Tuberculosis Vaccine Development

Progress, Challenges & Future Direction

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Pathogen, disease and unmet medical need

The Global Burden of TB

2 billion people latently infected with *M. tuberculosis*

5-10% infected people progress to disease

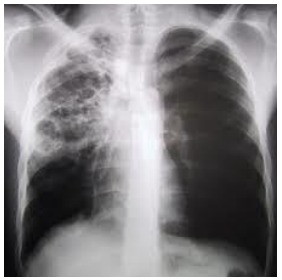
9 million new TB cases each year

1.5 million TB deaths each year

Equivalent to 20 passenger aircraft crashes each day

Pathogen, disease and unmet medical need

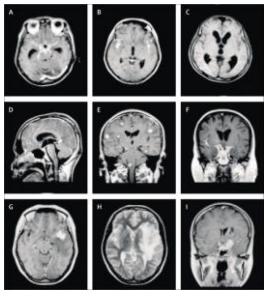
TB is transmitted by adults with cavitatory disease



HIV infected people carry greater burden of disease,

but are not responsible for increased transmission (paucibacillary disease)

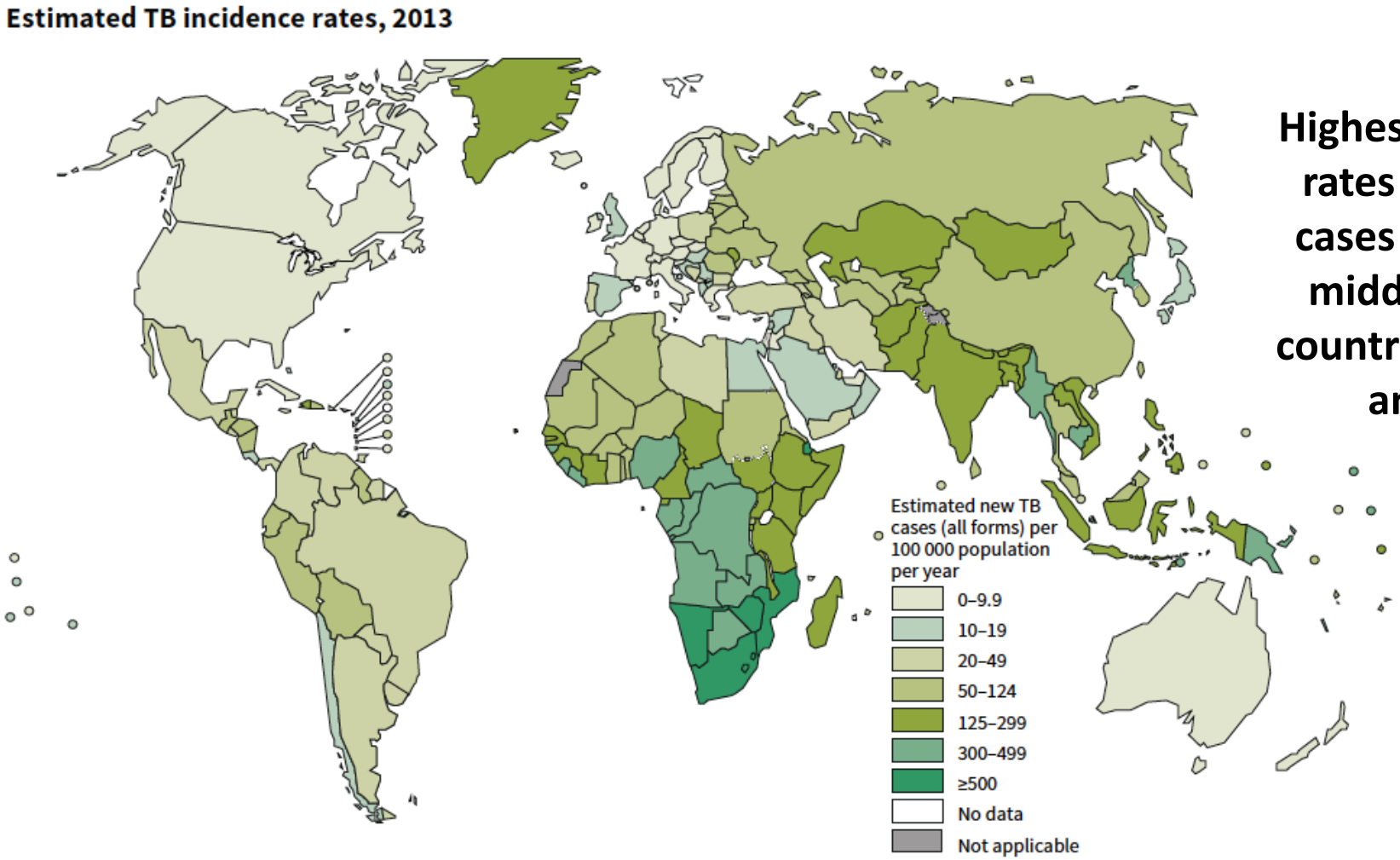
Children are sentinels for transmission



Young children most vulnerable

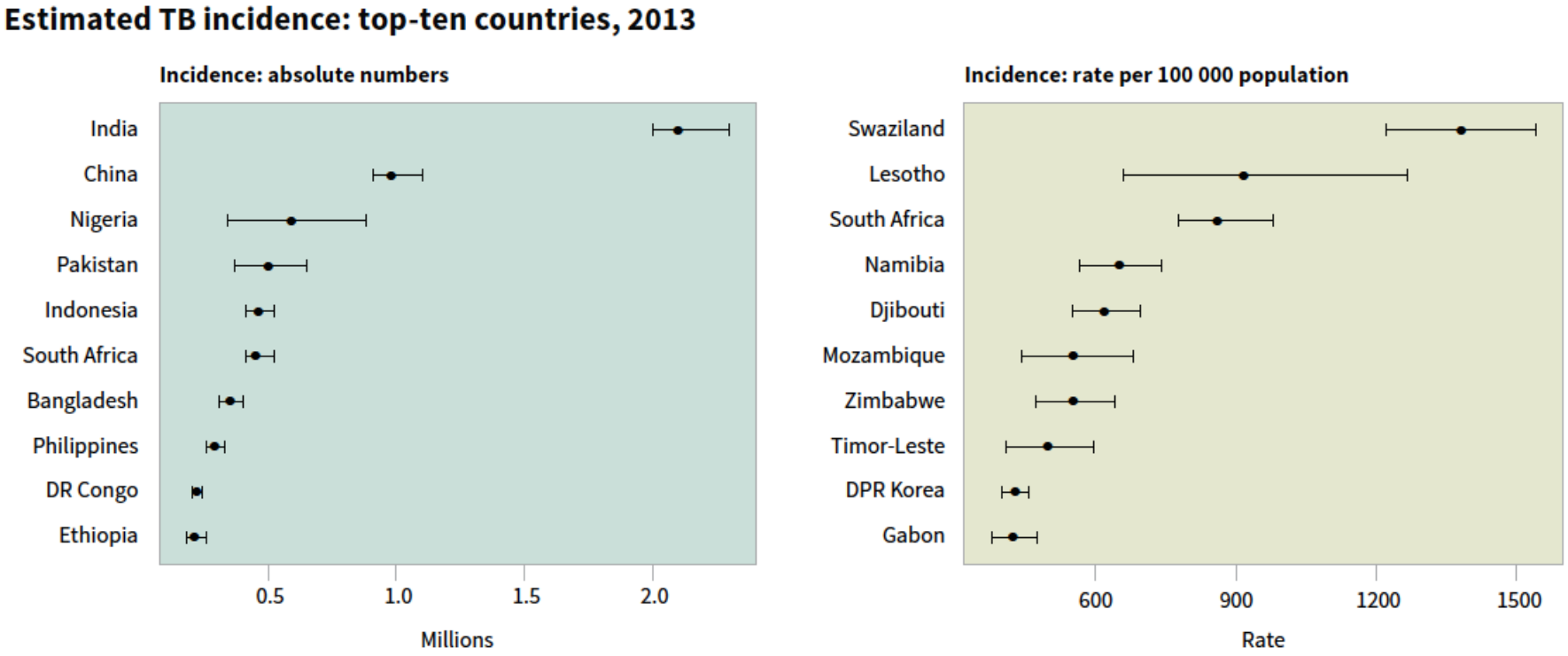
Highest risk of progression from TB infection to active disease, and worst TB morbidity and mortality, compared to older children and adults

Pathogen, disease and unmet medical need



Highest per capita rates of new TB cases in low and middle income countries of Africa and Asia

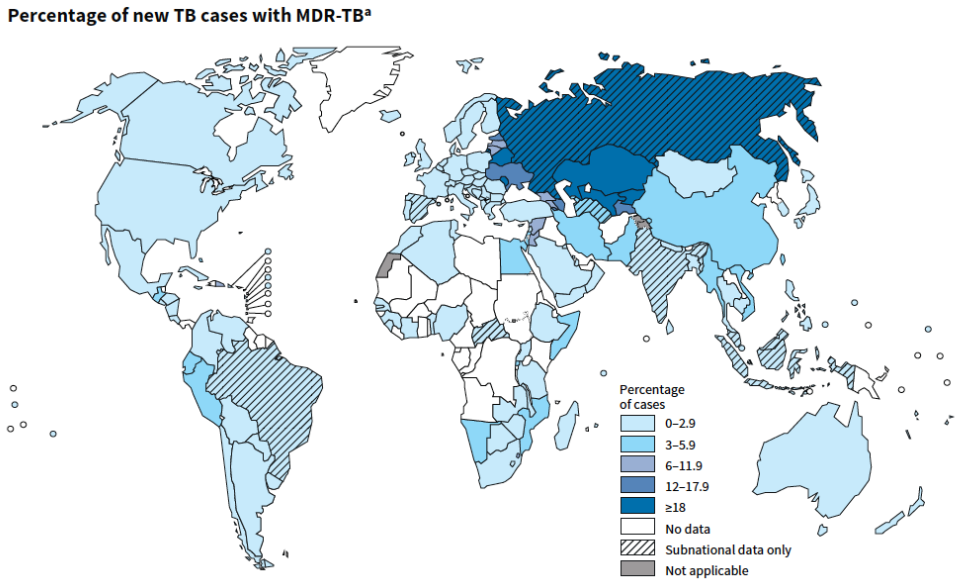
Pathogen, disease and unmet medical need



Largest absolute number of TB cases in Asia (India, China 35%)
Aging of the epidemic

Highest per capita incidence in Southern Africa (HIV and mining)
Incidence in Africa >2x global average incidence (126 per 100,000)

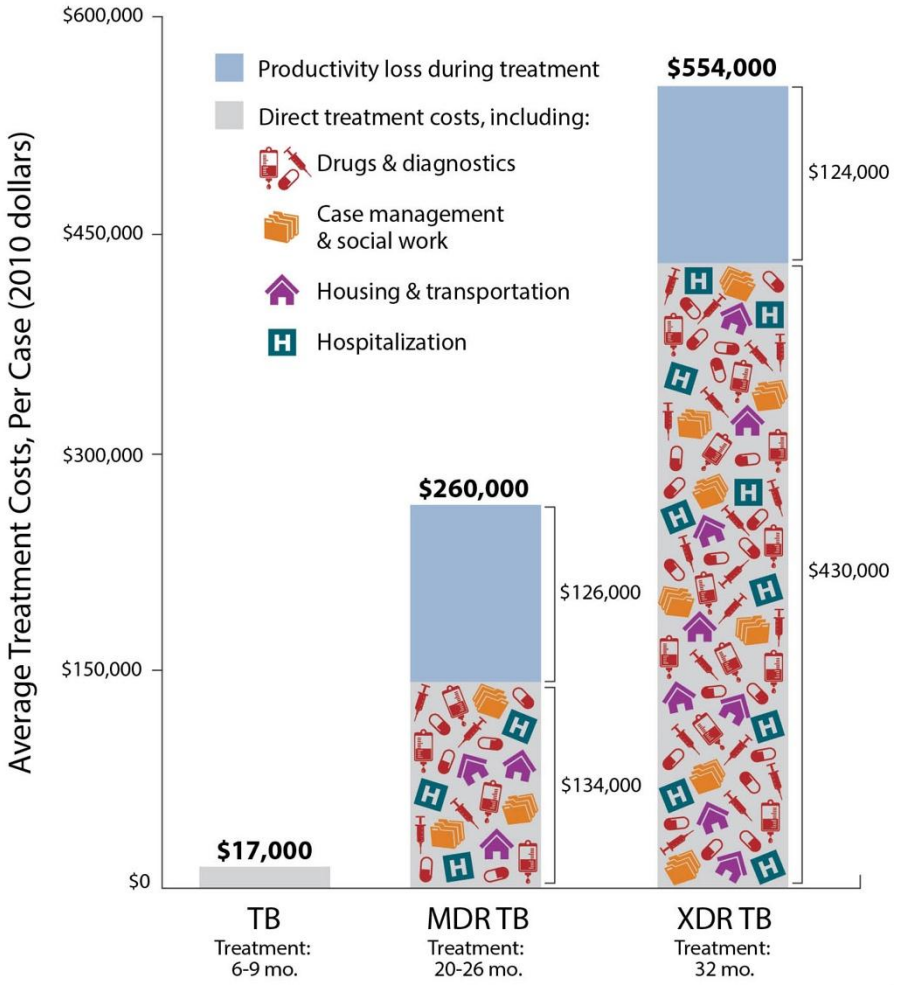
Pathogen, disease and unmet medical need



Average 3.5% of new TB cases multidrug resistant (MDR-TB)

Emerging threat to TB control
Treatment cost 15x DS-TB

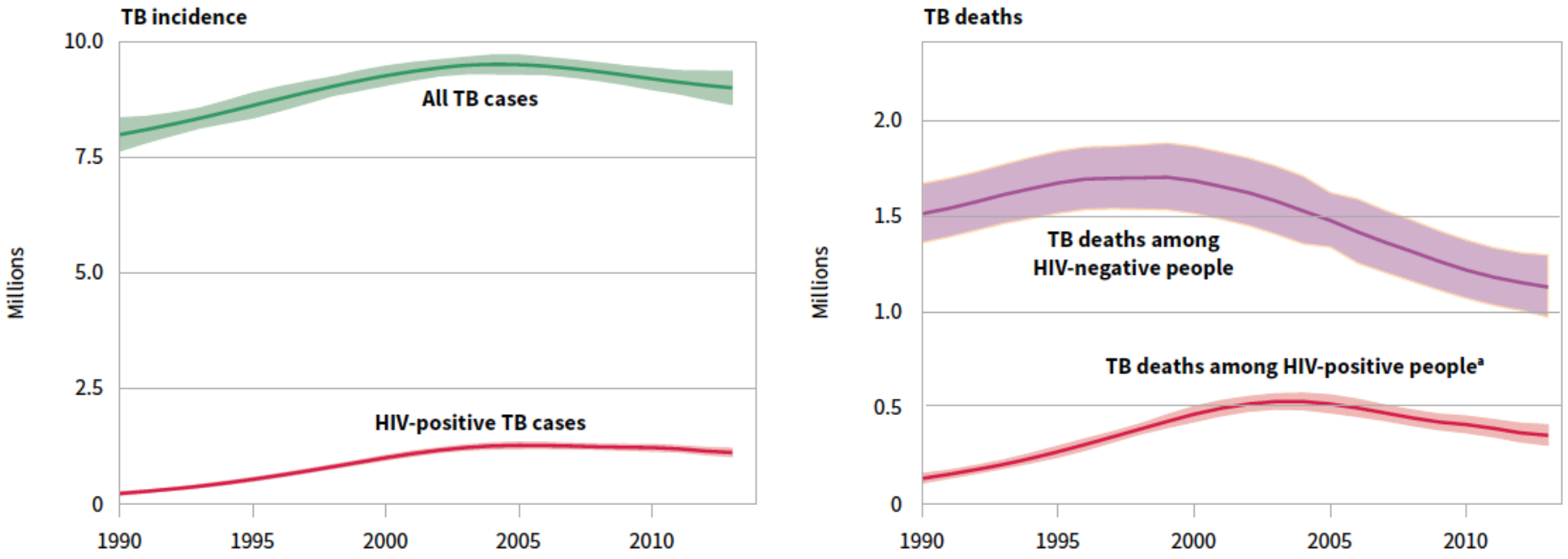
→ Potential for new TB vaccines



Source: CDC

Pathogen, disease and unmet medical need

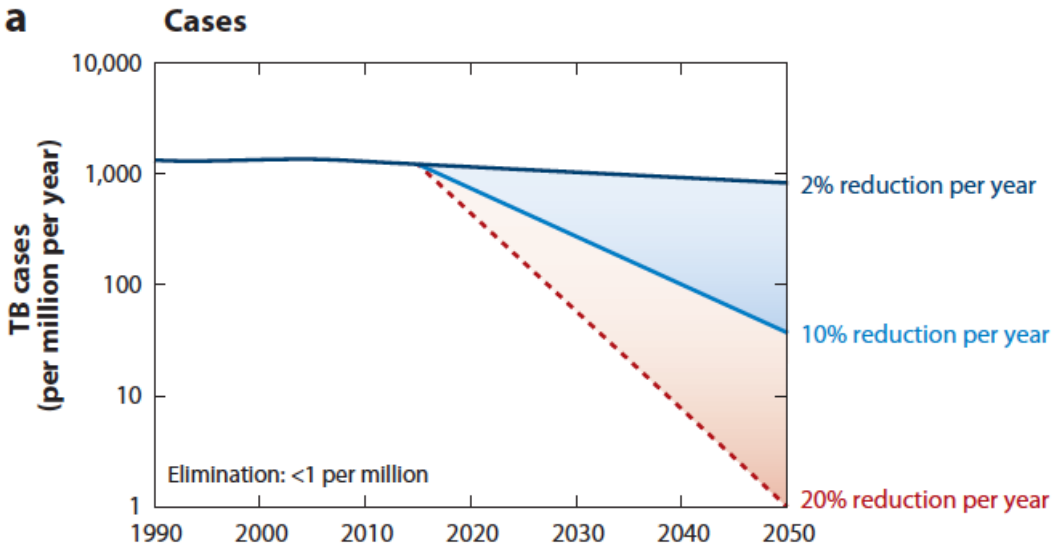
Estimated absolute numbers of TB cases and deaths (in millions per year), 1990–2013

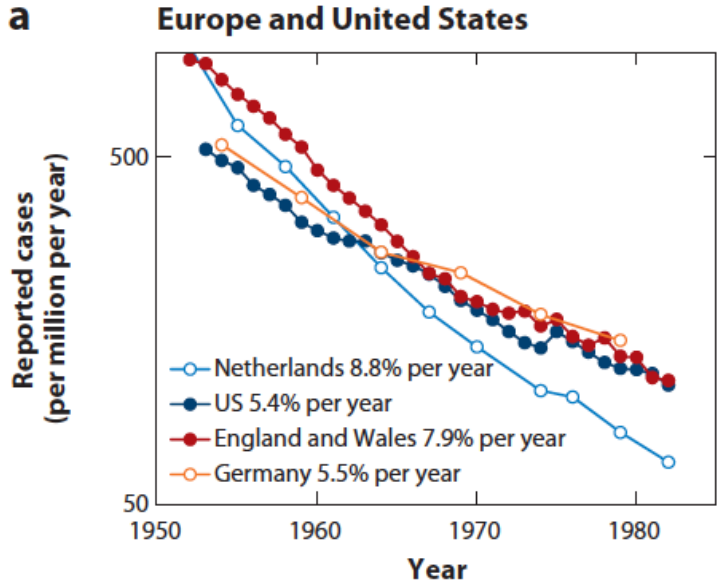


[a] HIV-associated TB deaths are classified as HIV deaths according to ICD-10.

The global TB epidemic has peaked
TB incidence rate falling at 1.5% per year
Not fast enough to meet TB control goals

Pathogen, disease and unmet medical need



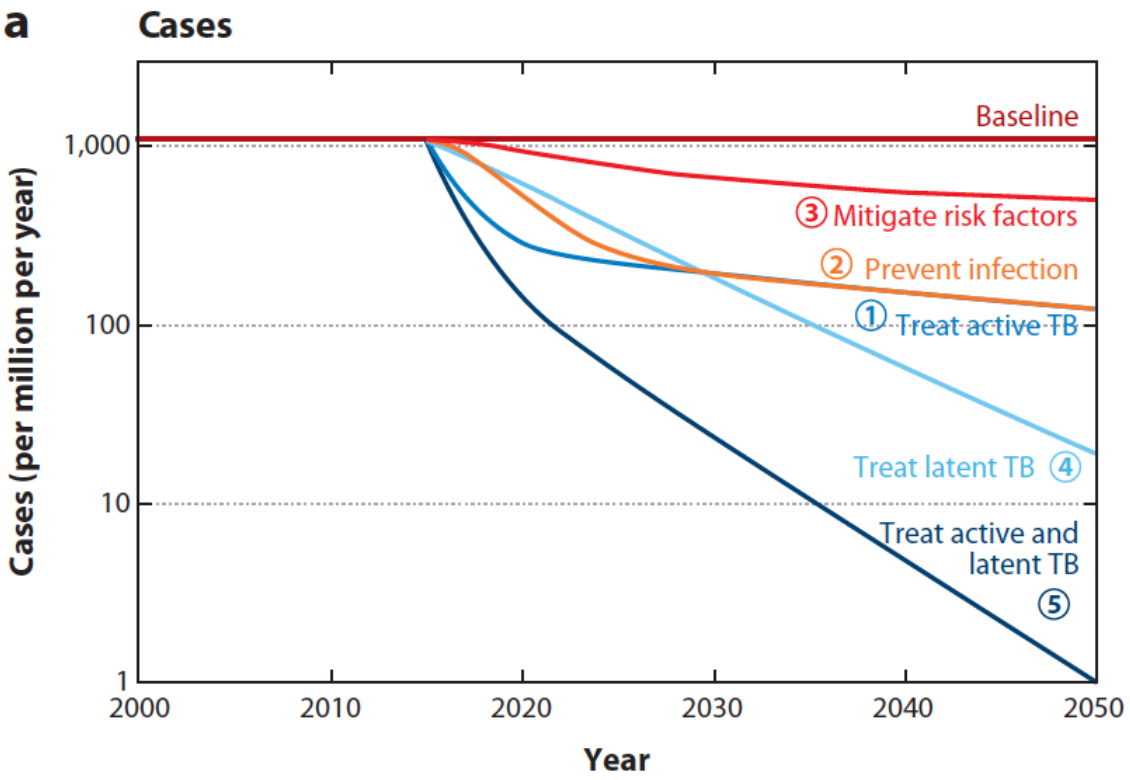


Target for TB elimination: Annual incidence <1 case per million population by 2050

Would need 1,000-fold reduction in 35 years
20% annual reduction is faster than historical examples

Dye, Annu Rev Public Heath 2013

Pathogen, disease and unmet medical need



2014 World Health Assembly "End TB Strategy"

Reduce TB deaths by 95% and new cases by 90% by 2035

Need optimal use of existing tools PLUS

New tools to prevent new infection and progression to disease – *including new vaccines*

***Impact of effective Prevention of Disease TB vaccine follows (4)**

Vaccine development: background

Why BCG is not good enough

Live attenuated M. bovis, first used in 1921

BCG protects against severe meningitic and miliary TB in infants and children (RR 0.15)

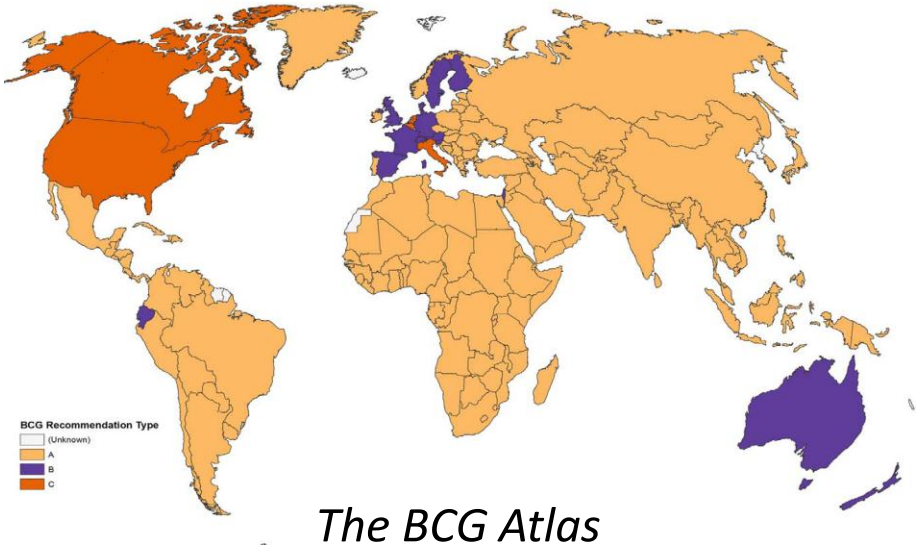
Billions of doses administered to infants since 1970's

Offers only partial protection against pulmonary TB in children

Little or no protection against pulmonary TB in adults

Meta-analysis, Mangtani CID 2014

1921 Model T Ford



The BCG Atlas

Vaccine development: background

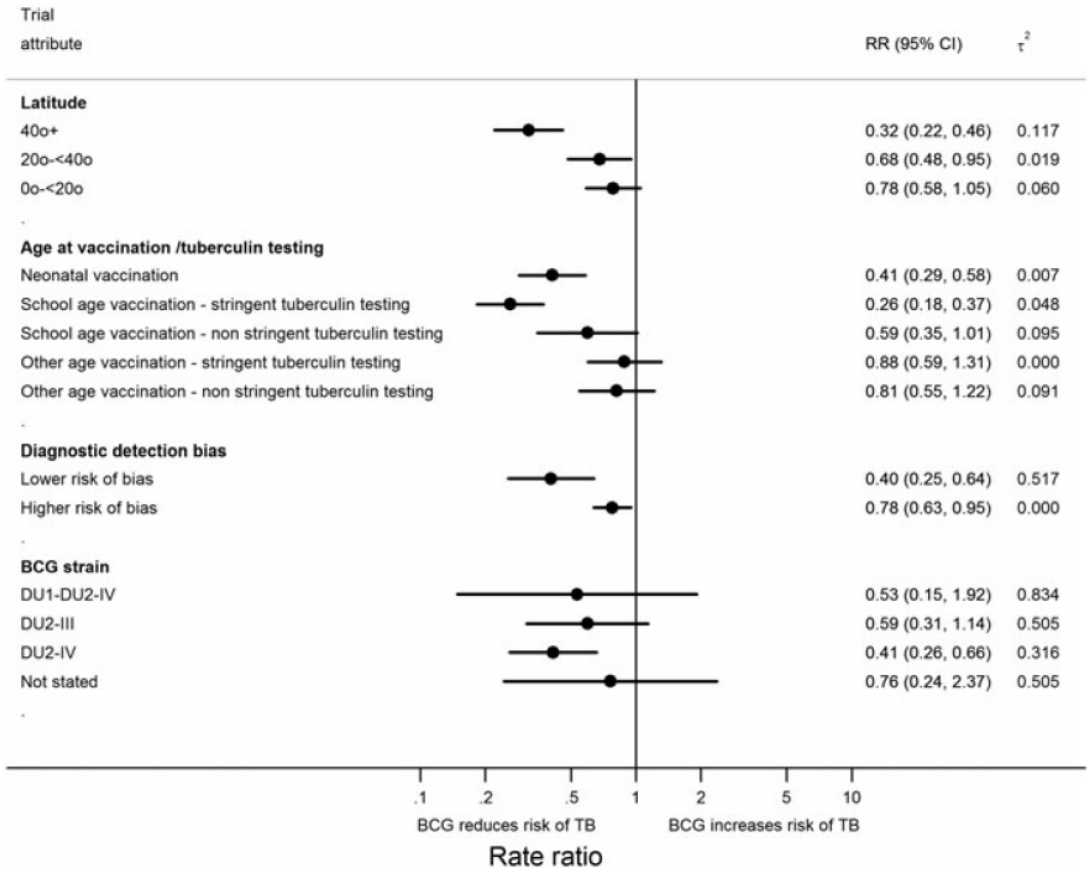
BCG efficacy is variable

Protection against pulmonary TB ranges from substantial (RR 0.22) to lack of benefit (RR 1.05).

Average RR 0.5 (0.35 – 0.72)

Highest BCG protection against TB disease in infants, and MTB uninfected children (RR 0.26), compared to MTB infected and uninfected adults (RR 0.88)

Implications for efficacy of novel live mycobacterial vaccines in high TB burden countries where 50 – 80% adults are MTB infected.



Meta-analysis, Mangtani CID 2014

Vaccine development: background

We need a new TB vaccine that offers longstanding, consistent protection against all forms of TB disease to infants, children, and adults, including MTB infected and HIV infected persons

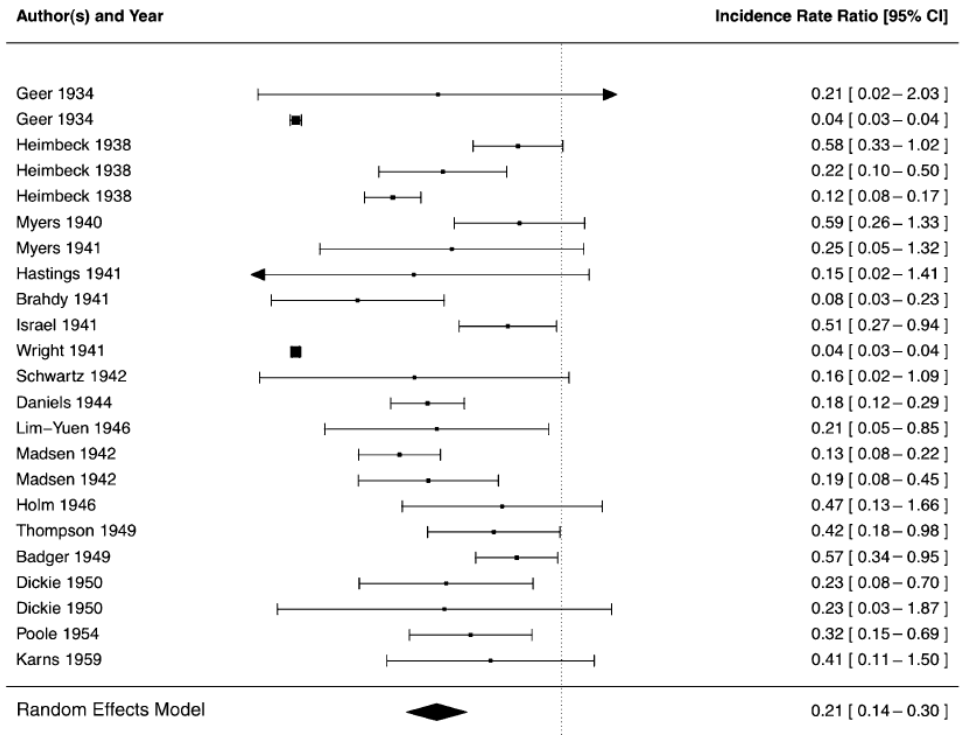
Is such a vaccine feasible?

Encouraging preclinical data from non-human primates

Humans control 90% of MTB infections

Longstanding MTB infection itself appears protective against new disease

Partial efficacy of BCG vaccine



Andrews CID 2012

Vaccine development: background

Challenges

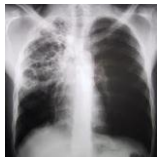
Murine model does not mimic human pulmonary TB disease

Limited access to NHP model

Lack of immune correlate of protection

Role of CD4 T cell IFN-gamma response?
Human T cell epitopes of MTB are hyperconserved in co-evolution (does the T cell response benefit the pathogen?)

Can MTB infected adults in TB endemic countries be protected?



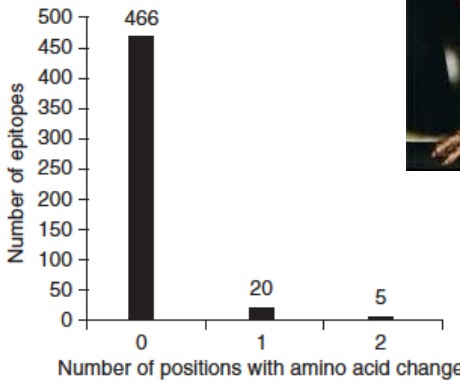
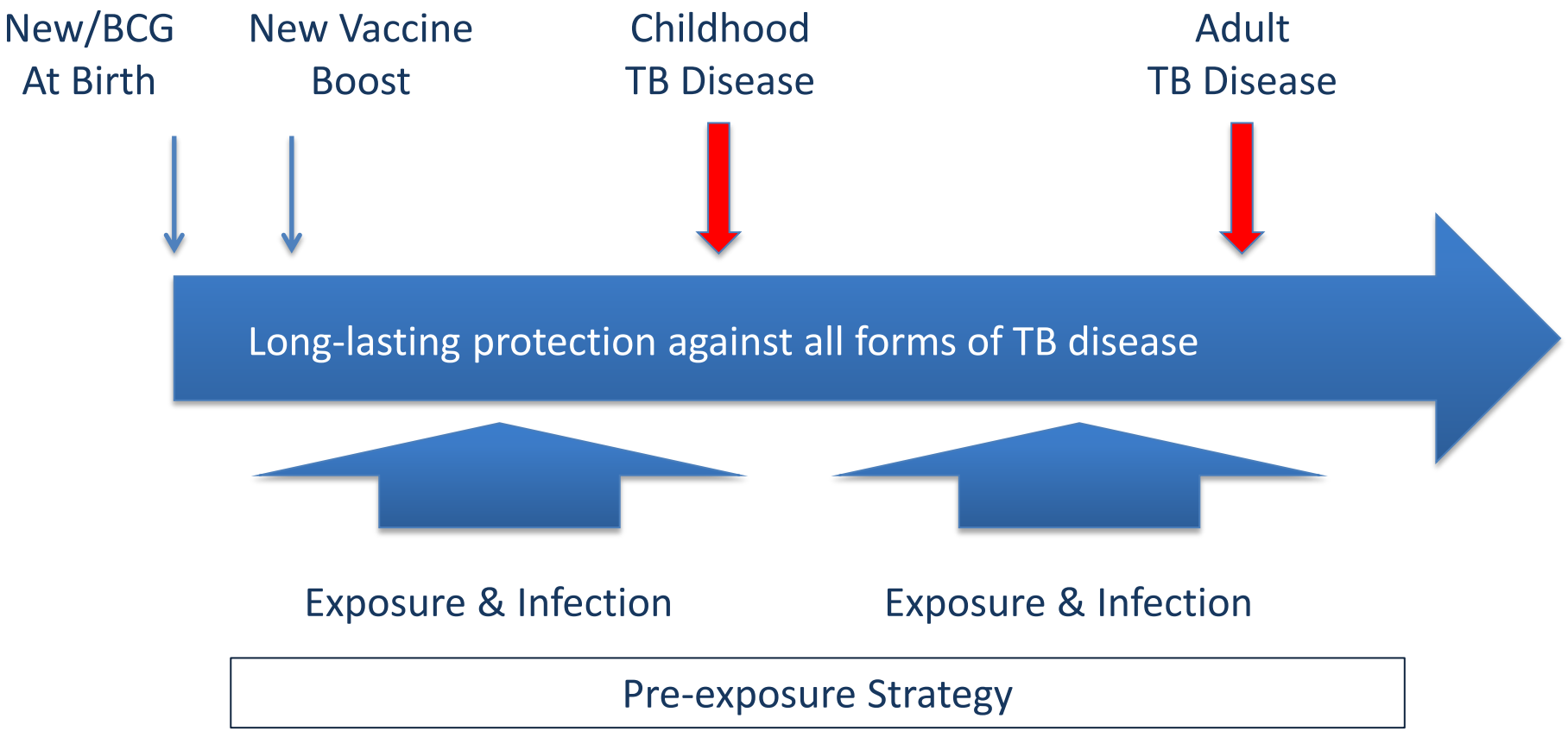


Figure 4 Number of variable amino acid positions in 491 human T cell epitopes of MTBC. This demonstrates the remarkable lack of genetic variability among the regions of the genome that interact with the human immune system.

Comas Nature Genetics 2010

Infant TB vaccination
BCG replacement vs. BCG Prime and Boost strategies



Vaccine development: background

Fallout from MVA85A

First infant TB vaccine efficacy trial in 50 years did not show added benefit compared to BCG alone

Preclinical data not convincing

Modest CD4 T cell responses in infants

(1) Shift towards TB vaccine strategy aimed at preventing TB in young adults to interrupt the epidemic

(2) Re-focus on upstream, pre-clinical data from NHP model to guide gating

(3) Progression only of 'Best-in-Class'

→ clinical trial hiatus

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*

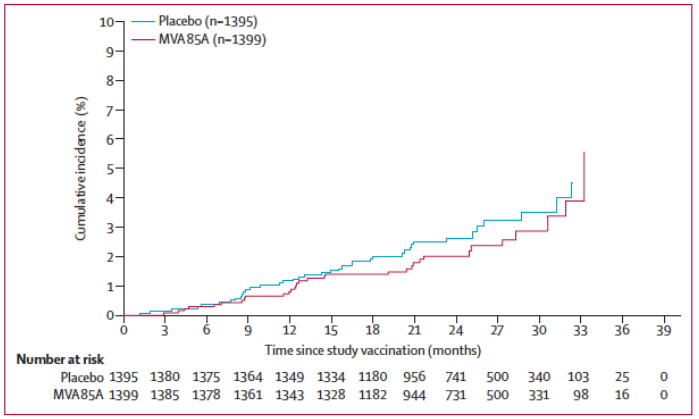


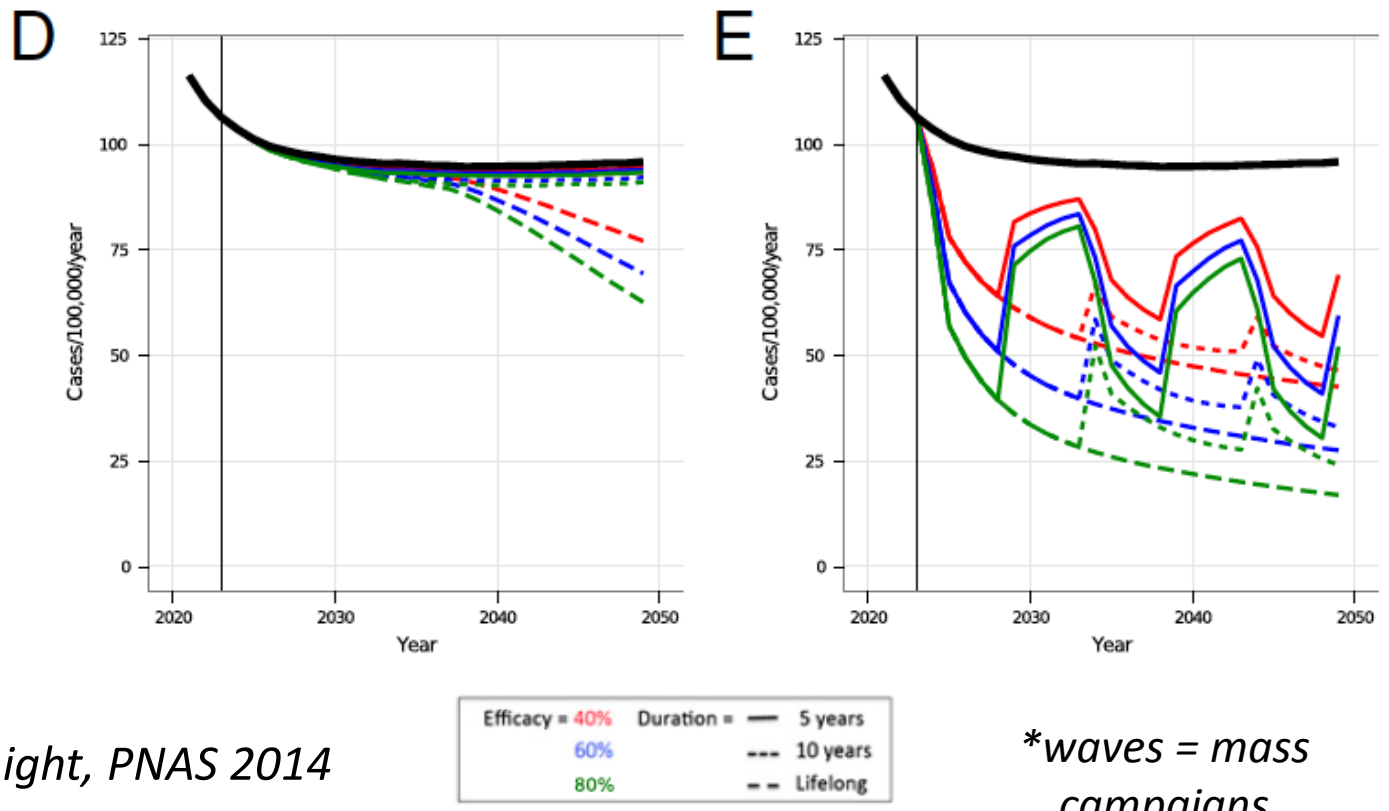
Figure 3: **Cumulative incidence of diagnosis of tuberculosis endpoint 1**

Vaccine development: background

Adult vaccine strategy (40% VE and 5-year protection) greater impact on TB incidence than infant vaccine (80% VE and lifelong protection) by 2050

Adult vaccine likely to prevent more infant TB cases than an infant vaccine
– due to reduction in transmission

Modeled impact of a new TB vaccine targeted at infants (D) or adolescents/adults (E)

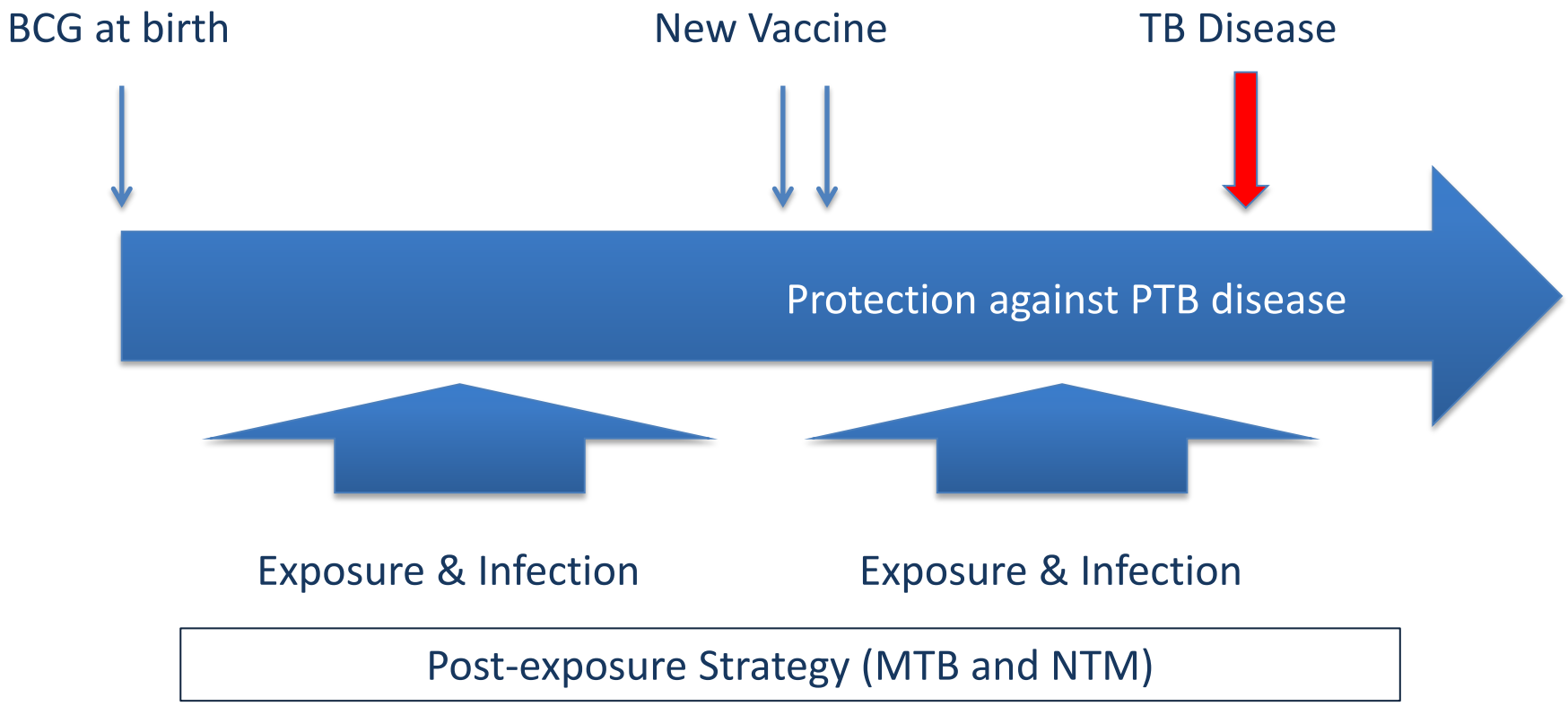


Knight, PNAS 2014

**waves = mass campaigns*

Adult TB vaccination
Prime and Boost strategy

Can MTB infected people be protected?
Potential blocking (live mycobacterial) or masking (<BCG) of vaccine effect

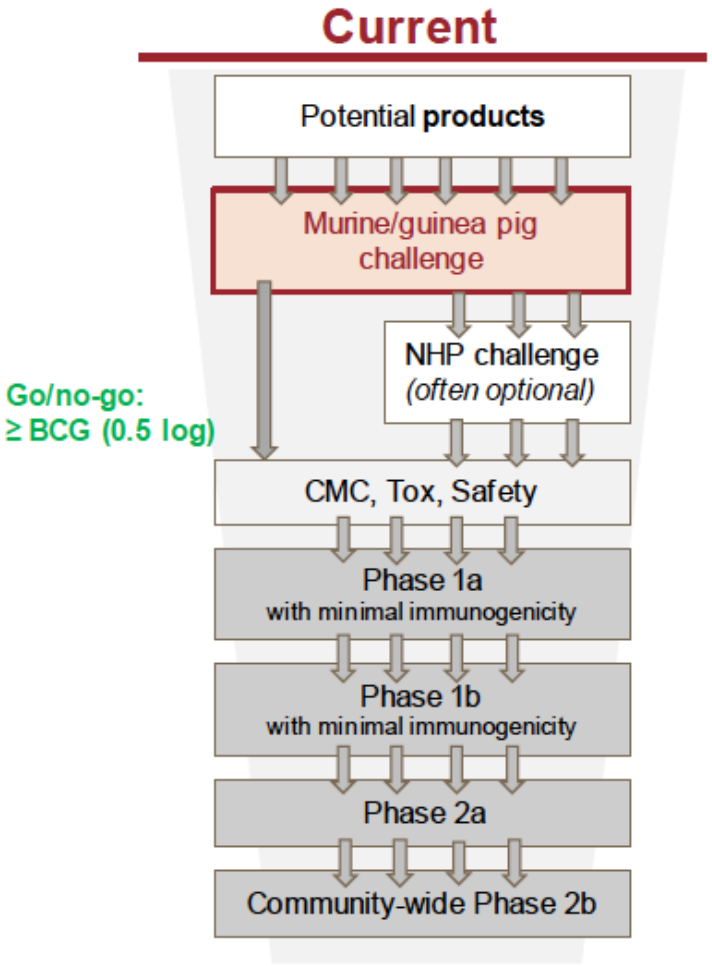


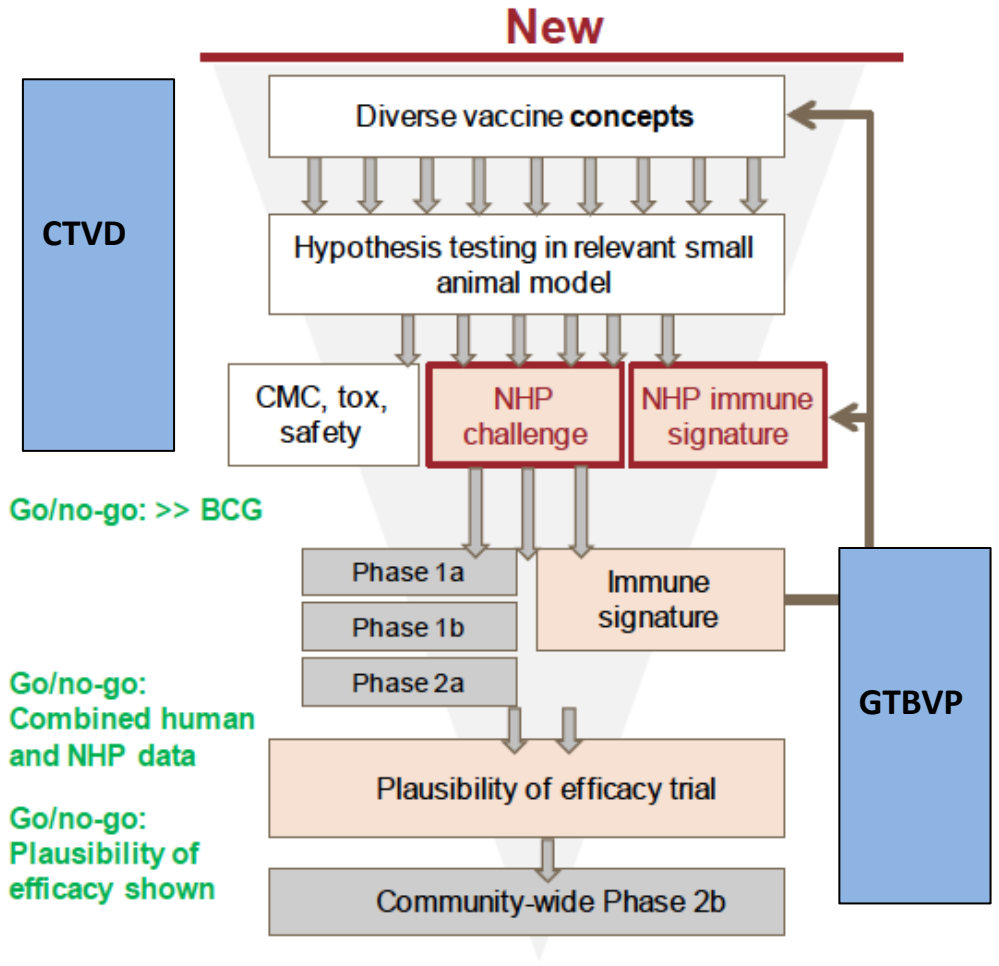
Phase 1	Phase 2a	Phase 2b	Phase 3
Ad5 Ag85A McMaster, Canada	**VPM 1002** (live attenuated rBCG) SII, TBVI	**M72+AS01E** (MTB32A and MTB39A) GSK, Aeras	**M. Vaccae** (lysate) Anhui Zhifei Longcom
DAR-901 (heat killed M. obuense) Dartmouth, Aeras	**RUTI** (lysate M. tuberculosis) Archivel Farma		
***TB/FLU-04L** (live attenuated influenza, ESAT-6, Ag85A) RIBSP, Russia	**H1 + IC31** (ESAT-6, Ag85B) SSI, TBVI, Aeras		
Aeras-402 (Ag85A, Ag85B, TB10.4) Crucell, Aeras ****MVA85A**, Oxford	***H4+IC31** (Ag85B, TB10.4) Sanofi, Aeras		
ChAdOx1.85A (chimp adenovirus) Oxford ****MVA85A**, Oxford	**H56+IC31** (85B, ESAT-6, Rv2660c) SSI, Aeras	*Prevention of Infection ** Prevention of Recurrence	
MTBVAC (live attenuated M. tuberculosis) BioFabri, TBVI	****ID93+GLA-SE** (Rv2608, Rv3619, Rv3620, Rv1813) IDRI, Aeras	*** Intranasal **** Also Aerosol	

Key – vaccine class

- Viral vector
- Mycobacterial whole cell/extract
- Protein subunit + adjuvant

The 'Shift to the Left': Concepts, Macaques, & Portfolio Management





Source: Bill & Melinda Gates Foundation

Collaboration for TB Vaccine Discovery (CTVD)
Global TB Vaccine Partnership (GTBVP)

Vaccine development: background

Experimental Medicine Studies in Humans

Demonstration of Proof of Concept

Prevention of Disease (POD)
Prevention of Infection (POI)
Prevention of Recurrence* (POR)
Therapeutic Vaccination

*Adjunctive Therapeutic Vaccination

Vaccine development: background

The rationale for a Prevention of Infection (POI) vaccine

Case-Control Studies
Evidence that BCG vaccination provides (modest) protection against IGRA conversion

Meta-analysis of 14 retrospective case-control studies (n=3,855)
BCG protective
RR for MTB infection 0.81
(95% CI 0.71 - 0.92)

Roy BMJ 2014

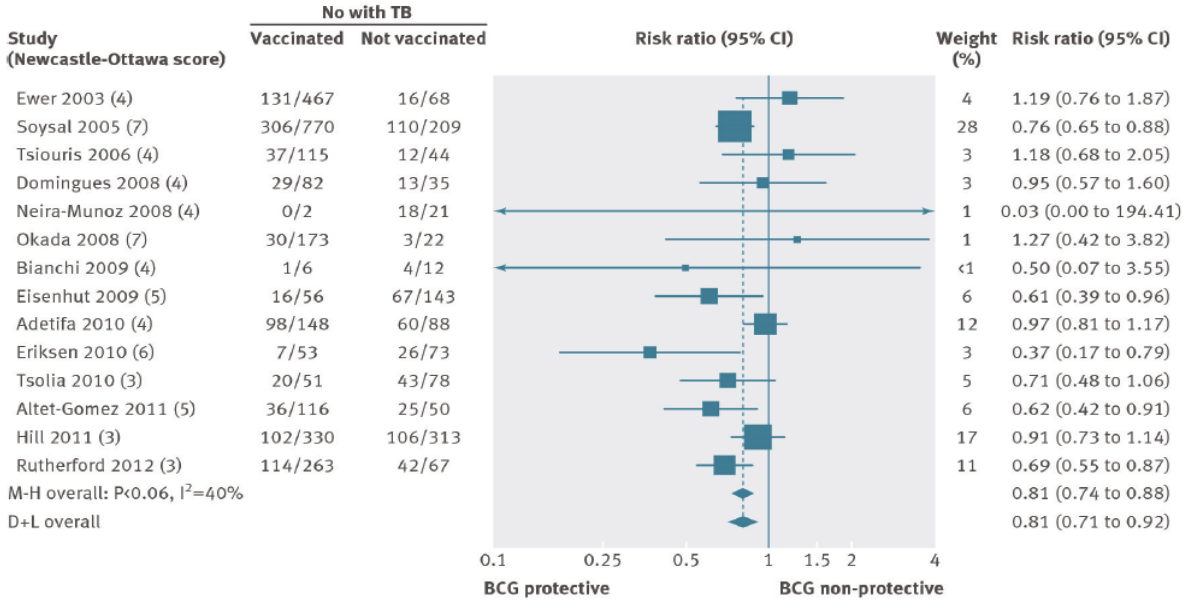


Fig 2 Protection against *Mycobacterium tuberculosis* infection (TB) as determined by interferon γ release assay (QuantiFERON) in children vaccinated with BCG. D+L=DerSimonian and Laird method; M-H=Mantel-Haenszel method. One test was used per paper and in cases where both ELISpot and QuantiFERON data were available data from QuantiFERON testing were used

POI Design

healthy, BCG-vaccinated, HIV uninfected adolescents

*Excludes: ESAT-6 subunit vaccines and attenuated MTB vaccines until new IGRA licensed

Vaccine development: background

Challenges for a Prevention of Infection (POI) strategy

Scientific Challenges
90% people control own MTB infection, never progress to TB disease

If *effective* POI vaccine prevented only this subset of MTB infections
→ no impact on epidemic

An *ineffective* POI vaccine, that did not protect against MTB infection, might protect against future progression to TB disease
→ major impact on epidemic

Regulatory Challenges
No gold standard for MTB infection
IGRA = measure of T cell response to MTB
Not adequate surrogate endpoint for disease

Development Pipeline Challenges
Excludes subunit and MTB vaccines containing IGRA antigens (ESAT-6)

Implementation Challenges
50-80% of individuals in TB endemic countries already MTB infected in high school

Vaccine development: background

Opportunities for a Prevention of Infection (POI) strategy

Rate of MTB infection (IGRA+) 10-fold greater than incidence of TB disease

Opportunity to conduct smaller, cheaper, faster human trials

Proof of concept → 'green light' expansion into POD efficacy trials

ClinicalTrials.gov NCT02075203

Evaluate safety, immunogenicity, and prevention of infection by BCG revaccination, or by the novel vaccine H4:IC31 (AERAS-404), compared to placebo, in 990 SA adolescents

Primary endpoint IGRA conversion from negative to positive

Will also evaluate sustained IGRA conversion and sensitivity to alternative threshold values

Vaccine development: background

Rationale for a Prevention of Recurrence (POR) vaccine

TB patients (Rx completed, confirmed cured) have several-fold higher risk of subsequent TB disease than surrounding community

Recurrent TB disease = true relapse (reactivation) and reinfection
Incidence recurrent TB 2-8%

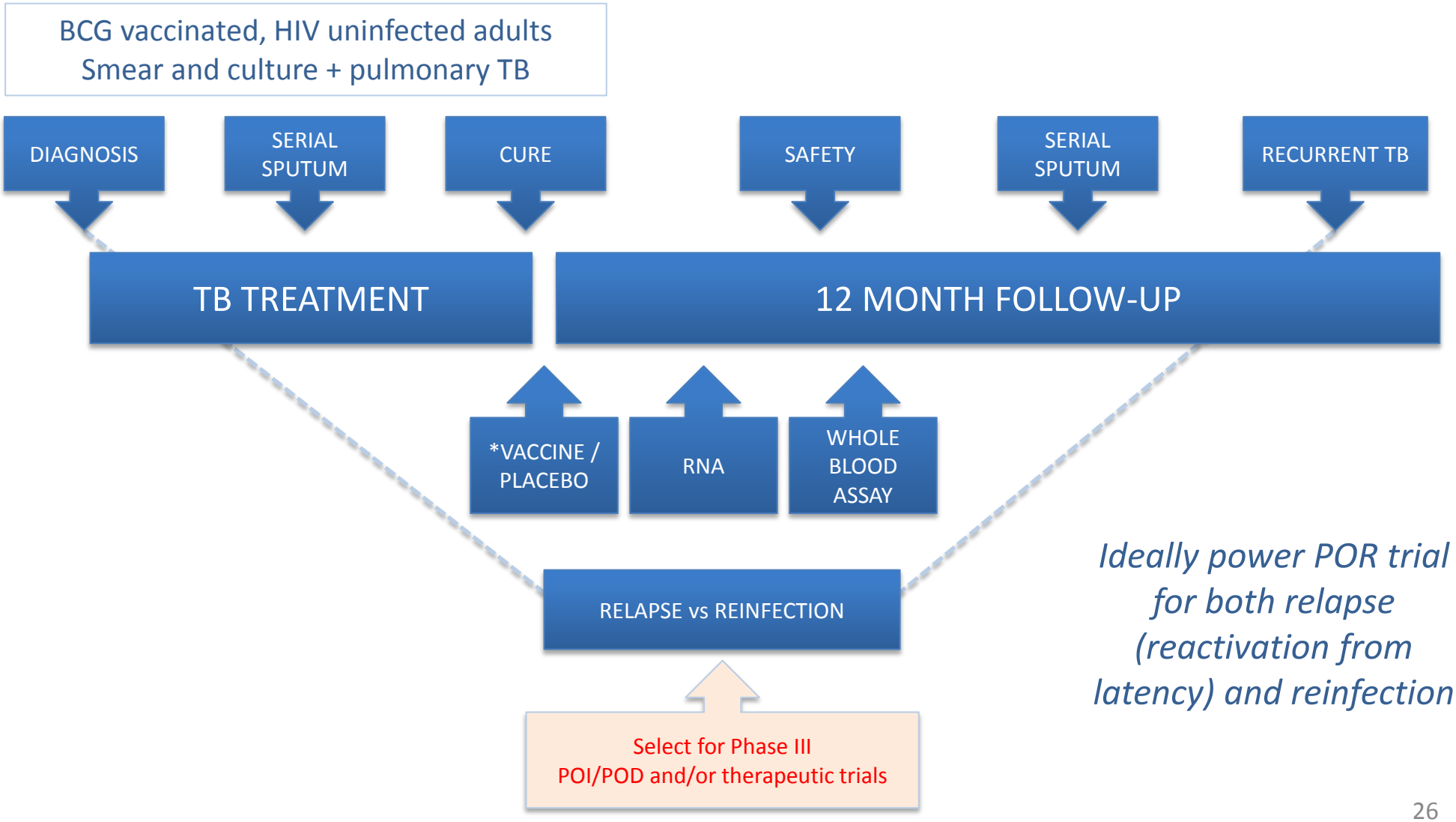
70-90% occurs within 12 months of TB treatment completion

Direct Public Health Impact
Modest impact on health services and MDR-TB control

TB Vaccine Development
Leverage high incidence to show proof of concept efficacy (small, but complex trials)

TB Drug Development
Therapeutic adjunct
Shorten treatment (Drug-Sensitive and MDR-TB)
Major public health impact
Pathway to true therapeutic indication…

POR Design



Ideally power POR trial for both relapse (reactivation from latency) and reinfection

Vaccine development: background

Challenges for a Prevention of Recurrence (POR) strategy

Is a POR vaccine feasible in TB patients?

No direct evidence from human studies
2 small safety & immunogenicity studies ongoing (subunit vaccines)

Setting a high immunological bar?

Indirect evidence from humans

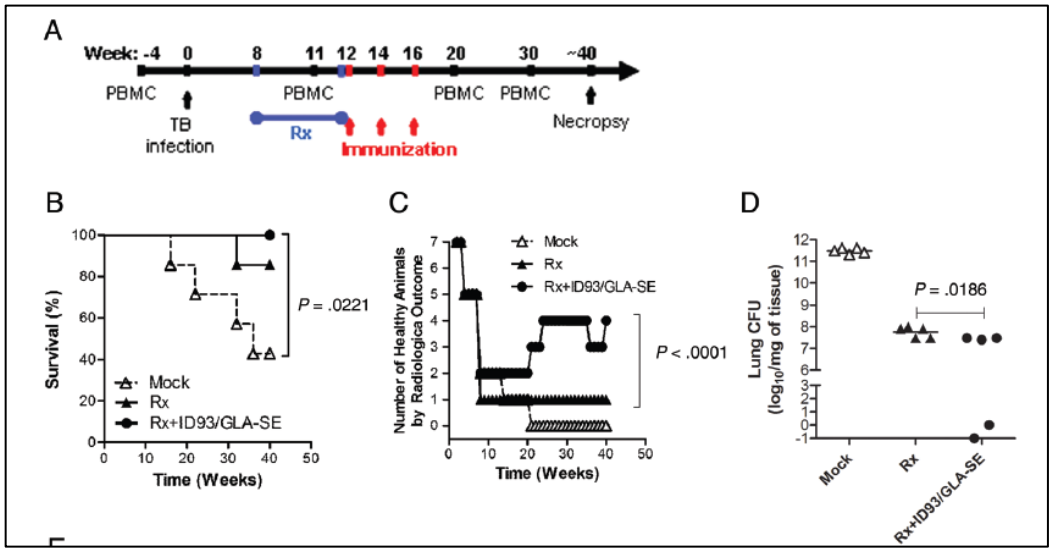
M. Vaccae

Therapeutic (meta-analysis 54 studies)

Time to sputum smear conversion

CXR resolutiion

Yang Plos ONE 2011



Therapeutic benefit in Cynomolgus macaques

Therapeutic Immunization against *Mycobacterium tuberculosis* Is an Effective Adjunct to Antibiotic Treatment

Rhea N. Coler, Sylvie Bertholet,[a] Samuel O. Pine, Mark T. Orr, Valerie Reese, Hillarie Plessner Windish, Charles Davis, Maria Kahn, Susan L. Baldwin, and Steven G. Reed

Infectious Disease Research Institute, Seattle, Washington

Vaccine development: pipeline

Most advanced BCG replacement candidates

VPM-1002 in HIV exposed/unexposed newborns in SA

MTBVAC in MTB uninfected adults and newborns in SA

Safety equivalent to BCG

Immunogenicity in newborns TBC ….

Role in POI for MTB uninfected adolescents?

To test efficacy…

Regulatory and ethical challenges to replace newborn BCG in an infant efficacy trial in a TB endemic country

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TB/FLU-04L (influenza) RIBSP	**H1 + IC31** SSI, TBVI, Aeras		
Ad35 / MVA85A Crucell, Oxford	**H4+IC31** Sanofi, Aeras		
ChAdOx1.85A/MVA85A (chimp adenovirus) Oxford	**H56+IC31** SSI, Aeras		
MTBVAC (live attenuated M. tuberculosis) BioFabri, TBVI	**ID93+GLA-SE** IDRI, Aeras		

Key

Viral vector

Mycobacterial whole cell/ extract

Protein + adjuvant

Ongoing, small-scale studies in infants

Limited funder appetite?

Vaccine development: pipeline

Most advanced boost vaccine candidates

M72+AS01E in Phase 2b POD in MTB infected adults in SA (n=3,500)

H4+IC31 in Phase 2 POI in MTB uninfected adolescents in SA (n=990)

H56+IC31 seeking funding for POI

ID93+GLA-SE seeking co-funding for POR

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Key

- Viral vector
- Mycobacterial whole cell/ extract
- Protein + adjuvant

Viral-vectored candidates

Experimental medicine: MVA85A aerosol delivery

Advancement of **H56+IC31** dependent on NHP studies and H4 POI

Best in Class?

Vaccine development: pipeline

Challenges for the pipeline

Limited number of concepts & vaccine classes

Candidates in ‘pipeline limbo’

NHP gating bottleneck

Fragmentation of efforts

POD - BCG replacement vs adult boost

POI and POR strategies untested, underfunded

Potential for therapeutic vaccination untapped

‘Shift to the left’

Limited funding options

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Protein + adjuvant

Awaiting positive signal from M72+AS01E POD or H4+IC31 POI

Likely 3 year hiatus in new large-scale clinical trials

Potential role for WHO

Advocacy for increased TB vaccine funding
preclinical (NHP) and clinical

Consensus building on portfolio priorities
(POD, POI, POR/Therapeutic)

Coordination
Pre-clinical
via Collaboration for TB Vaccine Discovery (CTVD)

Experimental medicine & portfolio management
via Global TB Vaccine Partnership (GTBVP)