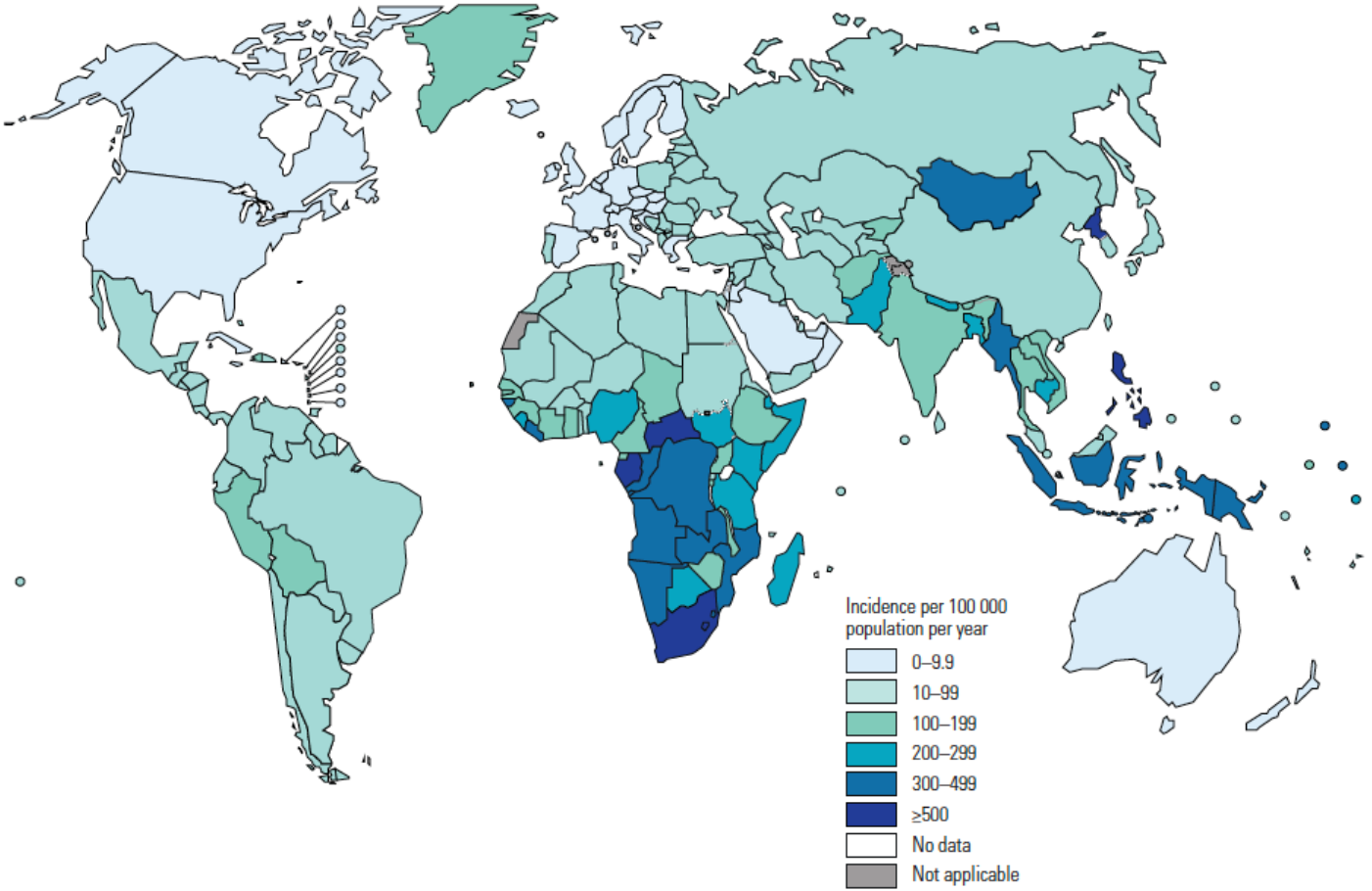
TB vaccines, anything but warp speed

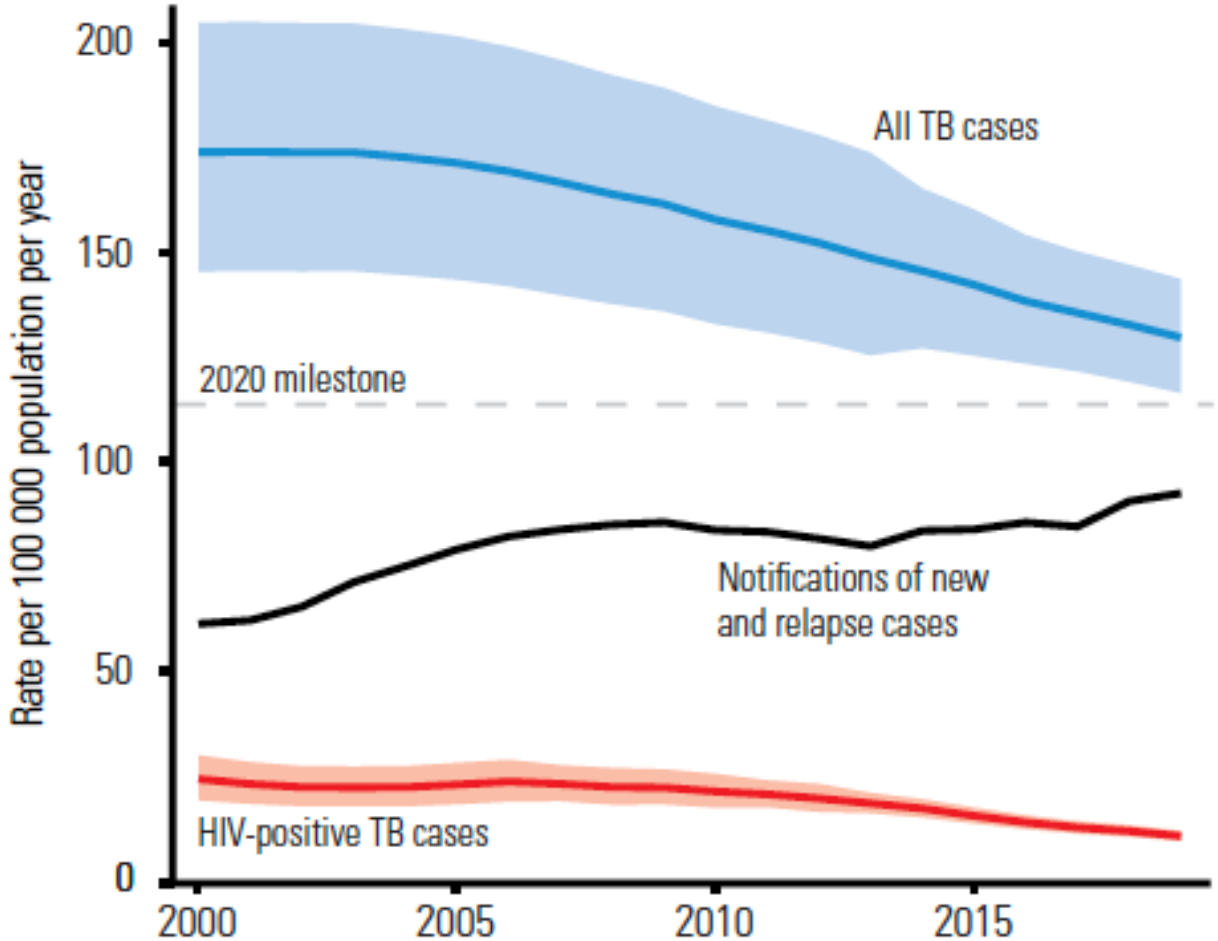
Tom Scriba, University of Cape Town

28 trials of 9 TB vaccine candidates plus BCG

10 million TB cases, 1.4 million deaths



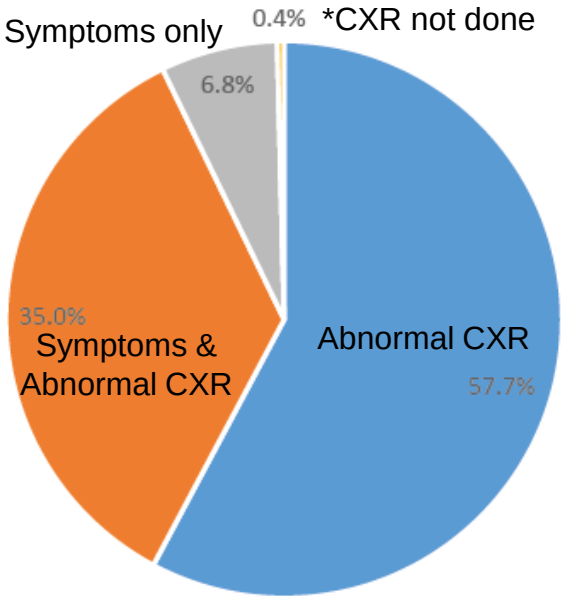
WHO Global TB Report 2020



WHO TB report 2020

The First National TB Prevalence Survey
South Africa 2018

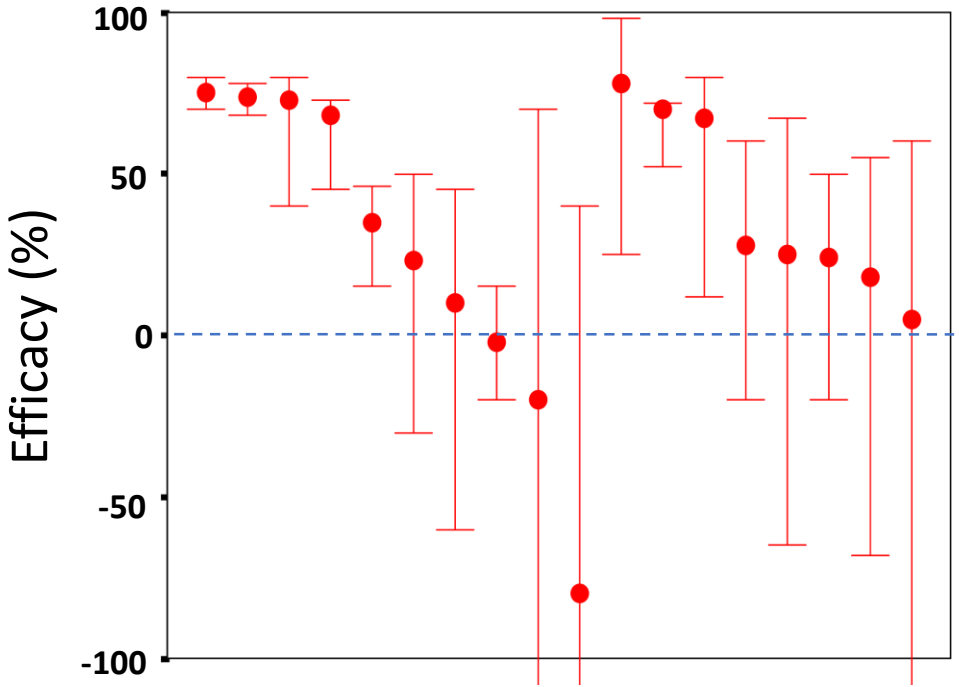
Prevalence per 100,000 population		95% CI
Sex		
Male	1,094	835 – 1,352
Female	675	494 - 855
Age group (years)		
15-24	432	232 - 632
25-34	902	583 – 1,221
35-44	1,107	703 – 1,511
45-54	1,063	682 – 1,443
55-64	845	505 – 1,186
≥65	1,104	680 – 1,528
All	852	679 – 1,026



https://www.knowledgehub.org.za/system/files/elibdownloads/2021-02/A4_SA_TPS%20Short%20Report_10June20_Final_highres.pdf

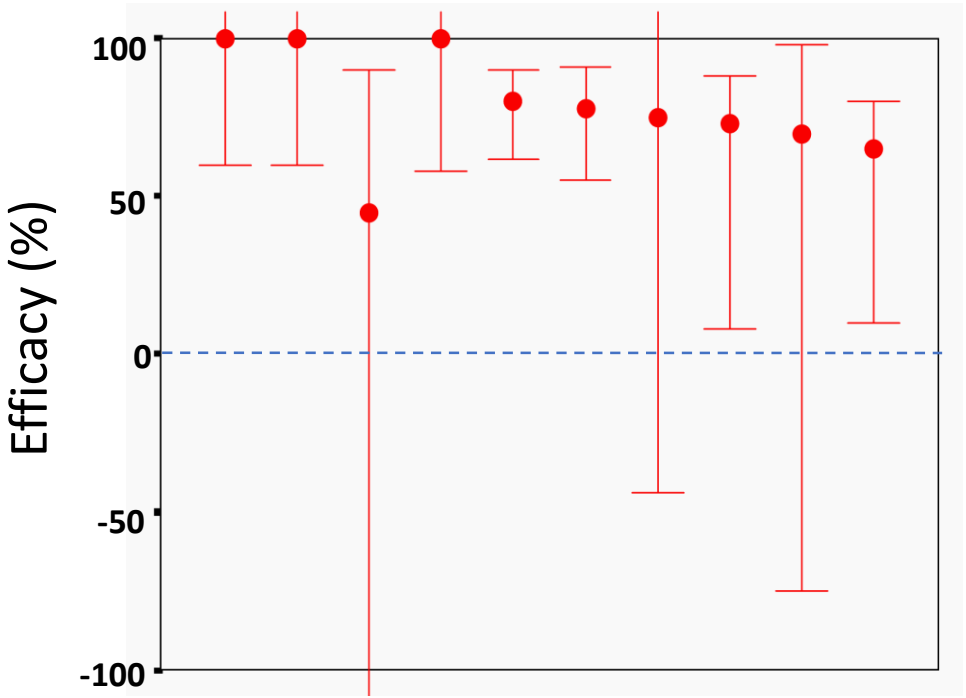
BCG – 100 years and counting!

BCG-induced protection against pulmonary TB is variable



*P. Fine. 2000. BCG Vaccines and Vaccination. In: L. B. Reichman and E. S. Hershfield. Tuberculosis. A comprehensive International Approach. 2nd Edition.

BCG protects against disseminated forms of TB in infants



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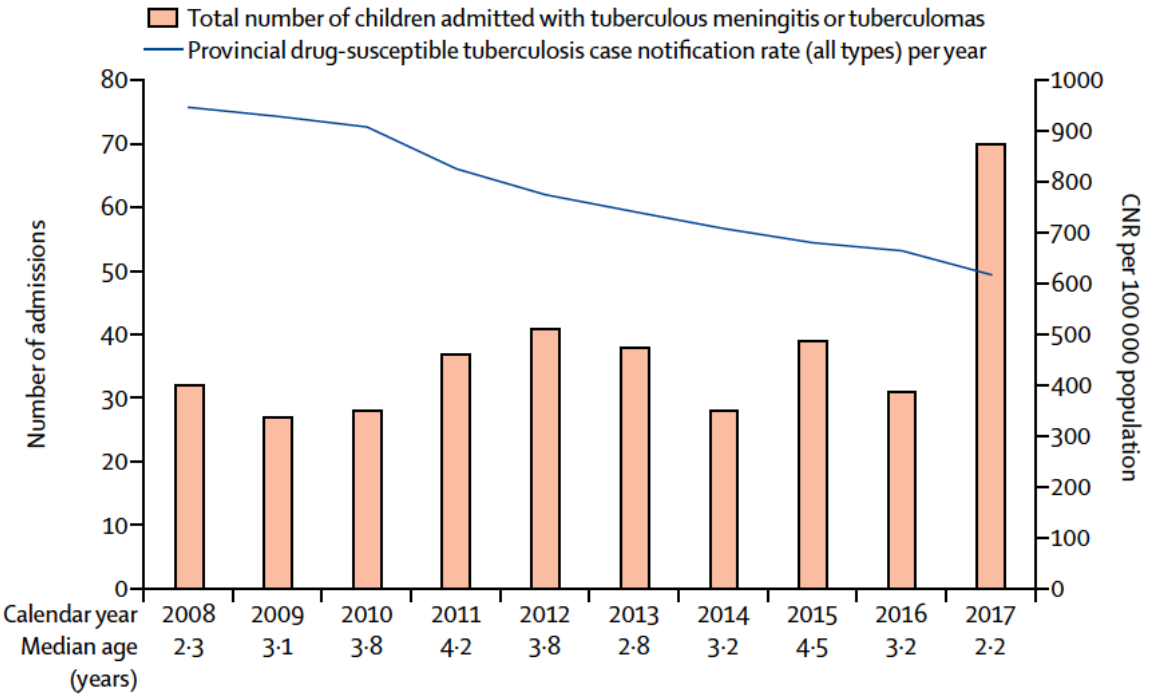
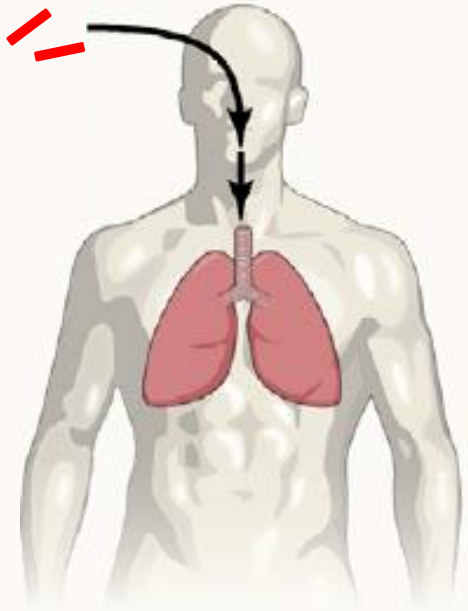


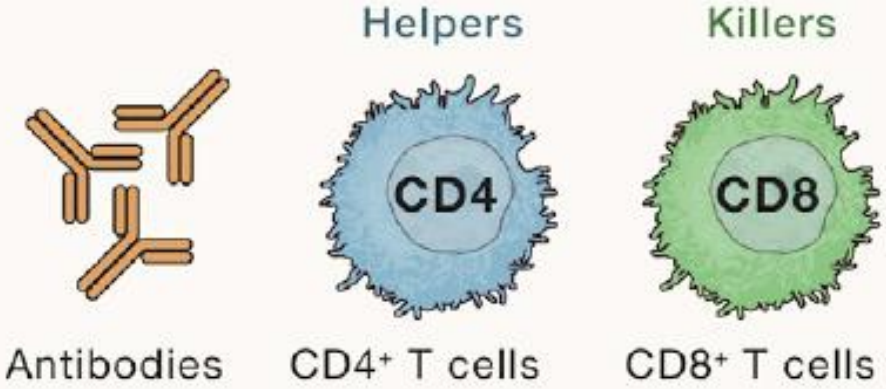
du Preez et al., Lancet Global Health 2019

Vaccine design

Which type of immune response protects against *M. tuberculosis*?

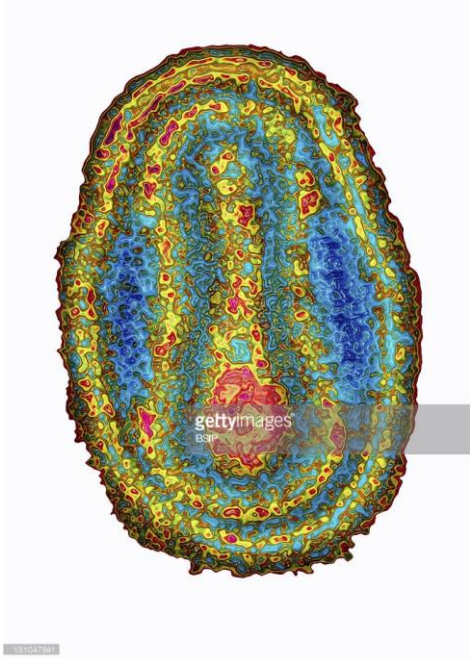
M. tuberculosis



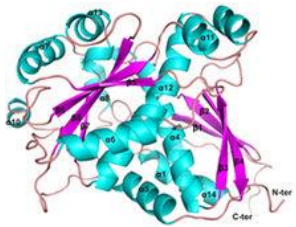


MVA85A – a good Th1 inducing vaccine candidate

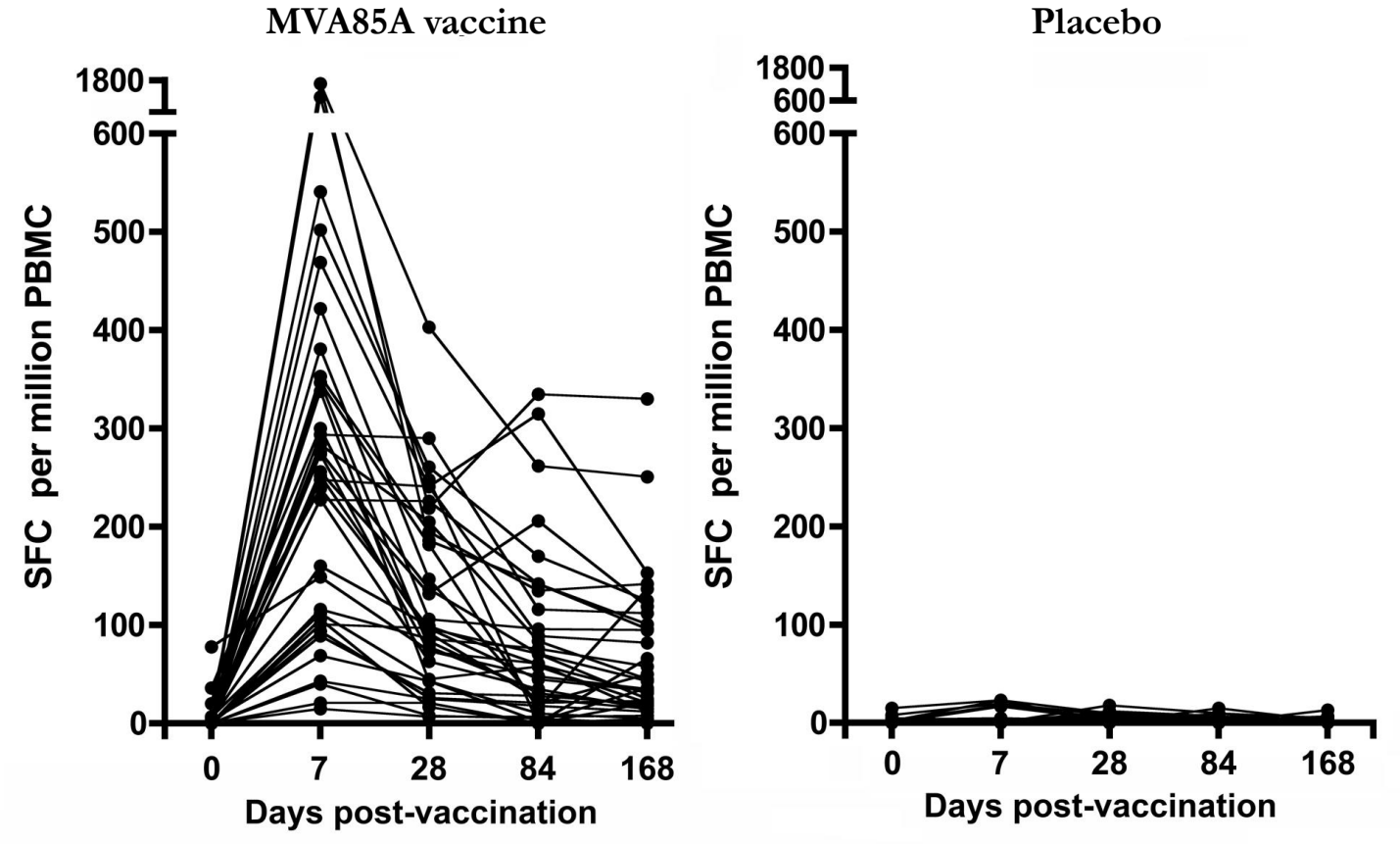
Modified vaccinia virus Ankara



Ag85A
Mycolyl transferase
gene (“blueprint”)

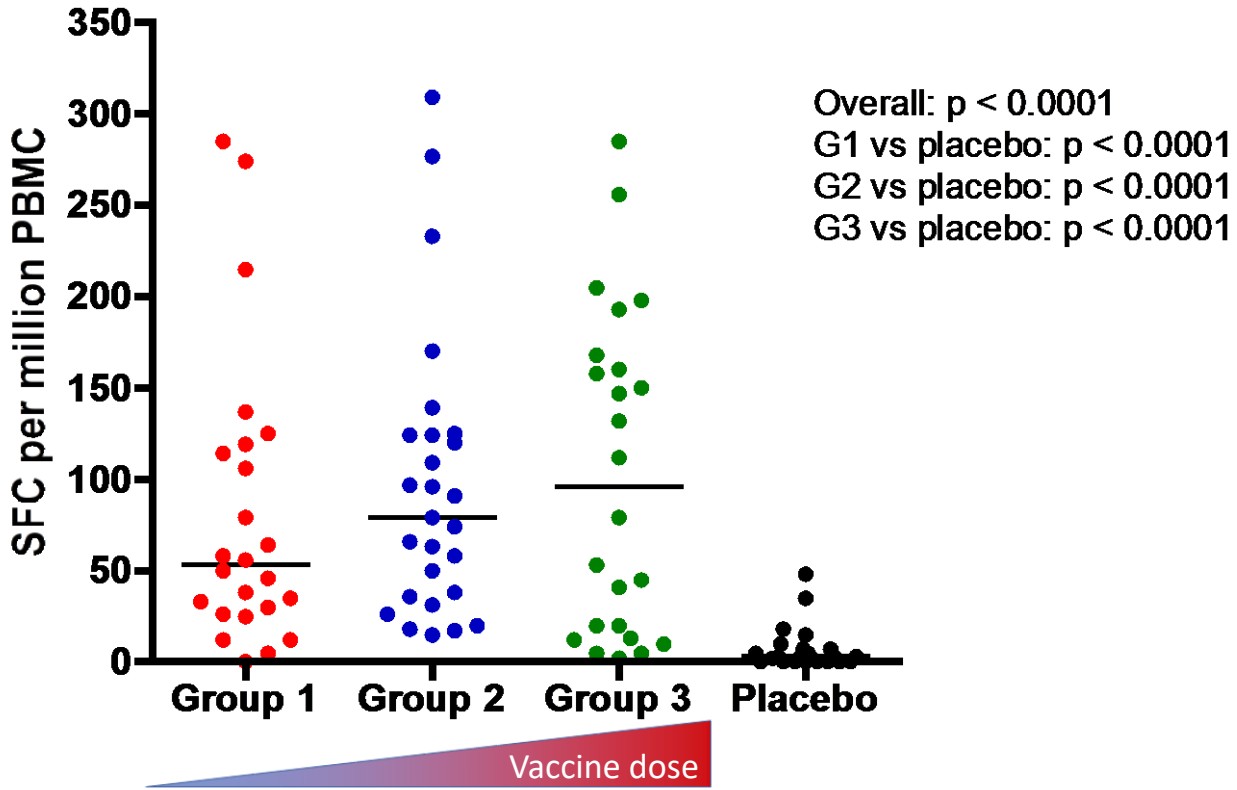


Evaluating T cell immunity



Scriba et al, JID 2011

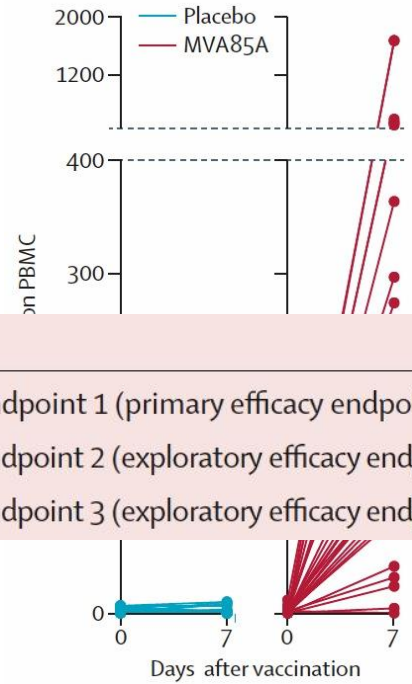
Infant responses >3 years after MVA85A vaccination

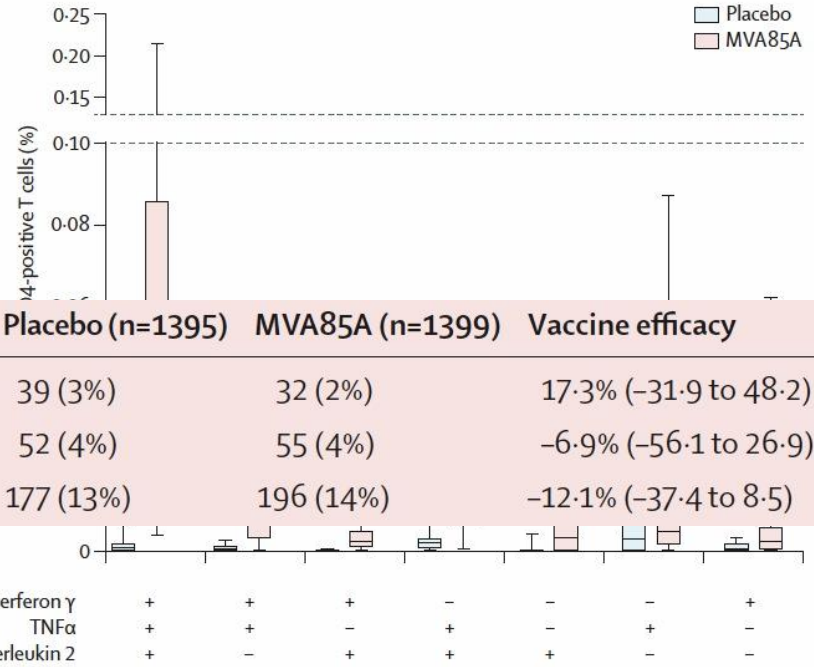


Tameris et al., Plos One 2014

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*

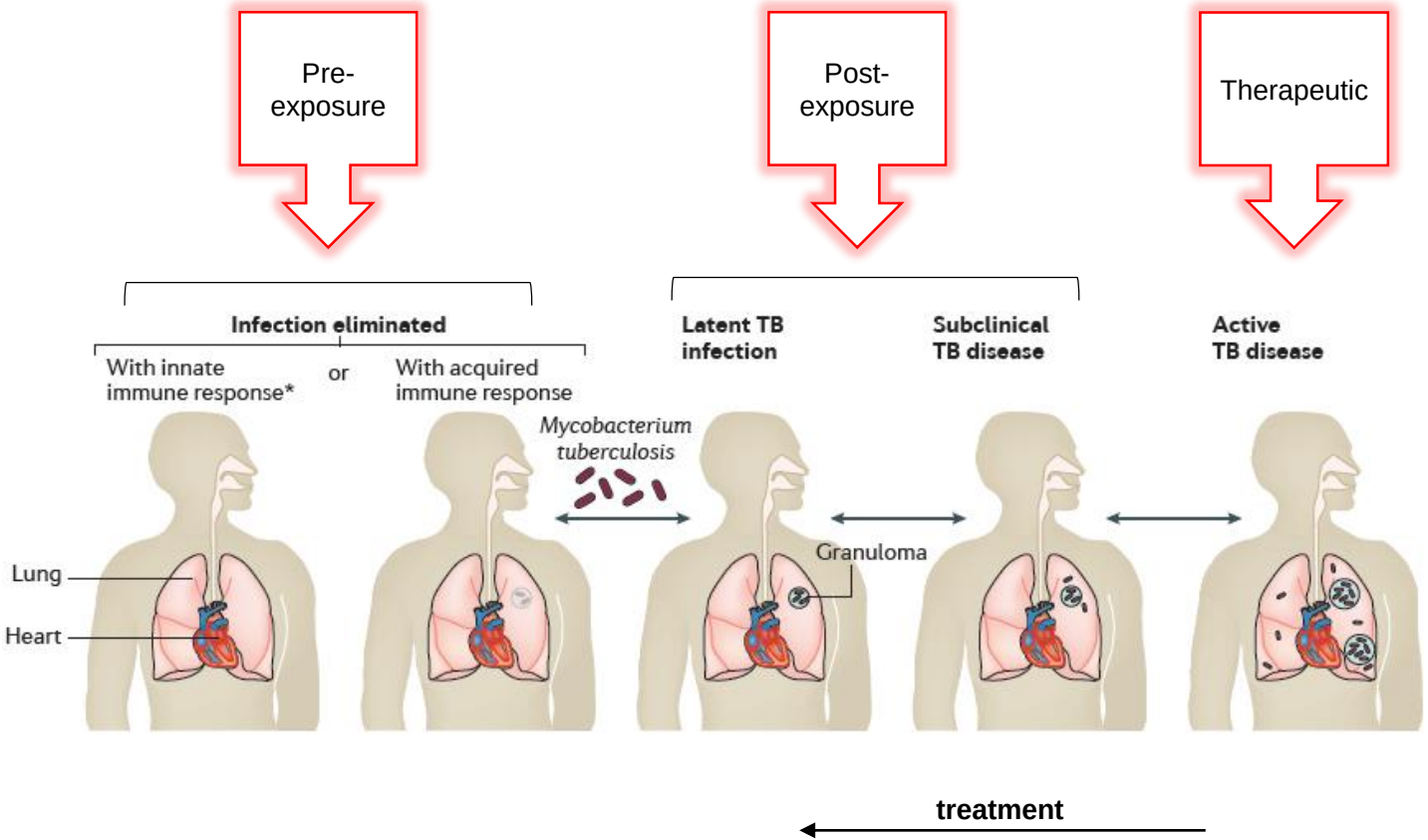




	Placebo (n=1395)	MVA85A (n=1399)	Vaccine efficacy
Endpoint 1 (primary efficacy endpoint)	39 (3%)	32 (2%)	17·3% (–31·9 to 48·2)
Endpoint 2 (exploratory efficacy endpoint)	52 (4%)	55 (4%)	–6·9% (–56·1 to 26·9)
Endpoint 3 (exploratory efficacy endpoint)	177 (13%)	196 (14%)	–12·1% (–37·4 to 8·5)

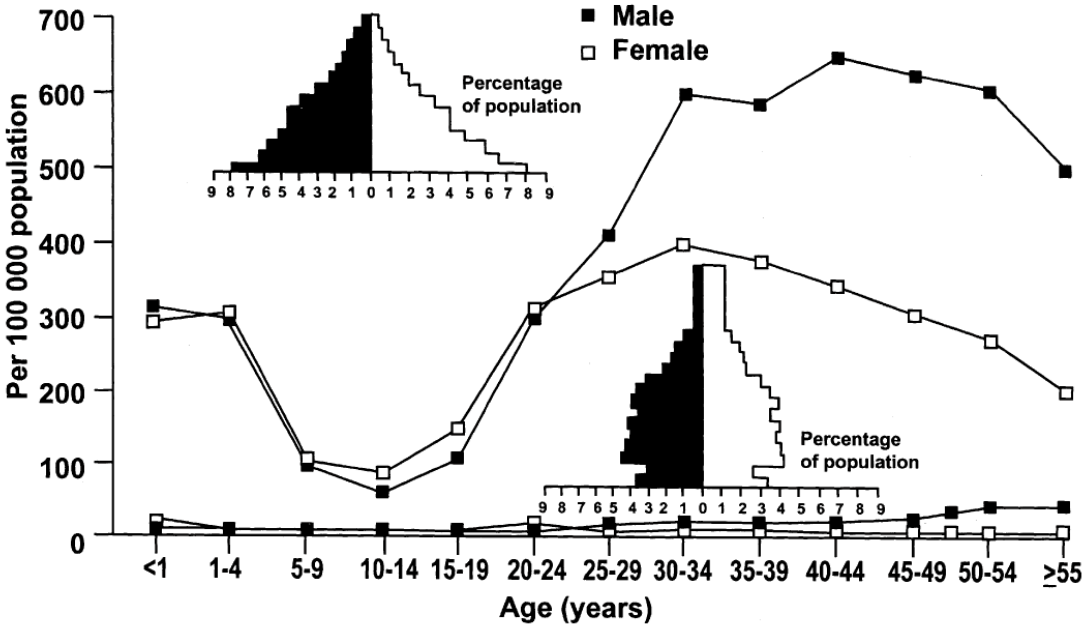
Tameris, Hatherill, et al. Lancet 2013

New vaccination strategies

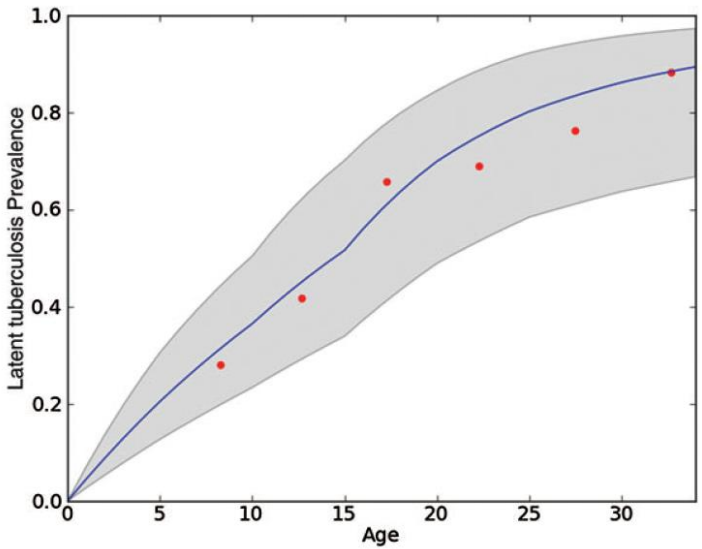


Barry 3rd NRI, 2009; Pai et al,. NR. Dis. Primer 2016

Can vaccination protect against infection?



Donald, et al. IJTLD 2004



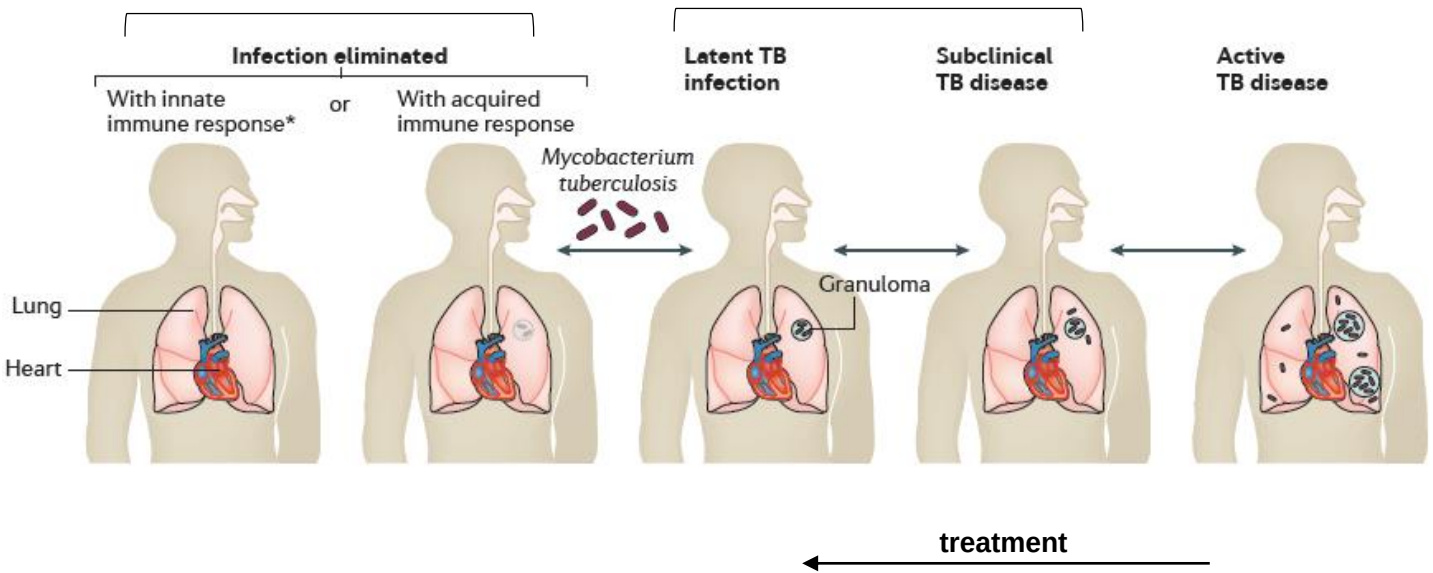
Andrews et al., JID 2014

Can vaccination prevent against *M. tuberculosis* infection?

Pre-exposure
Adolescents

H4 (Ag85B–TB10.4 in IC31)

BCG revaccination



Barry 3rd NRI, 2009; Pai et al,. NR. Dis. Primer 2016

Clinical trial of BCG re-vaccination to protect against M.tb infection

QFT- adolescents
N = 990

Placebo
BCG revacc.
H4:IC31

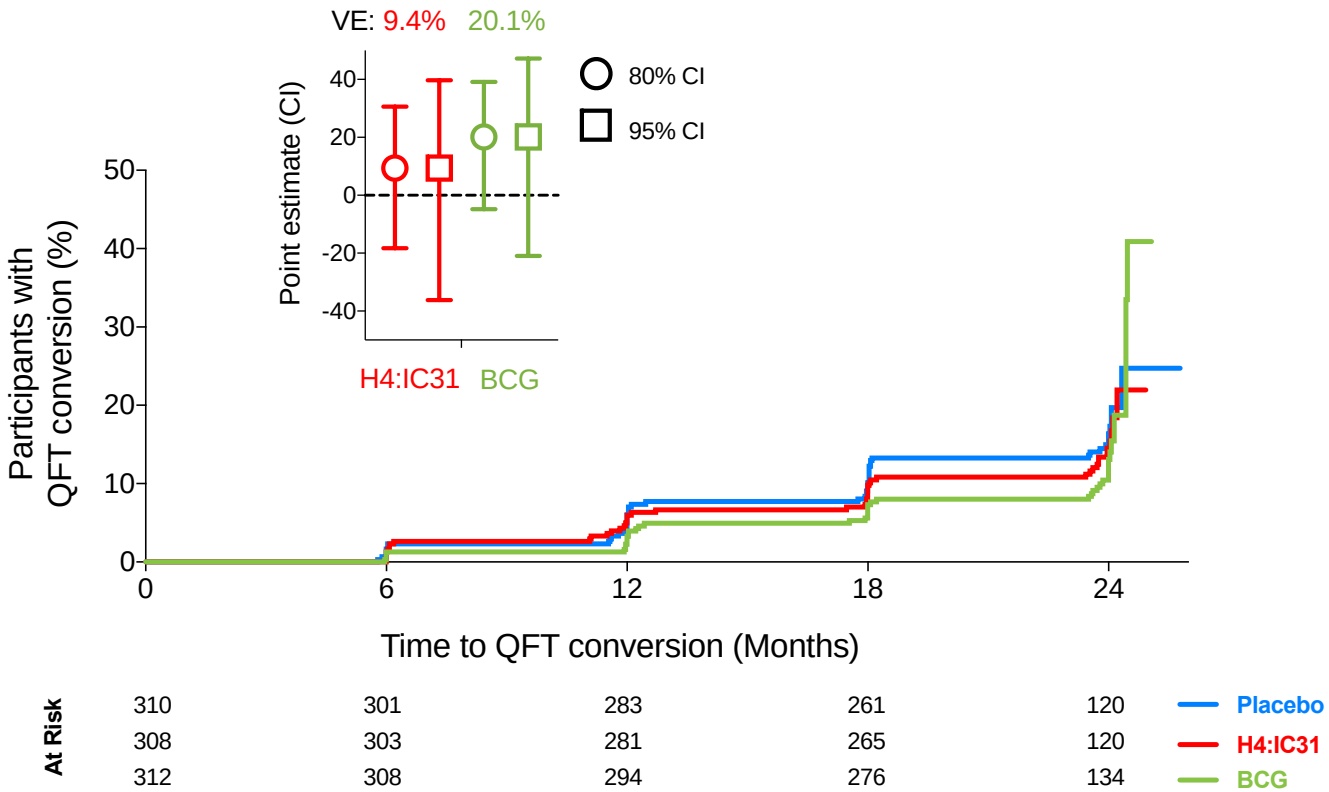
24 month follow-up
Endpoint: QFT

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†

Nemes et al., NEJM 2018

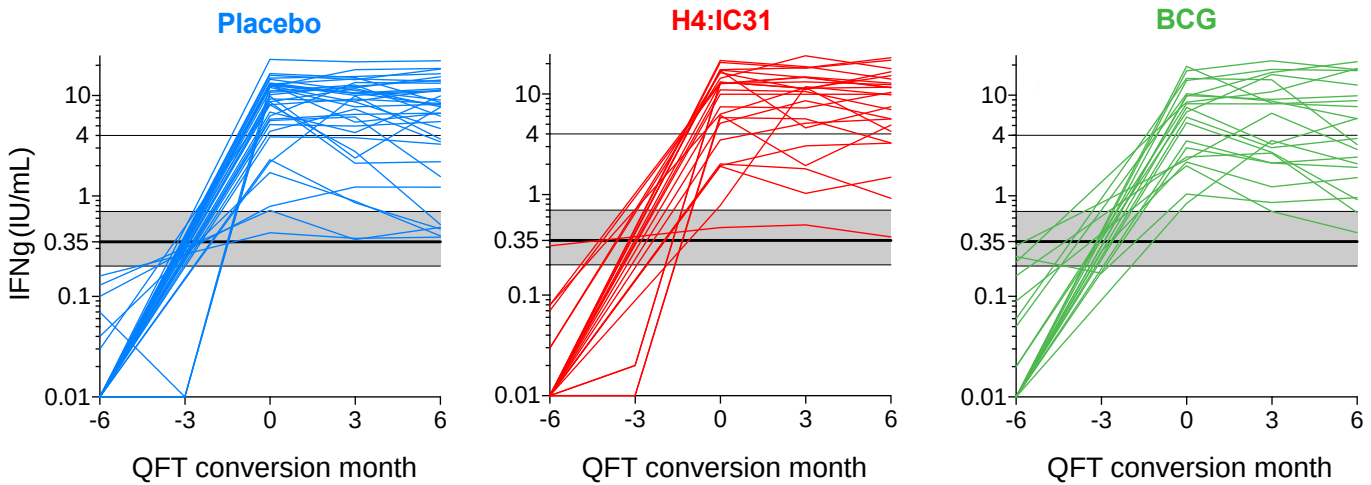
Efficacy: QFT conversion
(Initial infection)



Nemes et al., NEJM 2018

Efficacy: Sustained QFT conversion (Sustained infection)

82 QFT conversions from IFNγ <0.35 to ≥0.35 IU/mL after Day 84, without reversion through 6 months post-conversion



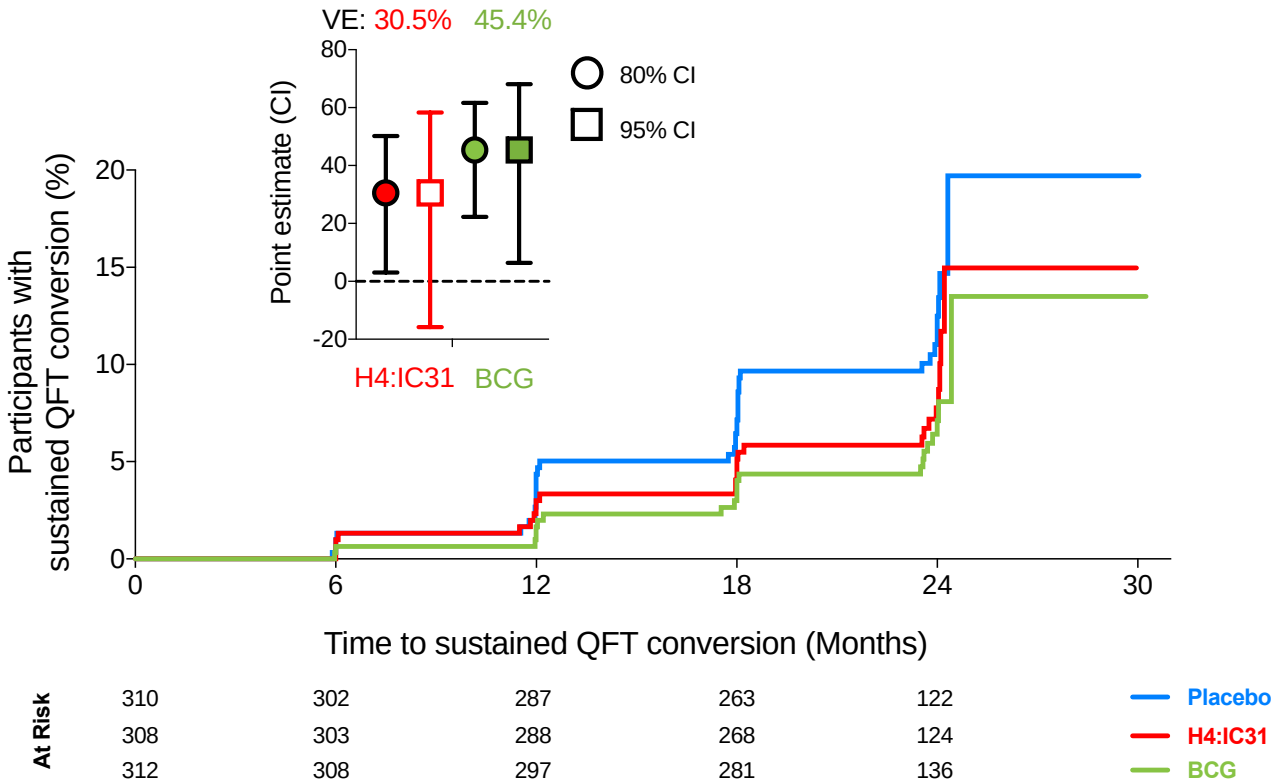
n = 36/310 (12%)

n = 25/308 (8%)

n = 21/312 (7%)

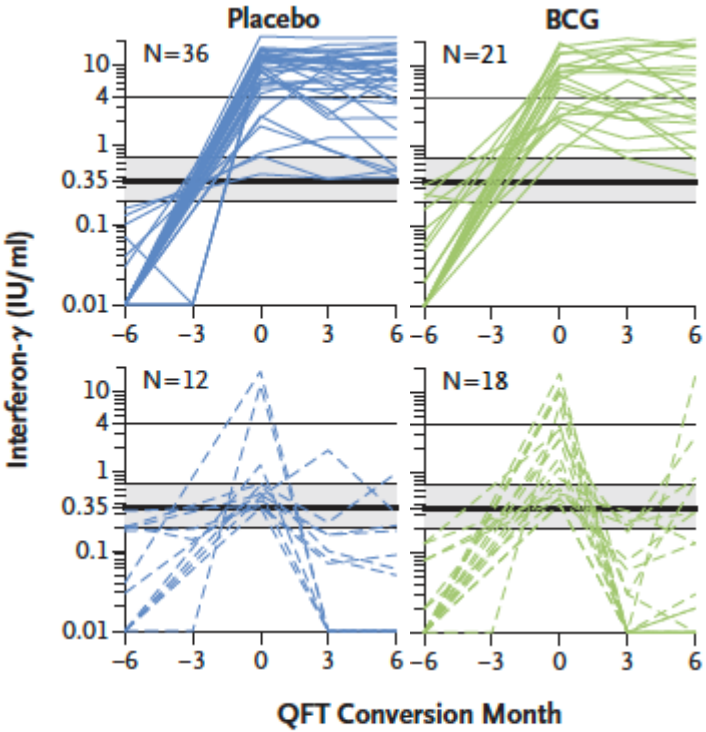
Nemes et al., NEJM 2018

Efficacy: Sustained QFT conversion (Sustained infection)

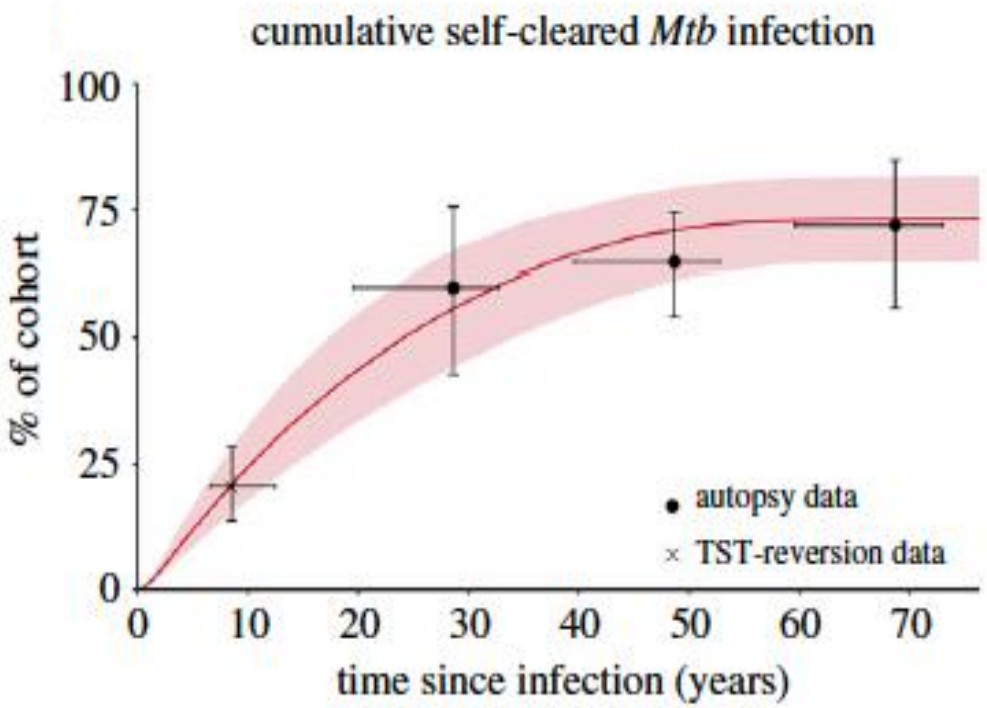


Nemes et al., NEJM 2018

What is **transient** or **sustained** Mtb infection?



Nemes et al., NEJM. 2018



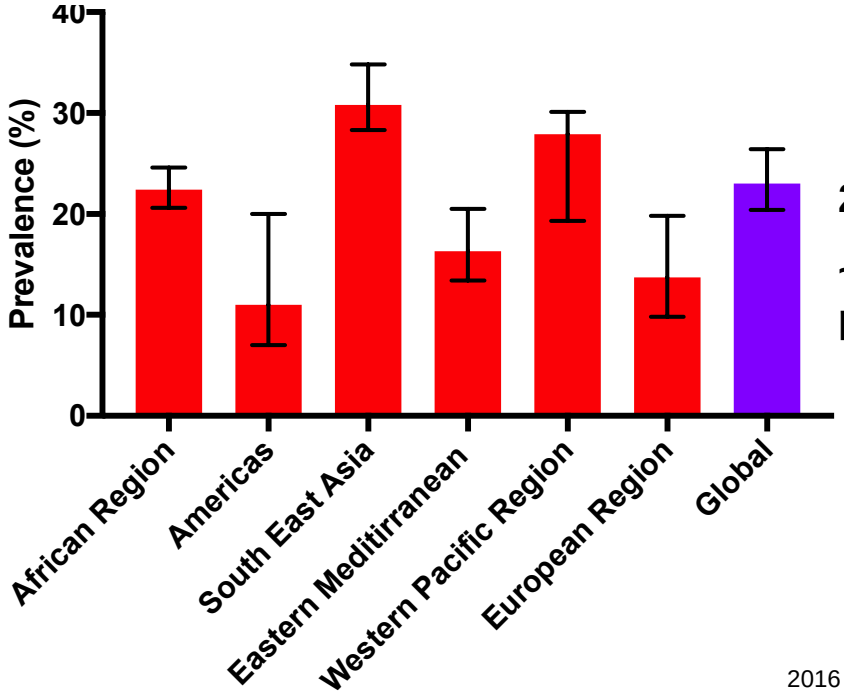
Emery et al., Proceed. B Royal Soc. 2021

PLOS | MEDICINE

RESEARCH ARTICLE

The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling

Rein M. G. J. Houben[1,2]*, Peter J. Dodd[3]

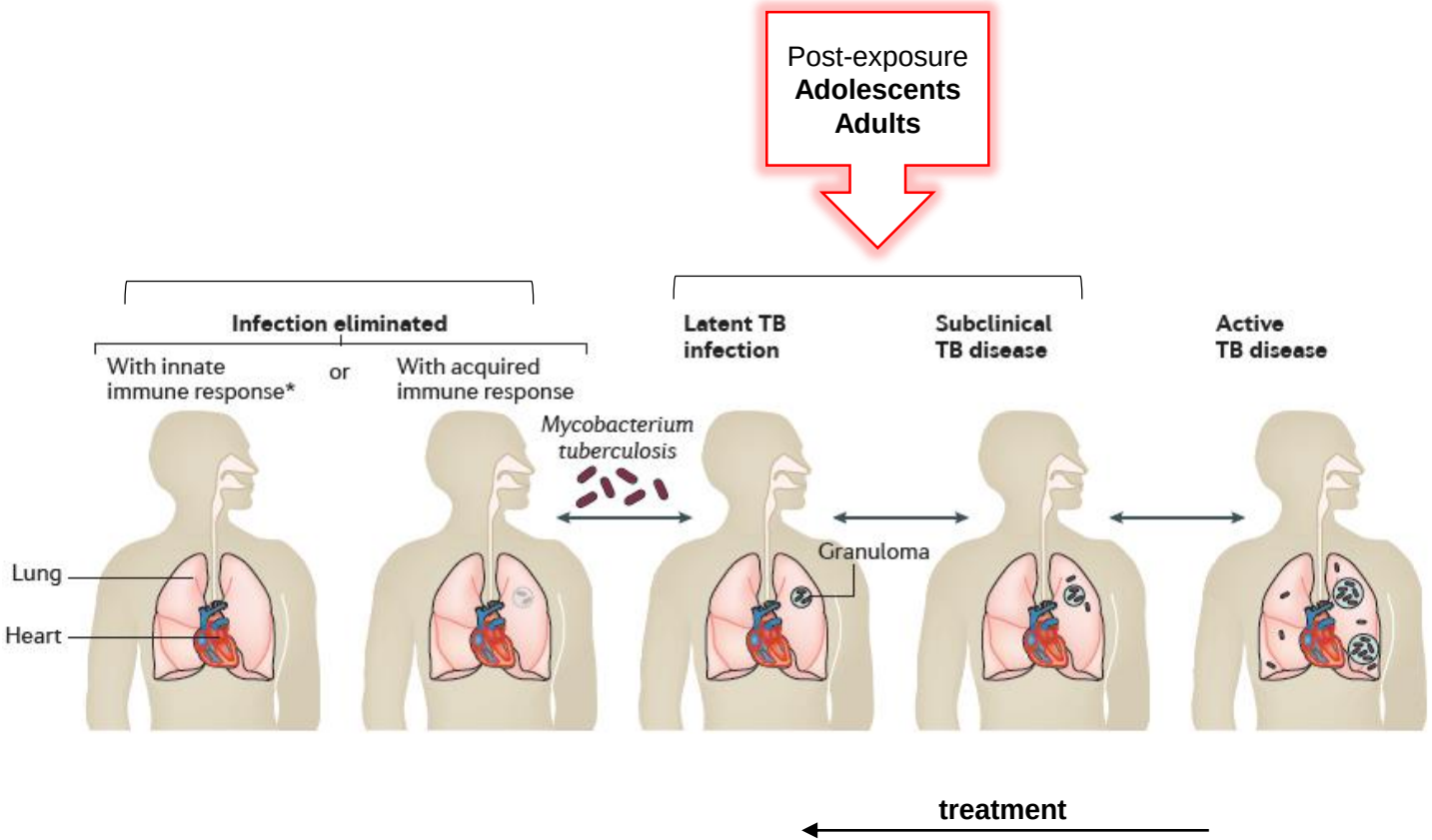


23%

~1.7 billion people

2016

Can TB vaccination protect infected individuals against TB disease?



Barry 3rd NRI, 2009; Pai et al,. NR. Dis. Primer 2016

M72 in $ASO1_E$

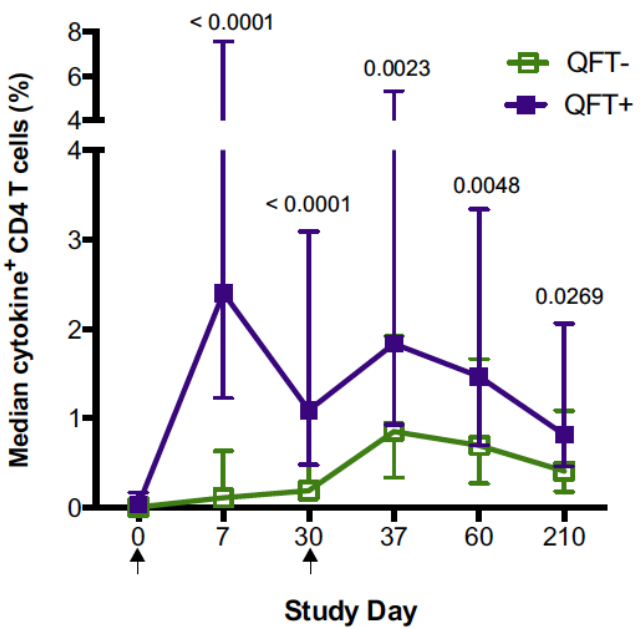
M72

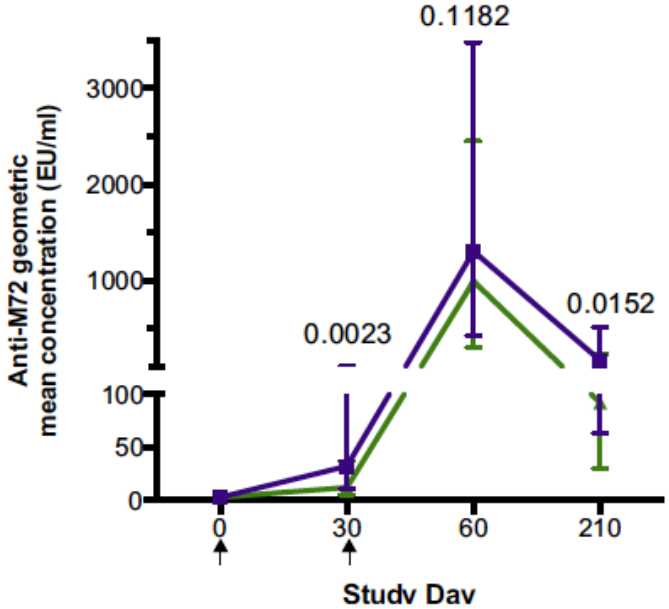
10 mg M72 polyprotein dissolved in 0.5 mL $AS01_E$ adjuvant

- 25 mg MPL (3-*0*-desacyl-4'-monophosphoryl lipid A)
- 25 mg QS21 (glycoside purified from bark of *Quillaja saponaria*)
- Adjuvants in suspension of liposomes in PBS

Soap Bark Tree
(*Quillaja saponaria*)

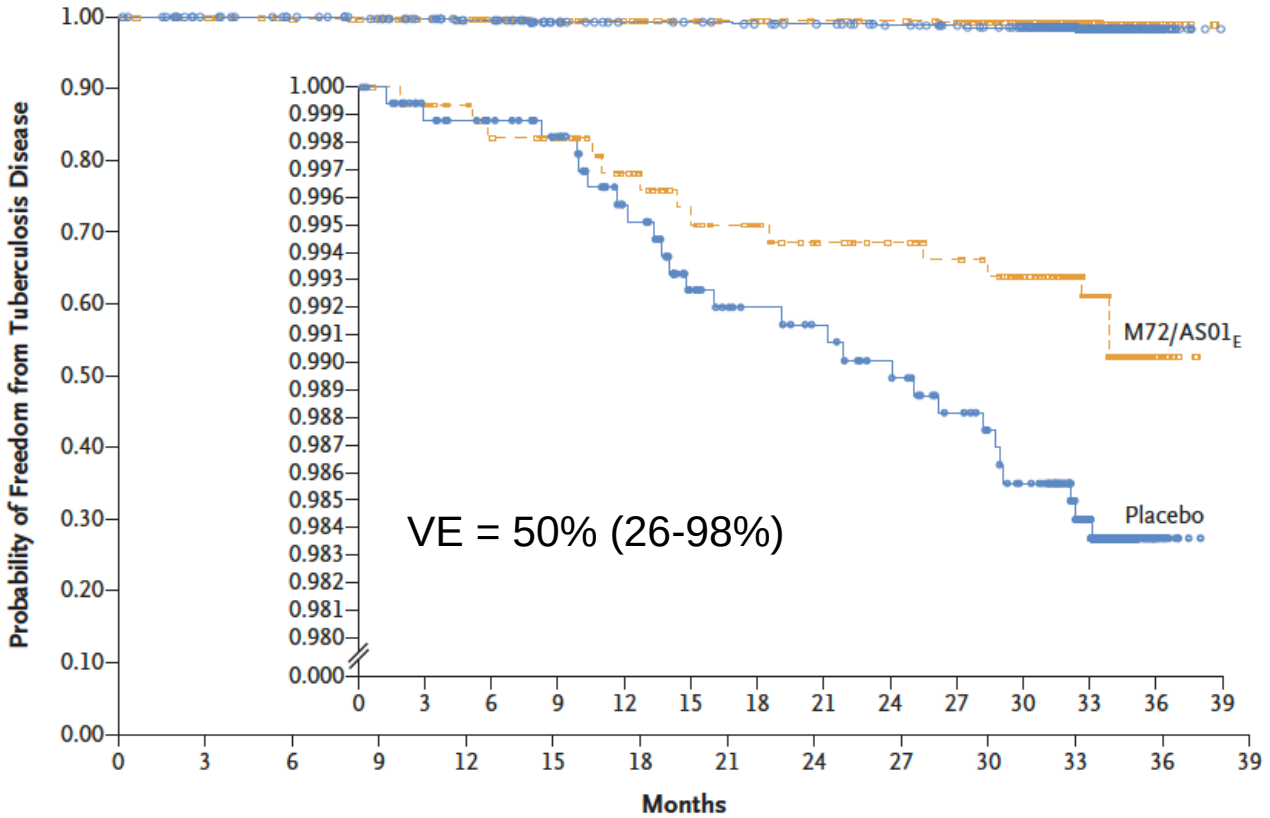
M72:AS01$_E$ is very immunogenic





Penn-Nicholson, Geldenhuys et al., Vaccine 2016

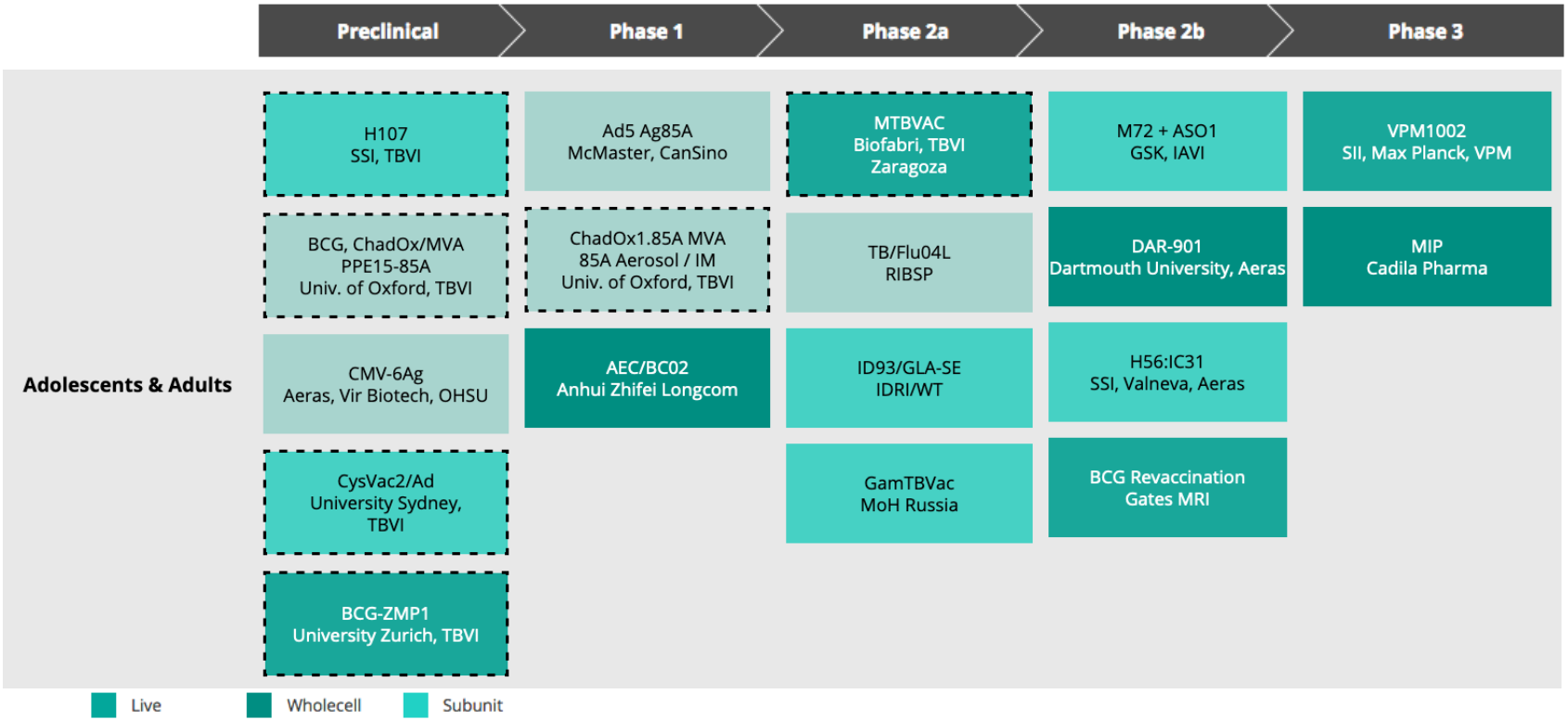
50% protection against TB disease in *M. tuberculosis*-infected adults



No. at Risk													
M72/AS01$_E$	1626	1621	1614	1609	1592	1580	1573	1566	1561	1557	1542	1468	12
Placebo	1663	1650	1642	1632	1610	1586	1576	1571	1564	1553	1539	1460	19

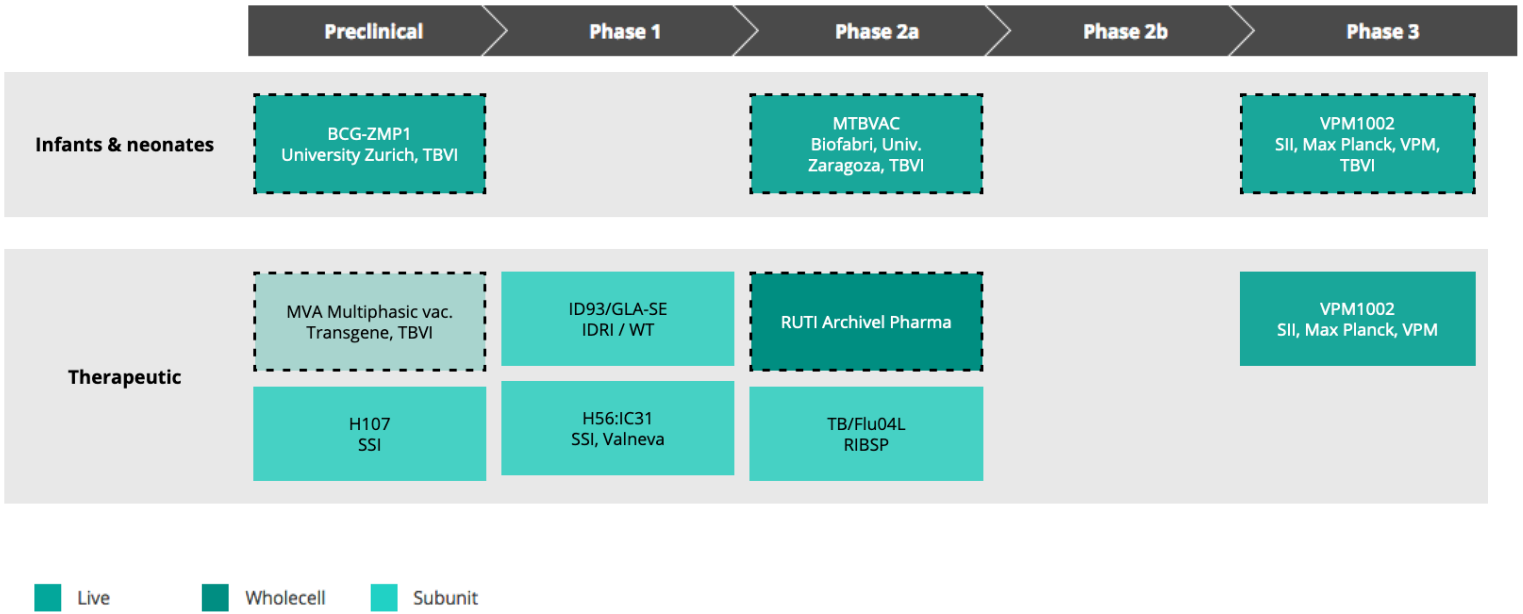
Tait et al., NEJM 2019

The TB vaccine development pipeline
(adolescent and adults)



https://www.tbvi.eu/what-we-do/pipeline-of-vaccines/

The TB vaccine development pipeline
(infants and therapeutic indications)



https://www.tbvi.eu/what-we-do/pipeline-of-vaccines/

Take home

- The burden of TB is enormous
- The complexity and heterogeneity of TB pathogenesis is considerable
- We need better tools to define this heterogeneity for effective vaccine development
- Natural immunity provides clues about protective mechanisms
- There is a “vibrant” pipeline of TB vaccine candidates
- Rational (data driven) advancement of candidates is critical
- Recent successes provide renewed impetus

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

IDM INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE

Elisa Nemes
Michele Tameris
Hennie Geldenhuys
Justin Shenje
Virginie Rozot
Claire Imbratta
Anele Gela
Munya Musvosvi
Adam Penn-Nicholson
Frances Ratangee
Angelique Luabeya
Mzwandile Erasmus
Mbandi Kimbung
Cheleka Mpande

Mark Hatherill
Simon Mendelsohn
Pia Steigler
Sara Suliman
Hassan Mahomed
Willem Hanekom
Nicole Bilek
Michele Tameris
Simba Mabwe
Miguel Rodo
Helen Mearns

Many, many others!

AERAS

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Ingrid Kromann
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