Insights from immunology that inform the development of new TB vaccines

Helen McShane

Jenner Institute

University of Oxford

The biggest challenge in TB vaccine R&D: lack of an immune correlate of protection

- **Definition**: A specific immune response (e.g., antibody level) that statistically associates with a lower risk of infection or disease.
- **Causality**: Does not automatically prove that the marker itself causes protection; it may simply be present alongside the real protective mechanism.
- An immune **correlate** is a measurable immune marker that shows a statistical association with protection against a disease
  - E.g., Measles, HBV
- An immune **surrogate** is a validated marker used to reliably predict vaccine efficacy or clinical endpoints when the true mechanism is unmeasured or complex
- A validated immune COP would be transformative for TB vaccine R&D

How can we identify immune COPs?

- Gold standard: human efficacy trials
- Other human studies
  - LTBI vs active disease; resisters vs LTBI
  - Phase 1-2a vaccine studies
- Controlled human infection models
- Animal challenge studies
  - NHP
  - Mouse – including gene deleted mice, adoptive transfer

What do we think we know about protective immunity against TB?

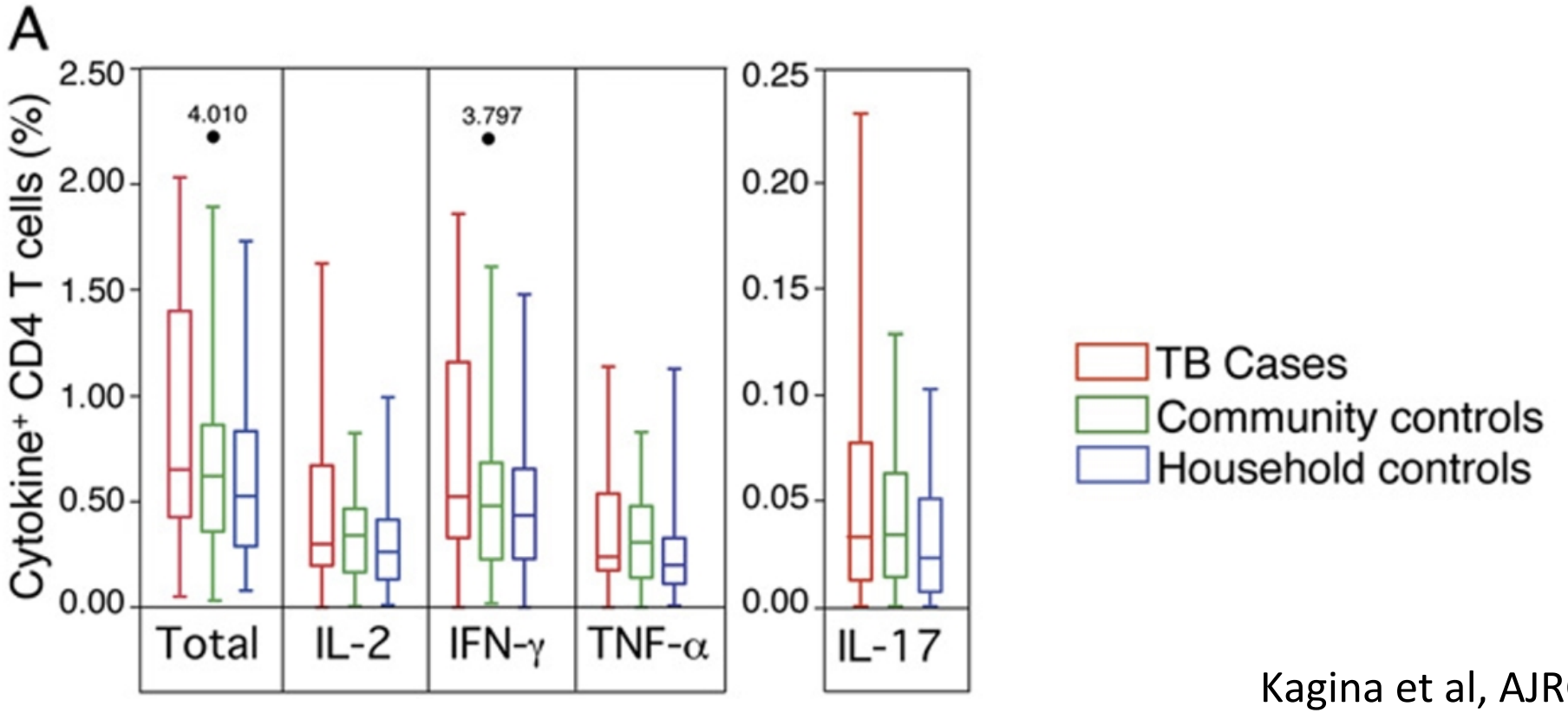
Antigen –specific class 2 restricted CD4+ T cells

- Mouse studies
  - Gene-deleted mice – CD4+ T cell / Class 2
  - Adoptive transfer
- People living with HIV
  - Higher risk of TB infection and TB disease
  - Risk increases as CD4+ T cell count declines
  - Risk reduced but not fully reversed by ARVs

Th1 cytokines are critical

- Interferon gamma
  - Gene-deleted mouse studies
  - Human genetic studies
- Tumour necrosis factor
  - Gene deleted mouse studies
  - Monoclonal antibodies against TNF
- IL2
- IL17

Specific T cell frequency & cytokine expression do not correlate with protection against TB in BCG-vaccinated newborns



Kagina et al, AJRCCM 2010

What about antibodies?

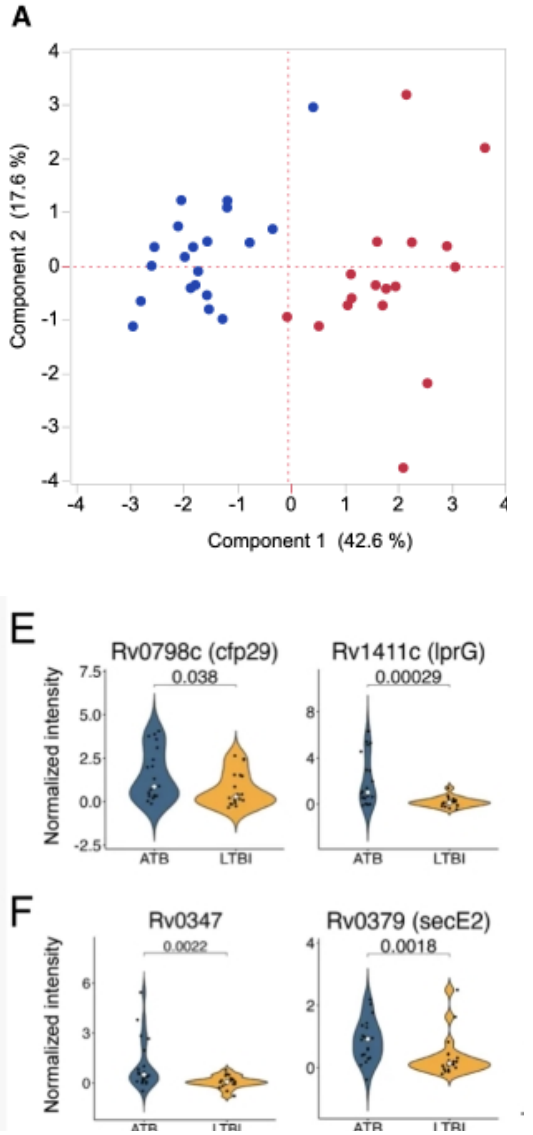
- Conventional wisdom:
  - Mycobacterium tuberculosis is intracellular
  - Antibodies in the serum cannot therefore protect against TB
  - Mouse studies with polyclonal sera support this dogma

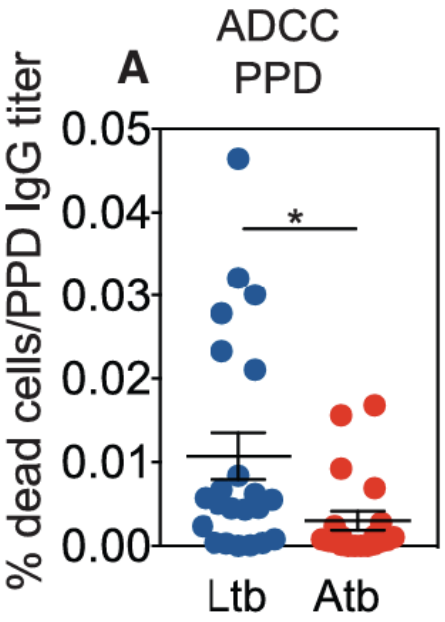
  BUT

- Recent evidence is accumulating to suggest antibodies may have a role…
  - Unclear whether as a correlate or a surrogate

Is there a functional role for antibodies in TB?

- Individuals with LTBI and active TB have different humoral signatures
- Antibodies in LTBI have enhanced Fc effector profiles
- Antibody glycosylation patterns can distinguish between LTBI and active TB
- Antibodies in LTBI drive macrophages to kill intracellular bacteria
- Individuals with LTBI vs active TB and resisters vs LTBI, have different IgG binding profiles

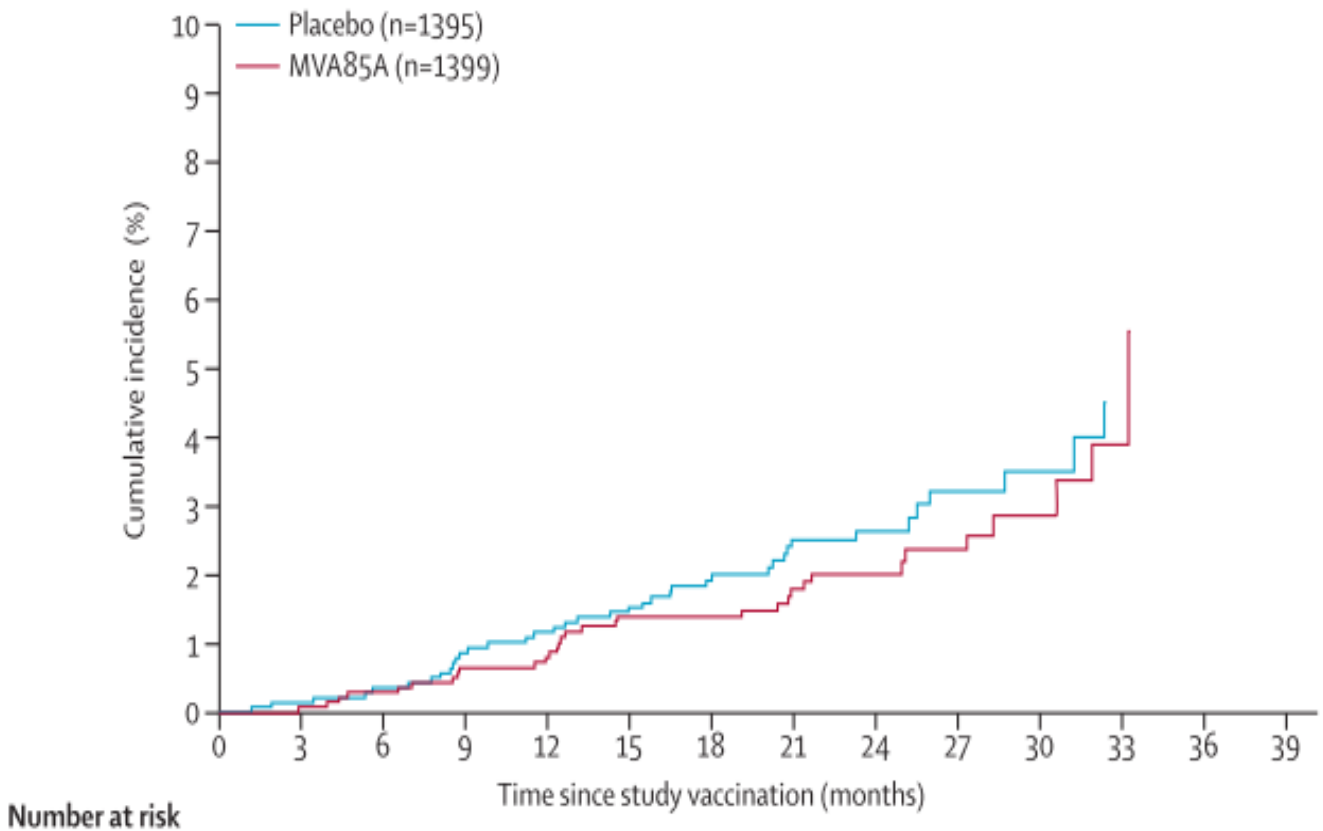




Lu et al, Cell 2016; Khan et al, Front Immunol 2026

Efficacy trial CoP data

MVA85A did not enhance BCG induced protection

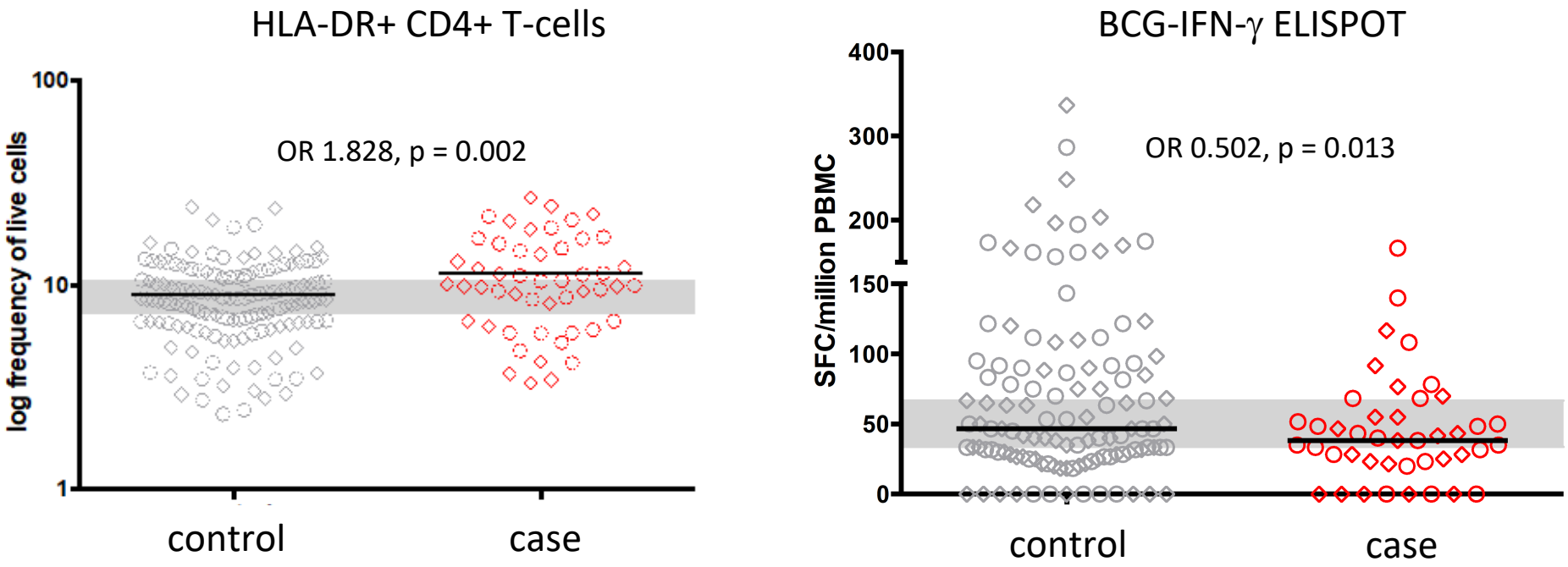


Number at risk

Placebo	1395	1380	1375	1364	1349	1334	1180	956	741	500	340	103	25	0
MVA85A	1399	1385	1378	1361	1343	1328	1182	944	731	500	331	98	16	0

Tameris M et al, Lancet 2013

T-cell activation and BCG IFN-γ ELISPOT are immune correlates of risk of TB disease in BCG-vaccinated infants

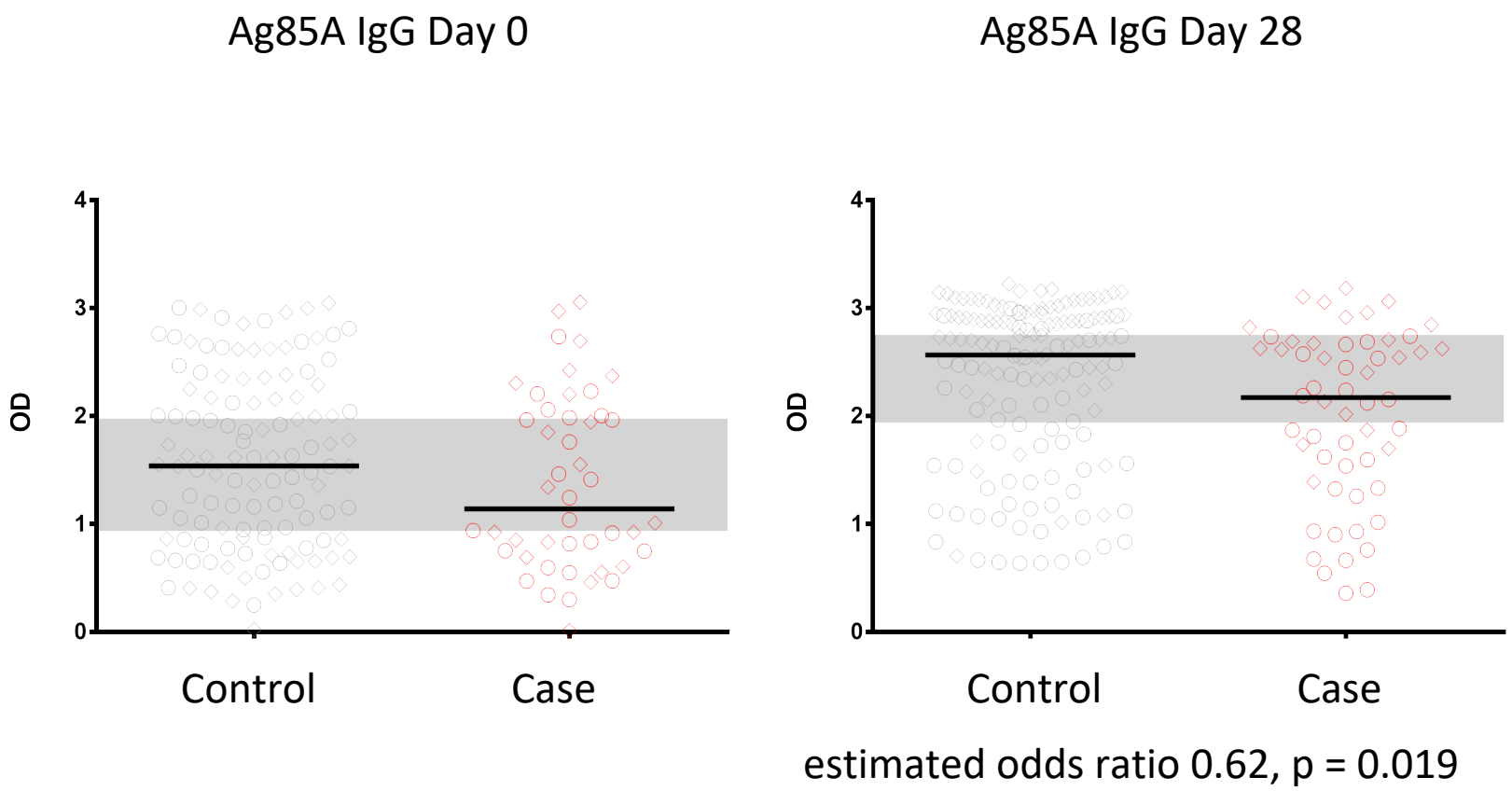


Result significant if Conditional Logistic Regression P<0.05 and FDR<2
Shaded bar indicates medium third of immune response level

Measured in healthy infants up to 3 years before disease develops

Fletcher HA *et al* Nature Communications, 2016

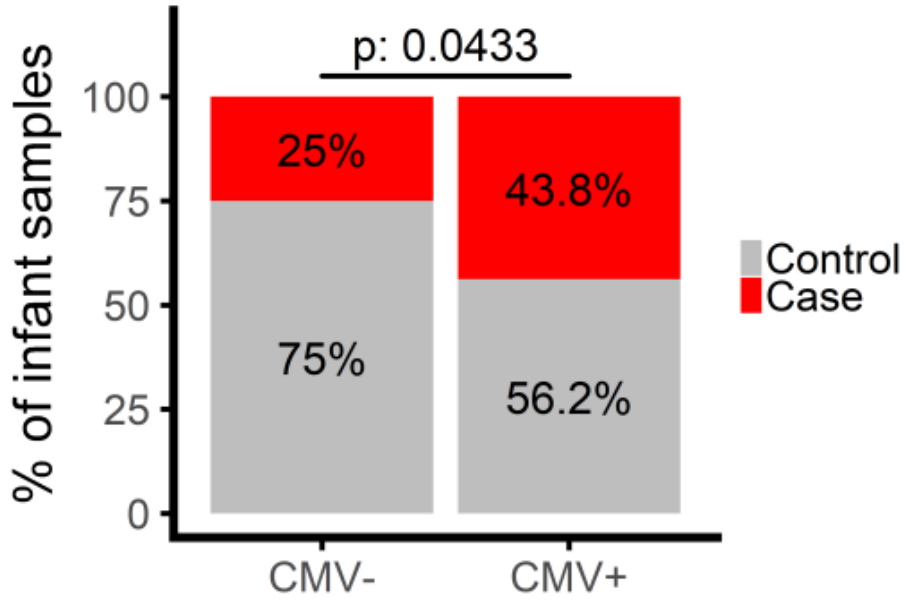
Antibodies correlate with reduced risk of TB disease

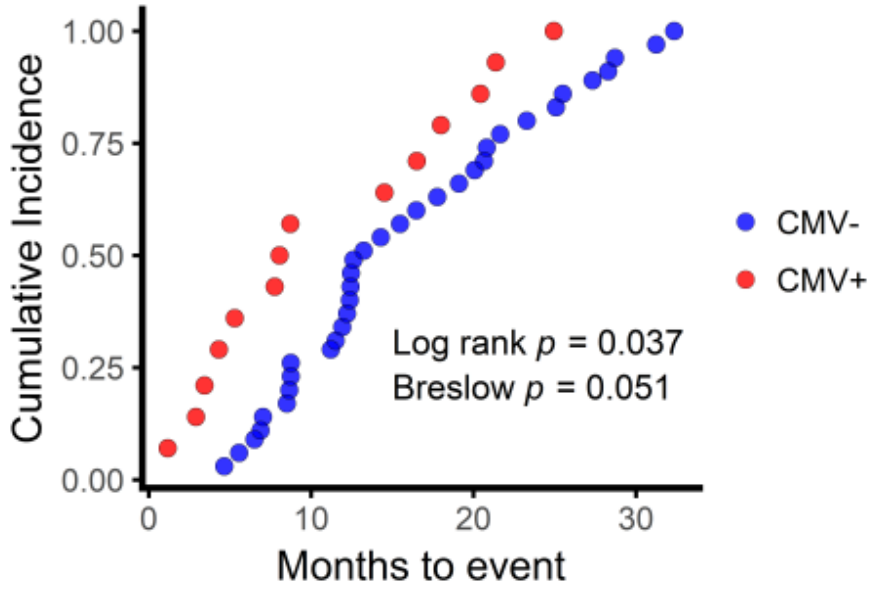


estimated odds ratio 0.62, p = 0.019

Fletcher HA *et al* Nature Communications, 2016

CMV infection is associated with risk of developing TB disease





Muller J et al JCI Insight 2019

Correlates of risk of M.tb infection

- HLA-DR expression on CD4+ T-cells (OR 1, 95% CI 0.95 – 1.06, p = 0.921) **did not** associate with risk of M.tb infection
- BCG-specific IFN-□ producing cells in PBMC (OR 0.99, 95% CI 0.97 – 1.01, p = 0.238) **did not** associate with risk of M.tb infection
- Plasma Ag85A-specific IgG responses on Day −7 was associated with **increased** risk of M.tb infection (OR 8.85, 95% CI 2.05 – 38.09, p = 0.003)
- Plasma levels of IFN-□2, TNF-□, CXCL10 (IP-10) and complement C2 were higher in infants that were subsequently infected with *M.tb*.

Satti et al, Nature Communications 2022

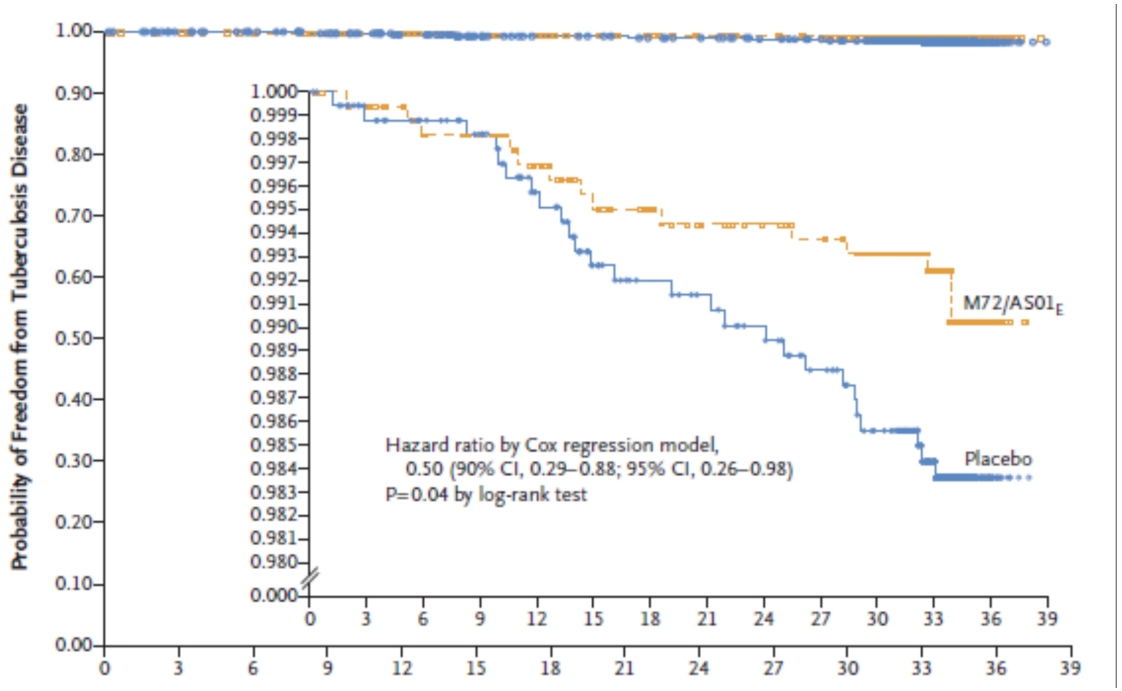
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

D.R. Tait, M. Hatherill, O. Van Der Meeren, A.M. Ginsberg, E. Van Brakel, B. Salaun, T.J. Scriba, E.J. Akite, H.M. Ayles, A. Bollaerts, M.-A. Demoitié, A. Diacon, T.G. Evans, P. Gillard, E. Hellström, J.C. Innes, M. Lempicki, M. Malahleha, N. Martinson, D. Mesia Vela, M. Muyoyeta, V. Nduba, T.G. Pascal, M. Tameris, F. Thienemann, R.J. Wilkinson, and F. Roman

- 3573 African adults
- HIV uninfected
- *M.tb* infected (QFT+)
- Endpoint
  - TB disease (C+ or GE+)
- 3 years follow up
- VE 49.7% (95% CI 2.1-74.2)



Comparison of VPM1002 with BCG in the prevention of tuberculosis in newborn infants: a multicentre, double-blind, randomised, phase 3, non-inferiority trial

*Videlis Nduba, Matsontso Mathebula, Victoria Nankabirwa, Megan Dempster, Francis Mhimbira, Issa Sabi, Anne Wajja, Mark F Cotton, Shaun Barnabas, Ayola Akim Adegnika, Stefan H E Kaufmann, Sina Brückner, Marcus May, Carsten W Höß, M Revathy, Vidya Niranjan, Aditi Bhargava, Manish Gupta, Dhananjay Kapse, Sajjad Desai, Leander Grode, Prasad S Kulkarni, Umesh Shaligram, and the priMe consortium**

	VPM (n = 3471)	BCG (n = 3469)	p value
QFT conversion	184	150	0.057
Sustained QFT conversion	44	33	0.22
TB disease	110	59	<0.0001

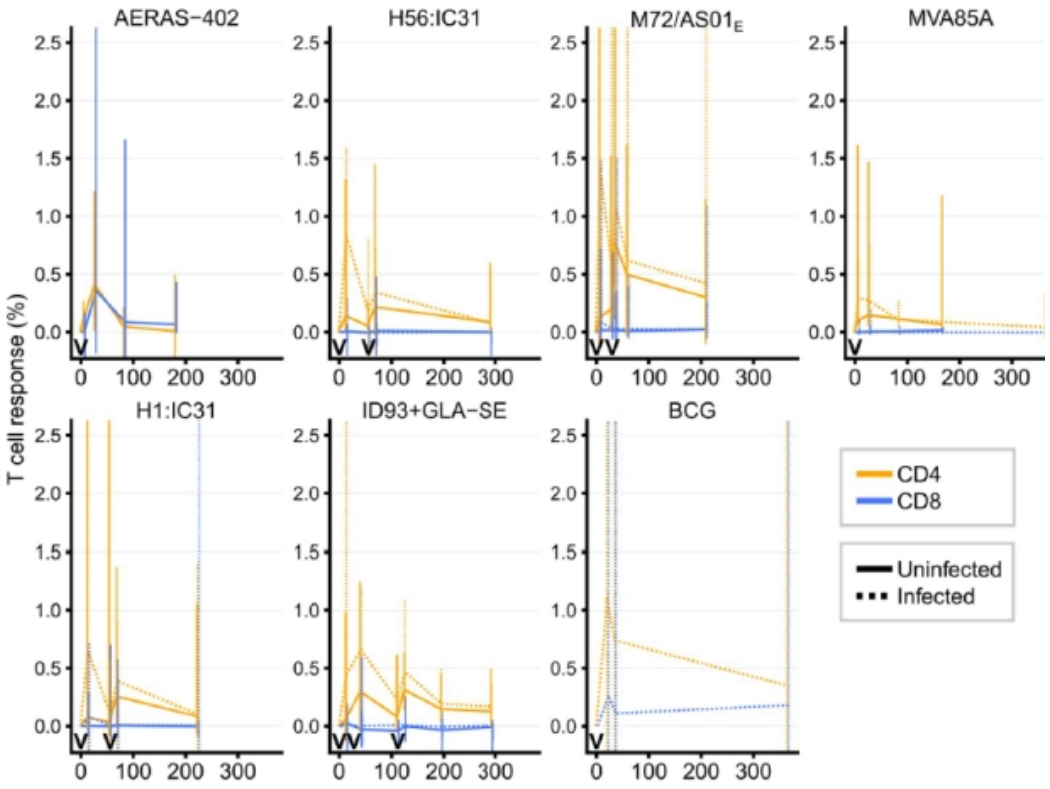
Nduba et al, Lancet Infect Dis 2026

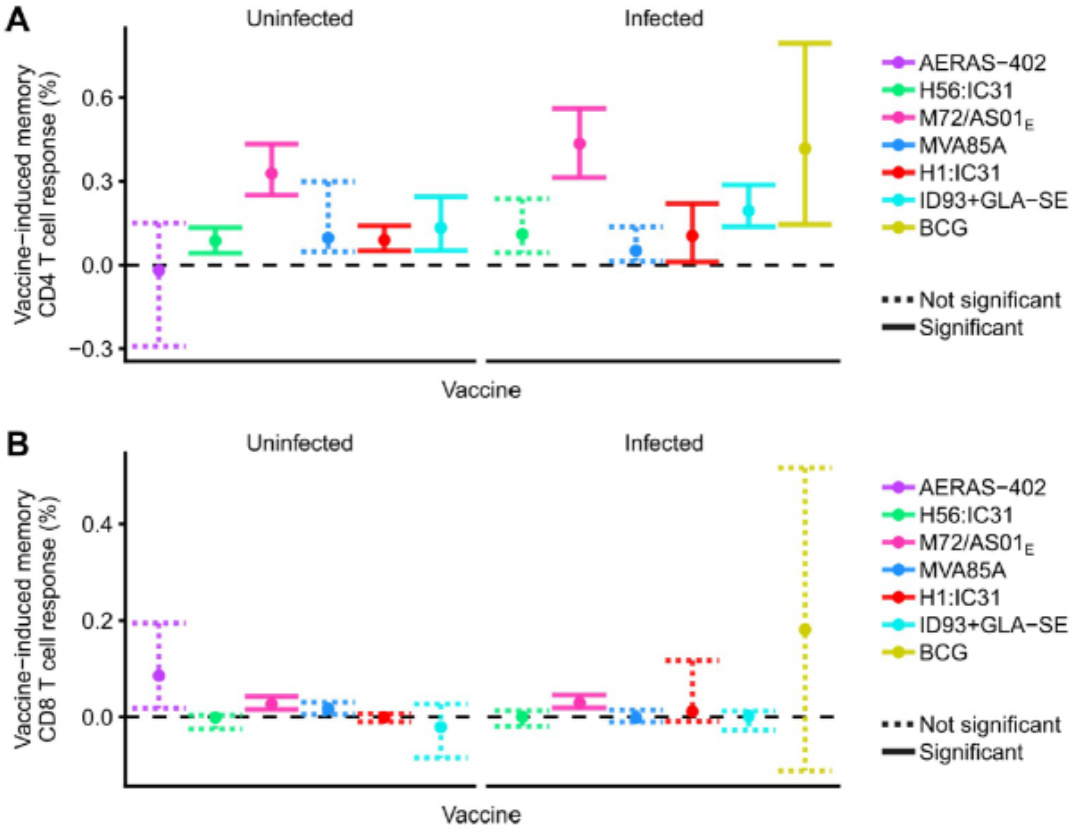
	IFNγ concentrations (pg/mL)		Difference (95% CI)	p value
	BCG	VPM1002		
Day 0				
Participants	37	102	..	..
Mean (SD)	0·55 (2·35)	2·59 (7·97)	..	..
Median	0	0	0 (0–0)	0·2206
Range	0–12·6	0–44·71	..	..
Day 14				
Participants	36	100	..	..
Mean (SD)	4·96 (10·85)	19·84 (34·49)	..	..
Median	0	0	0 (0–3·54)	0·0191
Range	0–53·31	0–191·77	..	..
Week 6				
Participants	37	102	..	..
Mean (SD)	601·40 (684·76)	214·56 (288·41)	..	..
Median	338·89	112·28	−190·02 (−344·23 to −67·79)	0·0005
Range	0–7589·77	0–1879·68	..	..
Week 12				
Participants	37	103	..	..
Mean (SD)	251·44 (272·59)	75·12 (83·75)	..	..
Median	170·43	48·23	−95·62 (−145·55 to −55·43)	<0·0001
Range	0–1150·60	0–341·12	..	..
Month 6				
Participants	37	101	..	..
Mean (SD)	91·81 (150·97)	33·17 (51·84)	..	..
Median	35·99	14·14	−19·71 (−35·99 to −5·44)	0·0033
Range	0–778·98	0–286·07	..	..
Month 12				
Participants	37	103	..	..
Mean (SD)	158·49 (589·69)	17·24 (28·30)	..	..
Median	29·97	0	−15·39 (−31·76 to 0)	0·0008
Range	0–3593·53	0–119·88	..	..

Table 4: Concentrations of interferon γ in the supernatant as determined by whole-blood ELISA after re-stimulation with tuberculin purified protein derivative for 7 h in VPM1002 and BCG groups

Cotton et al, Lancet Infect Dis 2022

Comparison of immunogenicity of various TB vaccine candidates

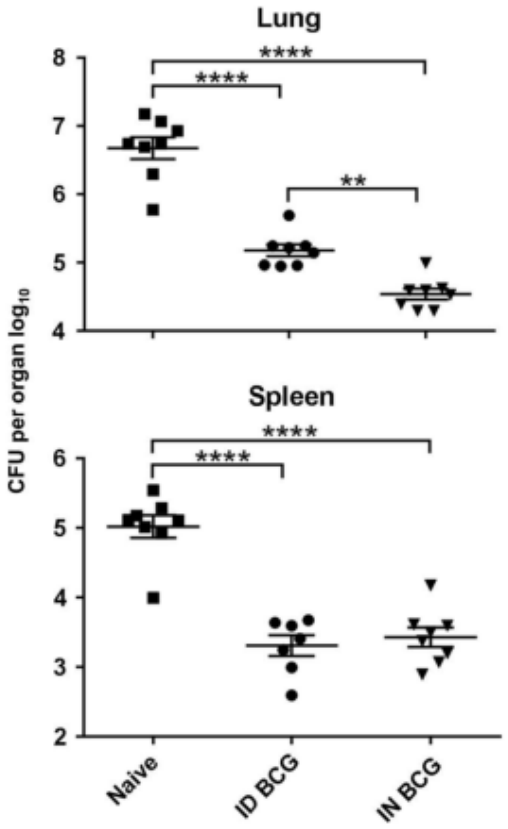


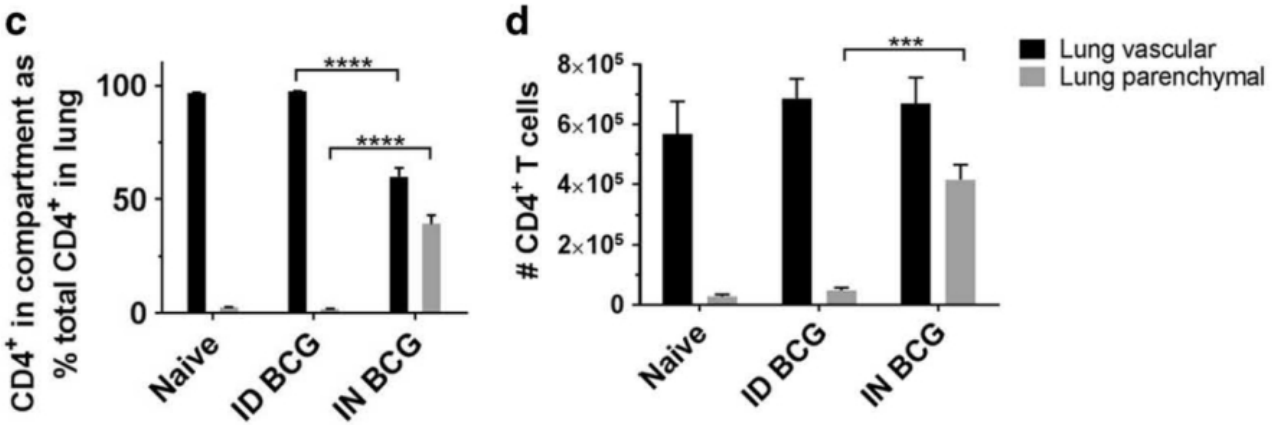


Rodo et al, PLoS Pathogens 2019

Preclinical animal data

PPD-specific lung parenchymal CD4+ T cells associate with protection after IN but not ID BCG in mice

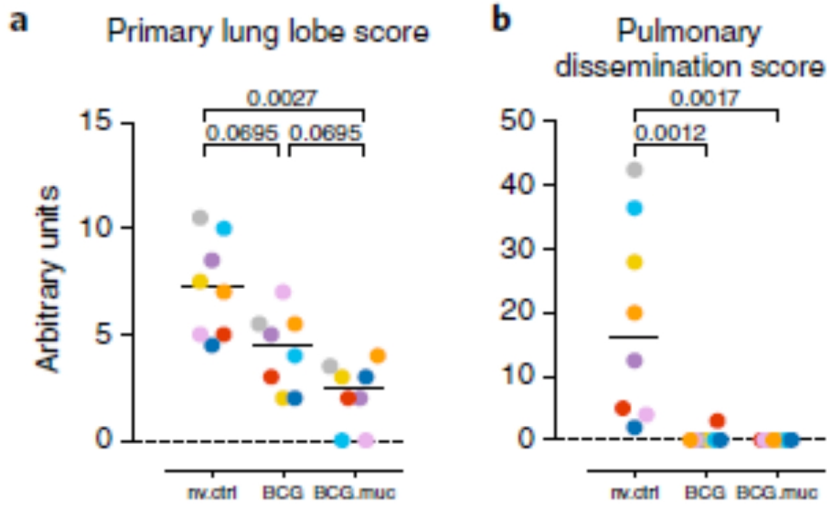


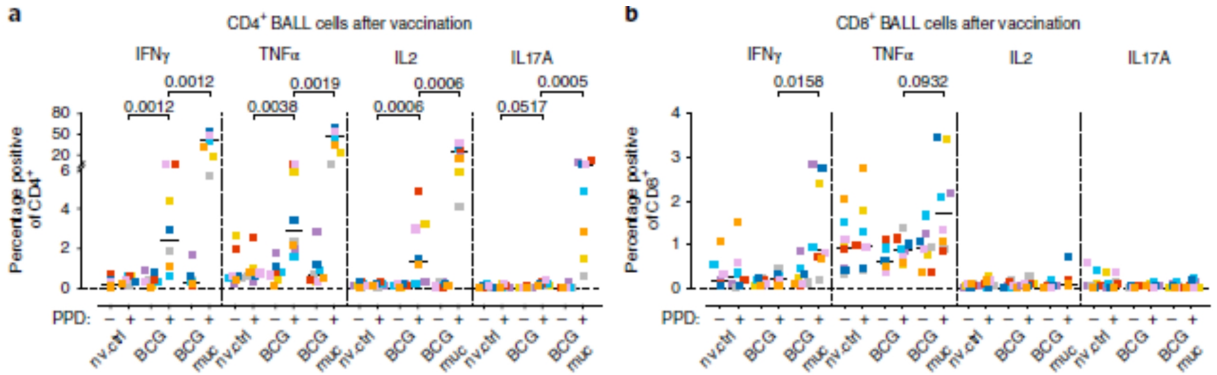


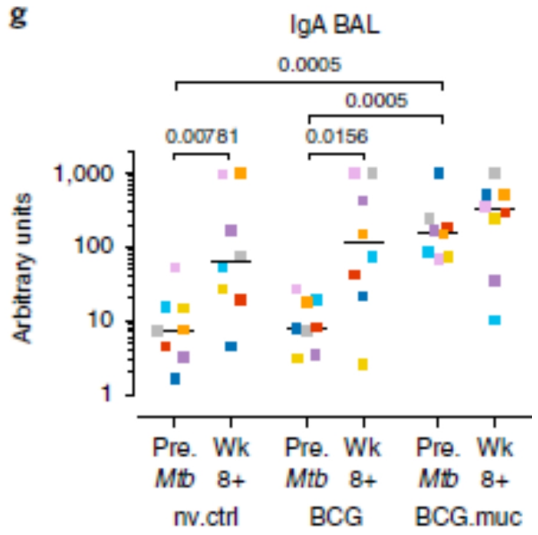
Bull N et al, Mucosal Immunology 2019

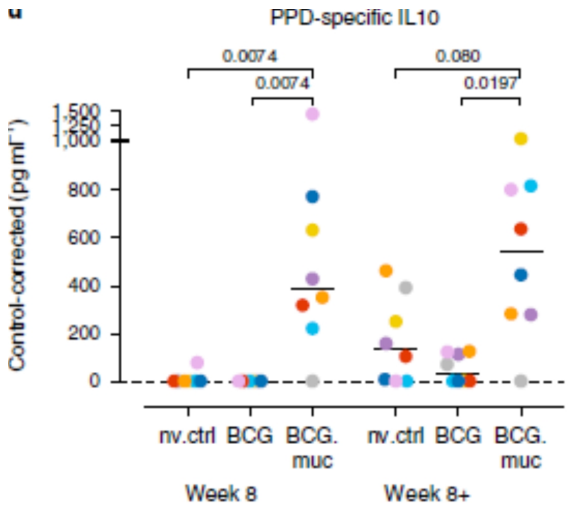
Mucosal BCG protects better against low dose *M.tb* infection than intradermal BCG in NHPs

Dijkman K et al NM 2019

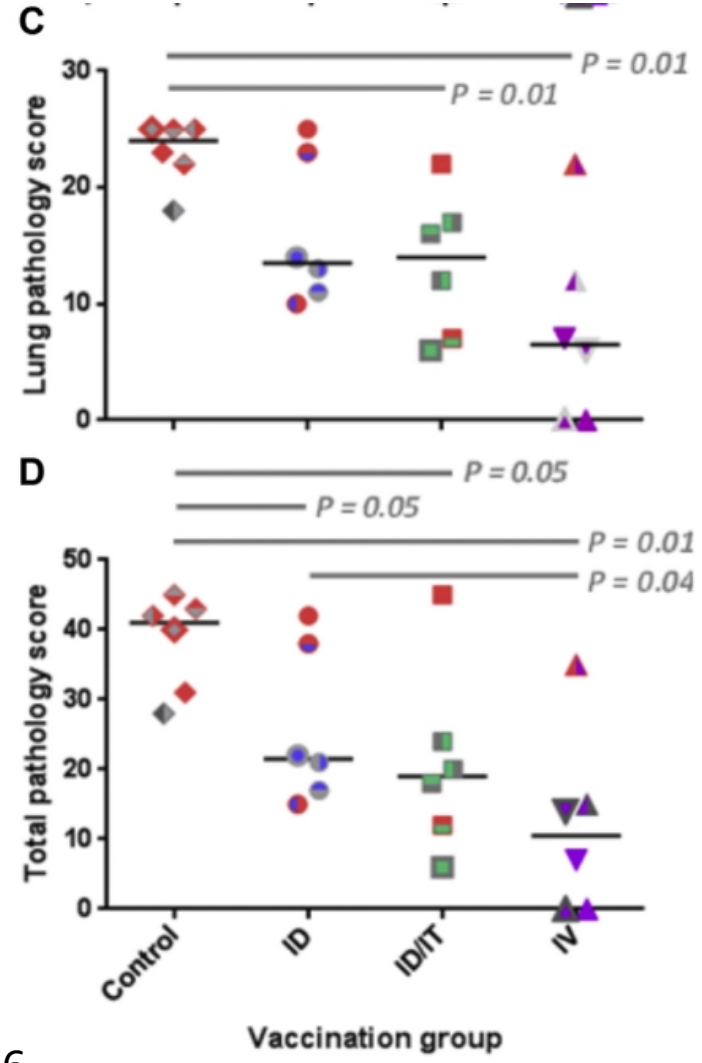




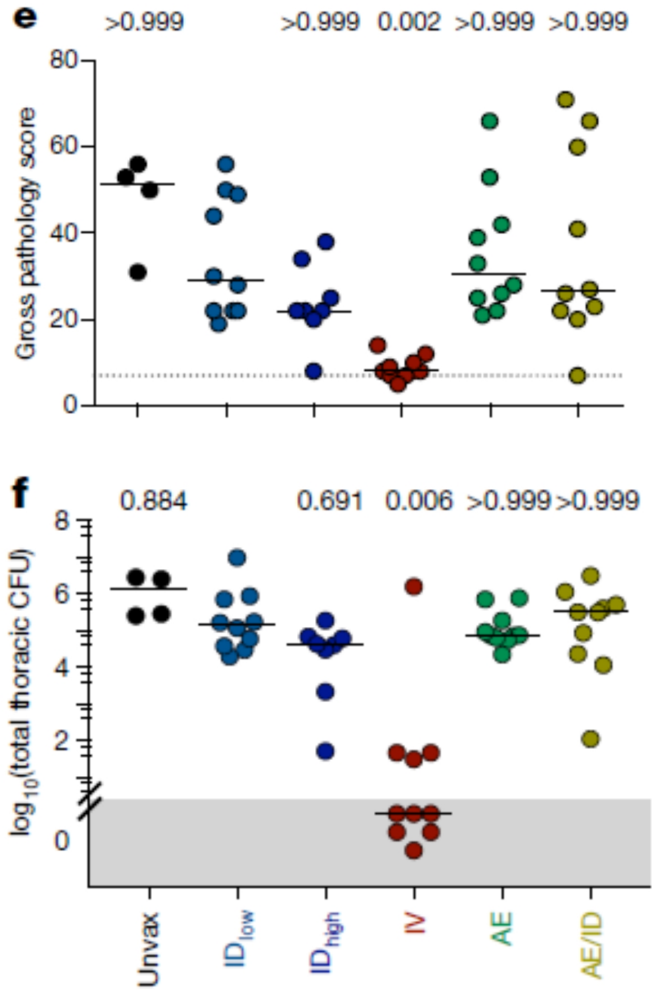




IV BCG profoundly alters the outcome of *M.tb* infection in NHPs



Sharpe S et al, 2016

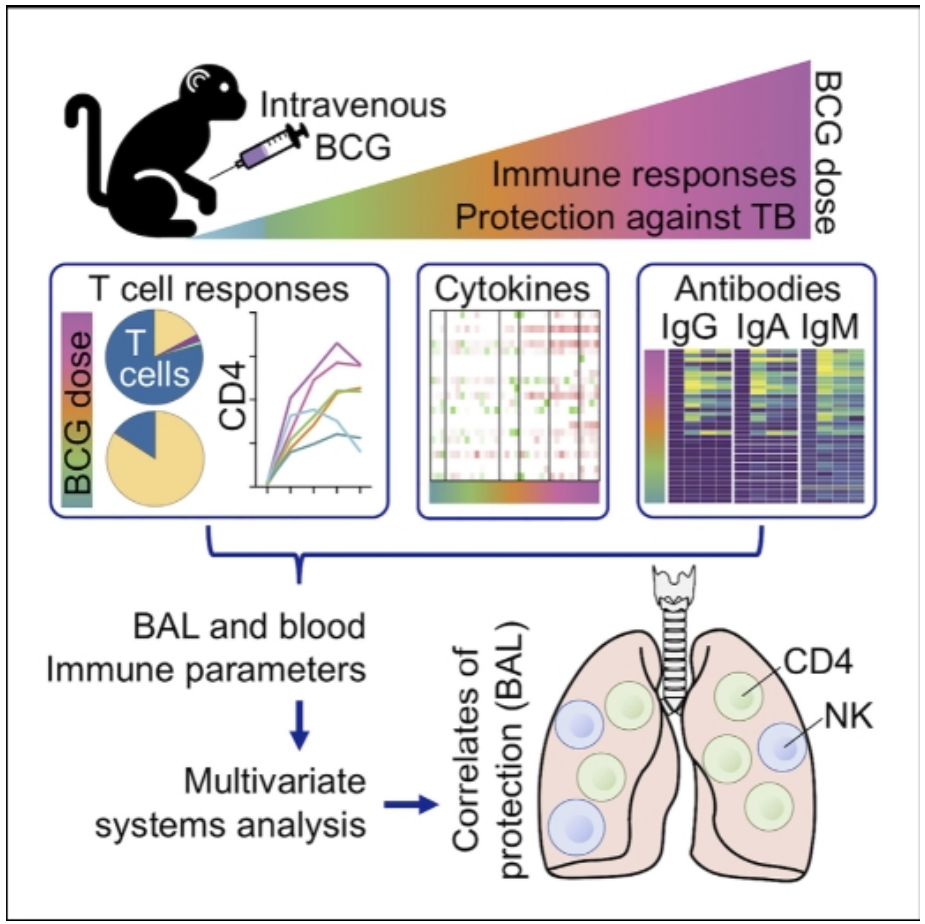


Darrah P et al, 2020

Article

Cell Host & Microbe

Airway T cells are a correlate of i.v. Bacille Calmette-Guerin-mediated protection against tuberculosis in rhesus macaques



Darrah et al, Cell Host Microbe 2023

nature immunology

ARTICLES

https://doi.org/10.1038/s41590-021-01066-1

Check for updates

OPEN

Robust IgM responses following intravenous vaccination with Bacille Calmette–Guérin associate with prevention of *Mycobacterium tuberculosis* infection in macaques

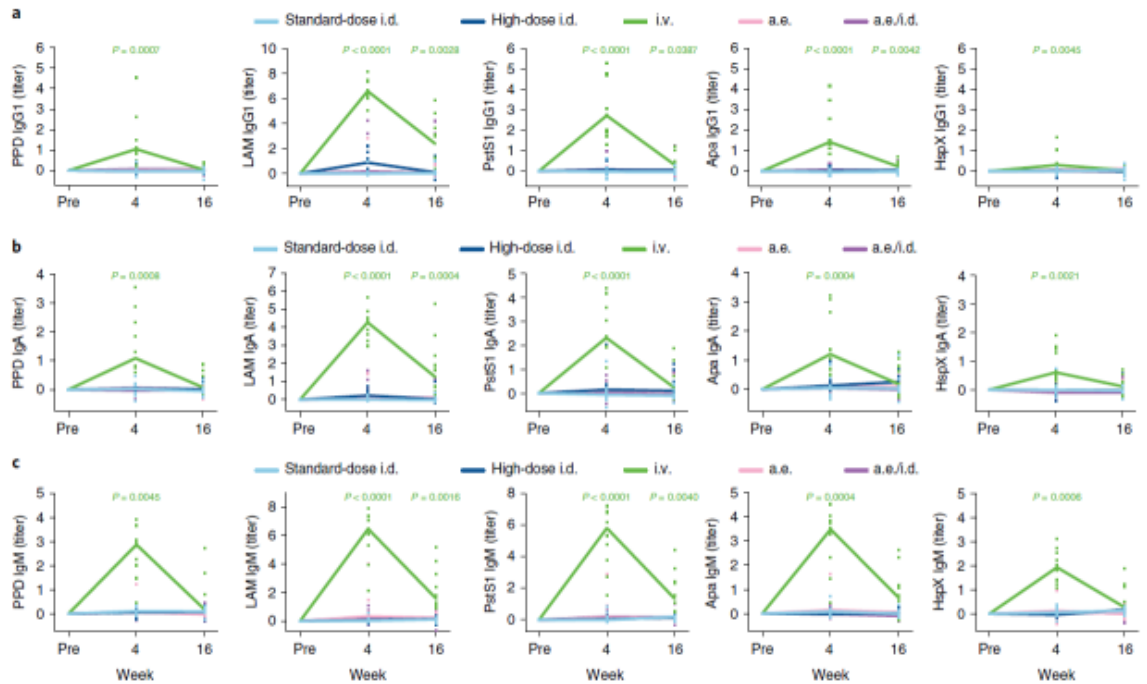
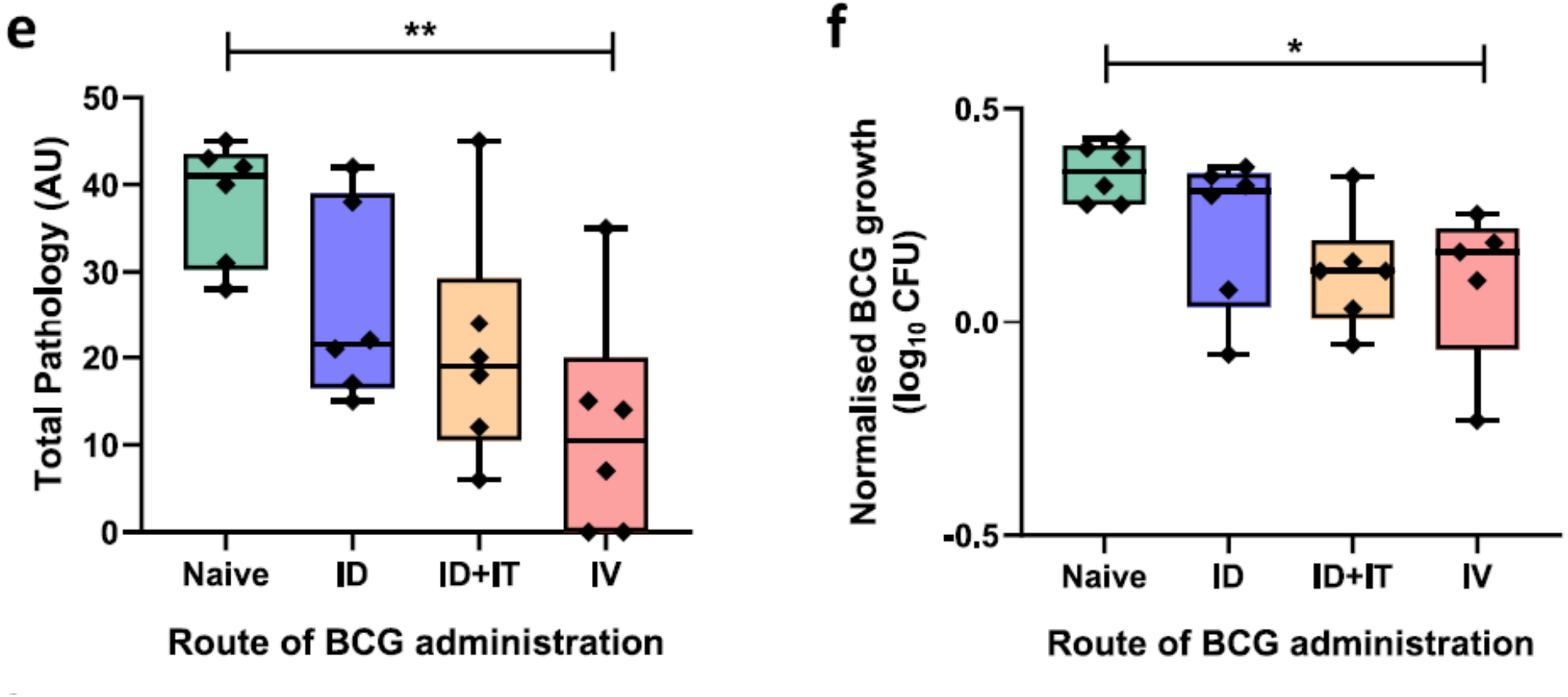


Fig. 2 | Intravenous BCG vaccination uniquely elicits a robust lung-compartmentalized antibody response. a–c, Fold change values in IgG1 (**a**), IgA (**b**) and IgM (**c**) titers present in the BAL fluid of each rhesus macaque following BCG vaccination. Fold changes were calculated as the fold change in Luminex MFI over the pre-vaccination level for each macaque. A base-2 log scale was used for the *y* axis. Each point represents the duplicate average from a single macaque. The lines represent group medians over time. Kruskal–Wallis with Dunn's multiple-comparison tests were performed on the fold change values at each time point, comparing each experimental BCG vaccination group to the standard-dose i.d. BCG group. Adjusted *P* values < 0.05 compared to the standard-dose i.d. BCG group are shown and are colored by vaccination group.

Irvine et al, Nature Immunology 2021

Mycobacterial growth inhibition in vitro associates with pathology in NHPs



Tanner et al, NPJ Vaccines 2021

Summary

- A potent cell mediated immune response, particularly Th1 CD4 T cells, is critical for protection
- Other cell types likely play a role, including innate immune cells in early defence.
- Antibodies may play a direct role, or be a marker for another, as yet undefined immune function
- Lung immunity is important
- More functional ‘sum of the parts’ assays may be better COPs
- We must take every opportunity to analyse CoP samples from human efficacy trials
- A validated CoP would be game-changing in TB vaccine R&D