University of California
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Big Picture Scientific Challenges in Developing New TB Vaccines

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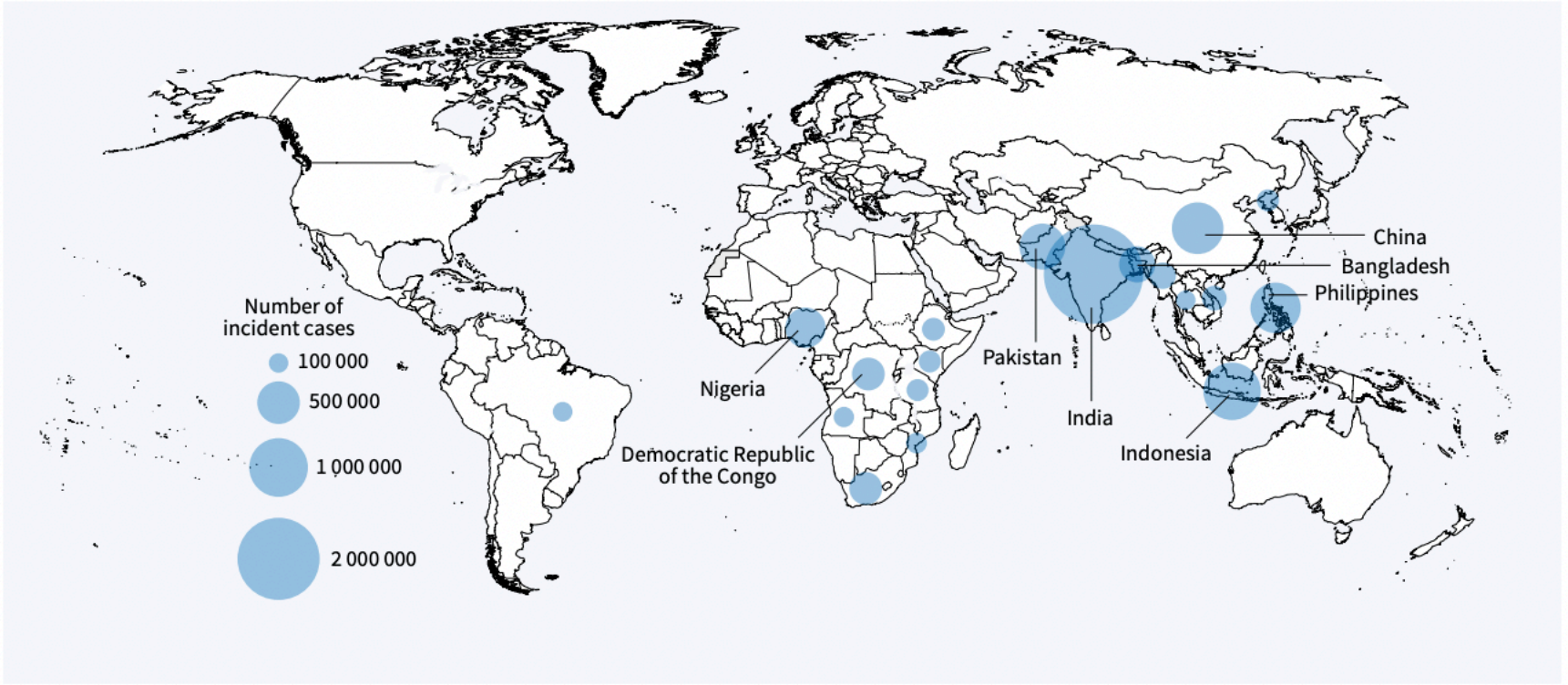
TB Vaccine Development: The Next Chapter Starts Now

Global burden of tuberculosis (TB) disease

FIG. 12

Estimated TB incidence in 2021, for countries with at least 100 000 incident cases

The countries that rank first to eighth in terms of numbers of cases, and that accounted for about two thirds of global cases in 2021, are labelled.



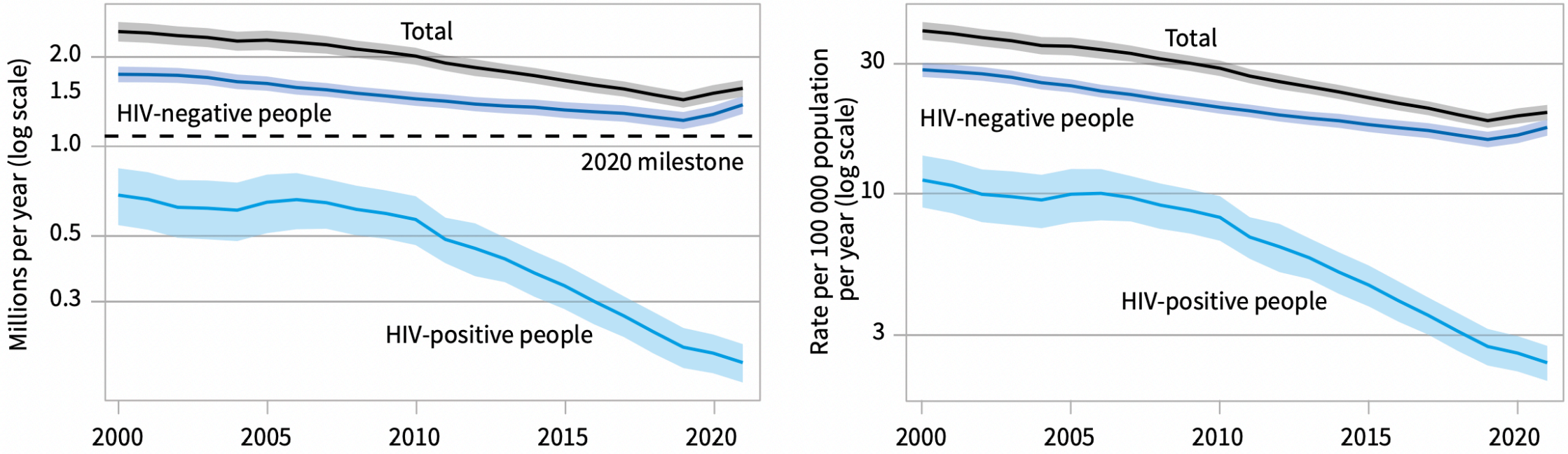
Global Tuberculosis Report 2022, *World Health Organization*

Post COVID-19 uptick in TB-related mortality

FIG. 6

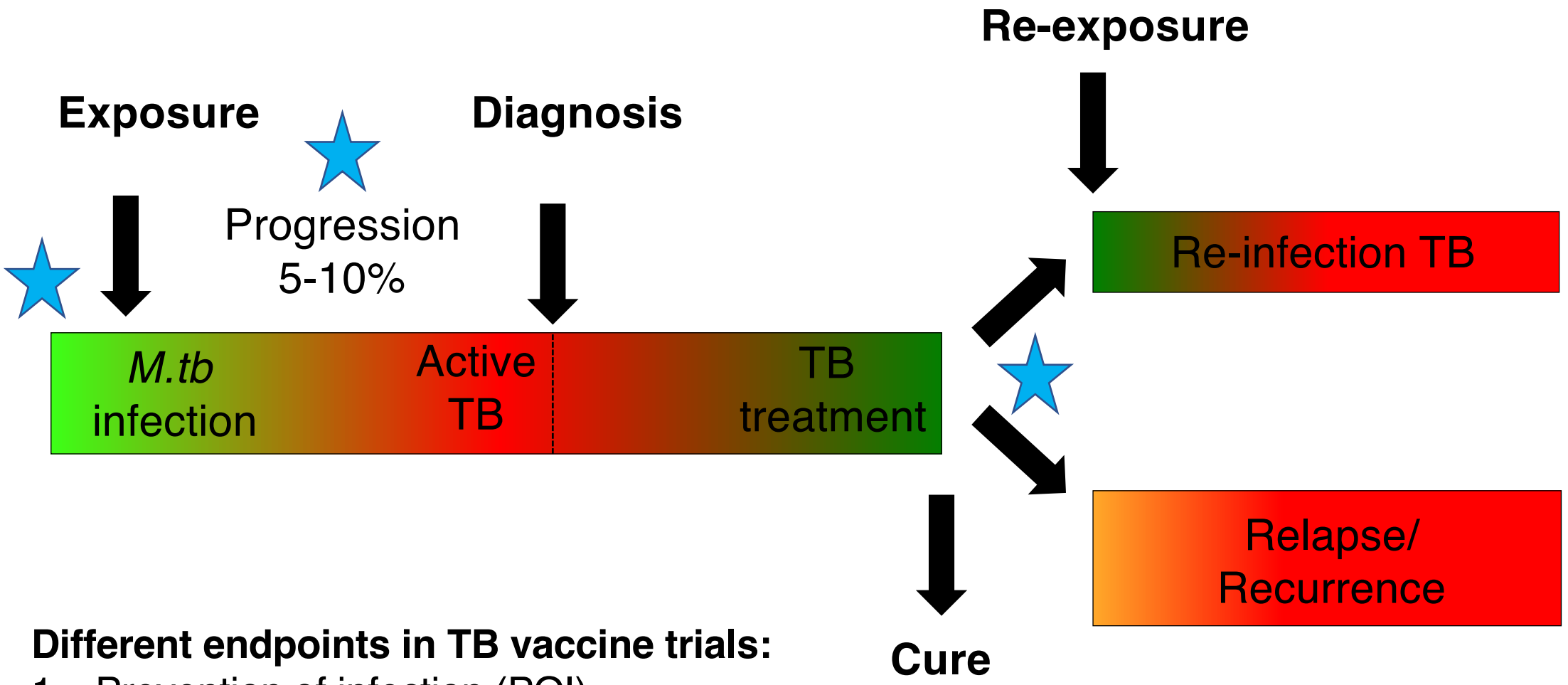
Global trends in the estimated number of TB deaths (left) and the mortality rate (right), 2000–2021

The horizontal dashed line shows the 2020 milestone of the End TB Strategy, which was a 35% reduction in the total number of TB deaths between 2015 and 2020. Shaded areas represent 95% uncertainty intervals.



Success in HIV-positive people largely attributed to advancements in antiretroviral treatments

Key transition stages in TB: vaccination opportunities



Different endpoints in TB vaccine trials:

1. Prevention of infection (POI)
2. Prevention of disease (POD)
3. Prevention of recurrence (POR)

Adapted from Thomas Scriba, University of Cape Town

Review of Vaccine Clinical Trial Stages

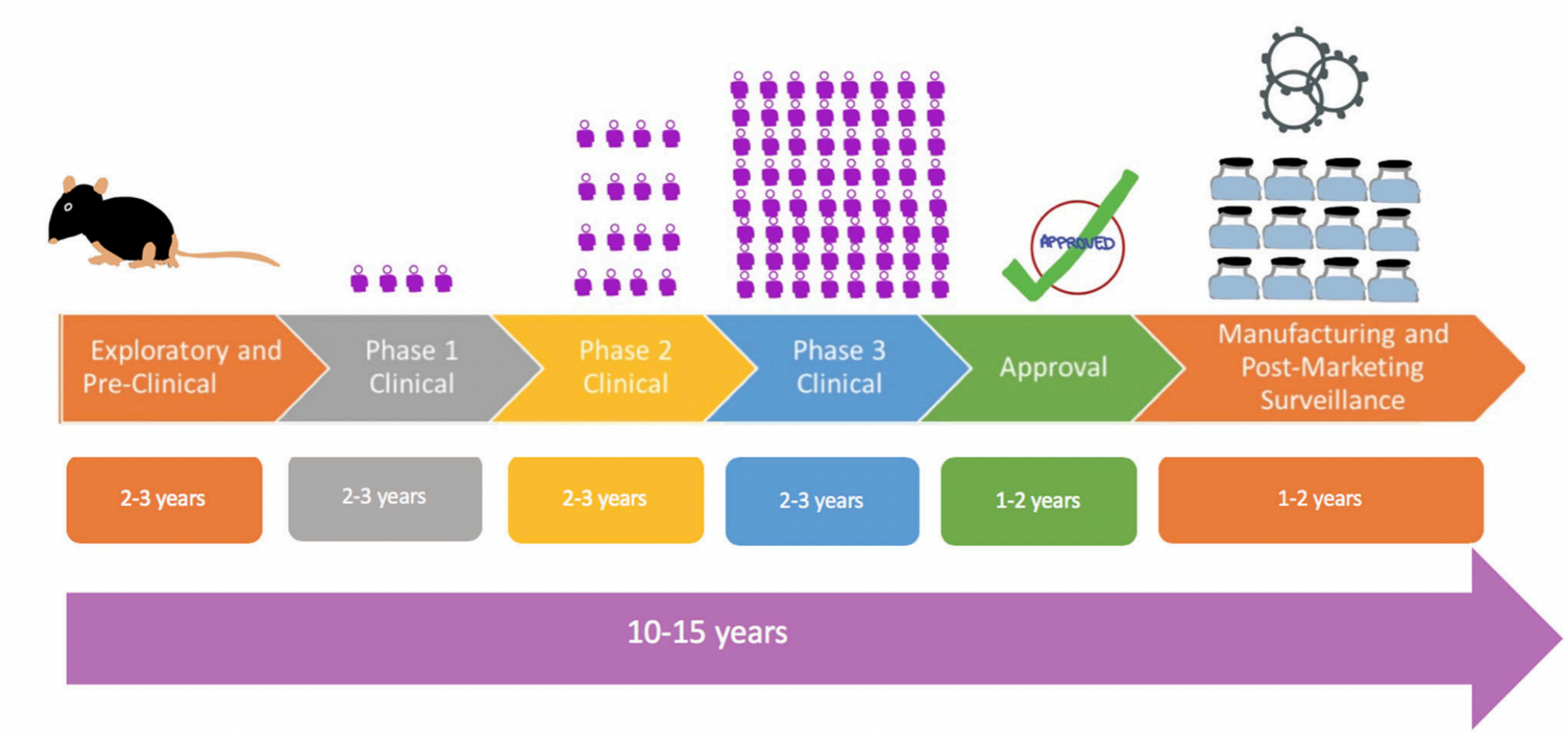


FIGURE 1 | Flowchart showing traditional process of vaccine development from exploratory, pre-clinical studies to Phase 1 studies in a comparatively few control volunteers as depicted by the figure to larger Phase 2 and Phase 3 studies. The symbol is a representation of the number of human subjects in trials.

Timelines are generally longer for TB vaccine trials!

Reference: PMID: 33163000 (2020)

What do we know about the efficacy of BCG?

Infant BCG vaccination and risk of pulmonary and extrapulmonary tuberculosis throughout the life course: a systematic review and individual participant data meta-analysis

Leonardo Martinez, Olivia Cords, Qiao Liu, Carlos Acuna-Villaorduna, Maryline Bonnet, Greg J Fox, Anna Cristina C Carvalho, Pei-Chun Chan, Julio Croda, Philip C Hill, Elisa Lopez-Varela, Simon Donkor, Katherine Fielding, Stephen M Graham, Marcos A Espinal, Beate Kampmann, Arthur Reingold, Helena Huerga, Julian A Villalba, Louis Grandjean, Giovanni Sotgiu, Uzochukwu Egere, Sarman Singh, Limei Zhu, Christian Lienhardt, Justin T Denholm, James A Seddon, Christopher C Whalen, Alberto L García-Basteiro, Rina Triasih, Cheng Chen, Jitendra Singh, Li-Min Huang, Surendra Sharma, Djohar Hannoun, Helena del Corral, Anna M Mandalakas, LaShaunda L Malone, Du-Lin Ling, Afrânio Kritski, Catherine M Stein, Richa Vashishtha, Fadila Boulahbal, Chi-Tai Fang, W Henry Boom, Eduardo Martins Netto, Antonio Carlos Lemos, Anneke C Hesseling, Alexander Kay, Edward C Jones-López, C Robert Horsburgh, Christoph Lange, Jason R Andrews

> 100 years old!

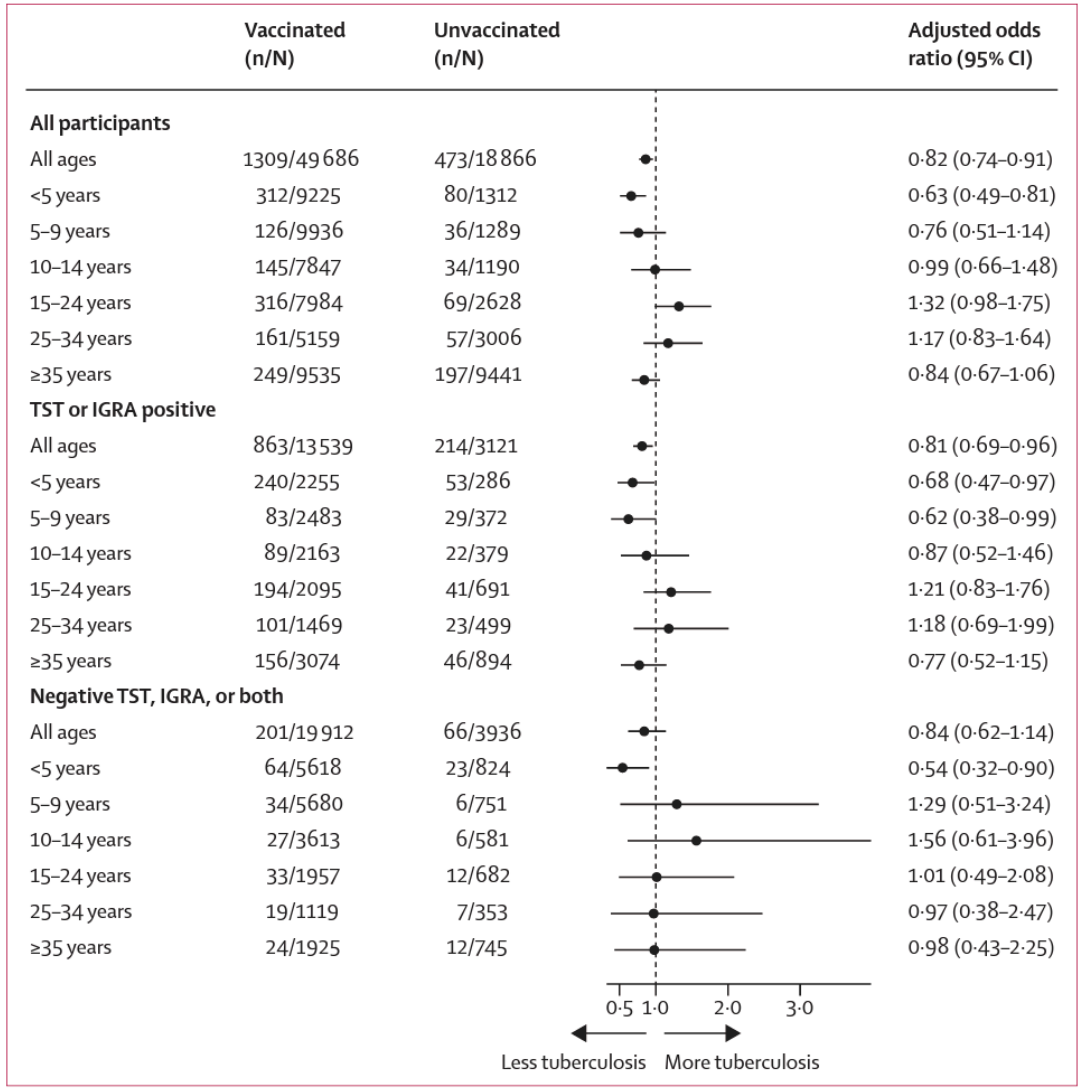


Figure 2: **BCG vaccination at birth and the risk of all tuberculosis, stratified by infection status and age**

Reference: PMID: 35961354 (2022)

TB Vaccine Pipeline

Vaccine candidates under clinical development

There are 15 vaccine candidates in the pipeline as of October 2022, of which nine are in active trials. The candidates are placed under the phase which corresponds to the most advanced ongoing or completed trial.

Platform

- Mycobacterial - Live attenuated
- Mycobacterial - Inactivated
- Viral vector
- Protein/Adjuvant

Trial staus

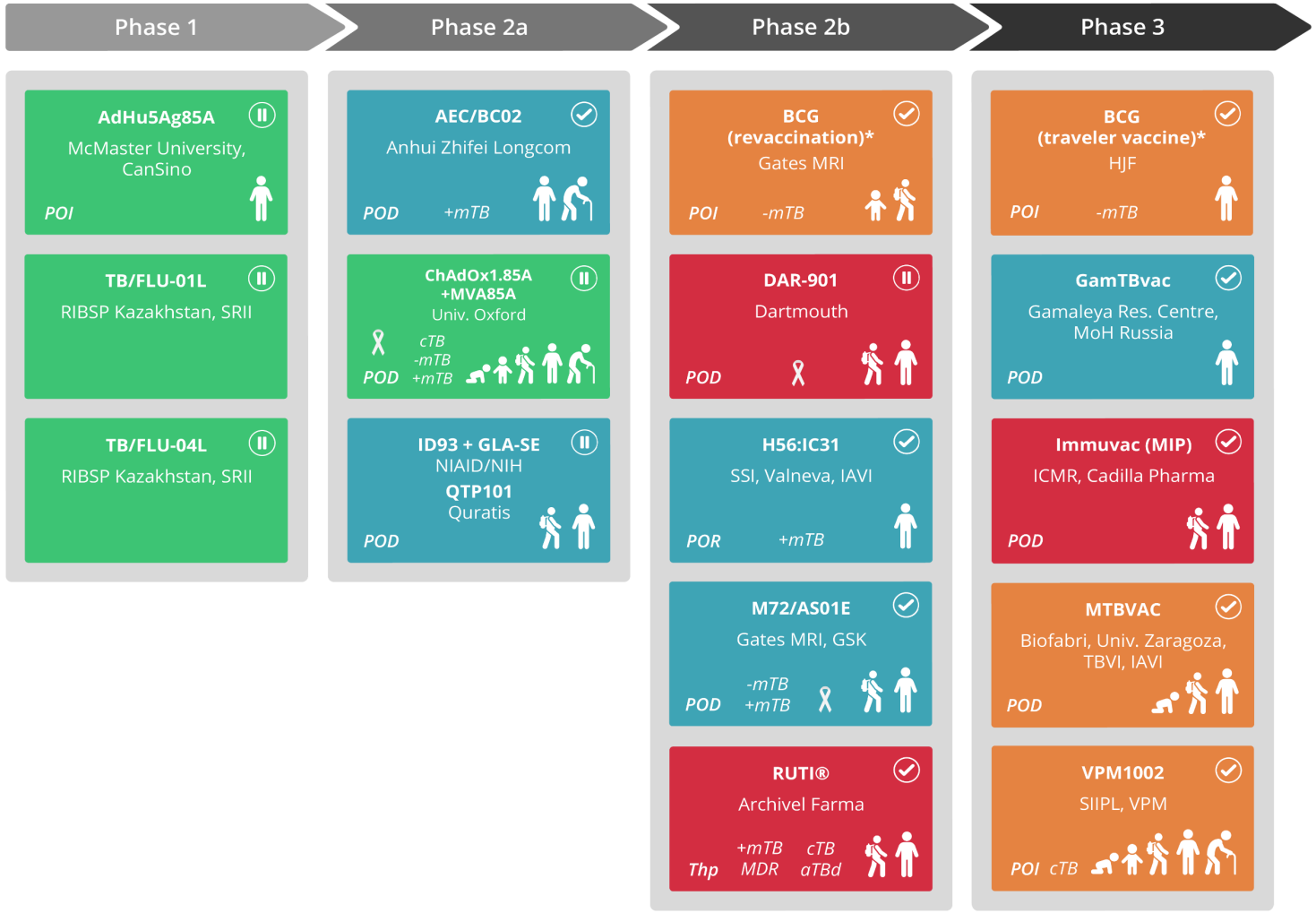
- Active trials
- No active trials

Candidate target population

- Elderly
- Adults
- Adolescents
- Children
- Infants
- People living with HIV
- -mTB — People without mTB infection
- +mTB — People with mTB infection
- aTBd — People with active TB disease
- MDR — People with MDR-TB
- cTB — People cured of active TB

Primary candidate indication

- *POI* — Prevention of Infection
- *POD* — Prevention of Disease
- *POR* — Prevention of Recurrence
- *Thp* — Therapeutic



**BCG appears twice in the pipeline to distinguish between the investigation of its use in BCG-naïve individuals (traveler vaccination) and in individuals who have previously been vaccinated with BCG (revaccination).*

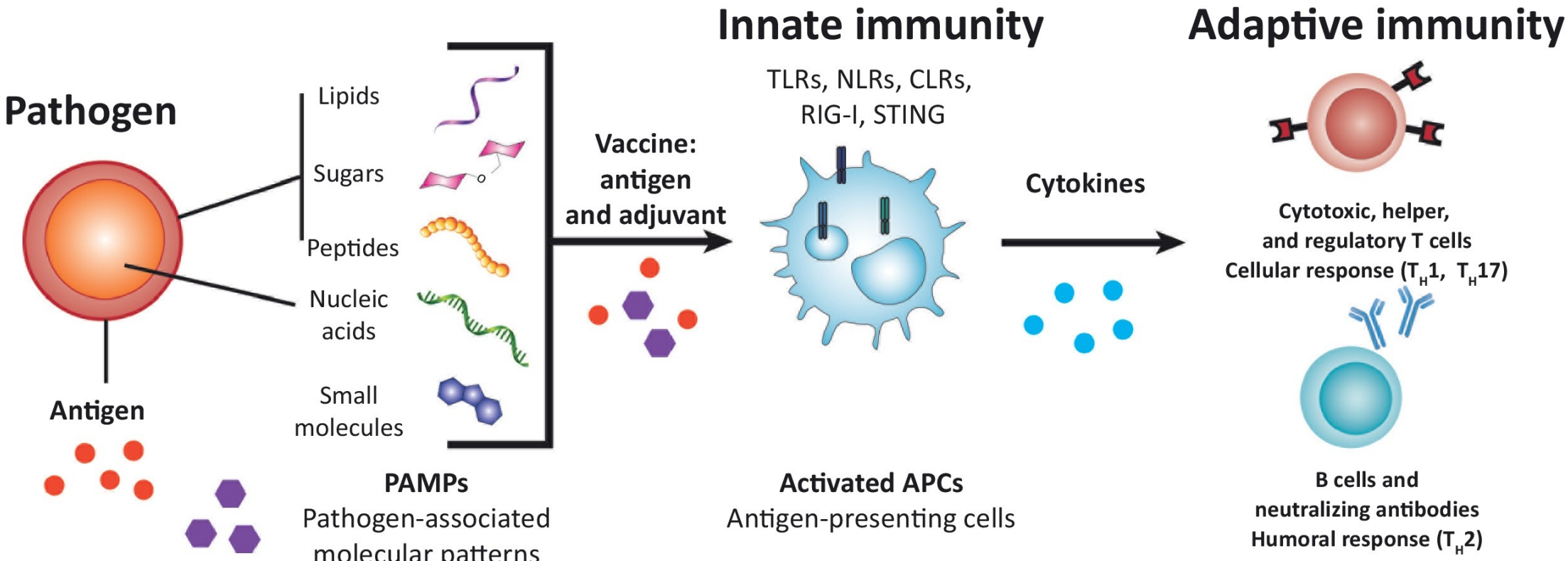
Stop TB Partnership
Working Group on New TB Vaccines

Information reported by vaccine sponsors or found in clinical trial registries or other public sources.

For the full list of completed trials for each candidate, visit www.newtbvaccines.org/tb-vaccine-pipeline/

Last update: 02 November 2022

Selection of antigens and adjuvants to include in the vaccine



- *Mycobacterium tuberculosis* has ~ 4000 genes, variably expressed in different lineages and disease states
- Which adjuvants can help stabilize a long-term memory response with minimal side effects?
- Promise of mRNA vaccines? New “adjuvant” effects?

PMID: 30470547

Selection of Populations

Infants:
Surpassing BCG
Paucibacillary TB
Maternal health status

Adults/adolescents:
BCG ‘revac’ or surpassing BCG
Clinical endpoints
Transmission chains

Elderly or immunocompromised:
Immunogenicity?
Comorbidities
Transmission chain (and myths)

We cannot assume that protection in one population can be generalizable to other populations

A shift in focus from infants to adolescents and adults

Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team*

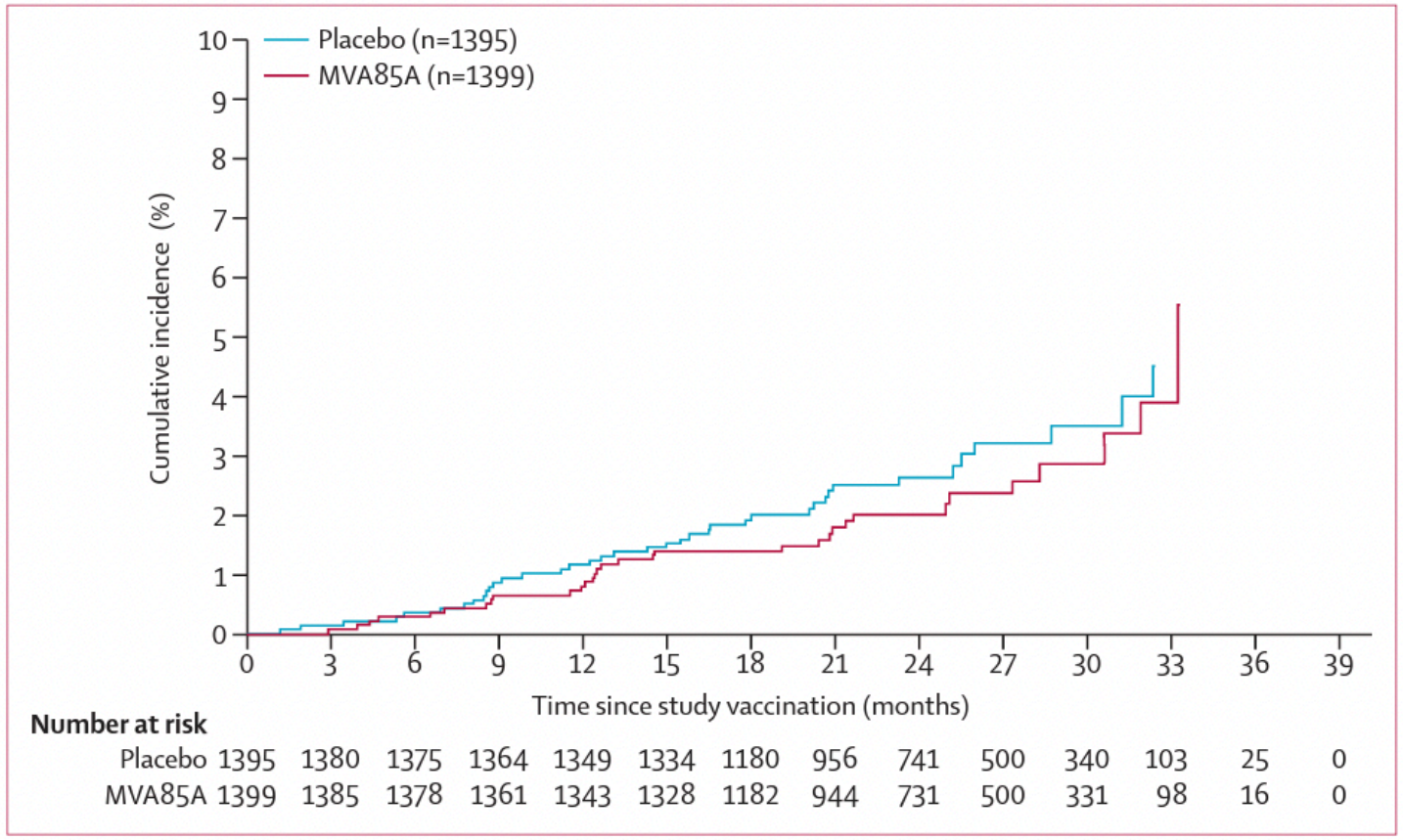


Figure 3: Cumulative incidence of diagnosis of tuberculosis endpoint 1

Reference: PMID: 23391465 (2013)

Recruitment and follow-up challenges

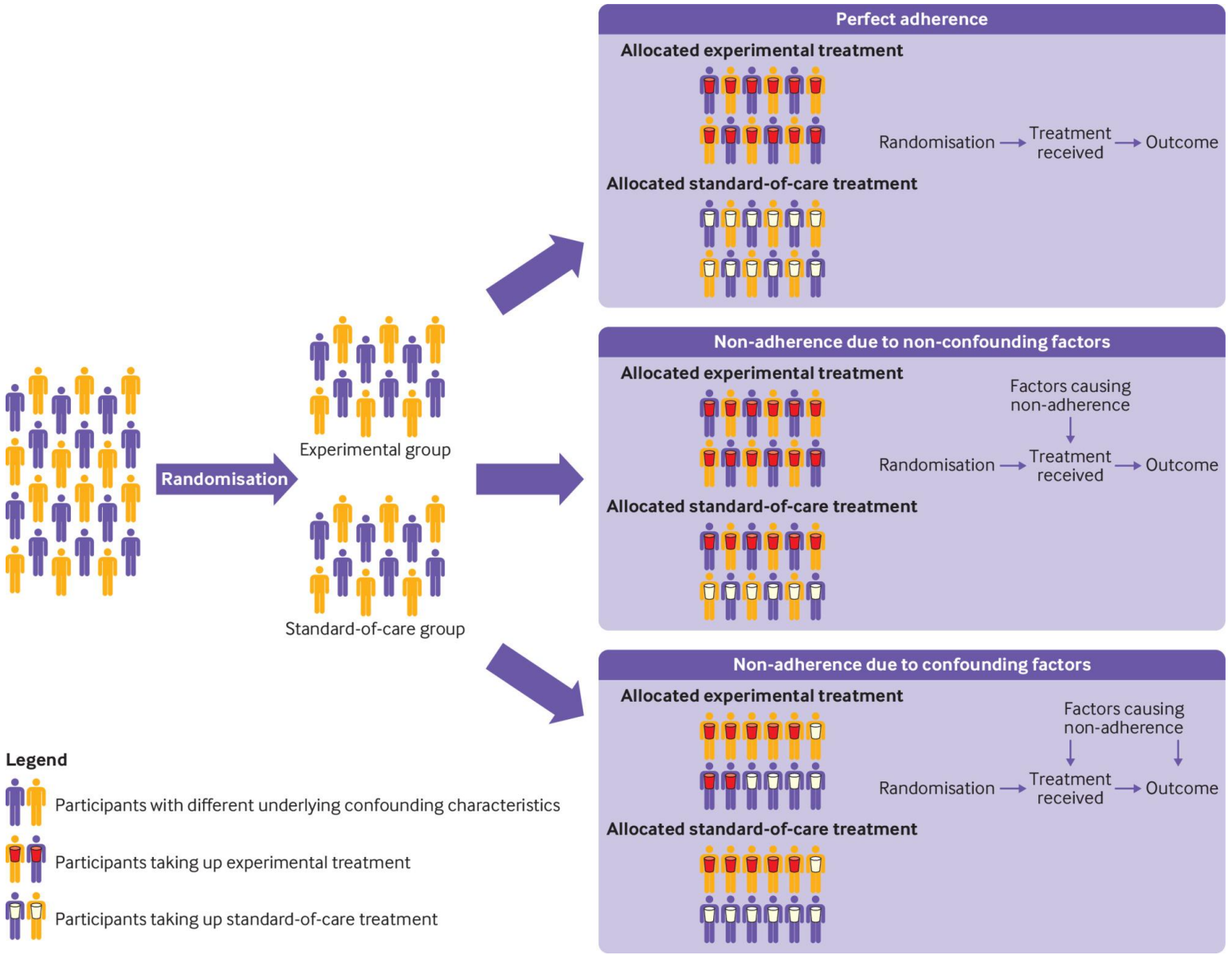
Challenges:

- Large sample size needed! Generally, a minimum of a few thousands in efficacy studies
- Long time to disease progression (2 years of follow-up is standard)
- Resources for follow-up: staffing, contact with participants, active case finding
- Is the disproportionate focus on adolescents and adults valid (BCG, transmission likelihood)?

Intention-to-treat vs. per-protocol analysis:

“Intention-to-treat (ITT) analysis maintained the original group composition achieved by randomisation”
“Per protocol (PP) analysis included only those participants who completed the protocol for their allocated treatment”
-Consolidated Standards of Reporting Trials (CONSORT) recommends ITT as standard practice in analysis of clinical trials

- Sedgwick, BMJ, 2015



Per Protocol

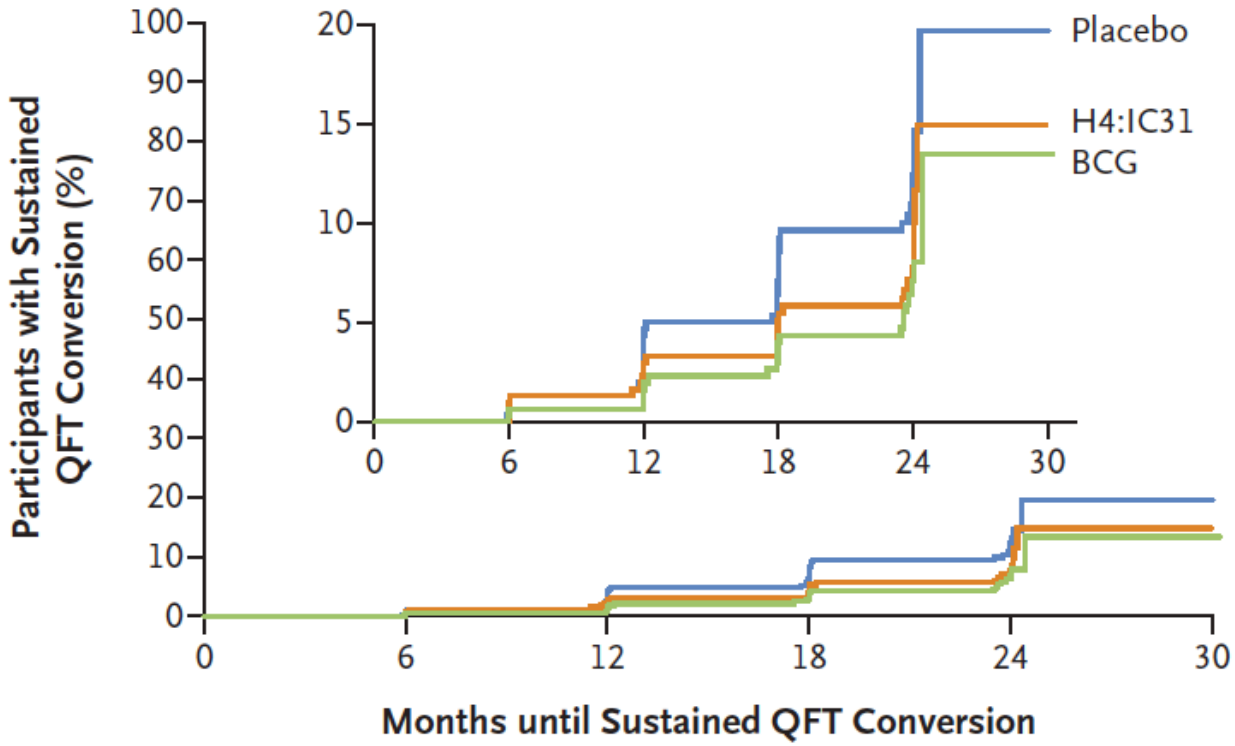
Intention to treat (non-confounded)

Intention to treat (confounded)

Non-adherence in non-inferiority trials: pitfalls and recommendations. PMID: 32651165

TB Vaccinology Achievements in 2018 (1)
Prevention of Infection (BCG and H4): NCT02075203

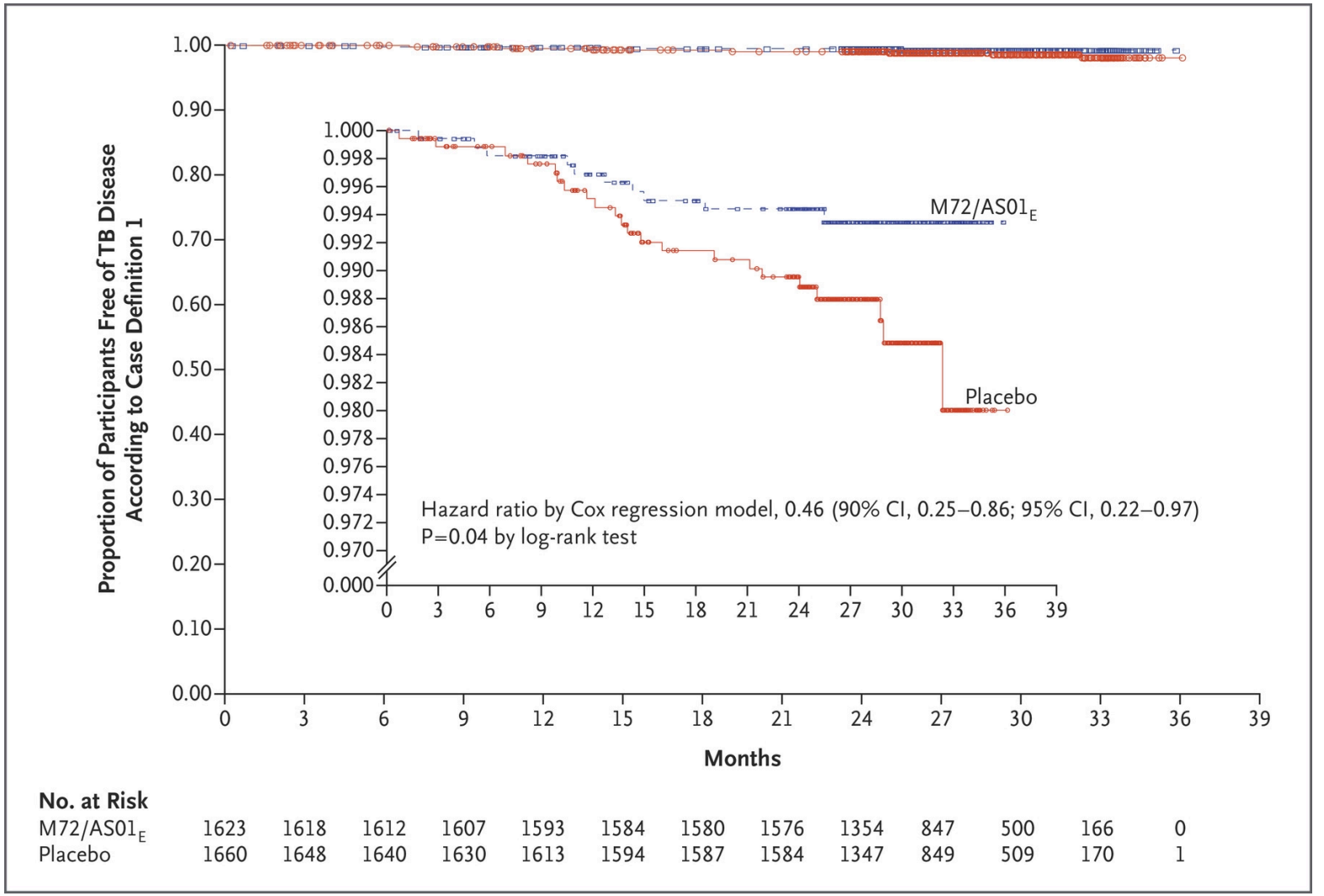
C Sustained QFT Conversion



No. at Risk					
Placebo	310	302	287	263	122
H4:IC31	308	303	288	268	124
BCG	312	308	297	281	136

Nemes, et al. NEJM, 2018

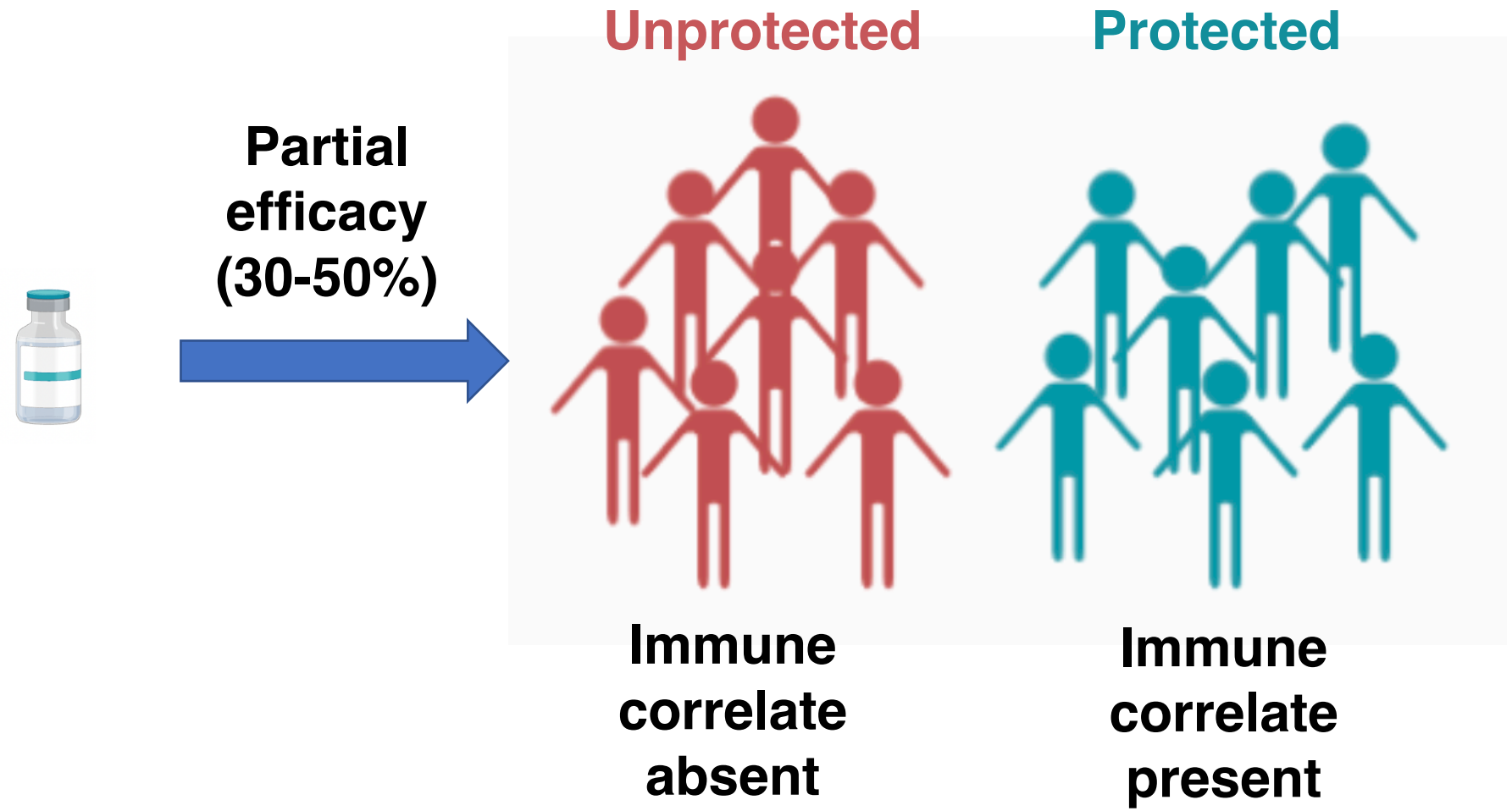
TB Vaccinology Achievements in 2018 (2)
Efficacy of GSK M72/AS01E (NCT01755598)



Promise for sub-unit TB vaccines

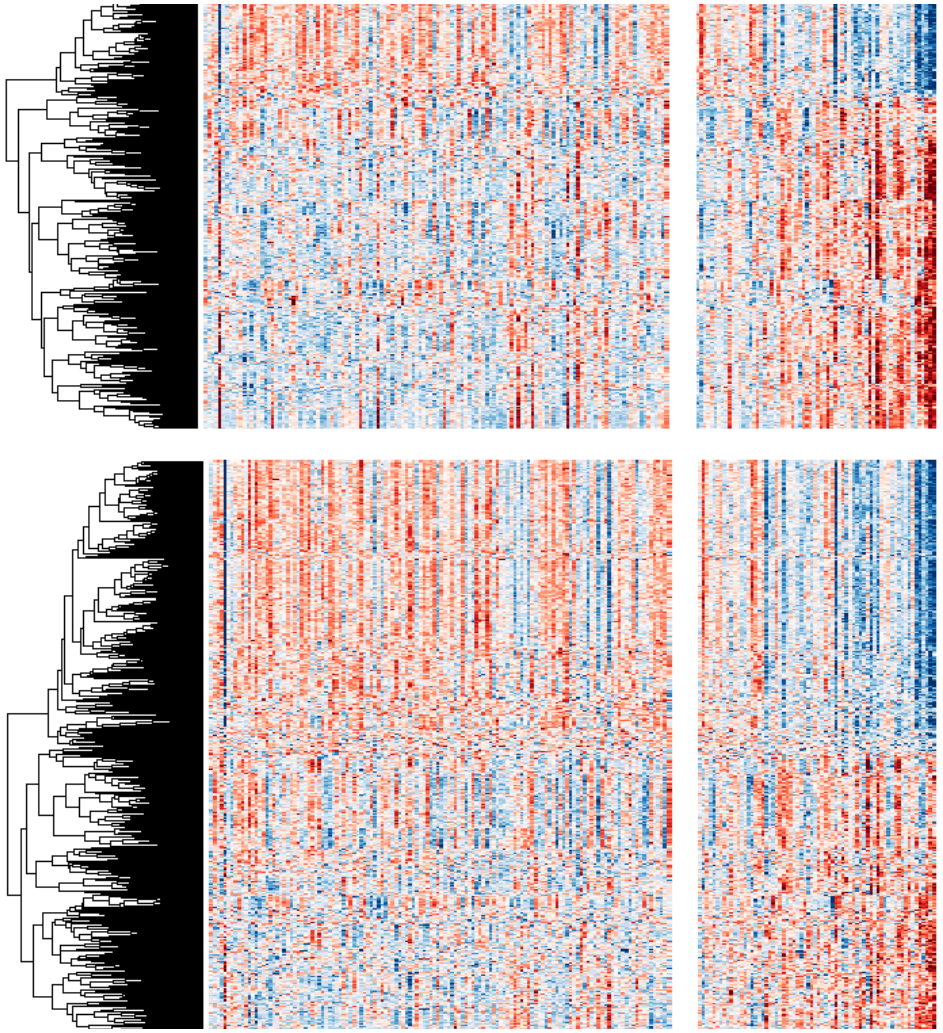
Van Der Meeren, et al. NEJM 2018

The Quest for the TB Correlates of Protection (COP)



Is the immune COP mechanistic (i.e. protection-driving), or just a passenger correlate?

Systems Biology: Biomarkers vs. Hypothesis Generation



Correlates:

Who is protected?

Mechanisms:

Why are they protected?

Special considerations to define COPs in people living with HIV (PLWH)

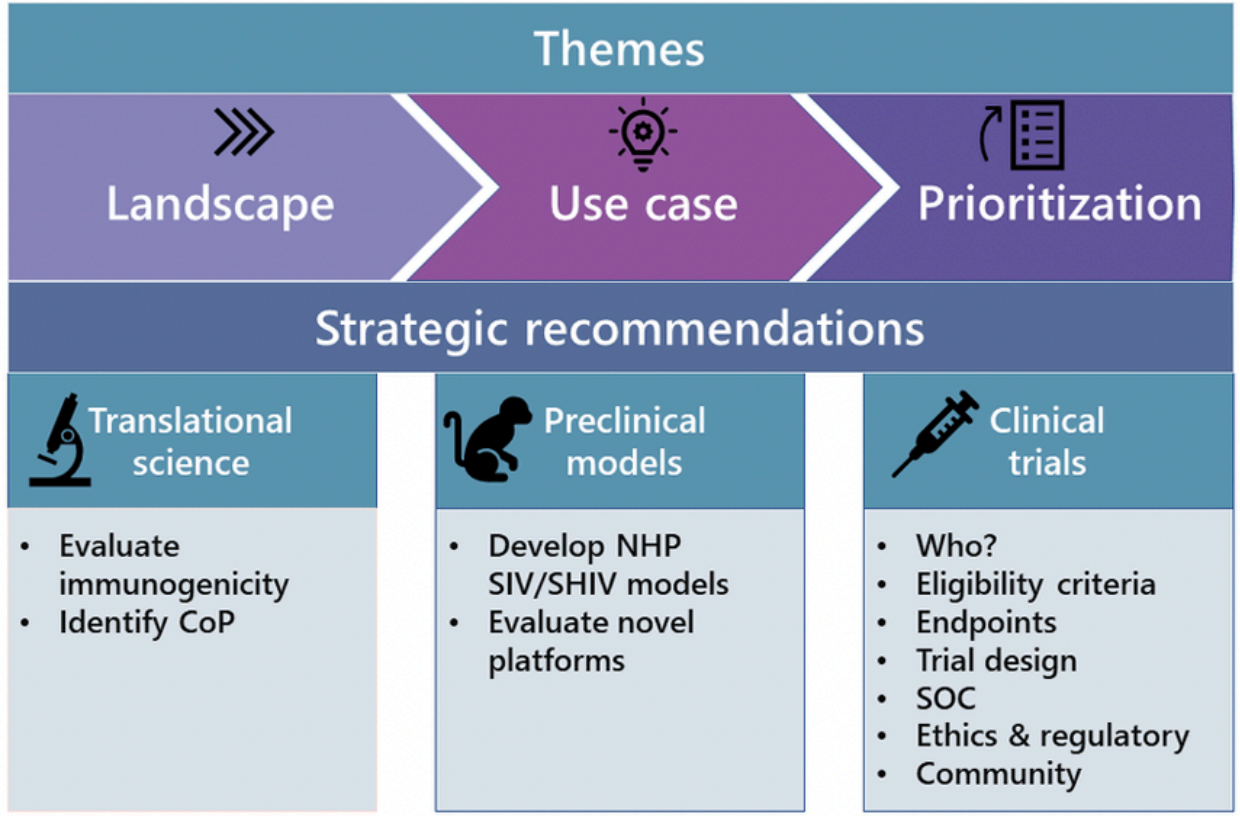


Figure 1

TB vaccine roadmap for people with HIV.

- Endpoints may be different:
POI: Latent infection detection tools are less optimal in PLWH
POD: paucibacillary disease, non-pulmonary presentations

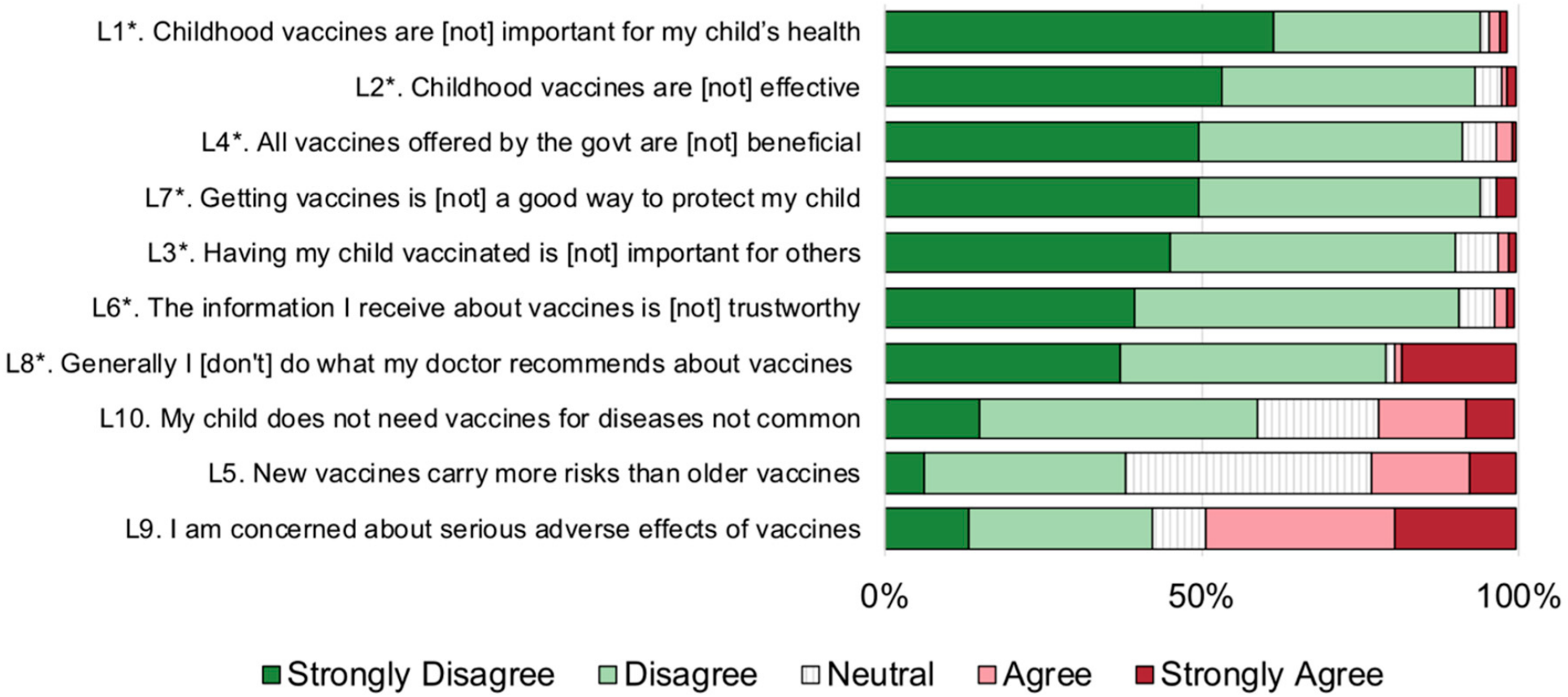
- **Special safety considerations:**

Risk from live attenuated vaccines should be carefully monitored

Unanticipated interactions with ARVs

Reference: Lancet HIV. PMID: 36240834 (2022)

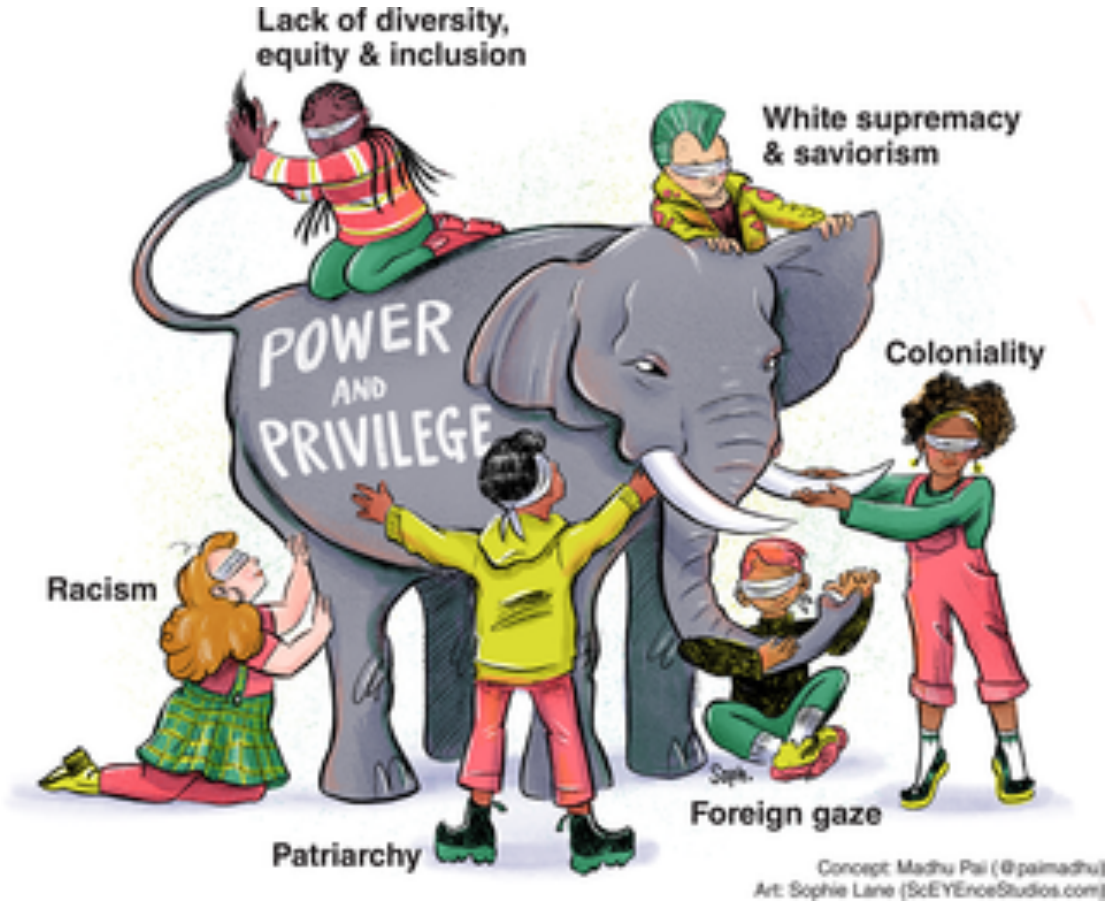
Engagement in Vaccine Clinical Trials in the Era of COVID-19



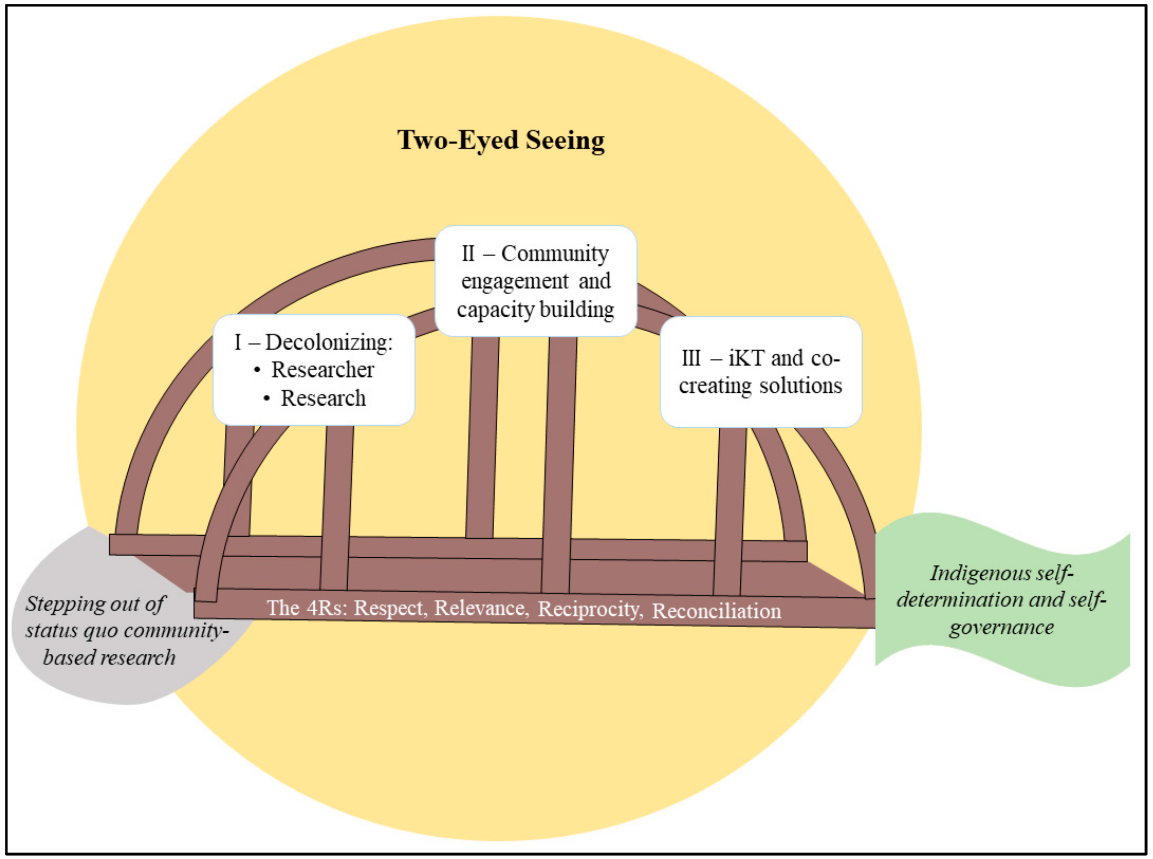
"Mothers of children in Sirajganj, Bangladesh (*n* = 60), Shanghai, China (*n* = 788), Addis Ababa, Ethiopia (*n* = 341), Guatemala City and Quetzaltenango, Guatemala (*n* = 767), and Chandigarh, India (*n* = 309), completed a survey between 2016 and 2018 using the WHO's 10-item Vaccine Hesitancy Scale."

Reference: Wagner AL, et al. Vaccines (Basel). 2019. PMID: 31635270

Decolonizing TB Vaccinology



Courtesy of Madhu Pai



Reference: PMID: 34097692