

EFFICIENCY OF LATE-STAGE TB VACCINE TRIALS RESTRICTED TO IGRA-POSITIVE PARTICIPANTS

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Phase 2b/3 trials of new TB vaccines may be conducted primarily among IGRA-positive participants because:

- the vaccine is expected to have better protective efficacy in those already sensitized to Mtb (**biology**)
- a trial with IGRA+ participants is expected to accrue more TB endpoints than a trial with mixed IGRA+/- participants (**efficiency**)

Evidence suggesting better efficiency:

- (1) TB incidence was 2.9 (95%CI 1.6-5.2) times higher in IGRA+ compared to IGRA- adolescents (cohort study, South Africa)
- (2) IGRA+ individuals had 9.4 (95%CI 6.5-13.5) times increased incidence of TB disease progression over ≥ 12 months compared to IGRA- individuals (meta-analysis, 33 cohort studies in high-risk populations)

(1) Zhou et al, Lancet Infect Dis 2020 (2) Mahomed et al. PLoS One 2011



However...



Pre-enrolment IGRA screening is laborious and costly

The apparent efficiency gain may be affected by:

- age cohort effects
- partial protection by previous Mtb infection
- age-varying annual risk of TB infection (ARTI)

Covariate and Group	No. of Participants/ Total No.†	Person-yr of Follow-up	Rate per 100 Person-yr (90% CI)
Overall			
M72/AS01 _E	13/1626	4427.62	0.3 (0.2 to 0.5)
Placebo	26/1663	4463.06	0.6 (0.4 to 0.8)
Age			
≤25 years			
M72/AS01 _E	3/706	1911.17	0.2 (0.1 to 0.4)
Placebo	16/724	1928.26	0.8 (0.6 to 1.3)
>25 years			
M72/AS01 _E	10/920	2516.45	0.4 (0.2 to 0.7)
Placebo	10/939	2534.80	0.4 (0.2 to 0.7)

TB incidence by age group, M72 phase 2B trial

So we asked:

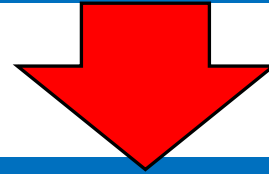
Taking these potential effects into account, what is the sample size requirement of a TB vaccine trial among adults and adolescents that only enrolls IGRA+ individuals compared to one that enrolls both IGRA+ and IGRA- individuals in the same population?



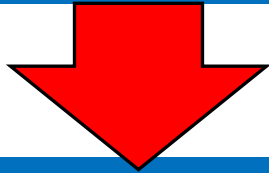
Methods: *difference equations model*



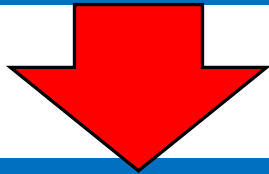
IGRA-positive prevalence for each year of age from birth in an imaginary population for a given ARTI



Incidence of TB disease based on assumed progression rate by year since (re-)infection, for each age



Number of expected TB endpoints in an imaginary TB vaccine trial that only enrolls IGRA+ participants
Number of expected TB endpoints in a similar trial that enrolls participants without IGRA testing



Compare sample size needed to accrue 50 TB endpoints in the placebo arm



Methods: *assumptions on infection and disease progression*



TB incidence by year of age since birth, by IGRA status

Assumptions	parameter	value	range
Closed population			
Infection incidence depends on ARTI	ARTI	0.04	0.02 – 0.06
ARTI constant over time (<i>endemic situation</i>)			
Reinfection occurs			
Infection leads to IGRA conversion			
IGRA reversion only occurs within 12 months post-conversion (<i>not modelled explicitly</i>)			
Disease progression independent of age	Overall progression rate	0.10	0.05 – 0.20
Disease progression occurs over 10 years post-infection following an empirical distribution	Proportion disease progression in first 2 years post-infection	0.82	0.65 – 0.97



TB incidence by year of age since birth, by IGRA status

Model	parameter	value	range
Reinfection only: progression rate does not depend on previous infections			
Partial protection: lower progression rate if previously infected	Reduction in progression rate	0.79	0.58 – 0.895
Age-varying ARTI: increase 13-18 years	Relative ARTI 0-12 years	0.50	0.25 – 0.75
Combined: models 2 and 3 combined			



Assumptions

Trial of 3 years follow-up, no attrition

Eligible ages for enrolment 15-44 years

Same number of enrolments for each year of age

In the mixed trial the number IGRA+ is proportional to that of the population (*randomly selected*)

Disclaimer

Exploratory – model simplifies reality

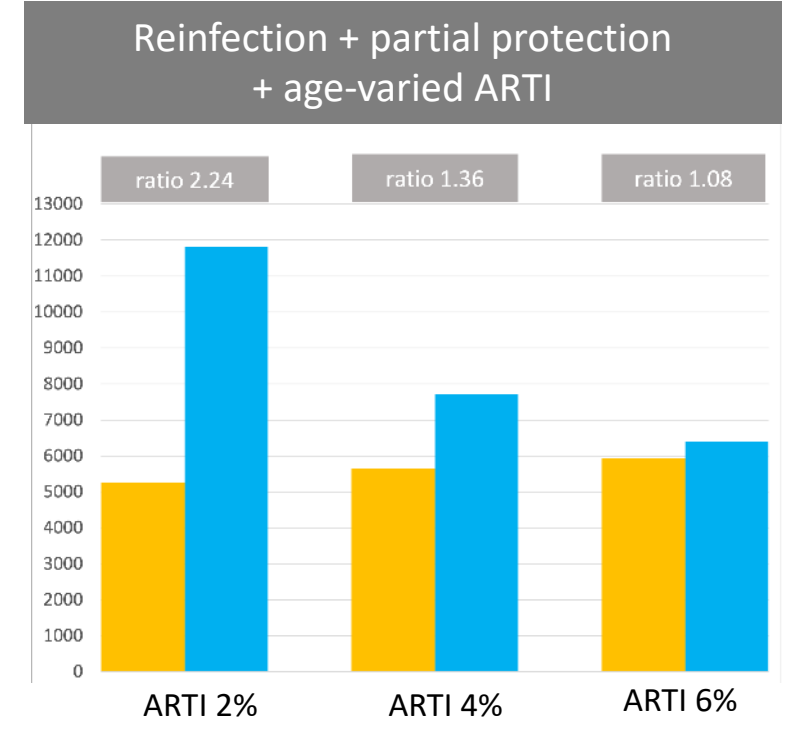
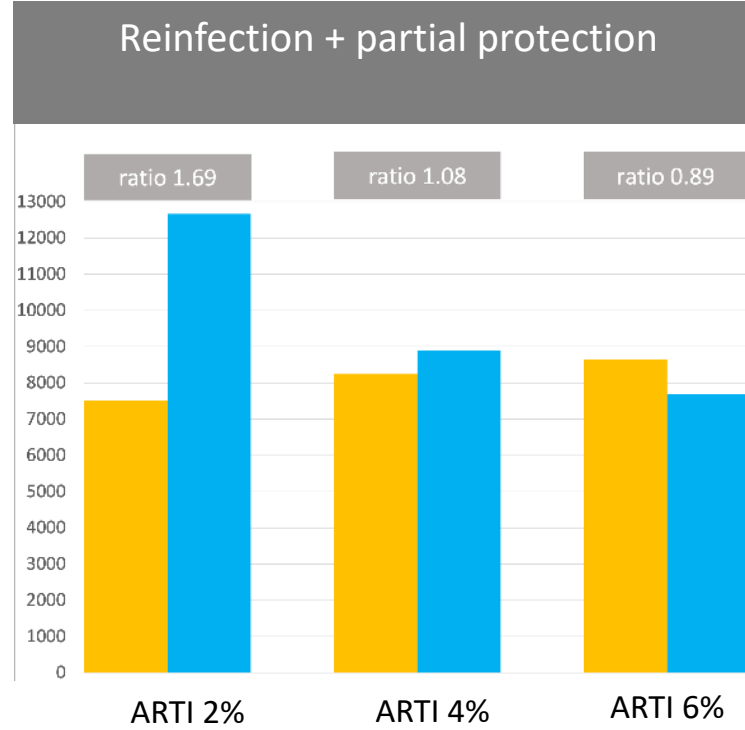
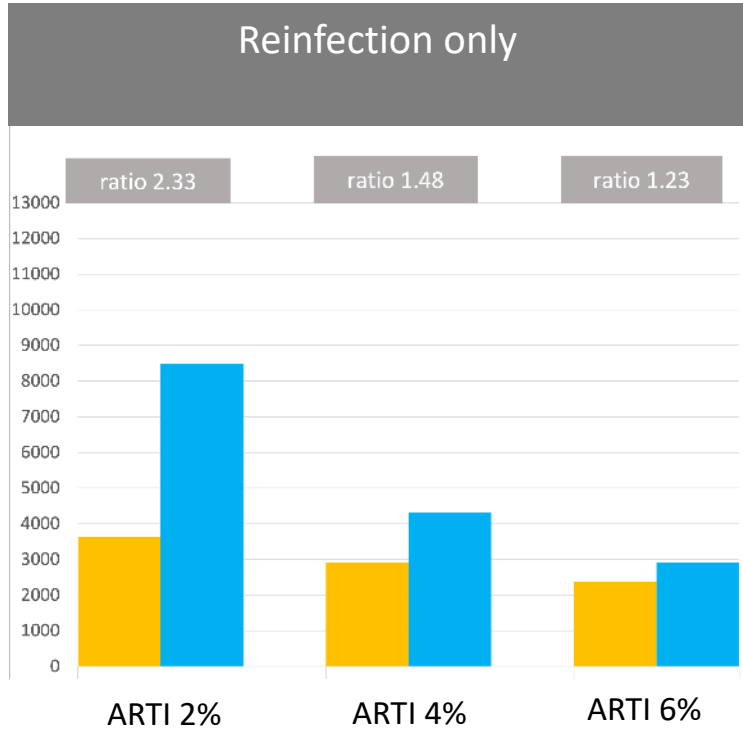
Focus on *relative* sample sizes



Key results



Sample size placebo arm required to accrue 50 incident TB cases



IGRA+ participants only trial



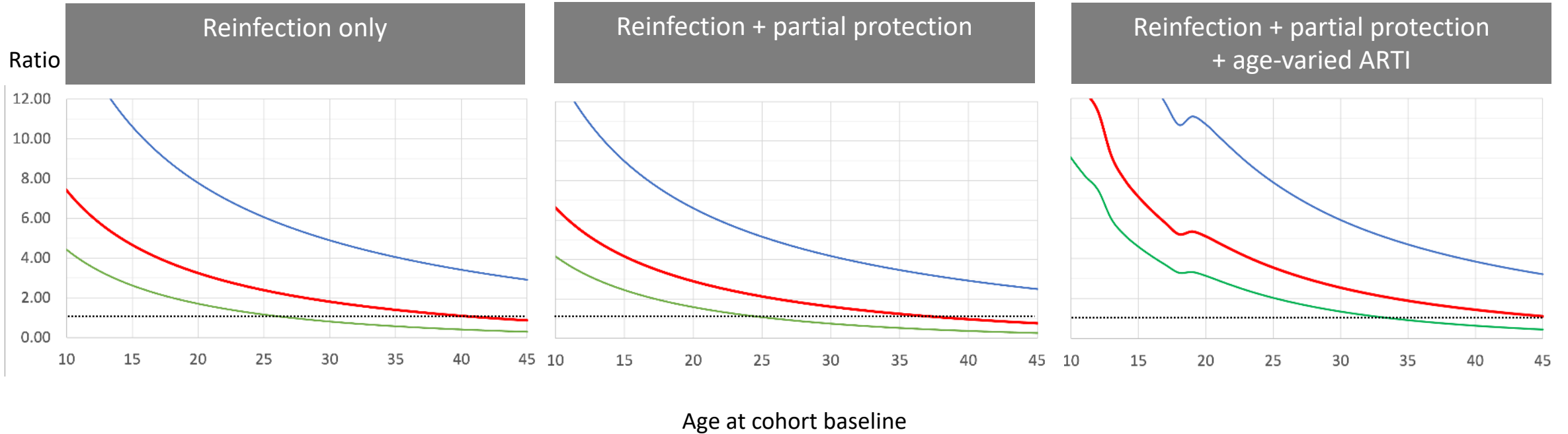
Mixed IGRA+/IGRA- participants trial



Ratio of TB incidence IGRA+ / IGRA- at baseline in a cohort with 2 years of follow-up



ARTI — 2.00% — 4.00% — 6.00%



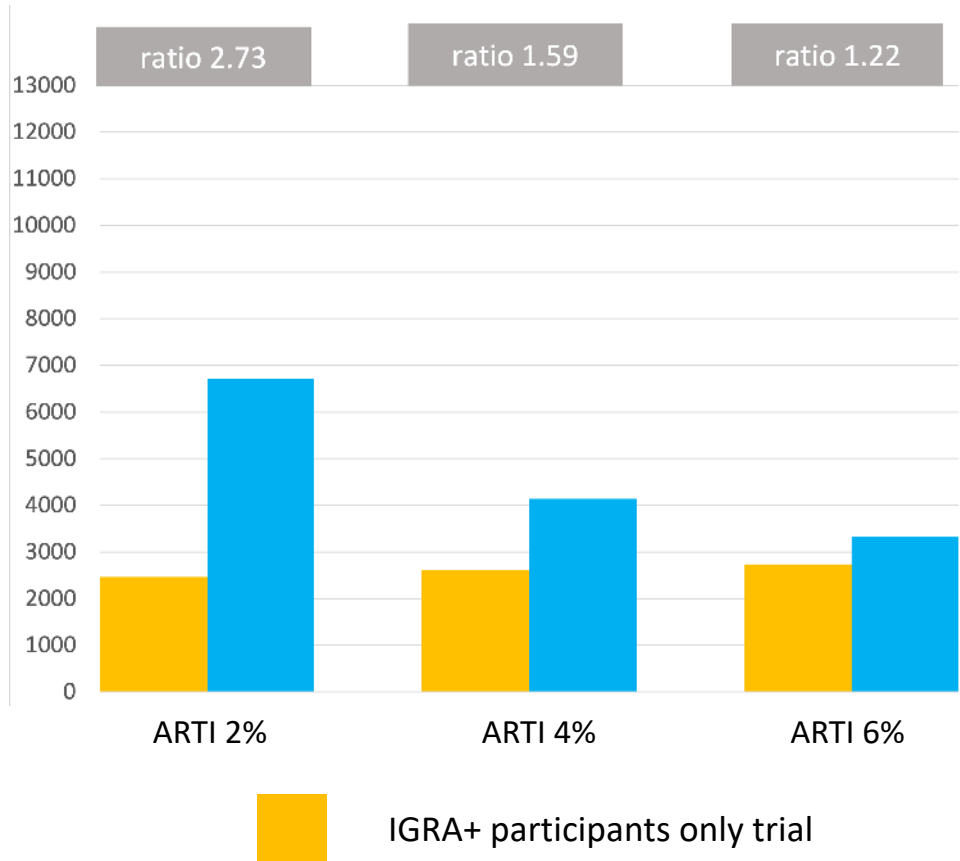


Effect of age-specific enrolment rates

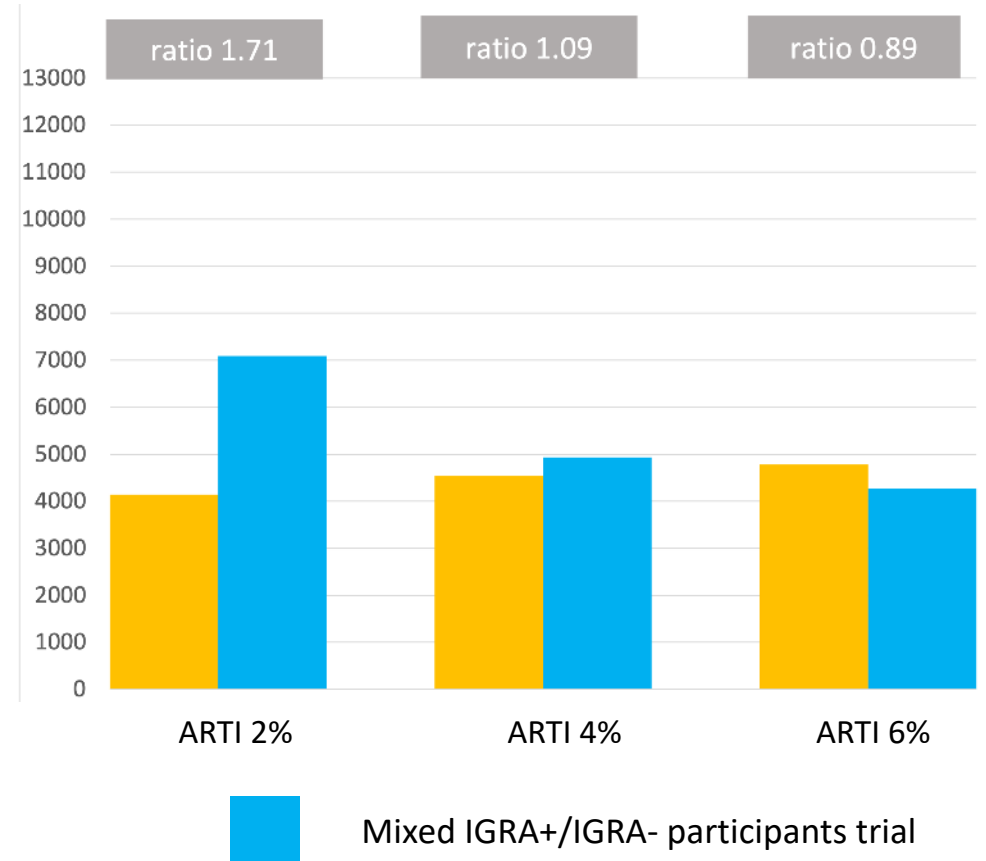


Sample size placebo arm required to accrue 50 incident TB cases
Combined model: children have 50% lower ARTI, 79% partial protection by previous infection

Enrolment 15-29 years is 3x that for 30-44 years



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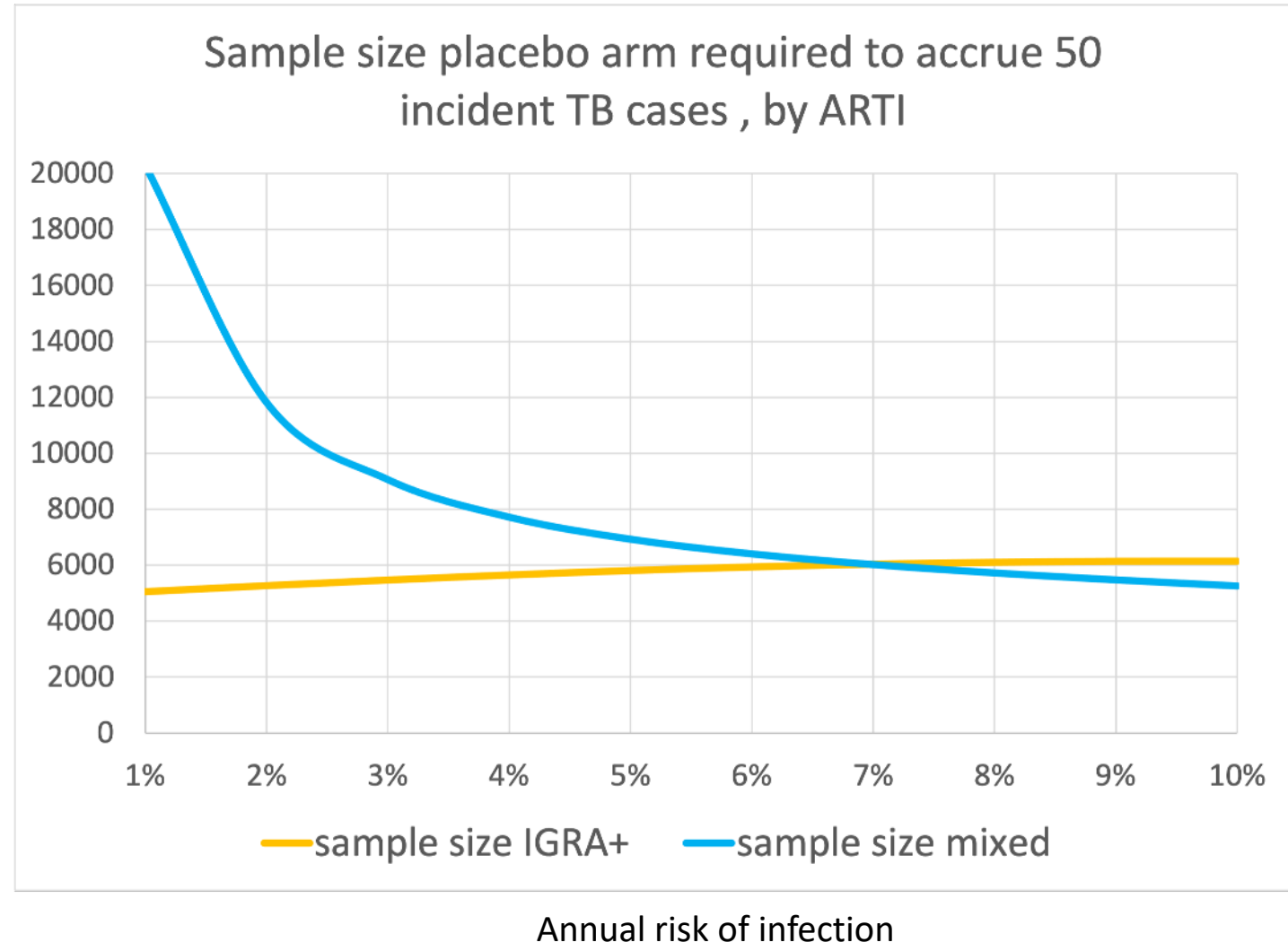




Effect of ARTI on sample size required in trial placebo arm



Combined model:
children have 50% lower ARTI,
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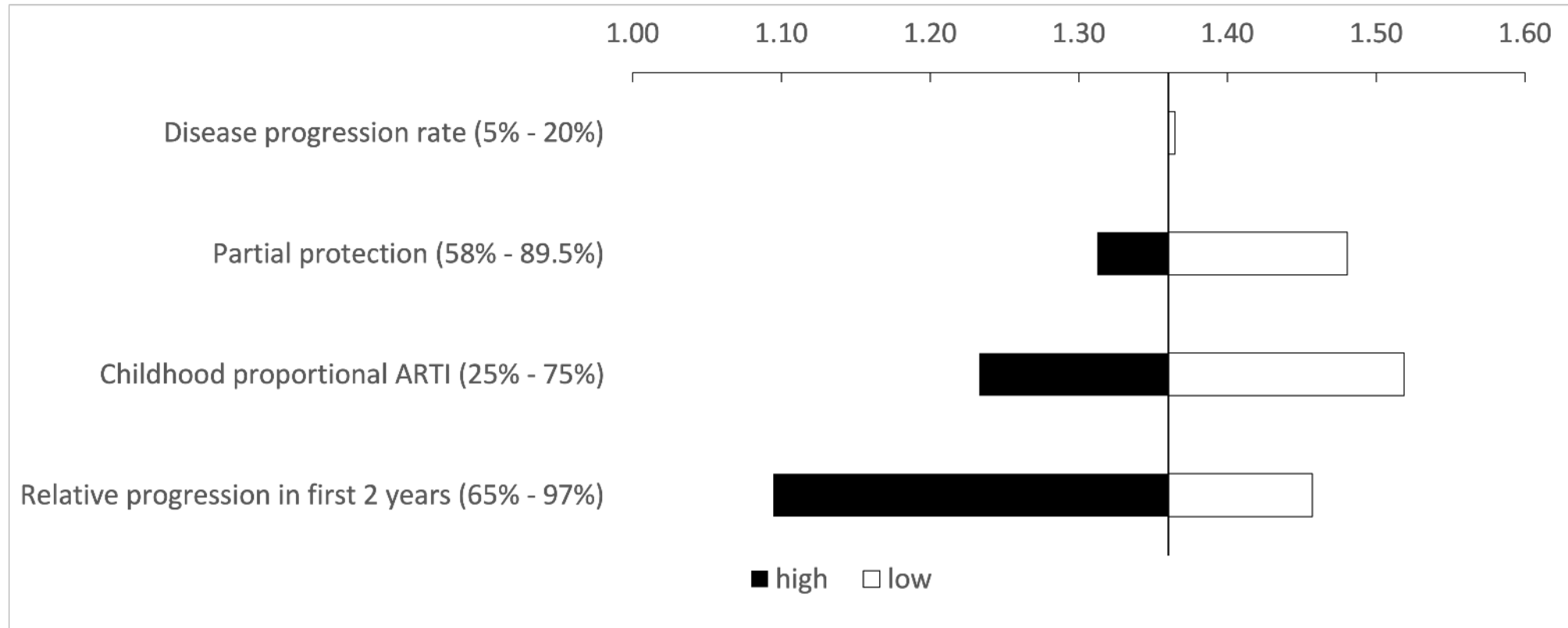
Sensitivity analyses



ARTI 0.04

Combined model: children have 50% lower ARTI, 79% partial protection by previous infection

Sample size ratio mixed vs IGRA+ only trial = **1.36**

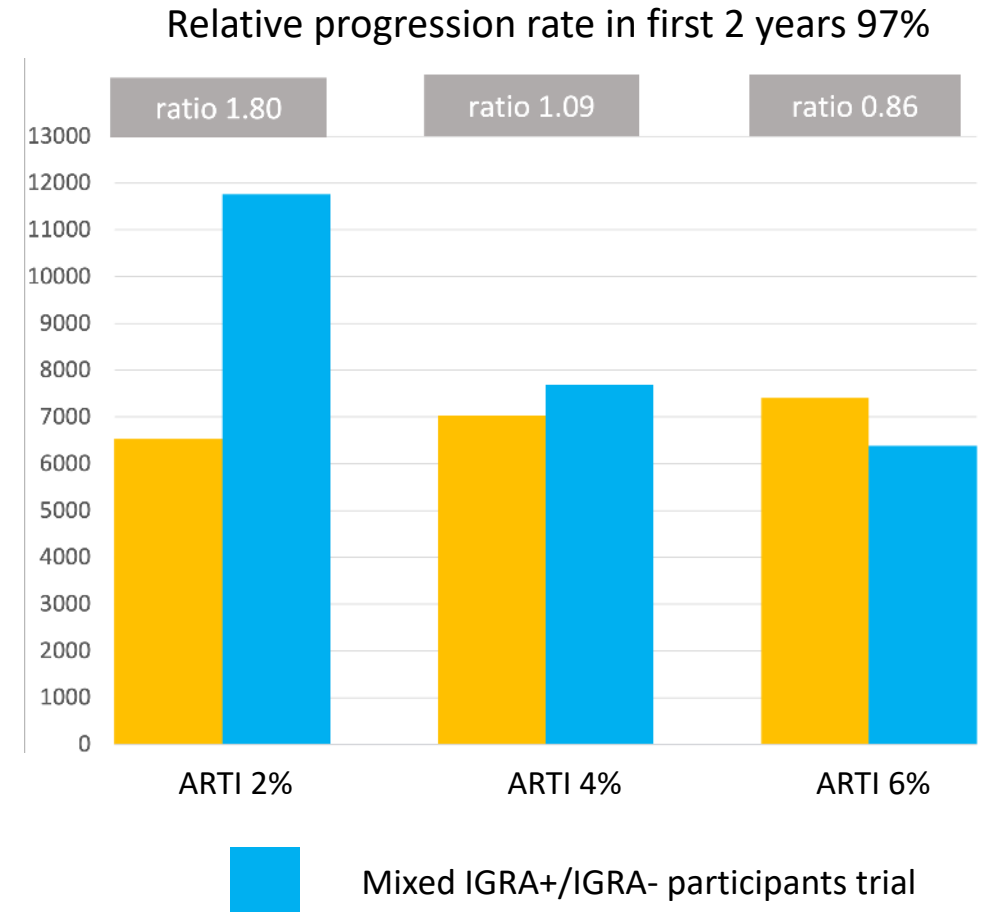
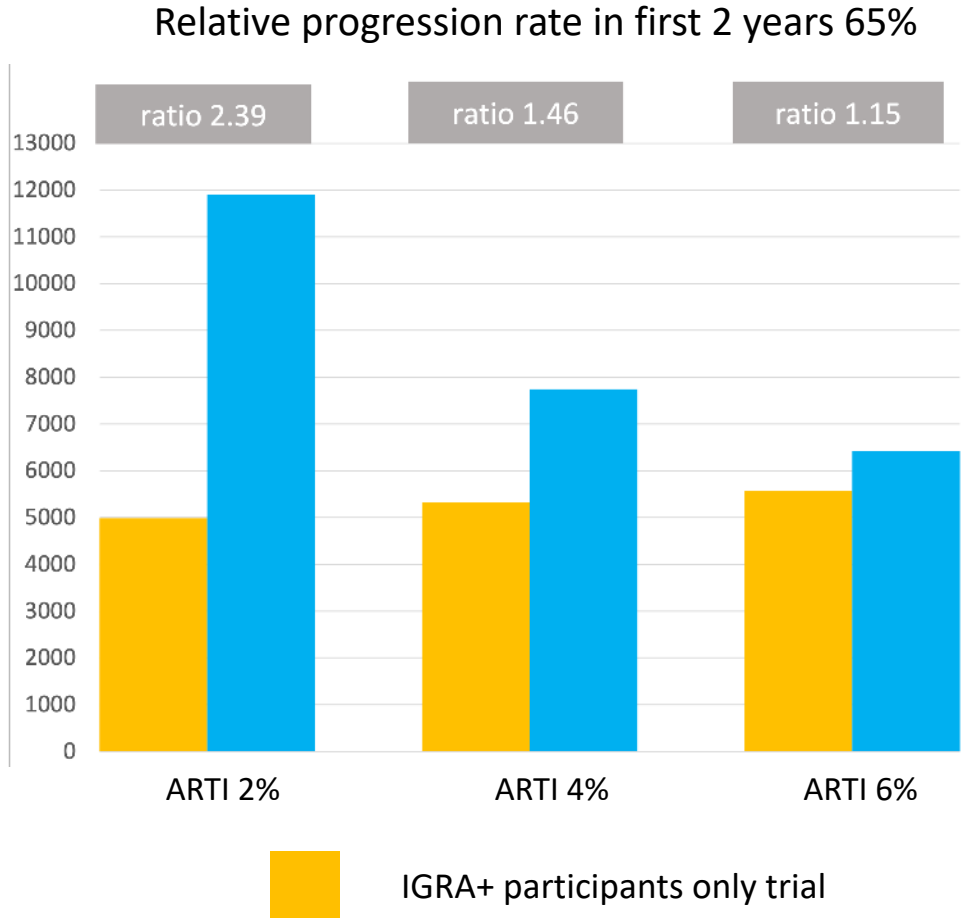




Effect of relative progression rate in first 2 years post-infection



Sample size placebo arm required to accrue 50 incident TB cases
Combined model: children have 50% lower ARTI, 79% partial protection by previous infection





1. The required sample size for a trial decreases with increasing ARTI, but much more so for a mixed trial without IGRA pre-enrolment screening than for a trial enrolling IGRA+ participants only.
2. As the ARTI increases, the required sample size for a mixed trial gets closer to that for an IGRA+ participants-only trial.
3. This due to an age-cohort effect (*with increasing age, the proportion IGRA+ that leads to disease progression decreases*): the observed difference in TB incidence between IGRA+ and IGRA- adolescents disappears with increasing age.
4. This effect is aggravated by partial protection due to previous Mtb infection but attenuated by age-varying ARTI.
5. Taking partial protection and age-varying ARTI into account, an IGRA+ participants-only trial is only one third more efficient than a mixed trial in high incidence (ARTI $\geq 4\%$) and equally efficient in very high incidence populations (ARTI $\geq 6\%$).
5. These results are largely unaffected by parameter assumptions within plausible value ranges but quite sensitive to the assumed distribution of progression rates over time since infection.
6. Age matters in trial enrolment: the younger the effective trial population, the smaller the sample size needed (conversely: the older the trial population, the bigger the risk of inadequate statistical power for a given sample size).



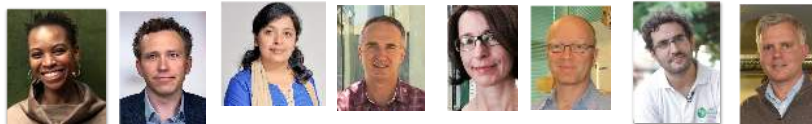
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