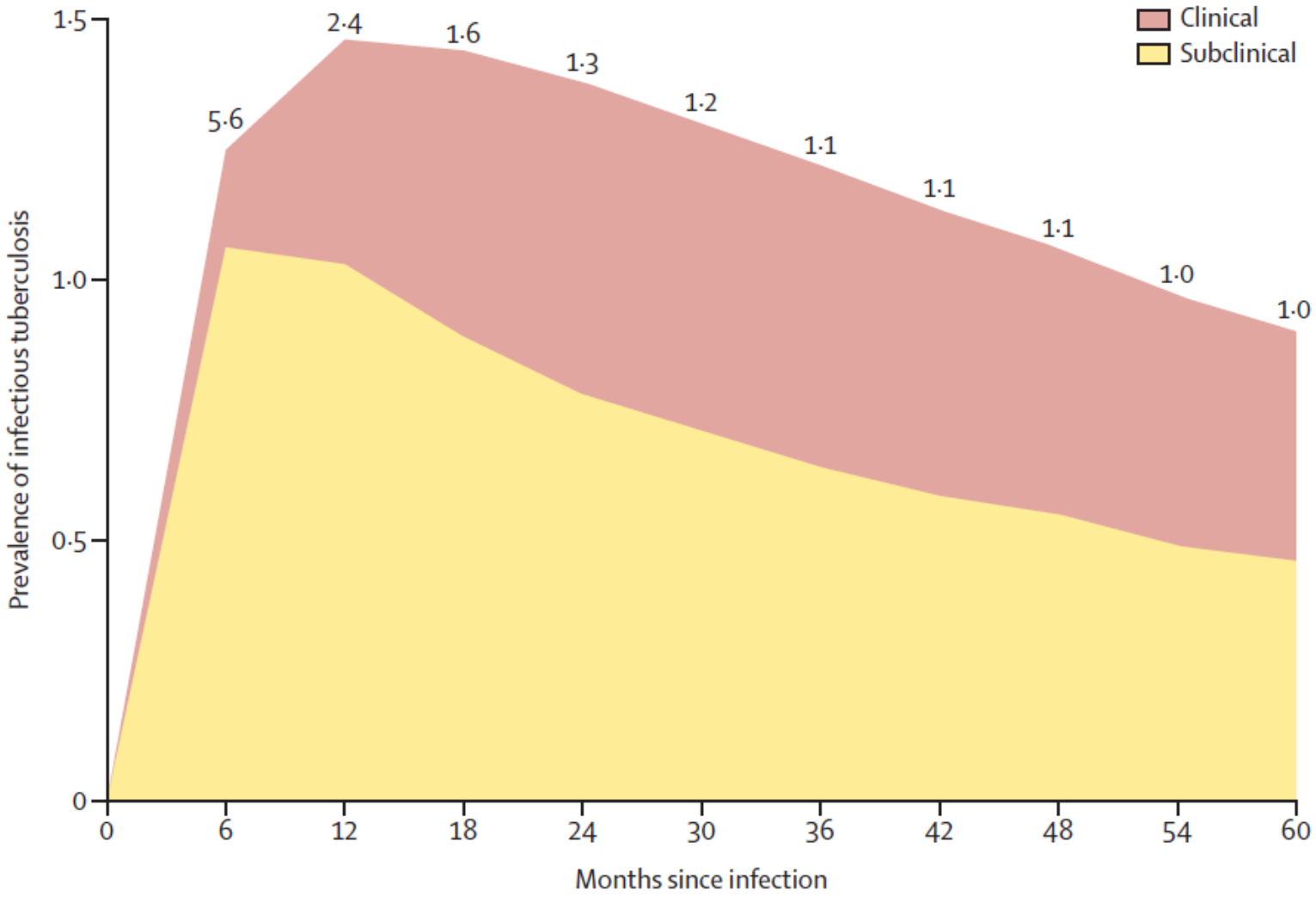
Ratio of scTB vs cTB after infection



Horton KC. Proc Natl Acad Sci USA. 2023

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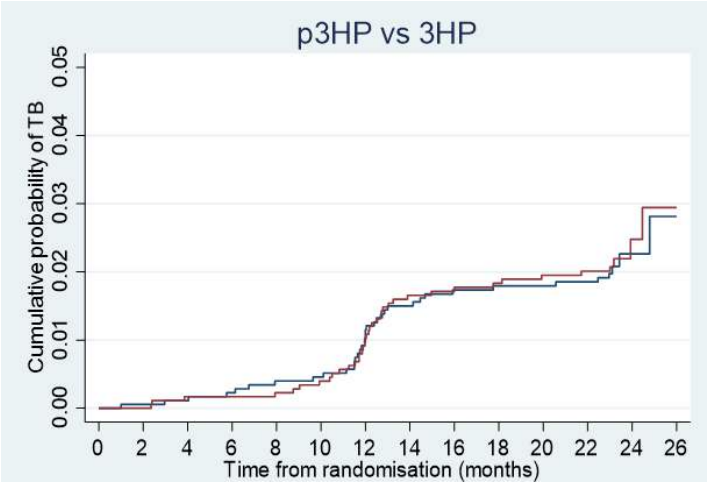
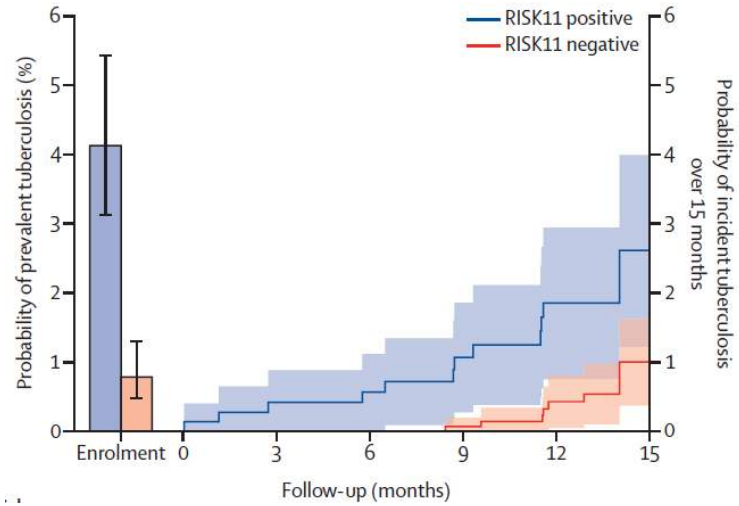
scTB & POD TB vaccines

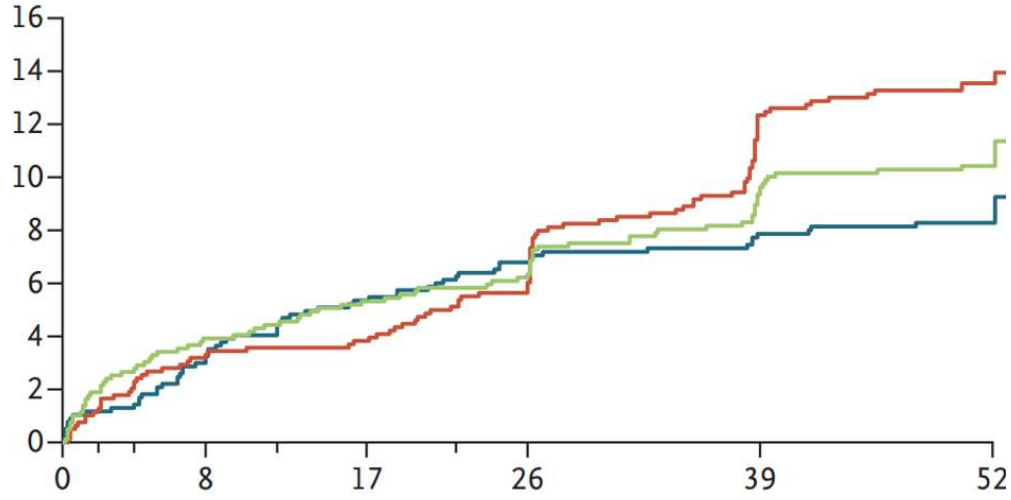
- Screening for TB in TB preventive treatment trials and treatment of disease trials detected a sizable burden of scTB



WHIP3TB
Annual screen



CORTIS
Screen end of trial



S31/A5349
Screened 6 monthly post end of Rx

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Clinical characteristics

Clinical characteristics

Scoping review of scTB (1)

- Not well described
- Less extensive disease
- Higher treatment success
- Lower mortality

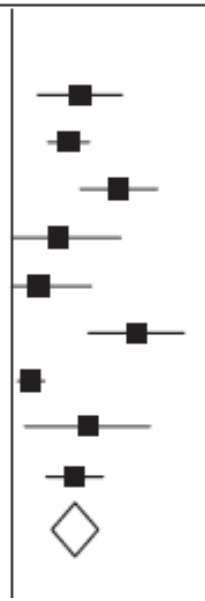
Comparison of chest computed tomography findings of active and subclinical tuberculosis diseases (2)

Radiographic findings	All patients (n = 412)	Active TB disease (n = 331)	Subclinical TB disease (n = 81)
Multiple lobe involvement	168 (36.1–45.6%)	144 (38.3–48.9%)	24 (20.8–40.3%)
Tree-in-bud sign	247 (55.1–64.6%)	191 (52.3–62.9%)	56 (58.4–78.1%)
Cavitation	165 (35.4–44.9%)	129 (33.9–44.3%)	36 (34.1–55.3%)
Consolidation	242 (53.9–63.4%)	204 (56.3–66.7%)	38 (36.4–57.7%)
Fibrotic scar	73 (14.3–21.7%)	65 (15.7–24.3%)	8 (5.1–18.3%)
Atelectasis	71 (13.9–21.2%)	62 (14.9–23.3%)	9 (6.0–19.8%)
Emphysema	58 (11.1–17.8%)	45 (10.3–17.7%)	13 (9.6–25.5%)
Bronchiectasis	82 (16.3–24.0%)	67 (16.3–24.9%)	15 (11.6–28.3%)

1. Teo. Eur Respir Rev. 2024; 2. Min et al. BMC Pulm Med (2020) 20:316

Progression from bacteriology negative to positive TB disease

	Patients who progressed (n)	Cohort size (n)	Follow-up (months)	Annualised rate (95% CI)
Active				
Frimodt-Moller et al (1965)[33]	25	86	36	0·10 (0·04–0·17)
Okada et al (2012)[52]	51	309	24	0·09 (0·06–0·12)
Cowie et al (1985)[31]	88	152	58	0·16 (0·11–0·22)
Nørregaard et al (1990)[51]	8	28	48	0·07 (0·00–0·17)
Borgen et al (1950, 1951)[28,29]	2	24	30	0·04 (0·00–0·12)
Aneja et al (1979)[24]	21	110	12	0·19 (0·12–0·26)
National Tuberculosis Institute (1974, 1976, 1978, 1982)[42–50]	36	271	60	0·03 (0·01–0·05)
Beeuwkes et al (1942)[25]	13	43	33	0·12 (0·02–0·21)
Hong Kong Chest Service (1979, 1981, 1984)[34–37]	71	176	60	0·10 (0·05–0·14)
Random-effects model				**0·10 (0·06–0·13)**
Heterogeneity: Q=40·8, df=8 (p<0·0001); I^2=77·4%, τ^2=0·0020				



Among persons with CXR evidence of TB, negative microbiology, untreated, and with, without or unknown symptoms suggestive of TB, 10%/year progressed to bact+ve TB

In 3 studies that included people with non-infectious subclinical TB, the rates of progression to bacteriologically positive TB were similar (range 4-12% per year).

(Sossen. Lancet RM. 2023)

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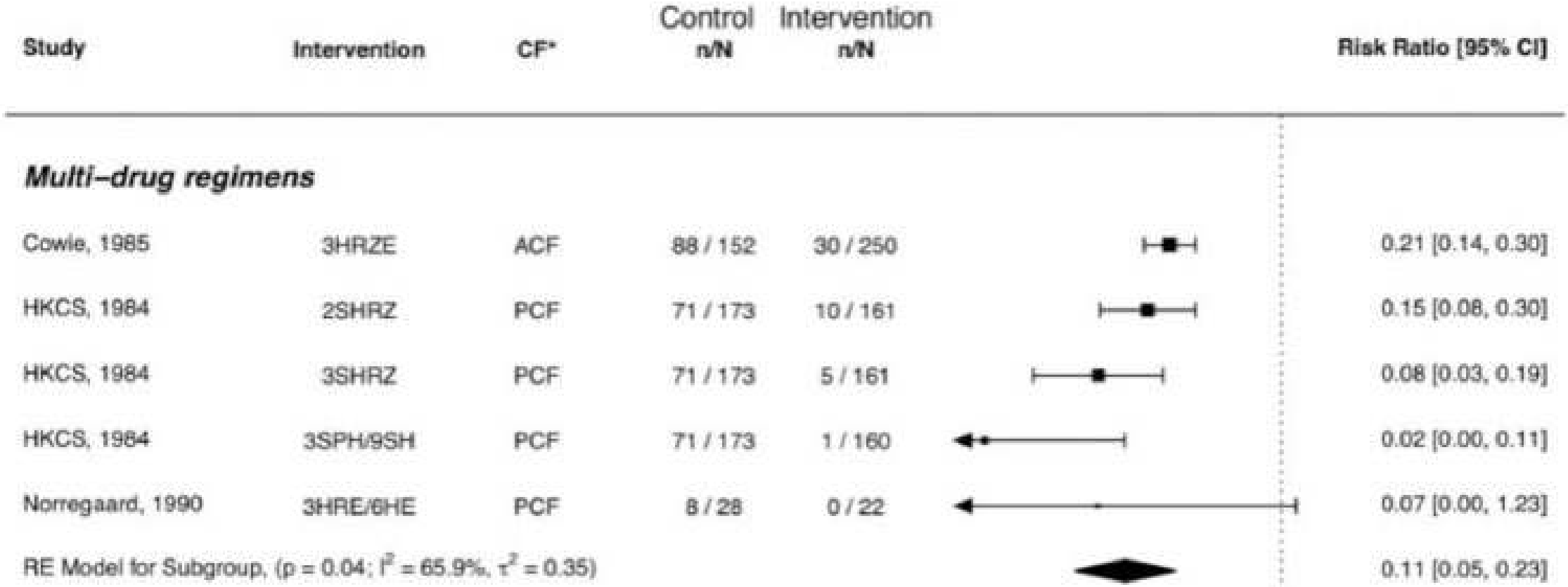
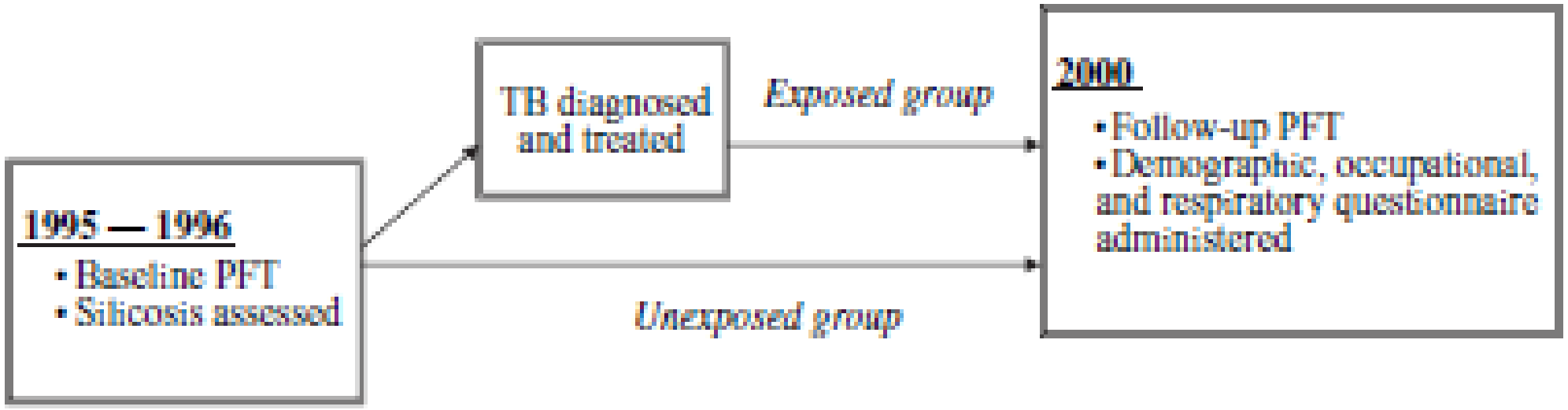
Treatment prevents progression

Multidrug treatment of patients with radiological TB and negative sputum cultures prevents progression to culture positive TB



(Gray. PLOS One, 2023)

Post TB lung function impairment



Lung function impairment was less in miners with TB: detected by CXR screening, less extensive disease, and smear negative

(Ross J. Thorax. 2010)

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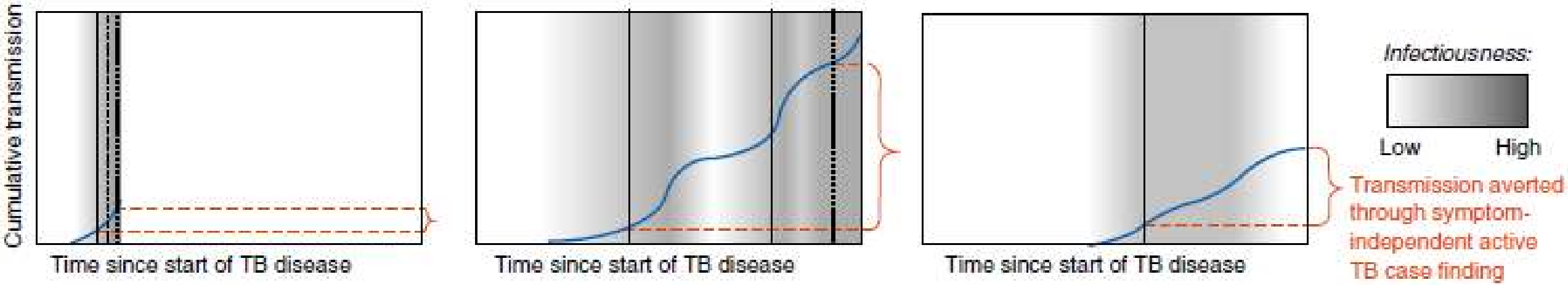
scTB and transmission



scTB may contribute substantially to transmission on a population level because of its high prevalence and long duration

Kendall. Am J Respir Crit Care Med, 2021

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TB vaccine POD trial design options for evaluating efficacy in preventing infectious scTB & cTB

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Trial design options

Design 1
Symptom TB screen

Endpoint
1°: cTB

Design 2
Symptom-independent TB screen at end of study follow up

Endpoint
1°: cTB

2°: scTB-end of follow-up

Design 3
Symptom-independent TB screen during & end of follow up. Testing differed to end of study

Endpoint
1°: cTB

2° : scTB during & end of follow-up

Design 4
Realtime symptom-independent TB investigations during and at end of follow up

Endpoint
1°: Composite scTB & cTB

In all designs, TB is excluded prior to enrolment using a symptom screen and sputum for Xpert

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Trial design options

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Trial design options

Design 1
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Design 4
Realtime symptom-independent TB investigations during and at end of follow up

Endpoint
1°: Composite scTB & cTB

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Special considerations: CXR screening

- Including a chest radiograph at study entry and or follow up for Designs 2–4 might yield important information to understand the effects of the vaccine on non-infectious scTB
- However, implications for inclusion criteria and treatment would need to be addressed
- Possible options for including chest radiography at study entry and follow up include
  - Do not look, therefore can’t treat
  - Look and do not treat
  - Look and treat

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Trial design options

Design 4a

Baseline: symptoms + sputum for Xpert

Follow up: realtime symptom-independent TB investigations (sputum for Xpert/culture)

Endpoint

Composite

scTB & cTB

Design 4b

Baseline: symptoms, ***CXR***, & sputum for Xpert

Follow up: Realtime symptom-independent TB investigations (***CXR***),

If new CXR abnormality, Ix for TB

Endpoint

Composite

CXR+/bact+

Symptom+/bac+

Benefit of Design 4a & 4b is that a smaller sample size, shorter time to complete the trial & be cheaper compared to Designs 1, 2 & 3 is likely

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Trial design options

Design 4a

Baseline: symptoms + sputum for Xpert

Follow up: realtime symptom-independent TB investigations (sputum for Xpert/culture)

Endpoint

Composite

scTB & cTB

Design 4b

Baseline: symptoms, ***CXR***, & sputum for Xpert

Follow up: Realtime symptom-independent TB investigations (***CXR***),

If new CXR abnormality, Ix for TB

Endpoint

Composite

CXR+/bact+

Symptom+/bac+

Risk of Design 4a & 4b is that if a vaccine has differential efficacy, a vaccine efficacious in preventing cTB may be rejected

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Regulatory & ethical considerations

- Regulators recognise cTB as the primary endpoint as it is well characterised, is associated with morbidity, mortality & transmission
- Symptom screening only during follow up accepted by regulators & ethics committees
  - scTB not detected & treated
- Screening for scTB at end of follow up acceptable to regulators and ethics committees
- Collection & storage of sputum for culture and Xpert during follow up may be acceptable to regulators & ethics committees
- Collection & real-time processing of sputum for culture and Xpert during follow up will be acceptable to ethics committees, but regulators may not accept scTB being included in a composite endpoint without further evidence
  - Treating scTB would prevent possible progression to cTB

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scTB: implications for TB vaccine trials

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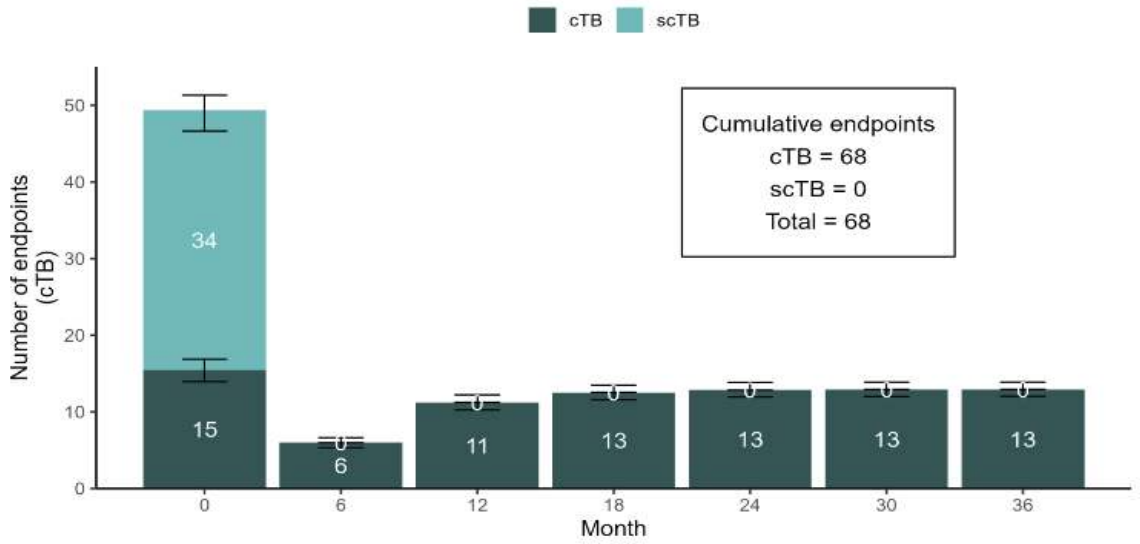
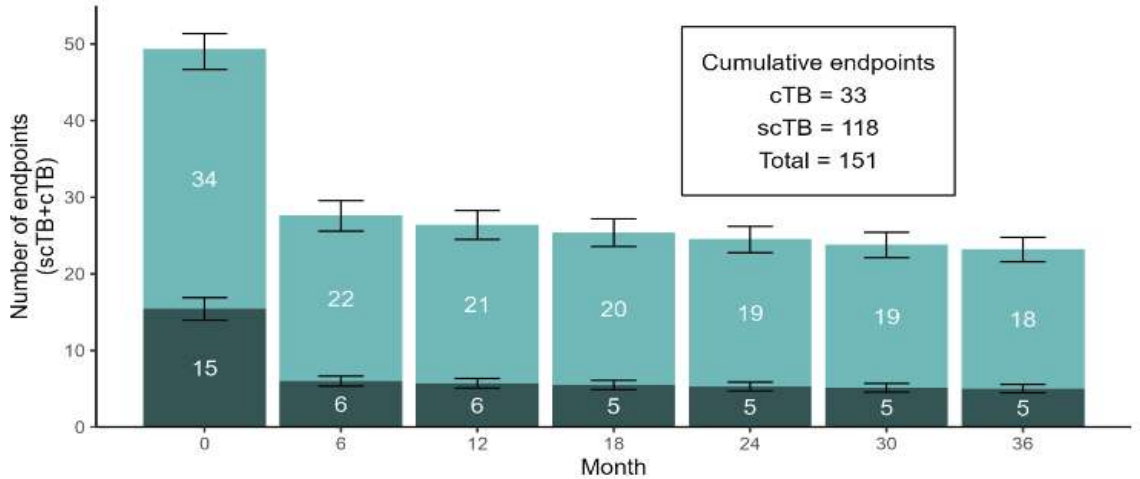
Estimated number of scTB & cTB endpoints, in the control arm of a POD TB vaccine trial



Symptom screen 6 monthly, and investigated for TB if positive. Only cTB detected



Symptom screen & sputum for culture / Xpert 6 monthly. Both scTB and cTB detected and treated

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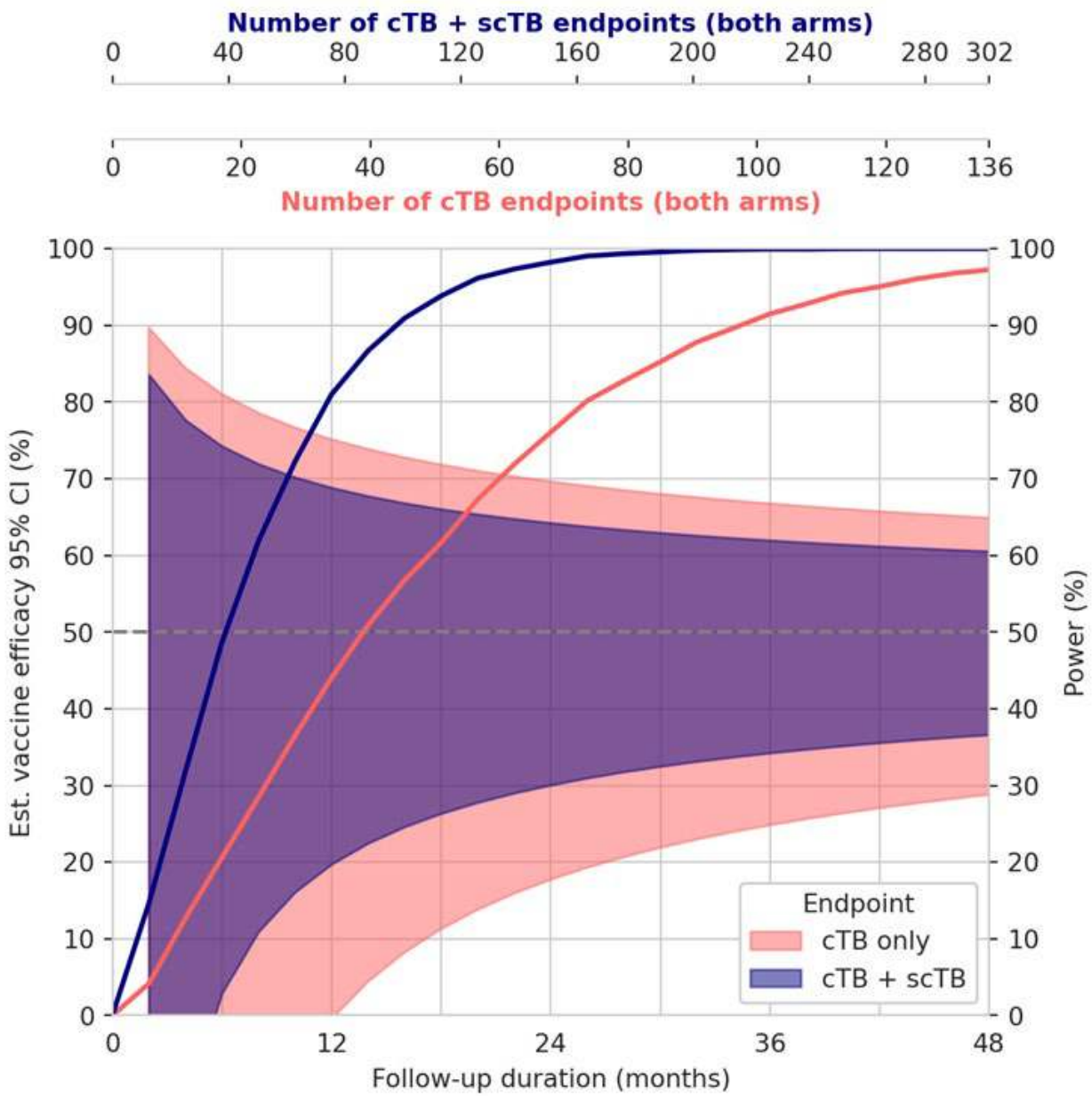
Time to accrual



Assumes 50% efficacy against scTB & cTB

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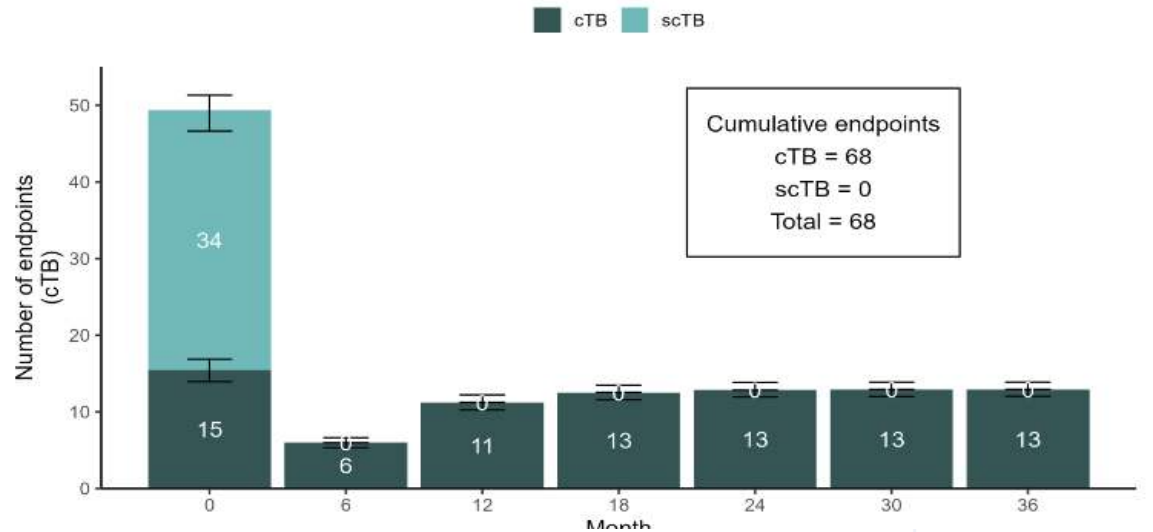

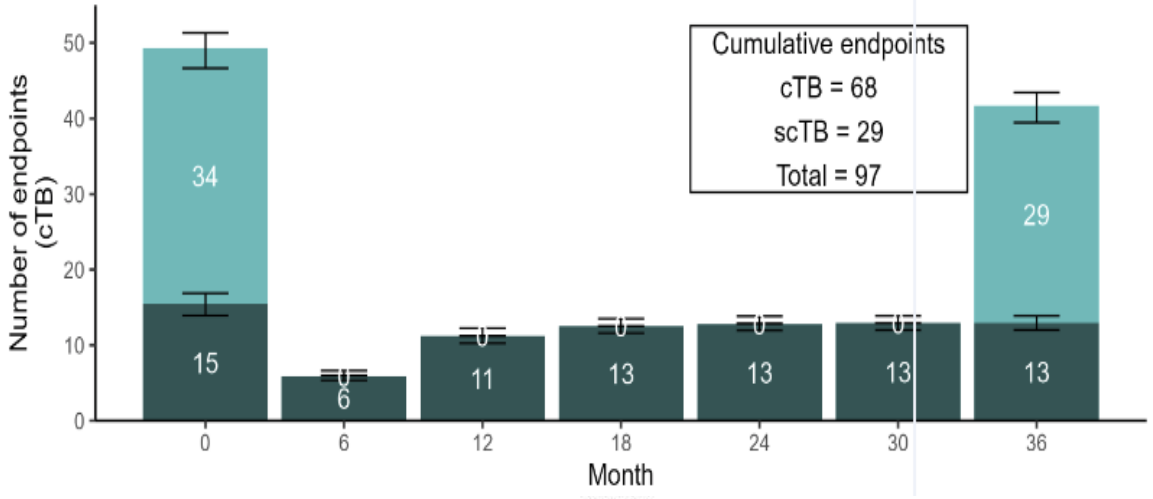

Symptom screen 6 monthly, and investigated for TB if positive. Only cTB detected

Only collecting sputum for culture/Xpert at last study visit would detect 1.4 X more endpoints than scenario 1

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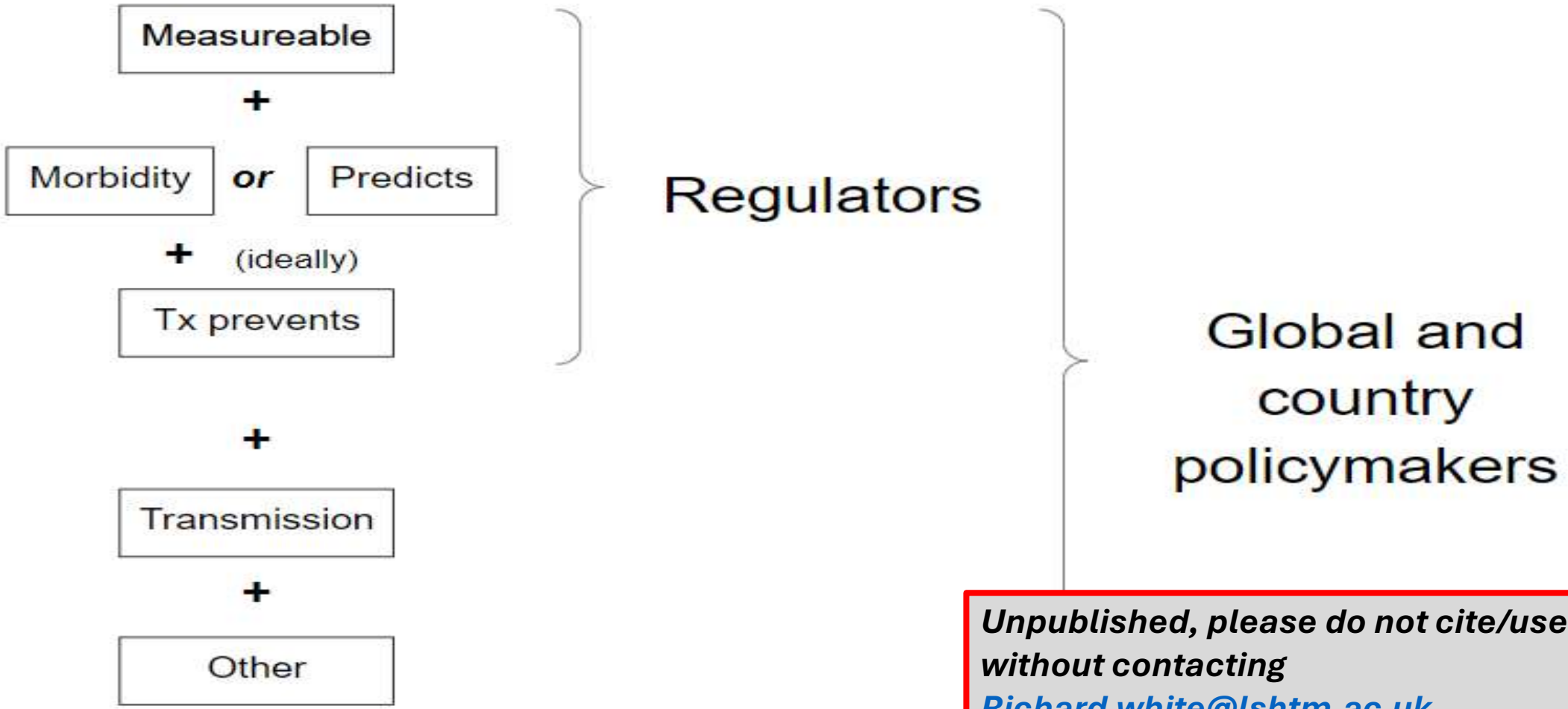
What evidence is required to include scTB as a co-primary endpoint?



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What evidence is required to include scTB as a co-primary endpoint?

Design	Morbidity	Predicts progression	Does Rx prevent cTB	Transmission
Systematic reviews and meta-analyses	X	X	X	X
Retrospective secondary analysis of existing data	X	X	X	
Cross-sectionally in a symptom-agnostic community-based screening	X			
Prospective cohort	X	X	X	
Natural history studies	X			
Cluster randomised trial of Rx or no Rx of scTB		X	X	
Symptom vs. symptom-agnostic ACF randomised trial				X

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Evolving landscape

- WHO recommends CXR screening and use of CAD in high burden settings
- WHO convening meetings (October 14-18) on scTB and TB screening to agree on definition of scTB, inform policy and set research priorities
- Global fund signalled intent to invest in scaling up CAD for TB diagnosis
- Adoption and implementation of active TB case finding in high burden countries is unknown, but likely to be heterogeneous & increasing

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Conclusion

- scTB accounts for half of prevalent TB and likely to be an important driver of transmission and result in morbidity
- If scTB is associated with morbidity and transmission, it is important to know whether TB vaccines are effective in preventing clinical and subclinical TB
- Various clinical trial design options would allow the efficacy of TB vaccines in preventing clinical and subclinical TB to be determined
- Evidence needed to support including scTB as part of a composite primary endpoint
- Policy and practice with respect to screening for and treating scTB is rapidly evolving

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