7TH GLOBAL FORUM ON TB VACCINES | 8-10 October 2024 Rio de Janeiro, Brazil

Driving innovation from discovery to access

Effectiveness of primary Bacillus Calmette-Guérin against the risk of Mycobacterium tuberculosis infection and tuberculosis disease: an individual-participant meta-analysis of trials and observational studies

Puck T Pelzer

10 October 2024

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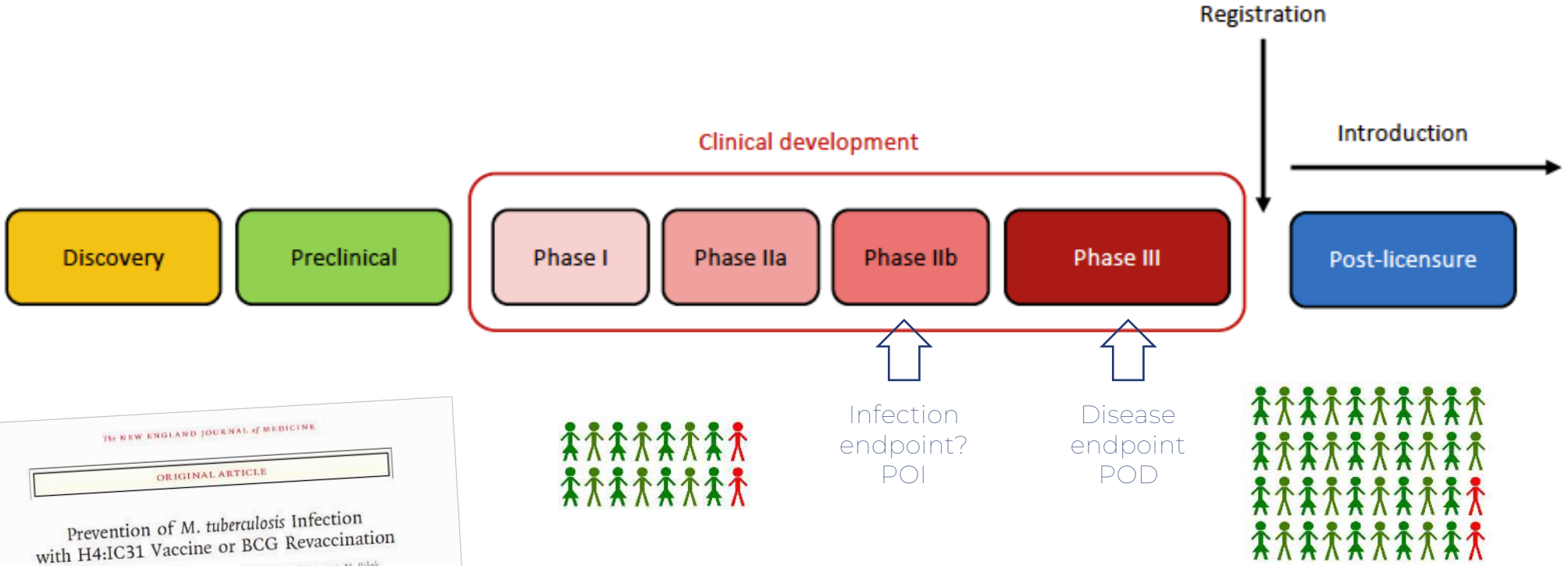
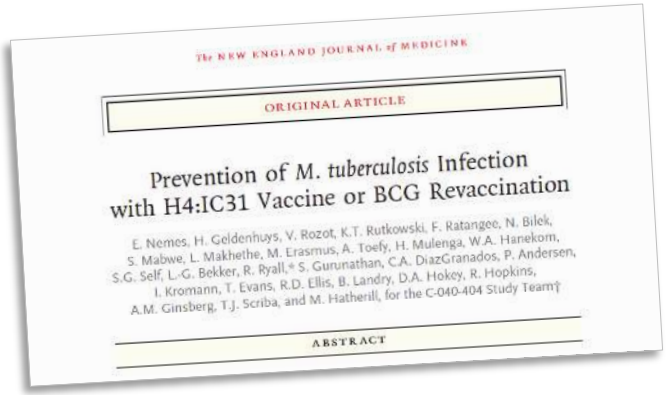
BACKGROUND





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination

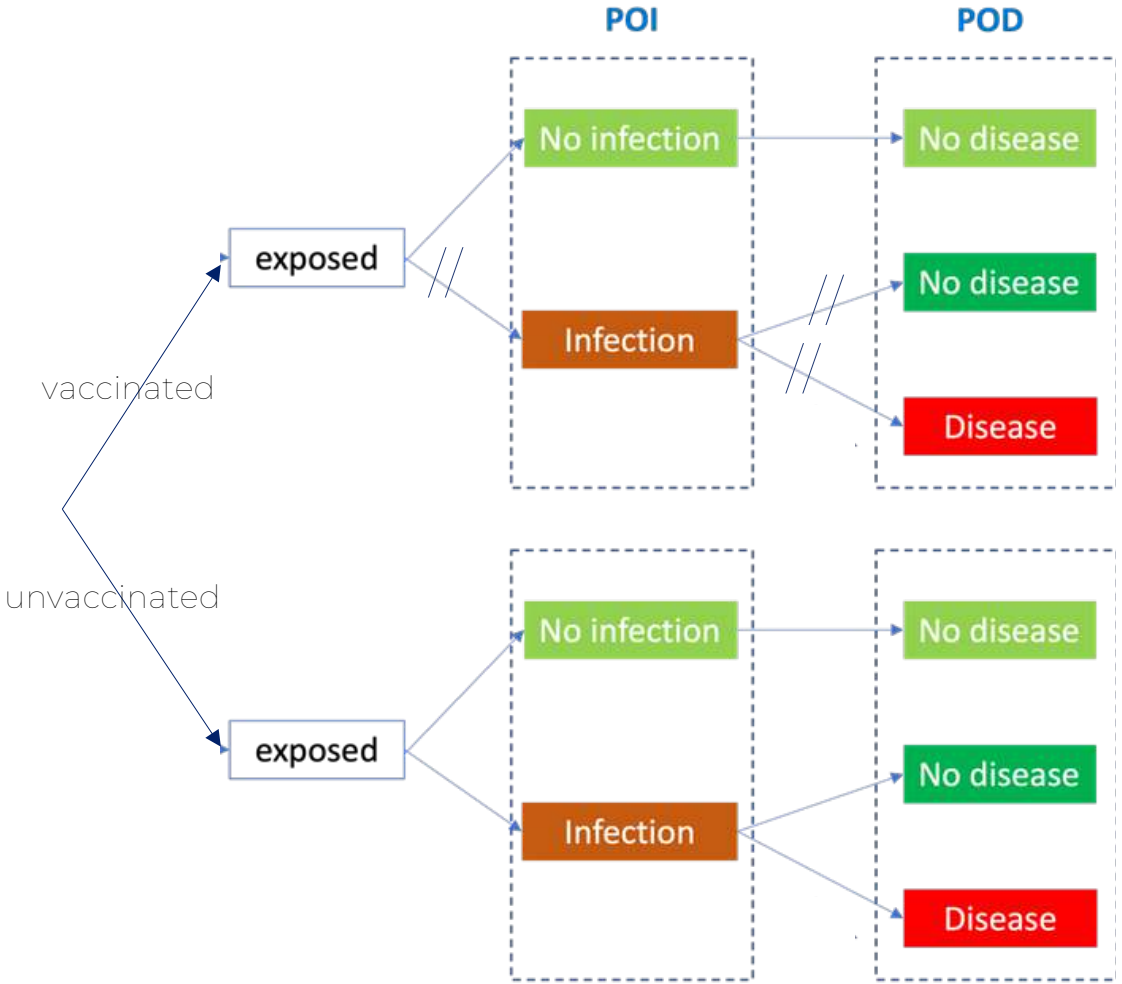
E. Nemes, H. Geldenhuys, V. Rozot, K.T. Rutkowski, F. Ratangee, N. Bilek, S. Mabwe, L. Makhethe, M. Erasmus, A. Toefy, H. Mulenga, W.A. Hanekom, S.G. Self, L.-G. Bekker, R. Ryall,* S. Gurunathan, C.A. DiazGranados, P. Andersen, I. Kromann, T. Evans, R.D. Ellis, B. Landry, D.A. Hokey, R. Hopkins, A.M. Ginsberg, T.J. Scriba, and M. Hatherill, for the C-040-404 Study Team†

ABSTRACT

POI → POD translation?

SLIDES COURTESY OF FRANK COBELENS

BACKGROUND



Vaccine (predominantly) blocks infection
→ POI ~ POD

Vaccine (predominantly) blocks disease
→ POI < POD

Wrongly discard efficacious candidate

Vaccine (predominantly) blocks infections that do not lead to disease
→ POI > POD

Wrongly move forward inefficacious candidate

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BACKGROUND

OBJECTIVE

Compare the quantitative relationship between incidence of Mtb infection test conversion and incidence of TB disease through individual participant data (IPD) meta-analyses of existing data

METHODS

Data

- Existing datasets from experimental and observational studies
- Longitudinal follow up
- BCG vaccination status, “Mtb infection” status, and TB disease status is known at baseline and tracked over time

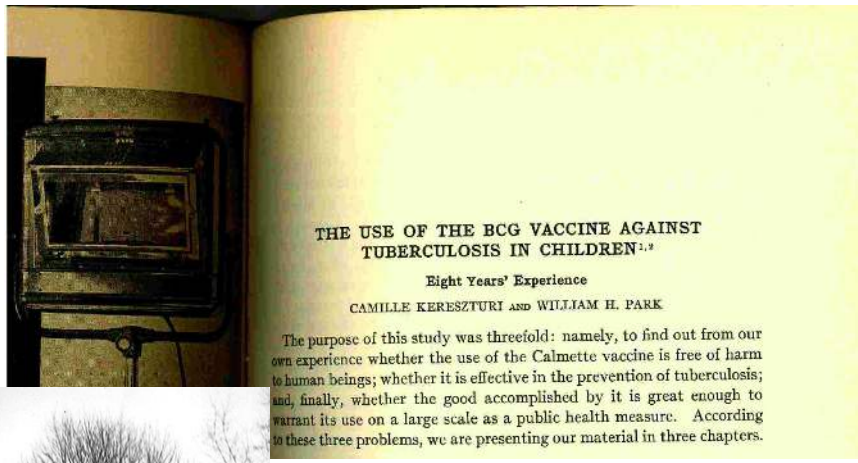
Study population

- All age groups
- General population, household contacts
- Observational studies: BCG vaccinated at birth

+ additional, study-type specific exclusion criteria (study level, participant level)

THE BCG RCT DATA CHRONICLES

- Started with Emails, Ended with sifting many Old Archives
- Following Leads from UK to US to South Africa… and Back
- The Case of the Missing Data (And the Retired Scientists)
- BCG on Potatoes and Beef bile and Unethical practices
- Calling Curators, Museal and trying to get access to Sanatoria Archives
- 90-year-old researcher to the Rescue
- Great-Grandkids and LinkedIn



SUMMARY

In 1947, a study was begun to determine insofar as possible the merits of BCG vaccine as a preventive for tuberculosis. The study was confined to resident patients of Lincoln (Illinois) State school, an institution for mental retardates.

THE USE OF THE BCG VACCINE AGAINST TUBERCULOSIS IN CHILDREN[1,2]

Eight Years' Experience

CAMILLE KERESZTURI AND WILLIAM H. PARK

The purpose of this study was threefold: namely, to find out from our own experience whether the use of the Calmette vaccine is free of harm to human beings; whether it is effective in the prevention of tuberculosis; and, finally, whether the good accomplished by it is great enough to warrant its use on a large scale as a public health measure. According to these three problems, we are presenting our material in three chapters.

METHODS

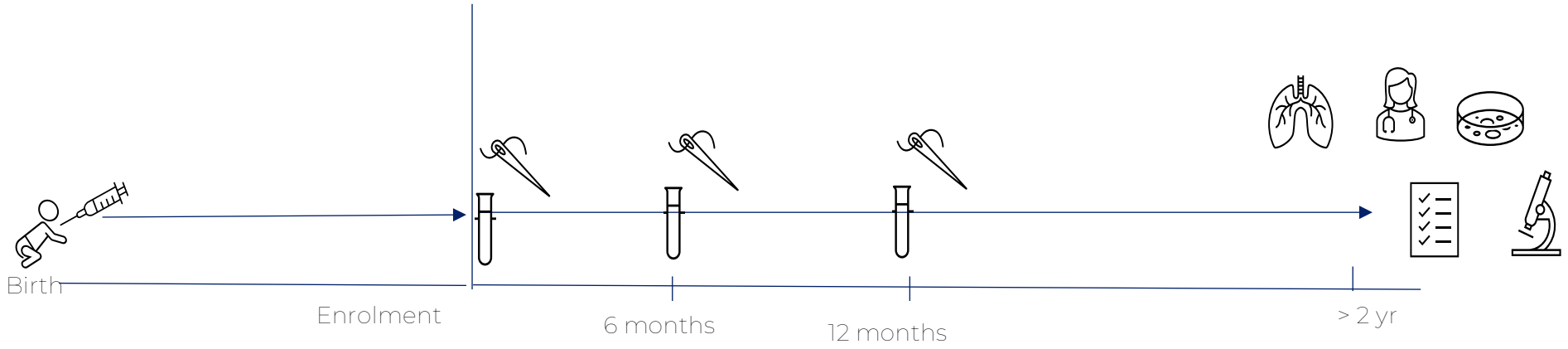
- neonatal vaccination
- IGRA
- TST
- CXR
- ssm
- culture
- Physical examination
- TB screening

Infection measured by TST or IGRA *conversion*

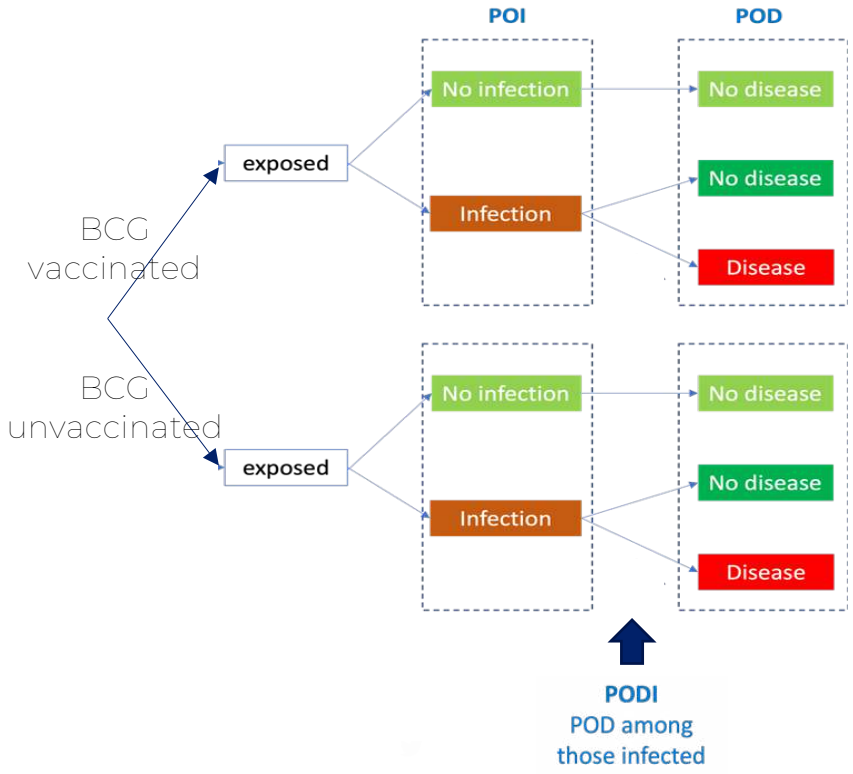
→excluded baseline positives

Study types:

1. ACS - Adolescent cohort studies
2. HHC - Household contact studies
3. RCT - Randomized controlled trials



ANALYSES



- Infection endpoint separately for TST and IGRA
- Disaggregated by study type
- Two-level mixed-effects Cox regression models, adjusted for study, age and sex
- Compared observed hazard ratio for "POI" with that for POD within the dataset
- Various subgroup and sensitivity analyses

SLIDES COURTESY OF FRANK COBELENS

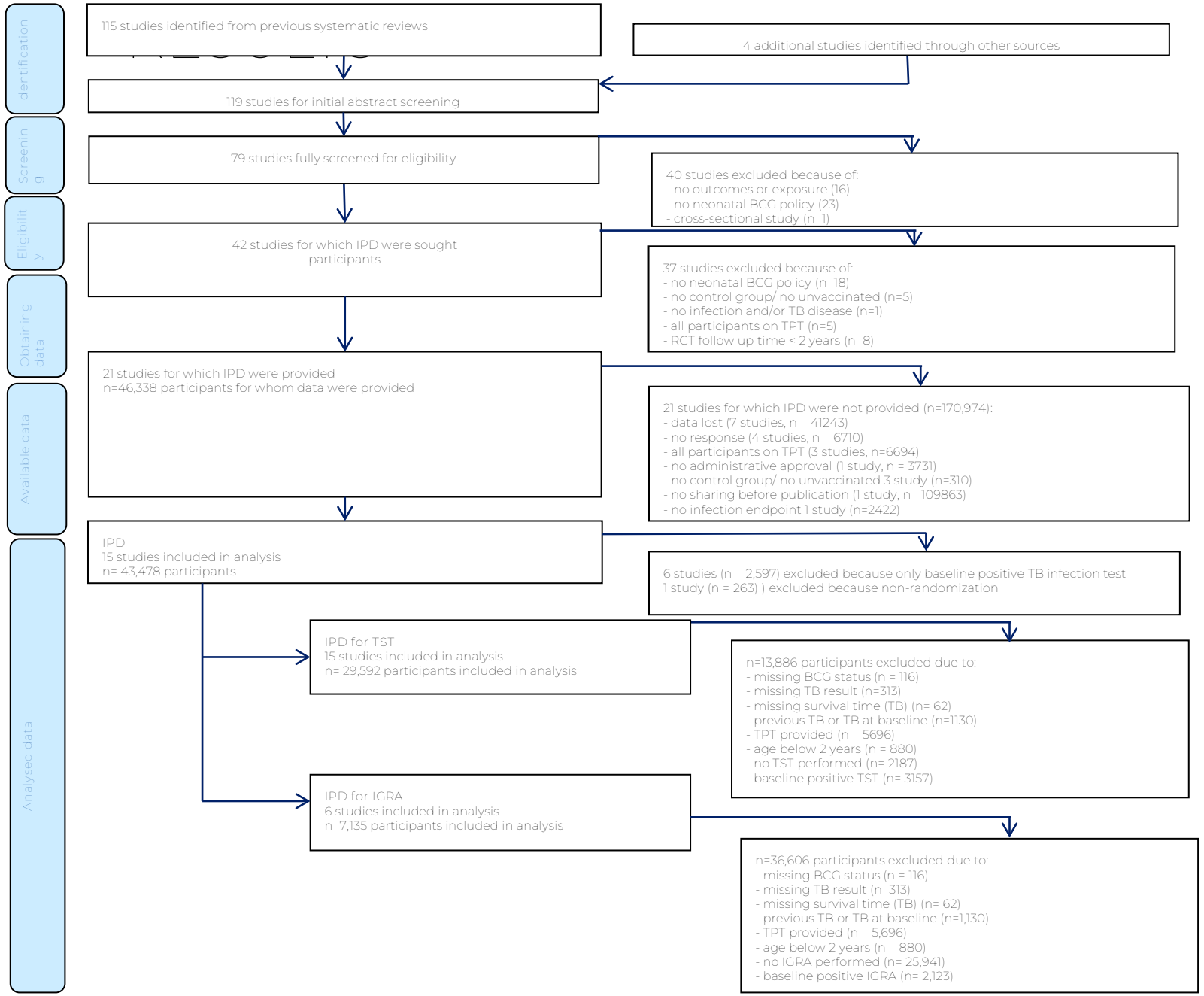
DEFINITIONS

TB Infection test conversion
TST: single conversion to ≥10 and ≥15 millimeter induration
IGRA: QFT with interferon-gamma-nil value ≥ 0.35 and ≥ 0.7 IU/mL

Sustained IGRA conversion
Two subsequent positive QFT results at ≥ 6-month interval

TB disease
As defined in individual studies

BCG vaccination status
Ascertained by typical scar



N = 43,741 participants

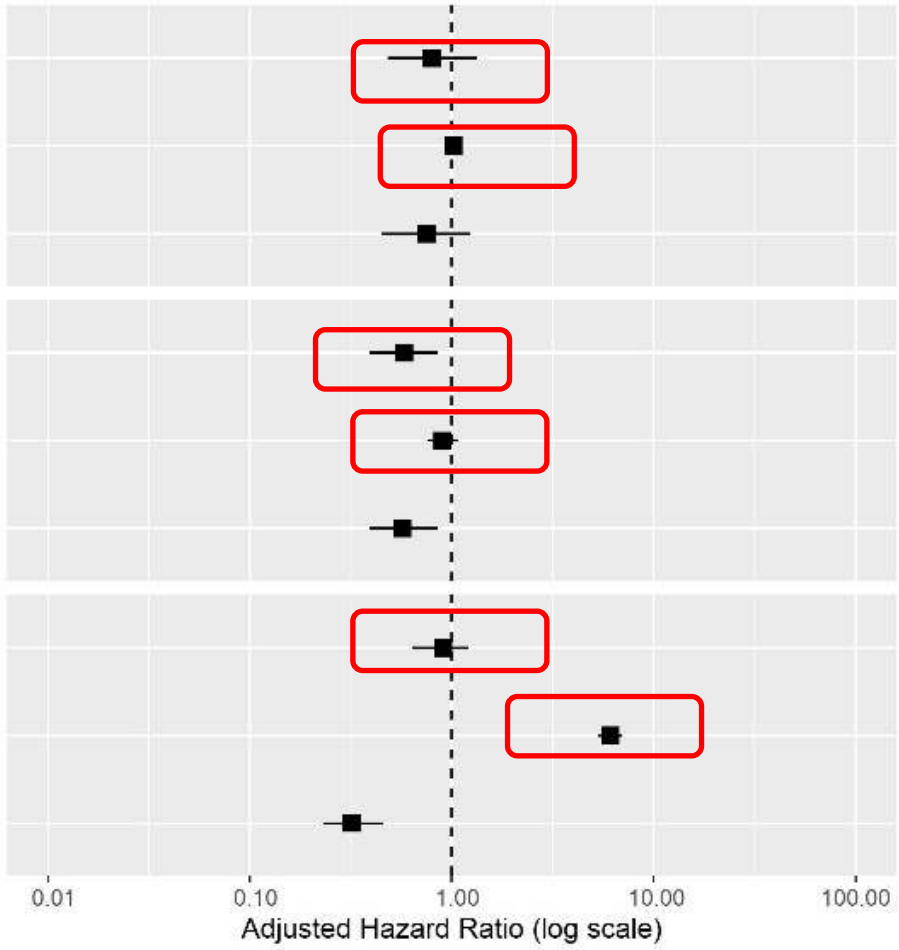
After applying exclusion criteria, remaining for analysis:

- 29,147 in 11 HHC
- 11,378 in 2 ACS
- 2,963 in 1 RCT

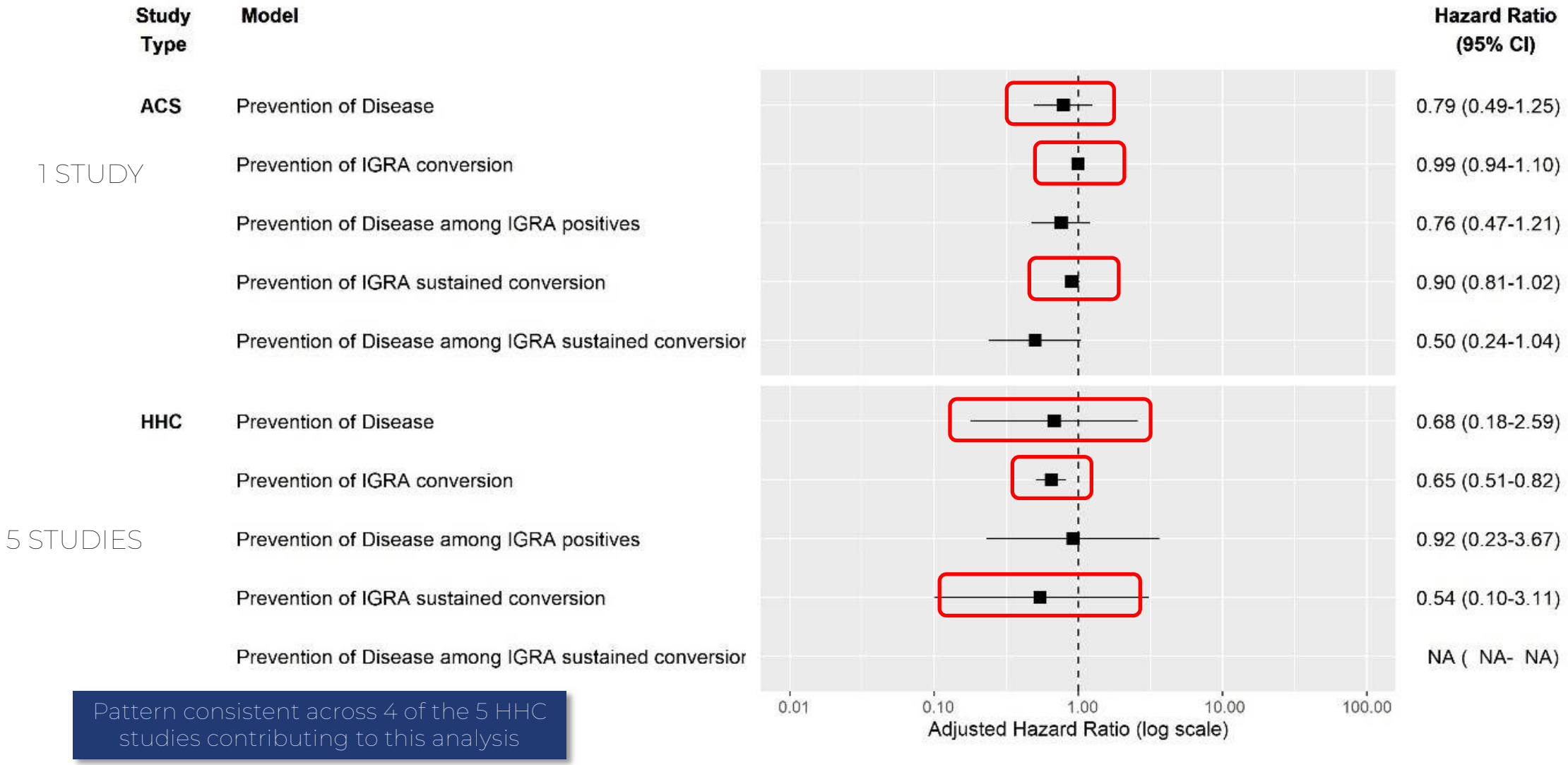
Additional exclusion criteria for TST and IGRA analyses

MODEL FOR TST, CUT-OFF ≥15 MM

	Study Type	Model	Hazard Ratio (95% CI)
2 studies	ACS	Prevention of Disease	0.80 (0.48-1.33)
		Prevention of TST conversion	1.02 (0.93-1.12)
		Prevention of Disease among TST positives	0.75 (0.45-1.24)
11 studies	HHC	Prevention of Disease	0.58 (0.39-0.86)
		Prevention of TST conversion	0.90 (0.76-1.07)
		Prevention of Disease among TST positives	0.57 (0.39-0.85)
1 study	RCT	Prevention of Disease	0.91 (0.64-1.21)
		Prevention of TST conversion	6.09 (5.35-6.92)
		Prevention of Disease among TST positives	0.32 (0.23-0.46)



MODEL IGRA, QFT CUT-OFF ≥0.7 IU/ML SINGLE AND SUSTAINED



Pattern consistent across 4 of the 5 HHC studies contributing to this analysis

SECONDARY ANALYSES

Alternative cut-offs

- TST ≥10 mm: more often positive HRs (cross-reactions)
- IGRA QFT ≥0.35 IU/ml: pattern largely consistent with QFT ≥0.7 IU/m

Age-stratified models

- Consistent patterns
- ACS, 5-12 years: non-significant protection against IGRA conversion (aHR 0.5) and disease (0.3)

Sex-stratified models

- TST: Consistent patterns
- IGRA: consistent patterns but different aHR for IGRA conversion between men (0.9) and women (0.5).

Latitude-stratified models

- HHC: significant protection against IGRA conversion in 20-40° band; other bands lack sufficient data

DISCUSSION

Interpretation

- Only find agreement with POD endpoint for IGRA conversion in the household contact studies
- Why not in adolescent cohort study? Age-dependent?
- TST-based "POI" likely affected by cross-reactions, even at cut-off ≥15 mm
- Predictive effect for POD of IGRA conversion (single or sustained) may fundamentally differ from predictive effect for POD of TST conversion

Study limitations

- Most included studies were observational
- Diverse cohorts and follow-up intervals
- Limited numbers of disease events, especially for (sustained) IGRA conversion
- Variability in disease endpoint definitions
- Potential for residual confounding

CONCLUSION

For BCG or a vaccine candidate with similar mode of action:

A TST-based endpoint lacks value as signal for PoD for phase IIb proof-of-concept trials.

Protection against QuantiFERON conversion, varies across different groups.

QuantiFERON conversion shows consistent results in groups with recent household exposure.
This consistency aligns with protection against disease.

QuantiFERON conversion could serve as a proxy for disease in TB vaccine trials in this group.

Further research and validation are necessary to confirm this.

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Declaration of interests

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