VALIDATE

"**VA**ccine deve**L**opment for complex **I**ntracellular neglecte**D** p**AT**hog**E**ns"

VALIDATE is an international network of researchers working together to accelerate the development of vaccines for:

- **TB**
- **Leishmaniasis**
- **Melioidosis**
- **Leprosy**

VALIDATE provides pump-priming grants, training grants, workshops, a mentoring scheme, seminars, & a website featuring news & opportunities.

Becoming a member is free – for details on how to join visit our website.

Find out more at www.validate-network.org

@NetworkValidate

or email Samantha.Vermaak@ndm.ox.ac.uk

MRC Medical Research Council

GCRF Global Challenges Research Fund

BBSRC bioscience for the future

Efficacy, challenges and aerosols: Novel approaches to human TB vaccine development

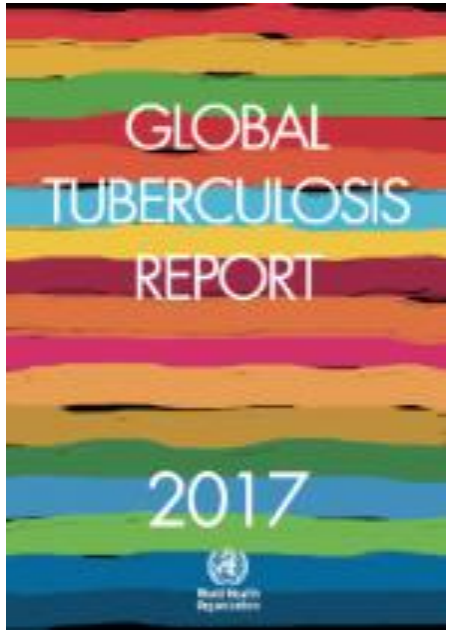
Helen McShane

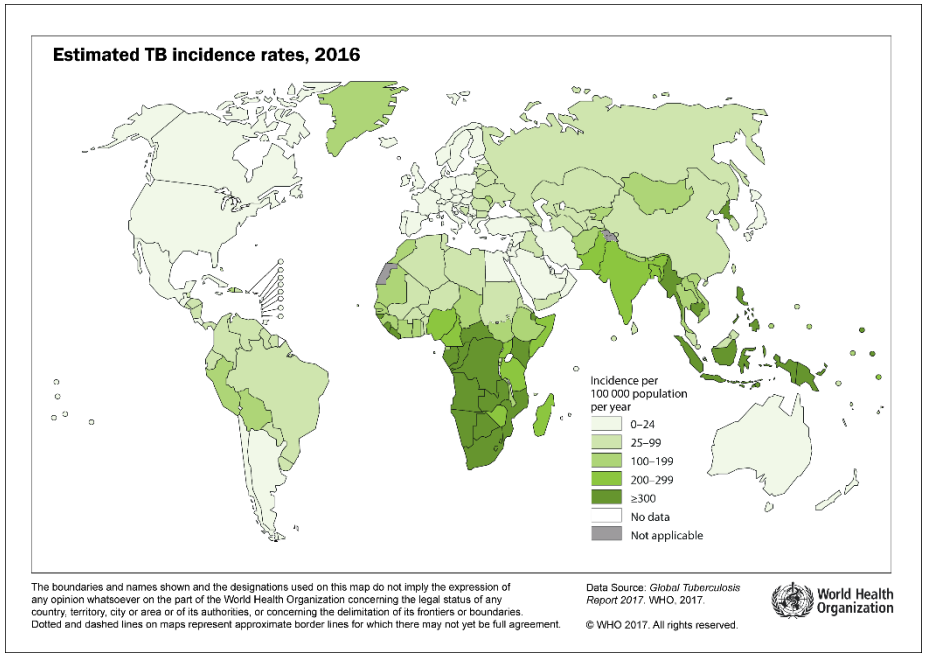
The Jenner Institute

University of Oxford

Epidemiology

- 10.4 million new cases in 2016
- 1.7 million deaths in 2016
- Resistance
  - MDR-TB (~490,000 in 2016)
  - XDR-TB
  - TDR-TB
- Overlap with HIV epidemic
  - 1.2m in 2015
- Burden of latent infection



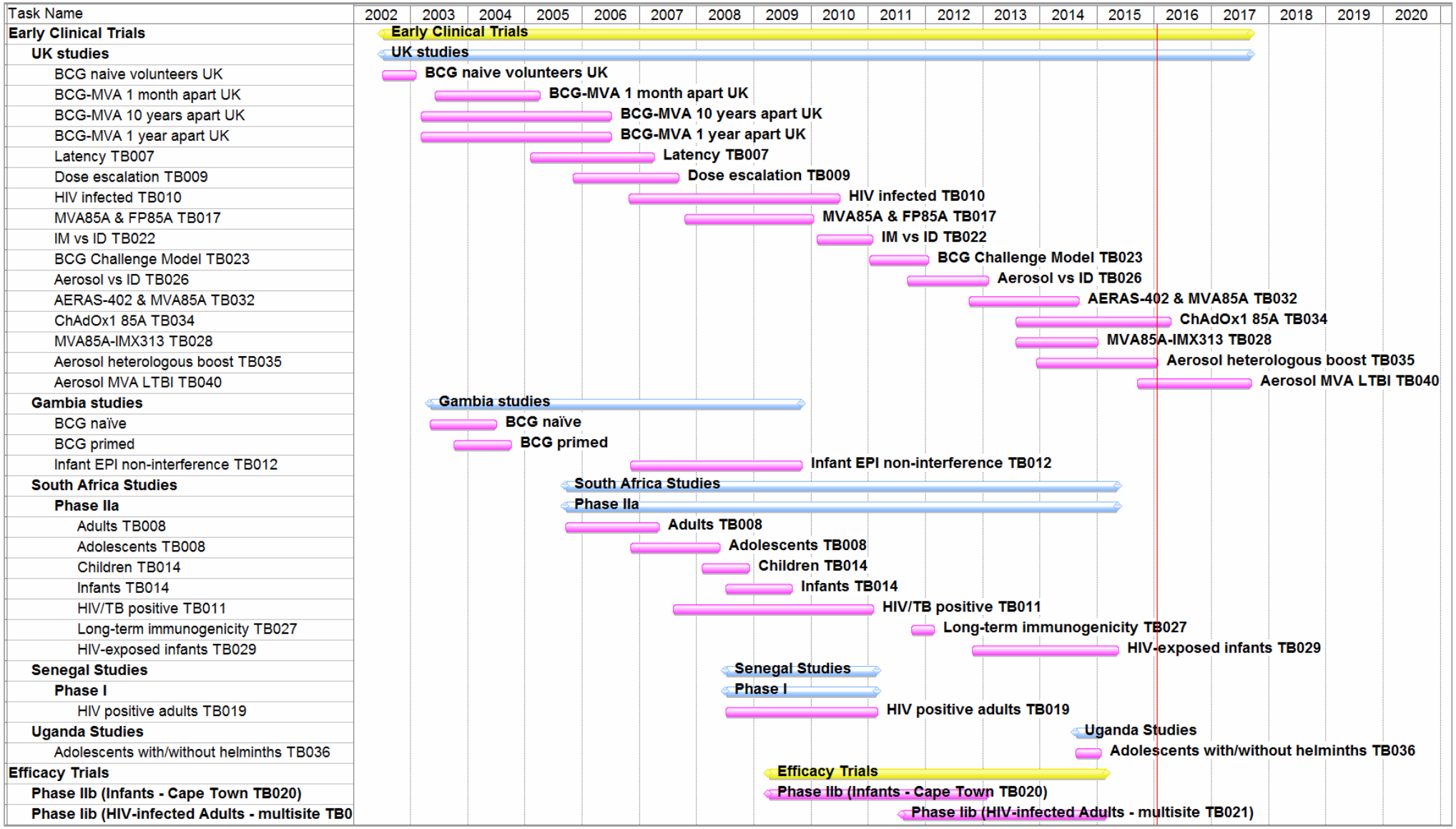


Challenges with TB vaccine development

- Uncertain predictive value of animal models
- Lack of immunological correlate
- Disease incidence
- Site infrastructure

EFFICACY

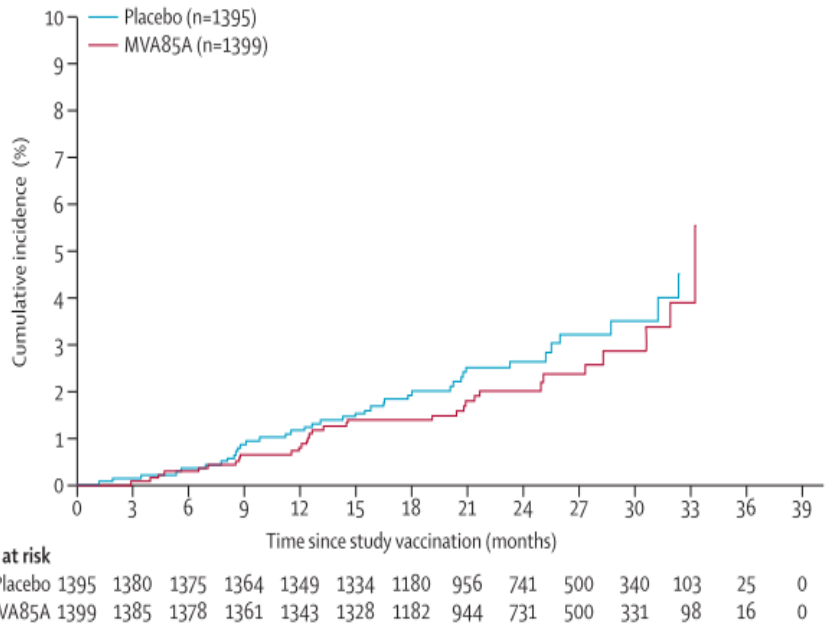
MVA85A Clinical Development Plan



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*

www.thelancet.com Published online February 4, 2013 http://dx.doi.org/10.1016/S0140-6736(13)60177-4



Lessons learnt from the MVA85A trial

- Vaccine efficacy trials are possible
- Prevention of disease
  - Isoniazid prophylaxis after TB exposure reduces disease from 13 to 8%
- Diagnosis
  - Role of clinical symptoms in diagnosis of TB
  - Quantiferon testing and risk of TB disease
  - Evaluation of Xpert in BAL and gastric samples

Future efficacy trials

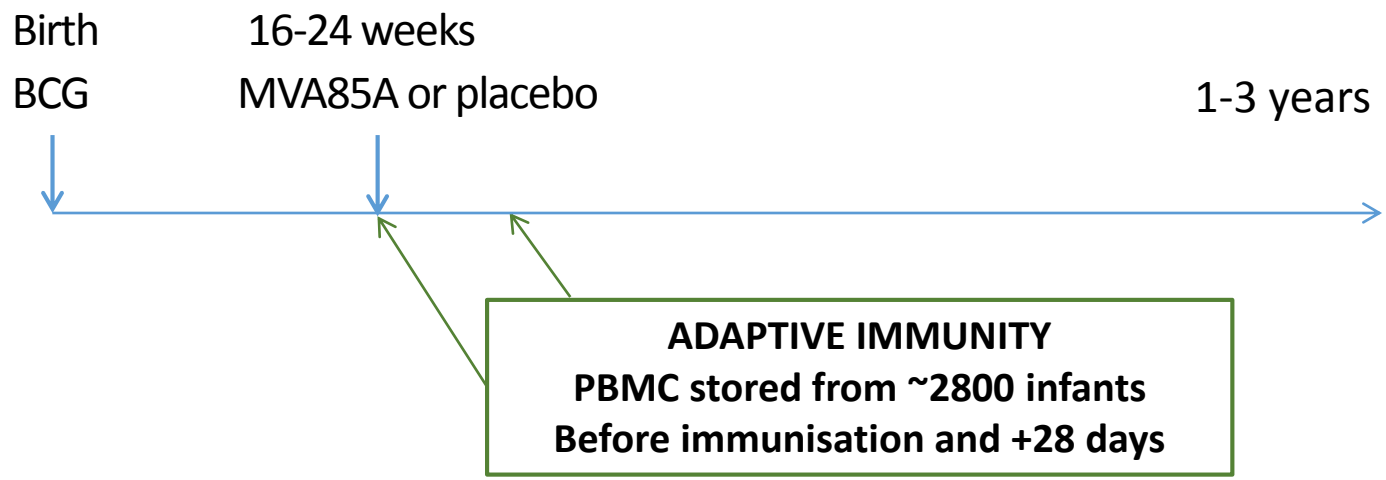
- Focus on adolescents/adults
  - Responsible for most transmission
  - Many vaccine candidates less immunogenic in infants
  - Incidence

- Prevention of infection
  - Faster (therefore cheaper) trial as many more endpoints

  BUT
  - Will a vaccine that prevents disease necessarily prevent infection?

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

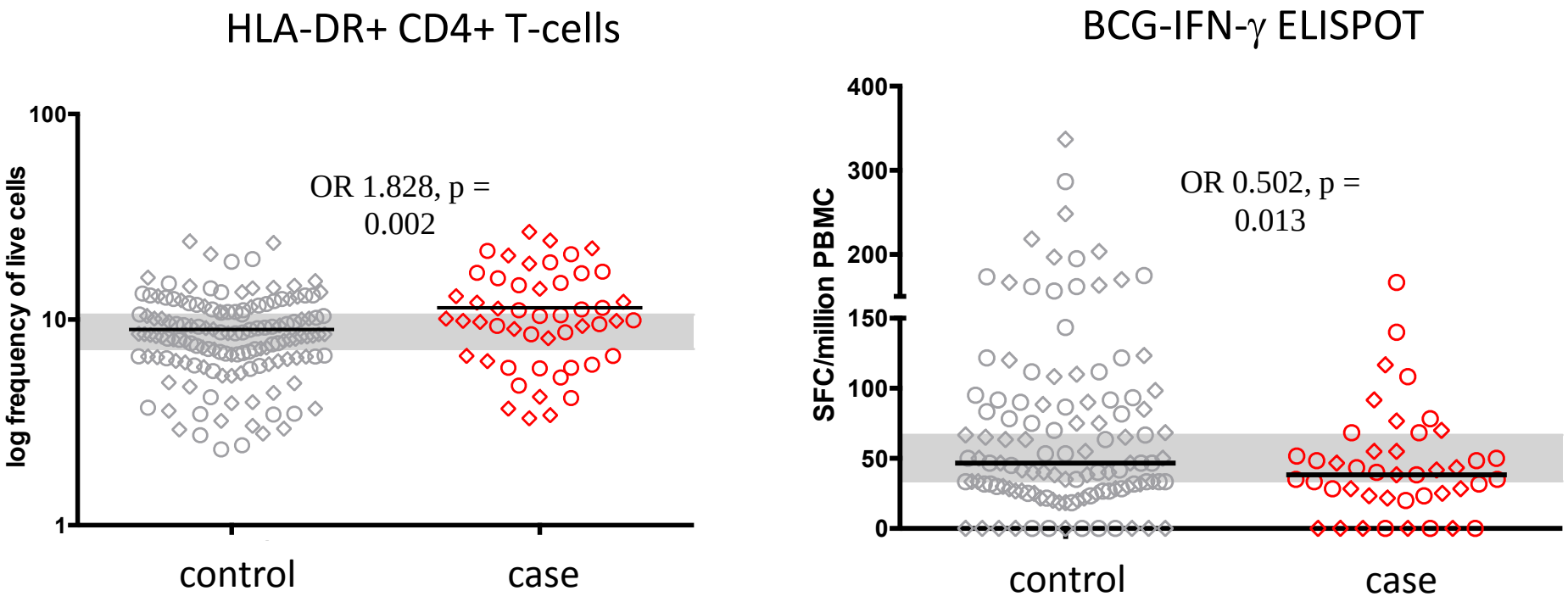
Michele D Tameris, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team*



Assays for immune correlates of risk analysis

- Transcriptional analysis
  - Illumina HT12 arrays
- Functional Assays
  - Mycobacterial growth inhibition assays
- Immune Assays
  - IFN-γ ELISPOT assays (UNS, PHA, BCG, 85A)
  - Antibodies on serum samples
  - Luminex on supernatants from above assays*
- Cellular phenotyping
  - Cell surface flow cytometry for lymphoid and myeloid cells
  - Markers of activation, exhaustion, T cell regulation*
- *Secondary assays performed on stored supernatant, RNA, frozen/fixed cells

T-cell activation and BCG IFNγ ELISPOT are immune correlates in BCG-vaccinated infants



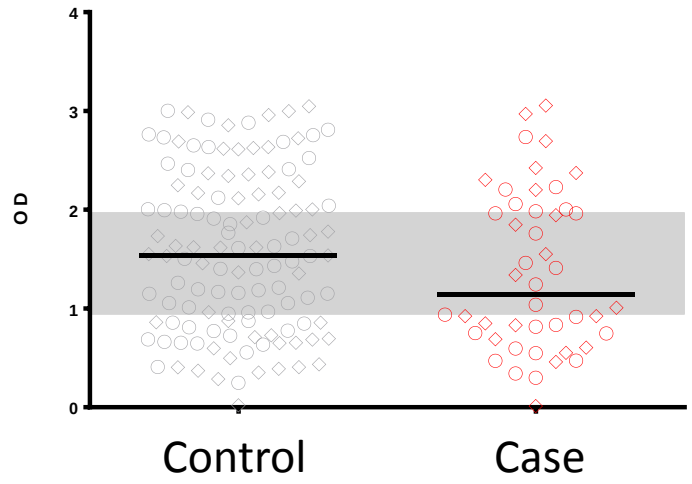
Result significant if Conditional Logistic Regression P<0.05 and FDR<2
Shaded bar indicates medium third of immune response level

Measured in healthy infants up to 3 years before disease develops

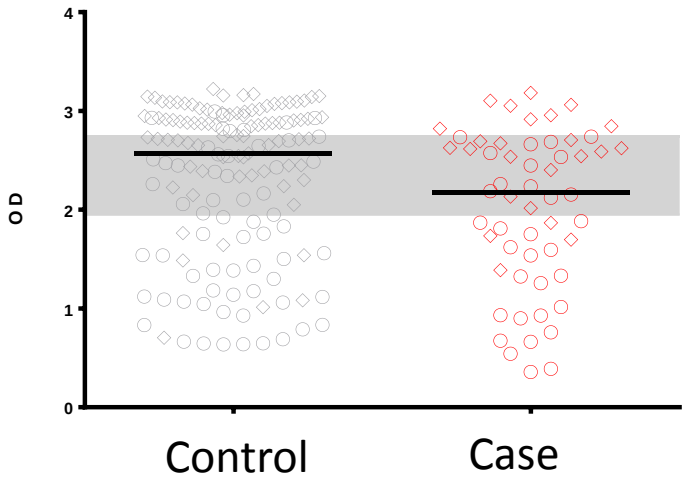
Fletcher HA *et al* Nature Communications, 2016

Antibodies correlate with reduced risk of TB disease

Ag85A IgG Day 0



Ag85A IgG Day 28

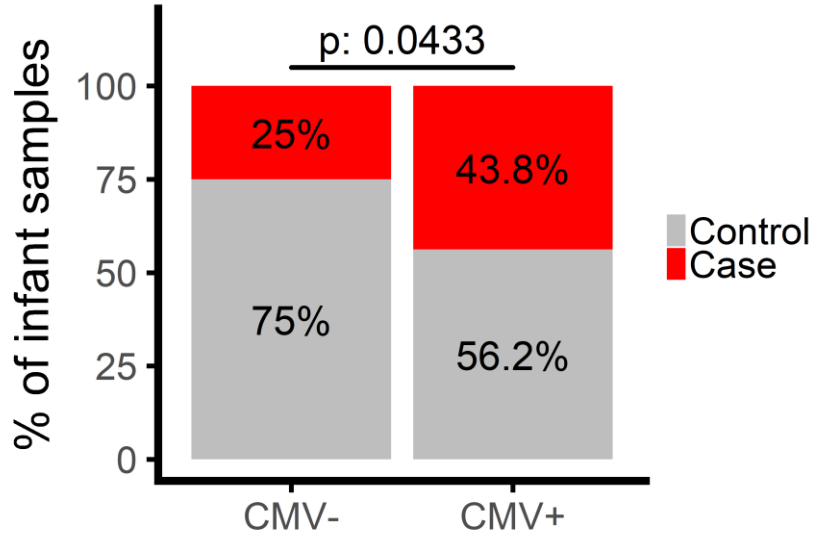


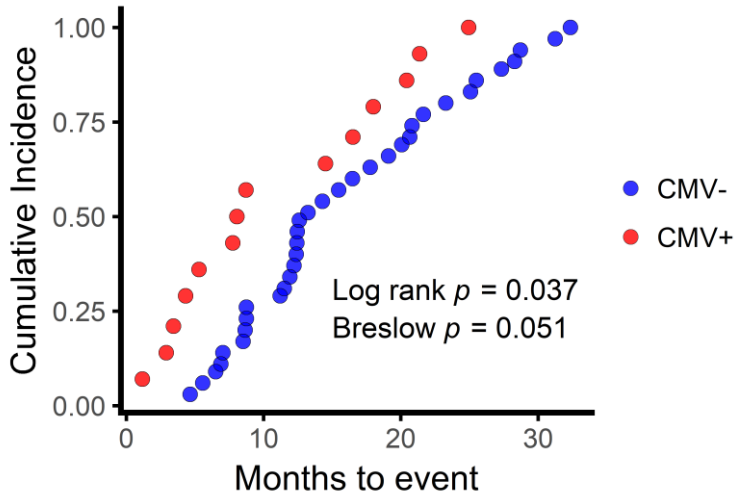
estimated odds ratio
0.62, p = 0.019

Are they directly involved in protection or correlating with another immune parameter?

Fletcher HA *et al* Nature Communications, 2016

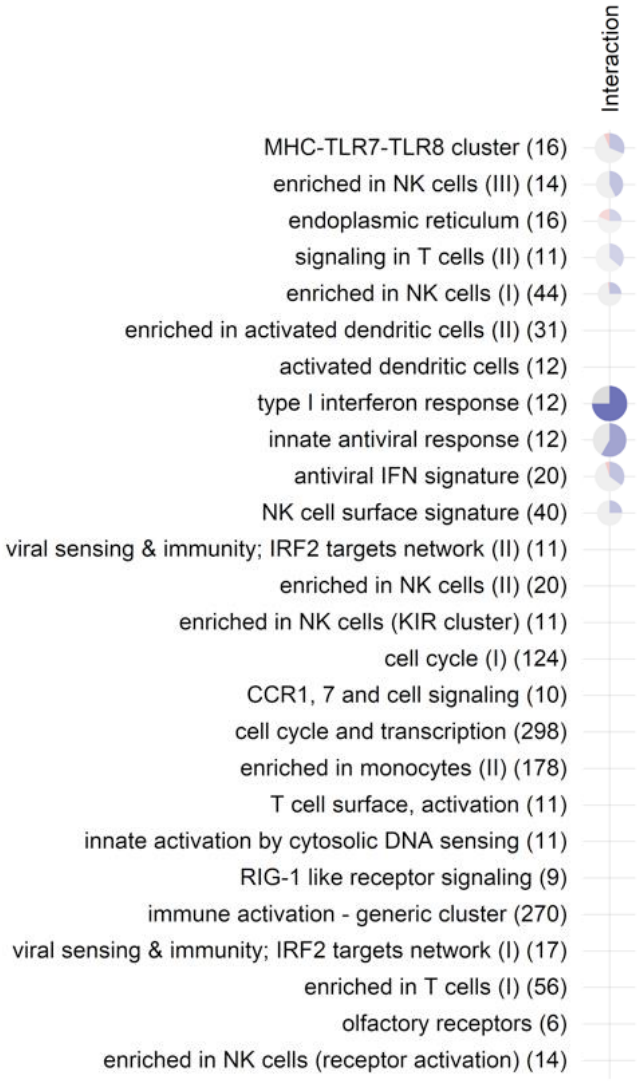
CMV is associated with risk of developing TB disease

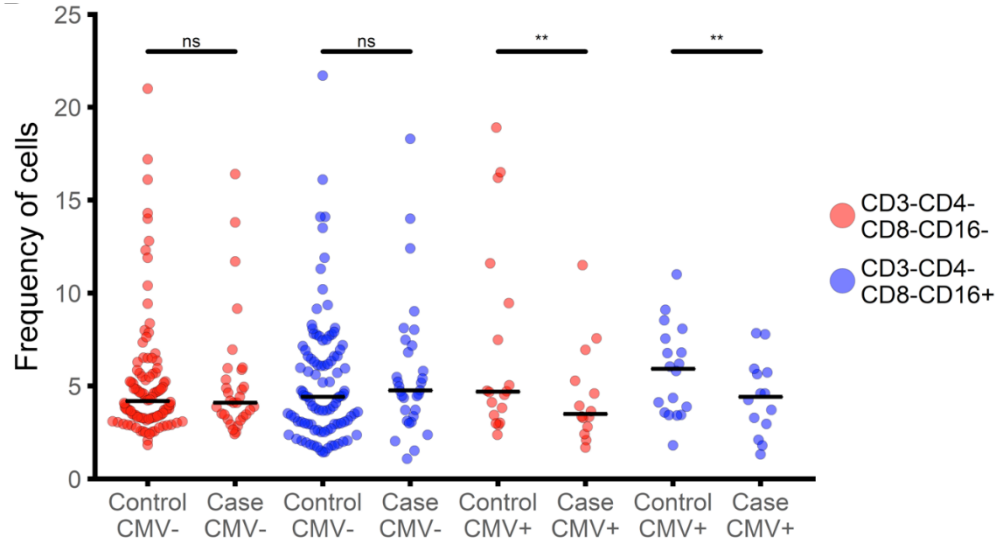




Muller J et al Submitted

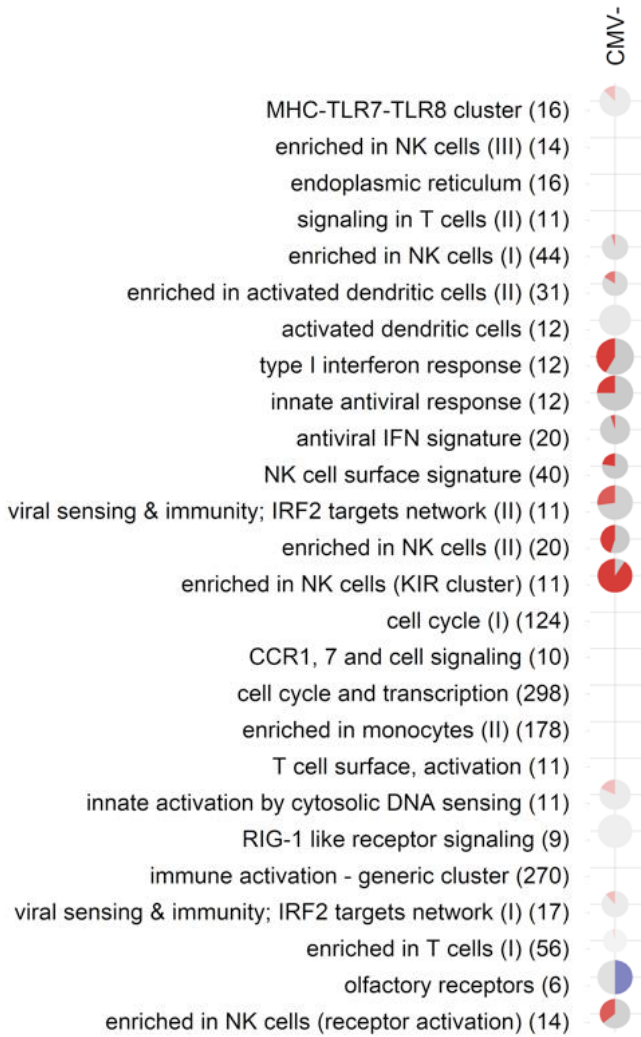
Lower NK & IFN responses among CMV+ infants who develop TB disease



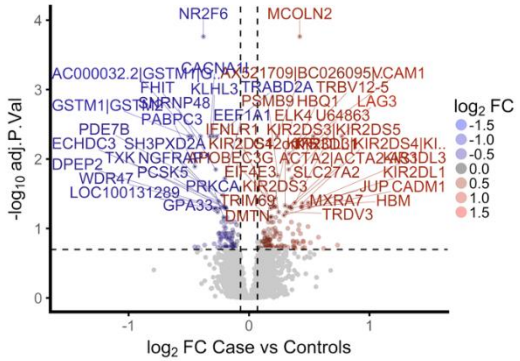


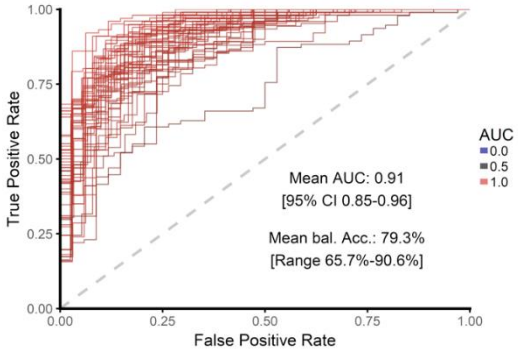
Muller J et al Submitted

CMV negative case infants look different



Type I/II IFN and immune activation strongly upregulated in CMV- case infants



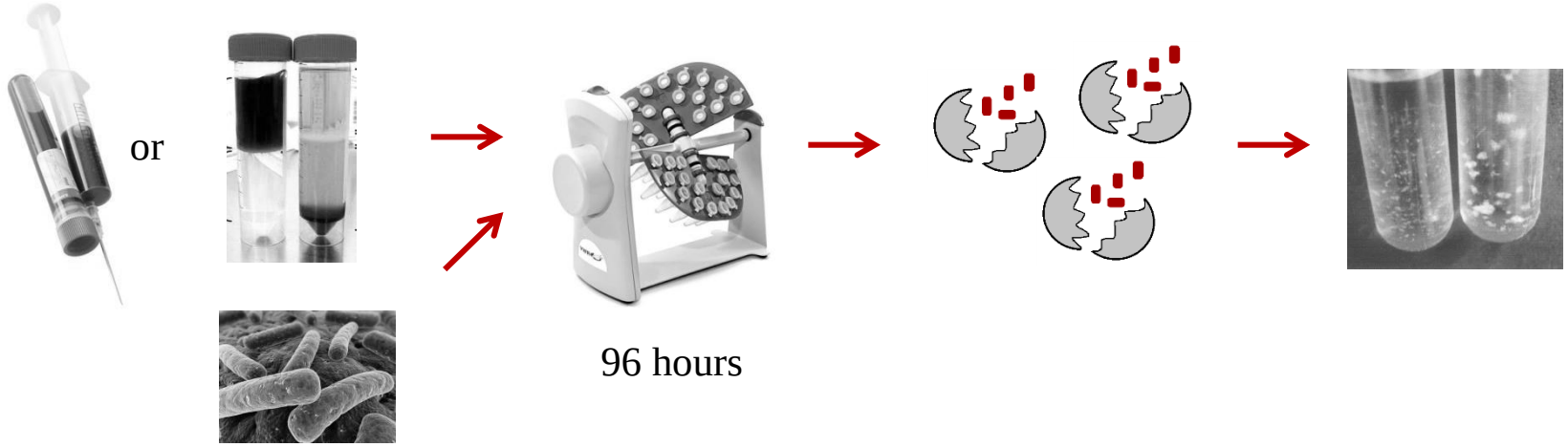


Muller et al Submitted

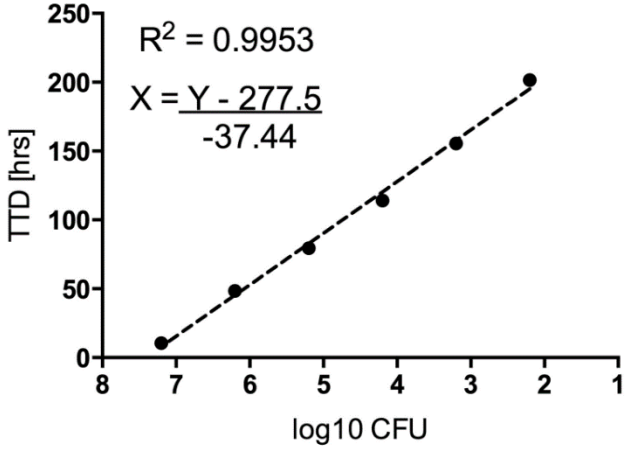
CHALLENGES

In-vitro and *in vivo* models for vaccine selection

Principles of the MGIT Assay



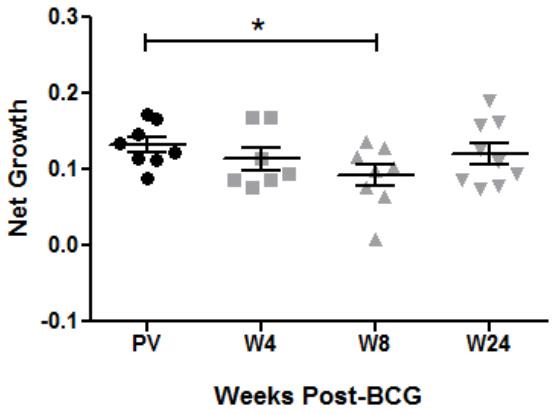
- 37°C + convection currents
- Oxygen-quenched fluorochrome -> UV light
- Intensity of fluorescence ∝ mycobacterial growth
- Read-out = time taken to detection (TTD) in hours
  (converted to Net Growth using std curve and ctrl)

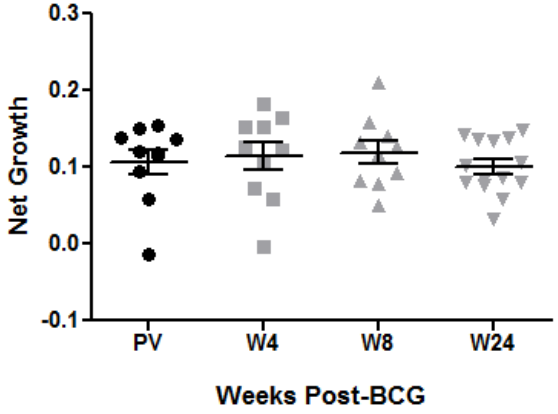


MGIA detects BCG vaccine effect in UK adults

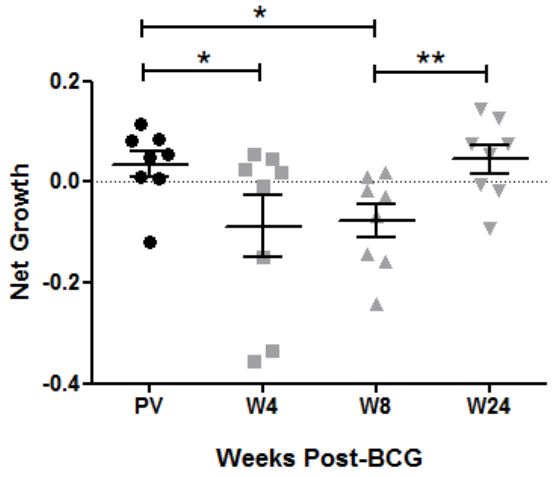
Primary Vaccination | **Revaccination**

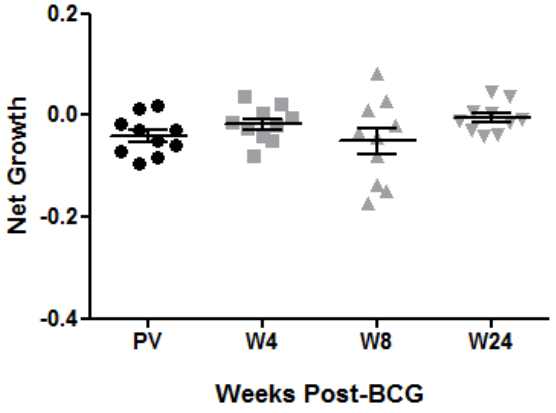
Whole Blood MGIT





PBMC MGIT



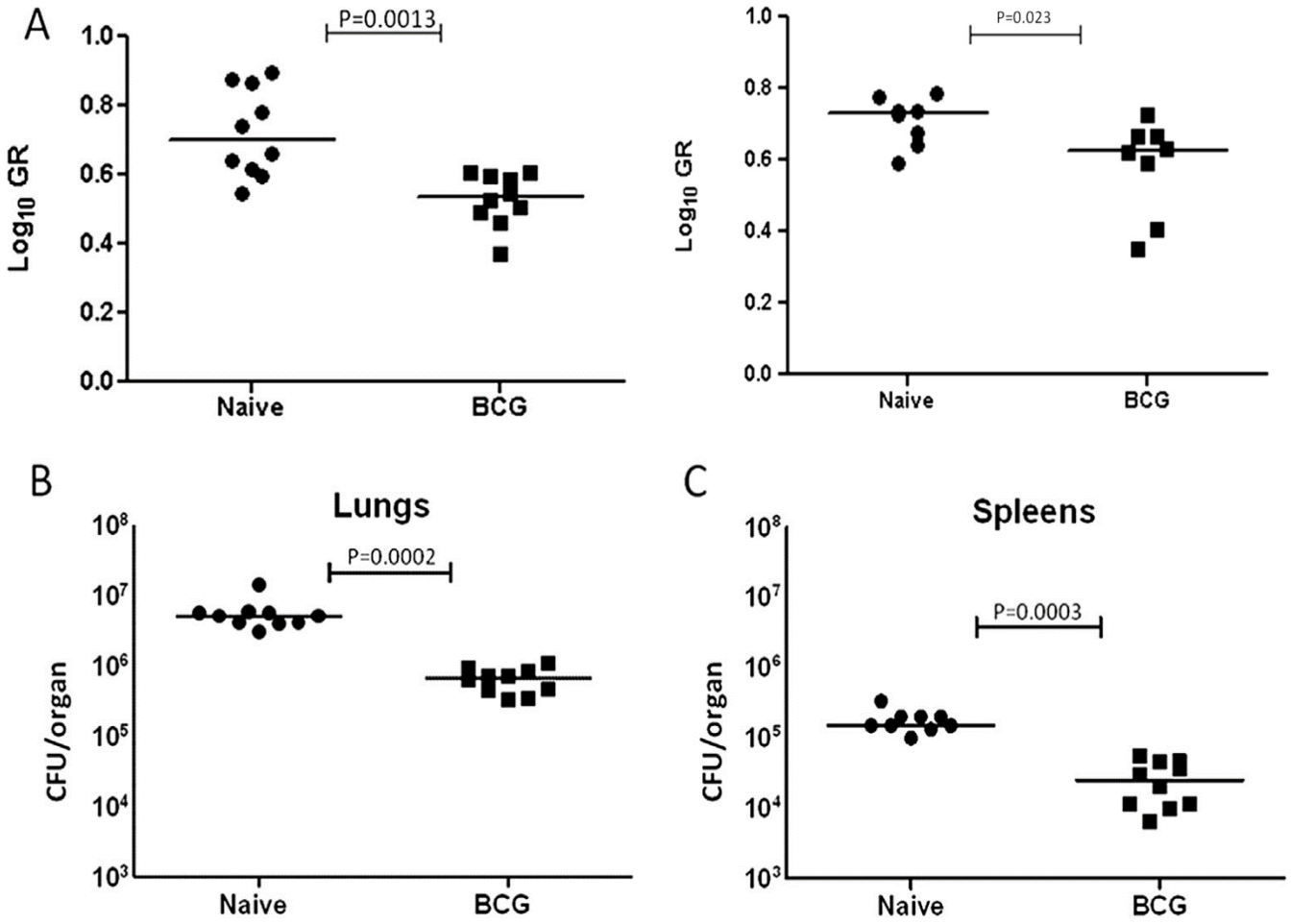


Fletcher H et al. CVI 2013

MGIA detects BCG vaccine effect in mouse splenocytes

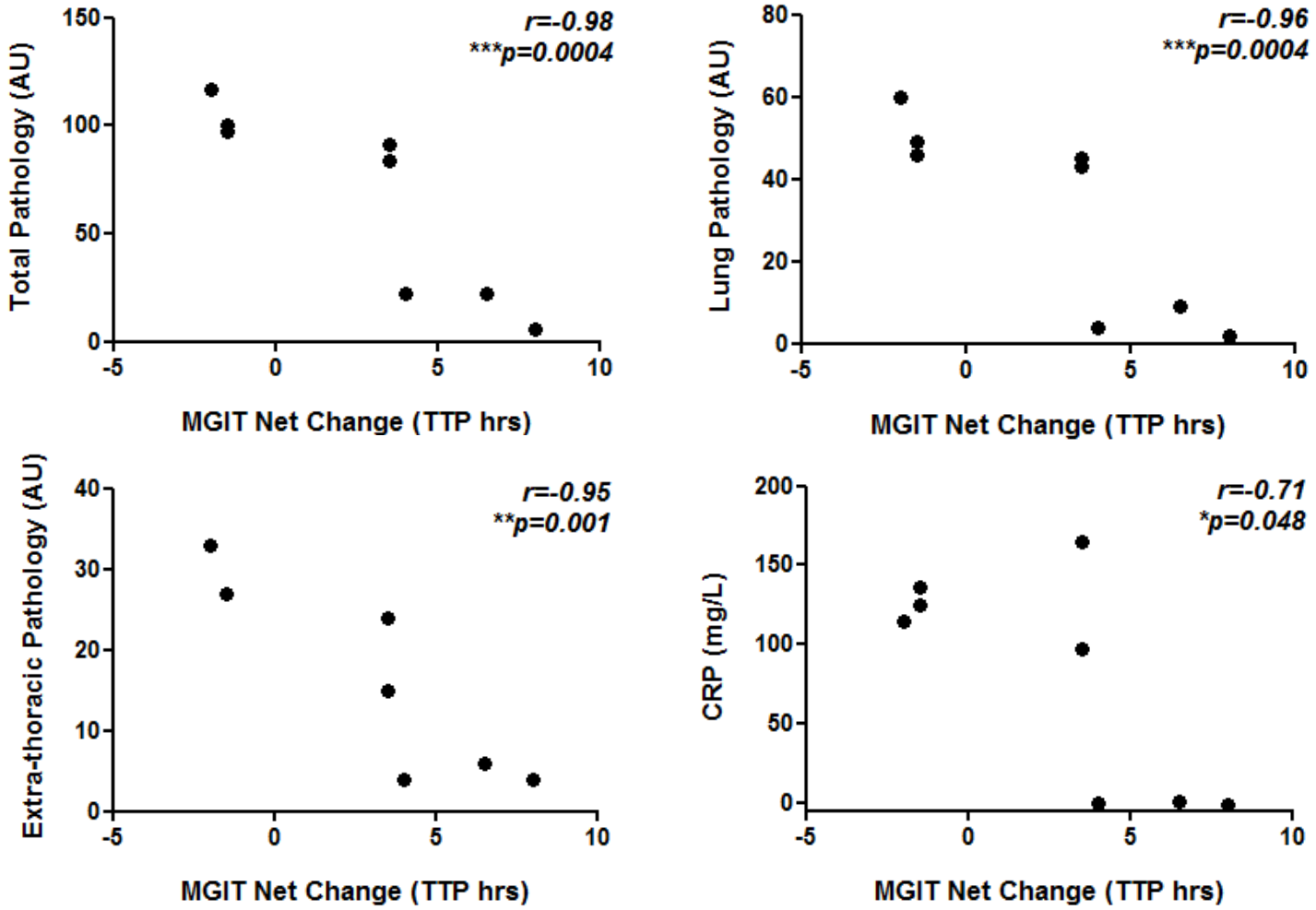
***In vitro* MGIT**

***In vivo M.tb* Challenge**



Marsay et al, Tuberculosis 2013

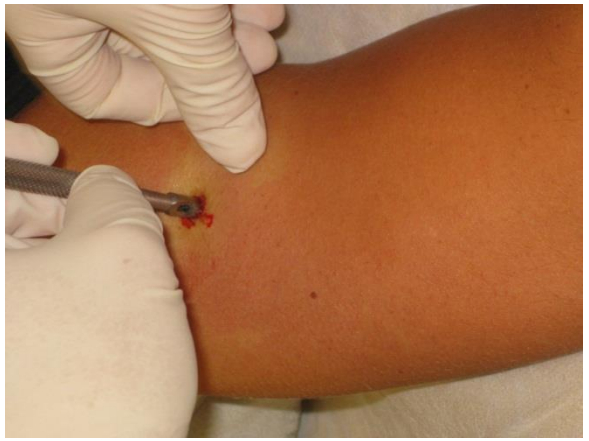
MGIA correlates with protection from *M.tb* challenge



Tanner R et al, unpublished

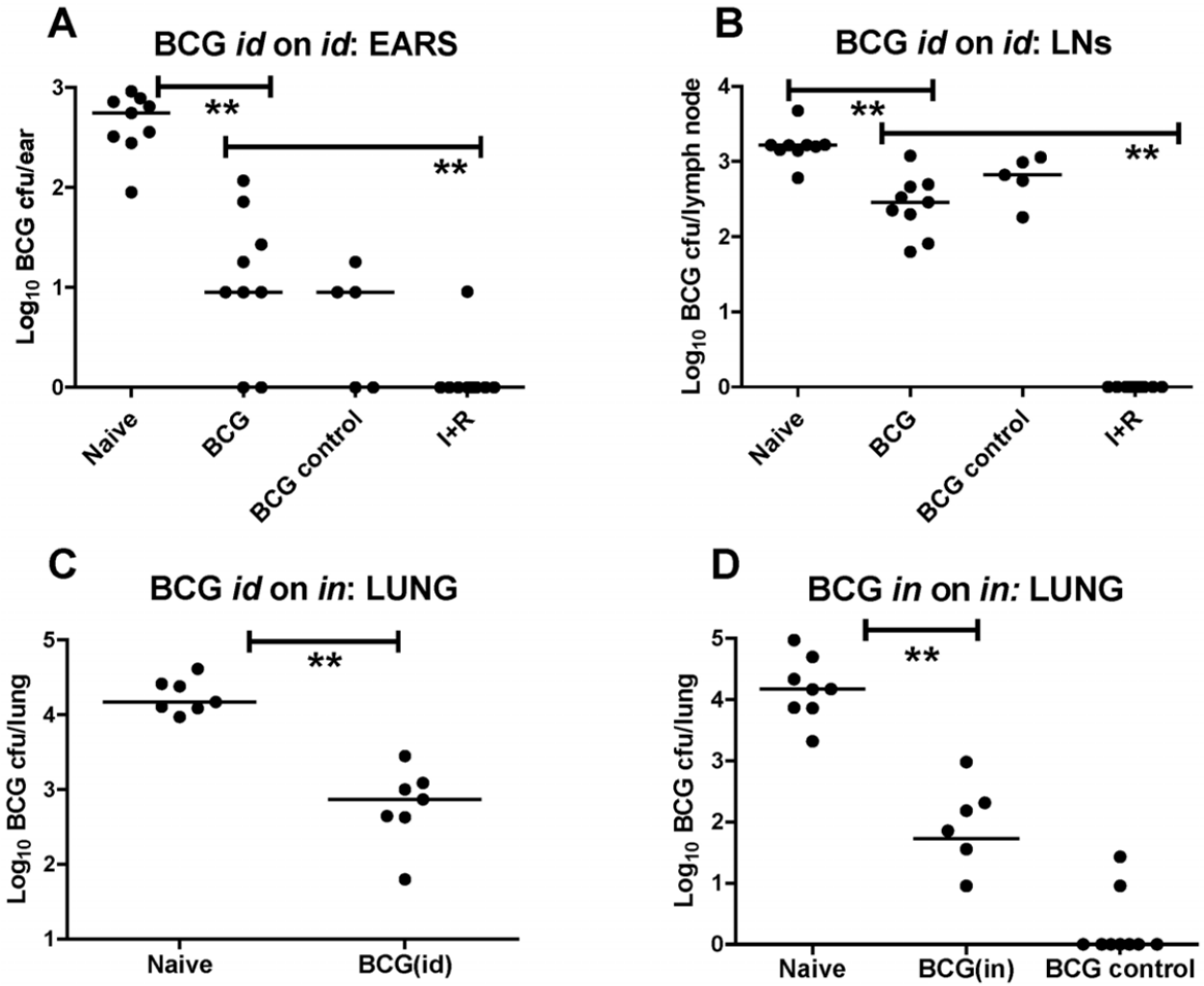
A human intradermal BCG challenge model

- An effective vaccine against BCG should also protect against *M. tuberculosis*
- Does intradermal BCG ‘challenge’ provide a good model for aerosol *M. tuberculosis* challenge?



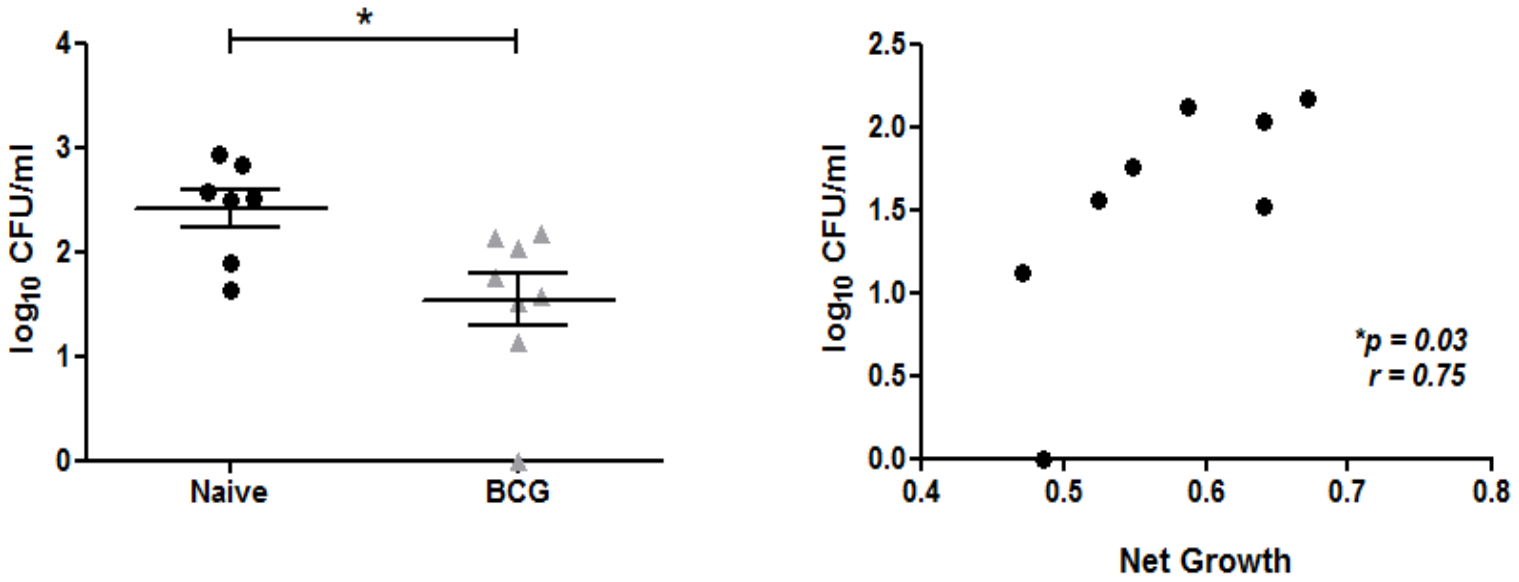
BIOLOGICAL VALIDATION IS CRITICAL ISSUE IN CHIM DEVELOPMENT

BCG vaccination protects against intradermal and intranasal BCG challenge in mice



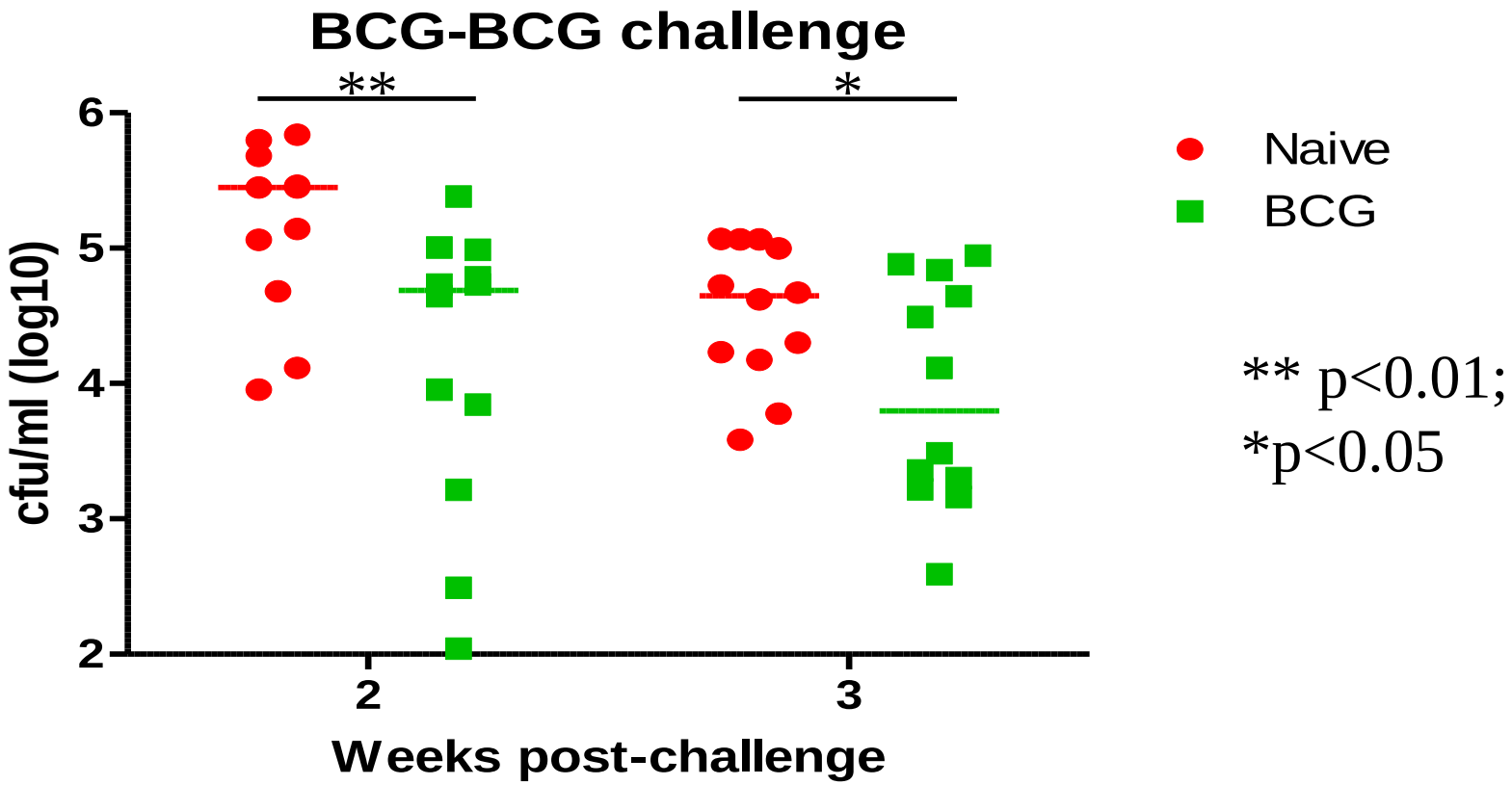
Minassian et al,
PLoS One 2011

BCG vaccination protects against intradermal BCG challenge in NHPs



Harris S et al, Tuberculosis 2017

BCG vaccination protects against intranodal BCG challenge in cattle

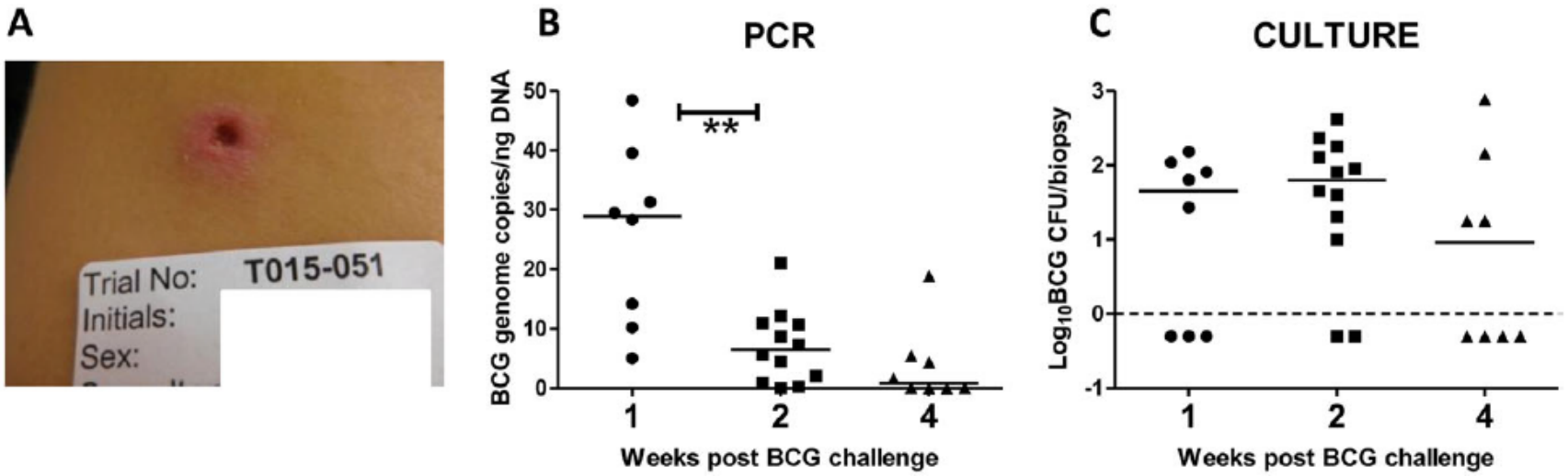


Animal Health & Veterinary Laboratories Agency

Villarreal-Ramos et al, Vaccine 2014

Pilot BCG challenge study

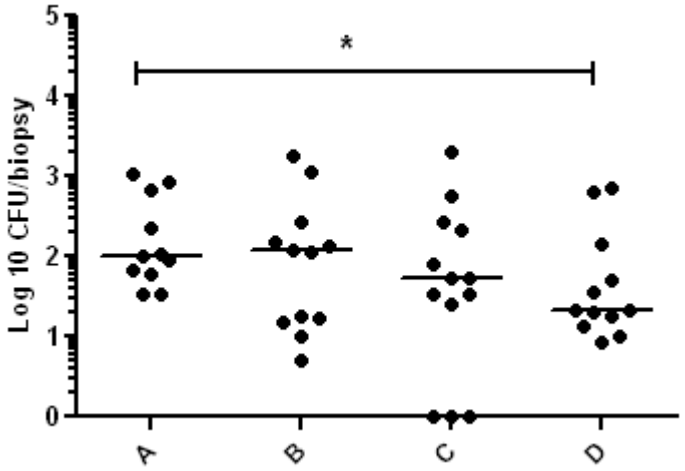
- BCG (SSI), 2-8 x 10^5cfu/ 100ul
- Route i.d
- Sampling: 4mm punch biopsy
- Biopsy at 1, 2, or 4 weeks post BCG



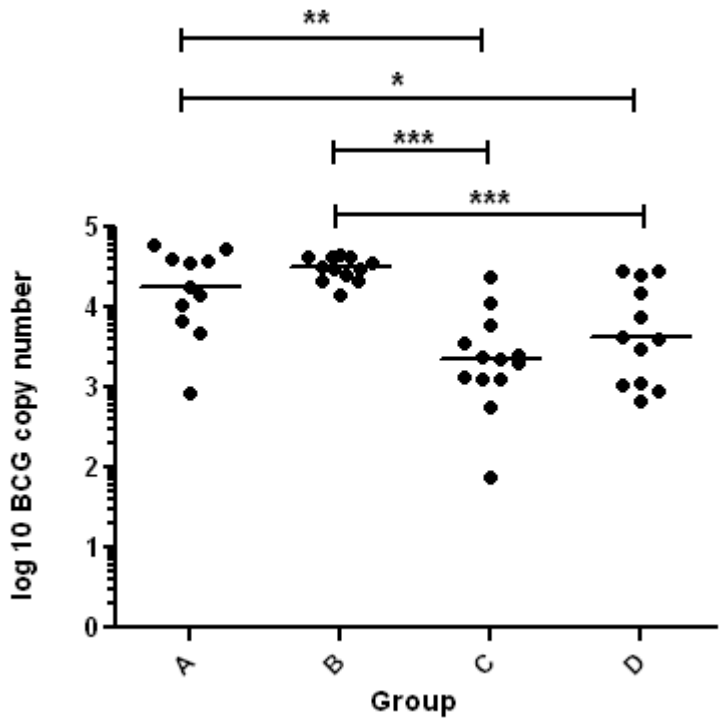
Minassian A et al, JID 2012

Prior BCG vaccination protects against intradermal BCG challenge in humans

Culture



PCR



A = naïve
B = MVA85A
C = BCG
D = BCG-MVA85A

*	$p < 0.05$
**	$p < 0.01$
***	$p < 0.001$

Harris S et al, JID 2013

A human aerosol BCG challenge model

Key issues:

- Safety and tolerability
- Is BCG recoverable from the BALF?
- Th1 immunogenicity in the blood and BALF post aerosol v ID immunisation
- Exploratory immunology
  - MAITs
  - B cells
  - Antibodies

Aerosol BCG

Arm 1 BCG SSI

- 3 subjects @ 10^3cfu
- 3 subjects @ 10^4cfu
- 4 subjects @ 10^5cfu
- 3 subjects @ 10^5cfu ID

No more BCG SSI

Arm 2 BCG Bulgaria

- 3 subjects @ 10^4cfu
- 3 subjects @ 10^5cfu
- 3 subjects @ 10^6cfu

Well tolerated

- 3 subjects @ 10^7cfu

BCG detection in BALF

Need MGIT + (viable) and PCR + (BCG specific)

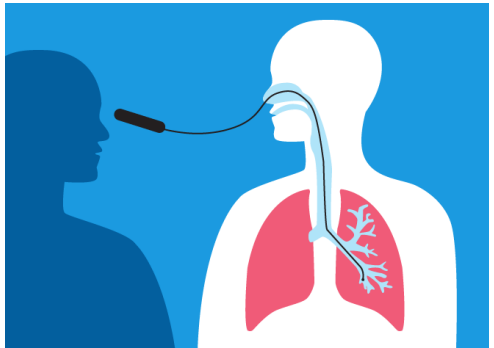
- 10^4 cfu
  - 1/3 -
  - 2/3 contaminated
- 10^5 cfu
  - 3/3 + on MGIT; PCR awaited
- 10^6 cfu
  - 3/3+ on MGIT; PCR awaited

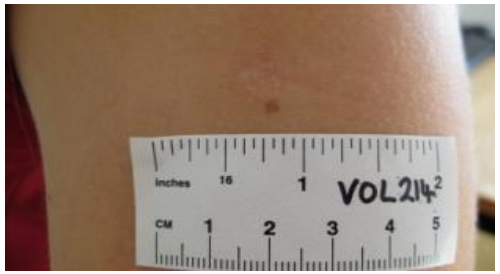
Animal models
- Toxicity
- Mechanisms
- Efficacy

Human safety & immunogenicity

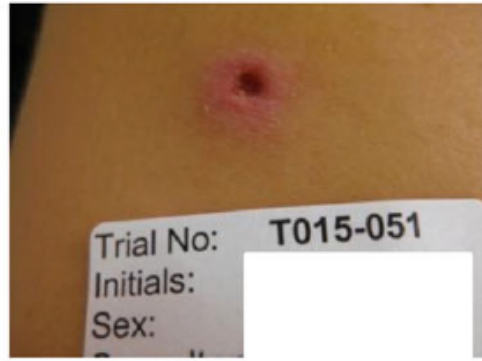
Human challenge model

Human field efficacy





A

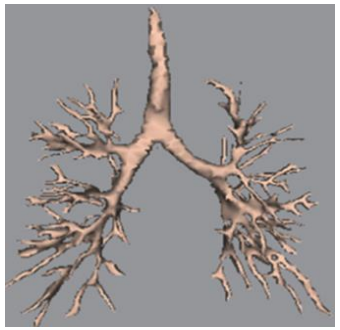


AEROSOL VACCINATION

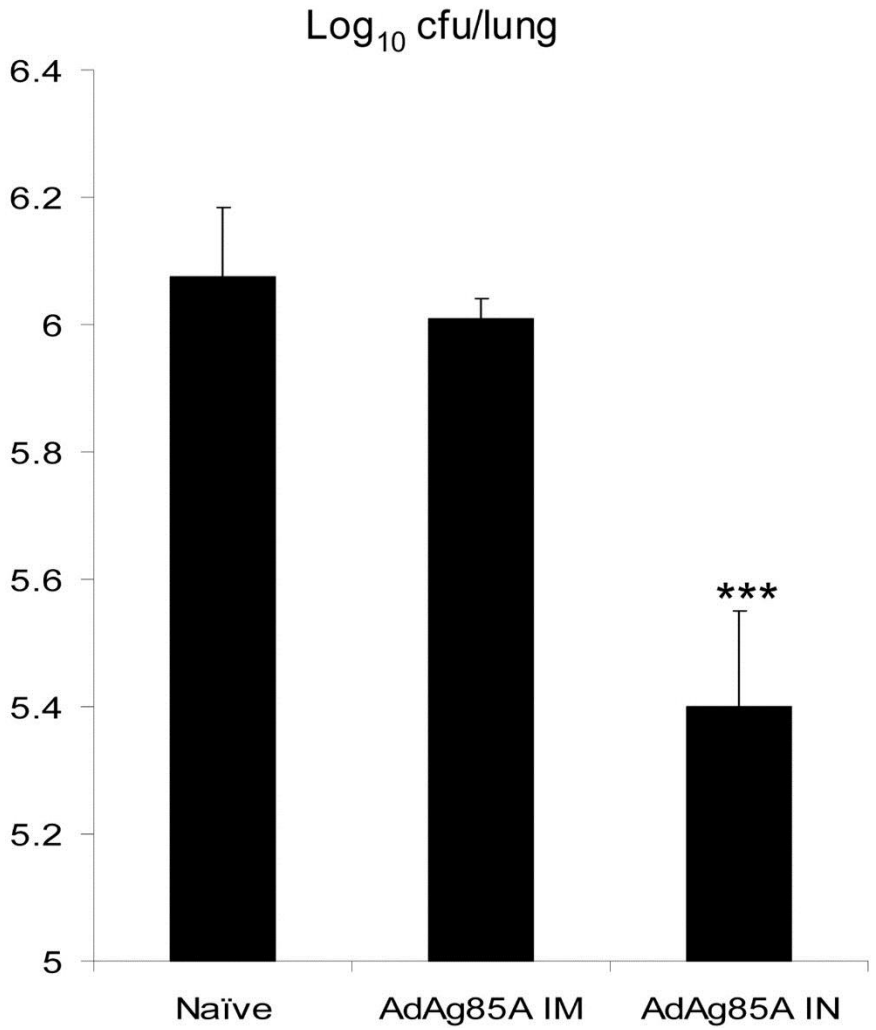
A more effective route of vaccination?

An inhaled TB vaccine

- Route of immunisation = route of infection
- BCG does not reliably protect against pulmonary TB
- Mucosal immunisation can generate potent durable immune responses
- Inhalation is a common route of drug delivery
- Feasible
- Needle and pain free
- Murine data to support this route of immunisation
- Not a new idea!



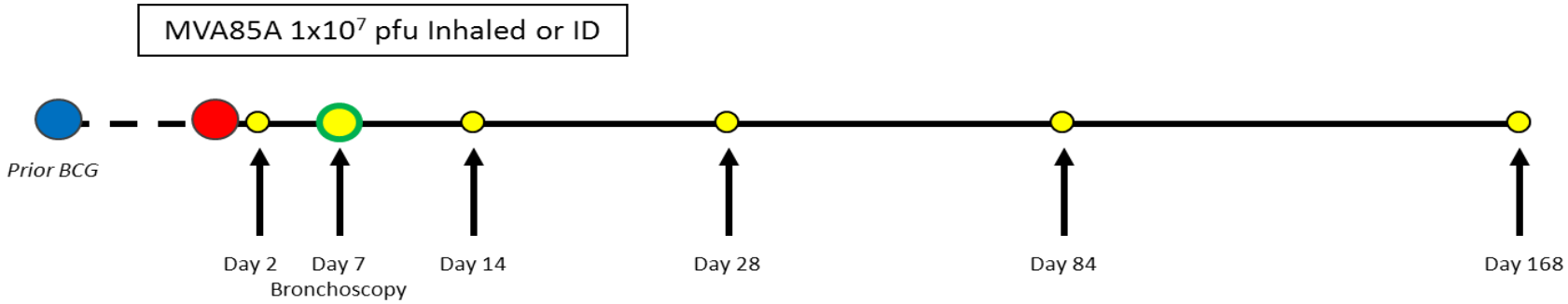
Protection by respiratory mucosal, but not parenteral, vaccination with AdAg85A



Michael Santosuosso et al. J Immunol 2005

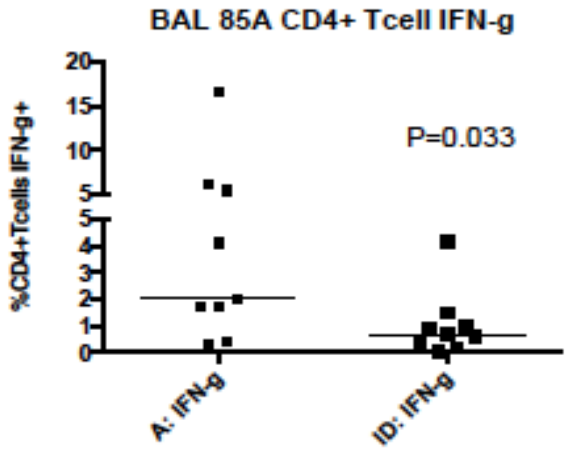
Assessing the inhaled route in a human clinical trial

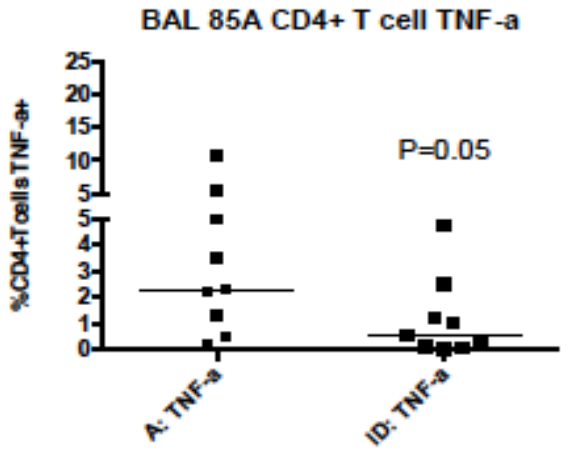
- Phase I trial
  - 22 BCG vaccinated adults randomised to 1 x 10^7 pfu MVA85A **inhaled or ID**
  - Randomised single blinded paired placebo design
  - Bronchoscopy day 7 BAL

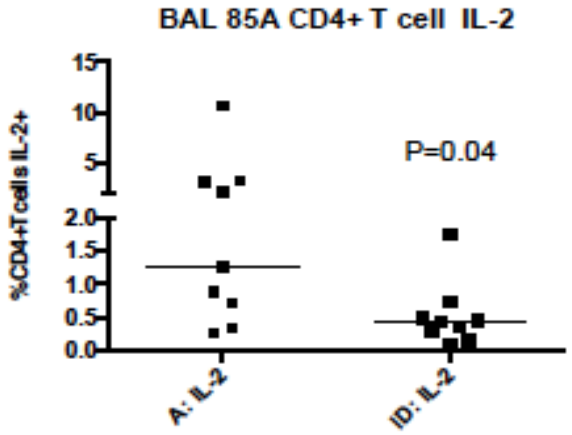


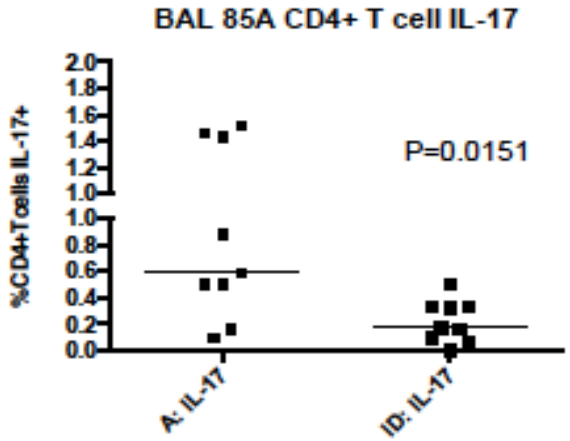
- Primary and secondary outcome
  - Safety: local & systemic AEs, S_aO_2, spirometry, bronchoscopy
  - Systemic and mucosal cellular immunogenicity: blood and BAL

BAL Ag85A specific CD4+ T cell responses stronger after aerosol than i.d administration





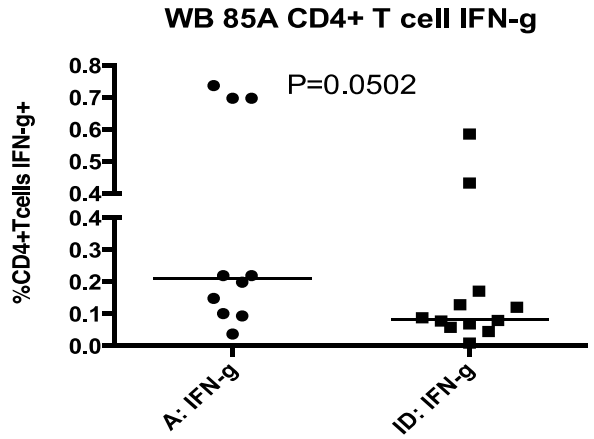


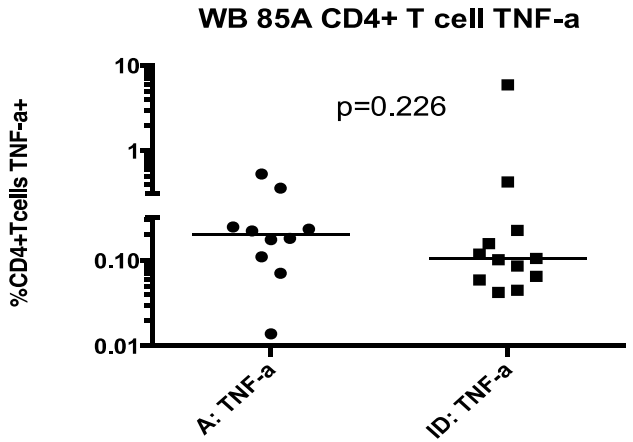


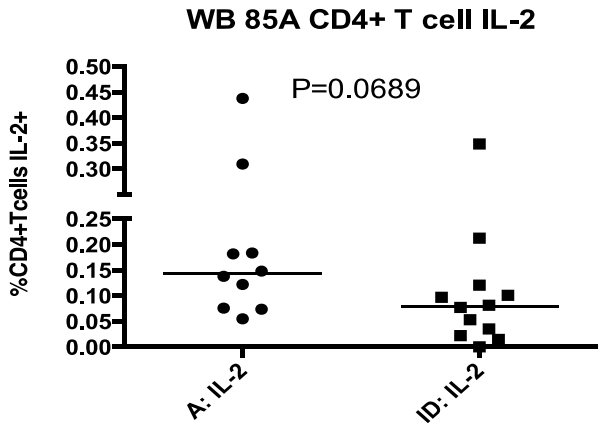
A: Aerosol
ID: Intradermal

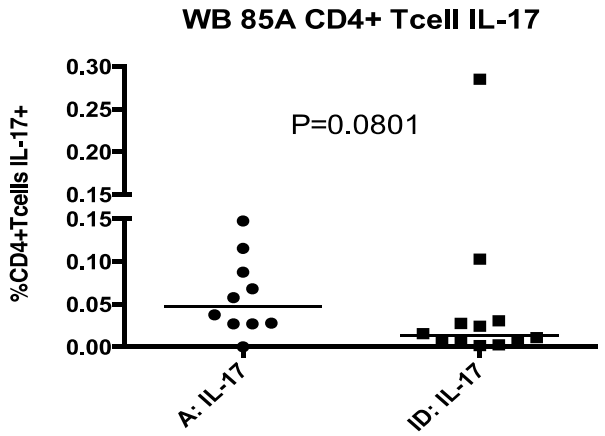
Satti I et al, Lancet Infect Dis 2014

Whole blood Ag85A CD4+ T cell responses at least as strong after aerosol than i.d administration









A: Aerosol
ID: Intradermal

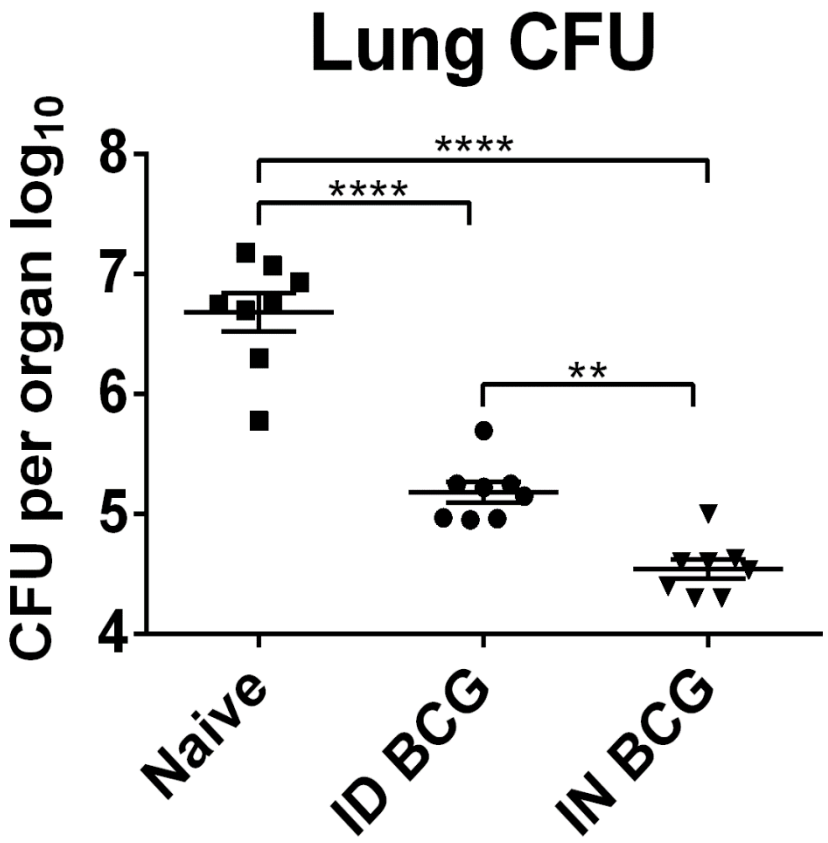
Satti I et al, Lancet Infect Dis 2014

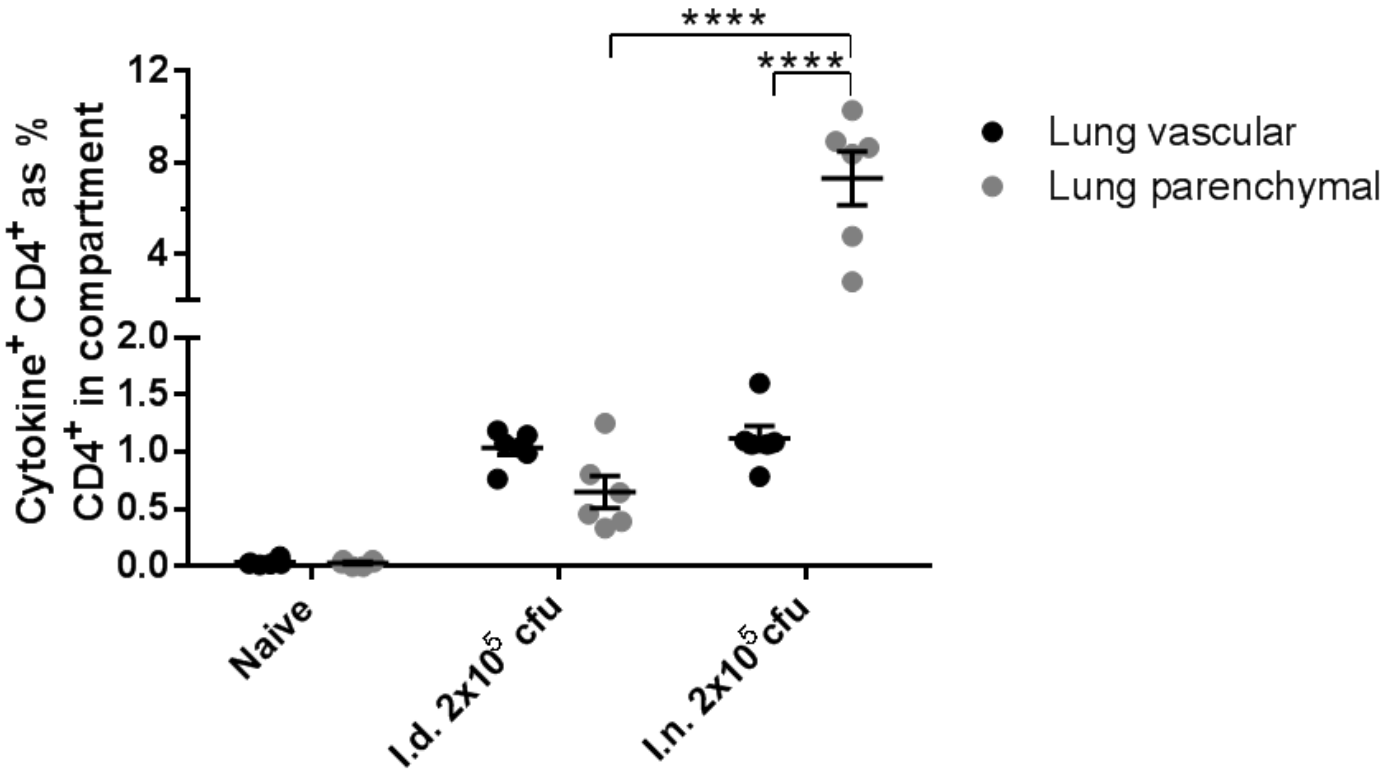
Aerosol BCG delivery

1. A more effective route of vaccination

2. A human mycobacterial challenge model:
   - For vaccine evaluation
   - To determine early innate events in the airway

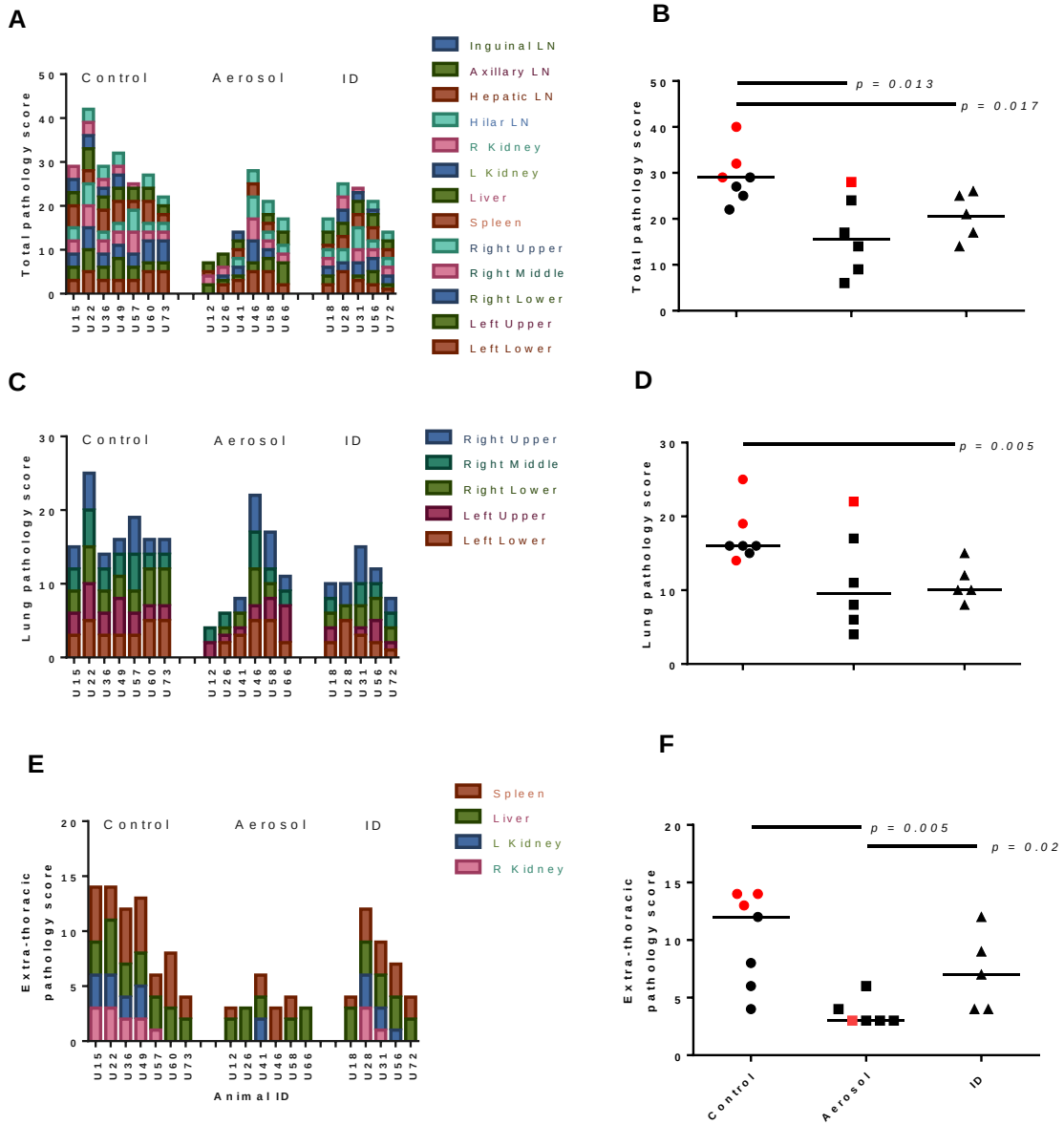
Protective efficacy of ID v IN BCG





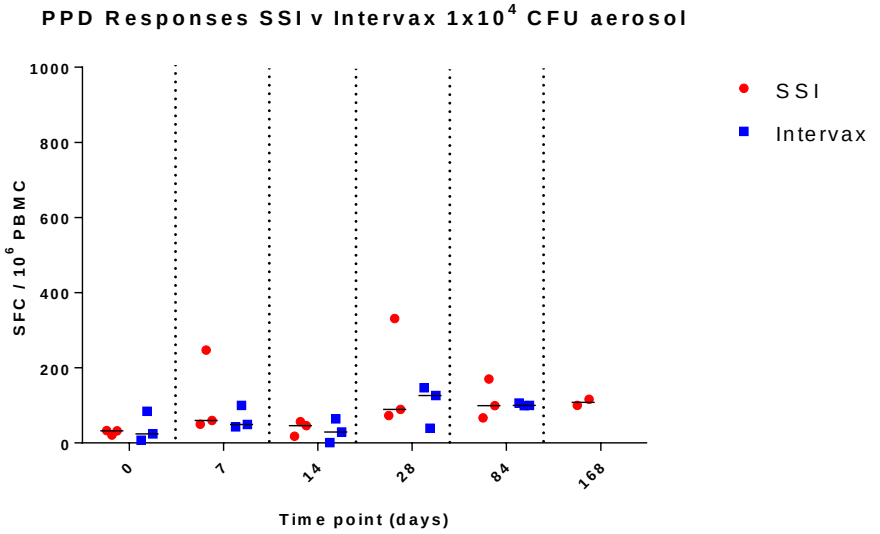
Naomi Bull, unpublished data

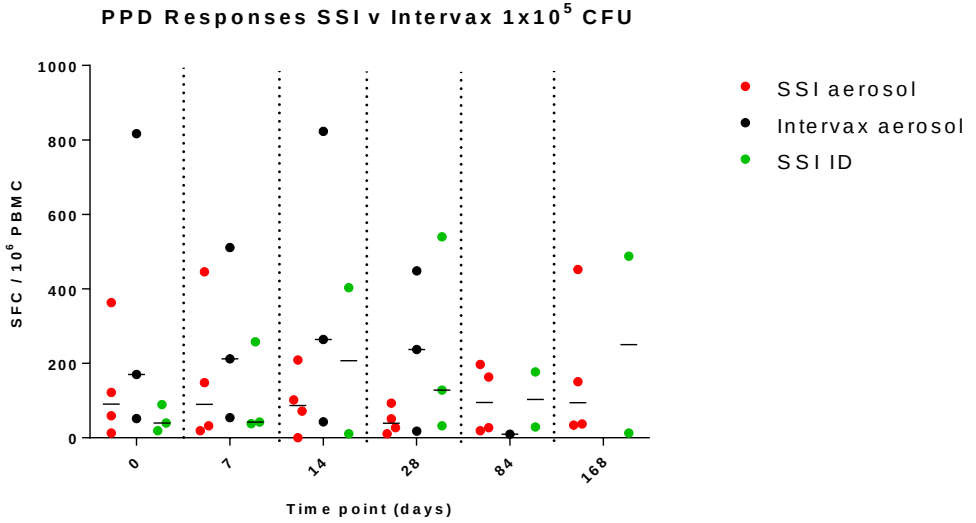
Aerosol BCG protects against extra-pulmonary dissemination

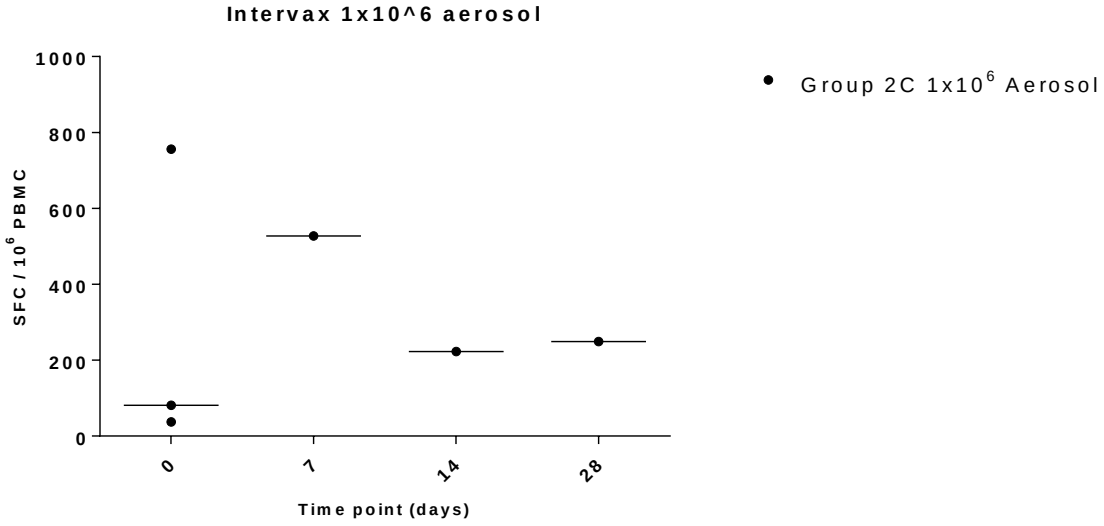


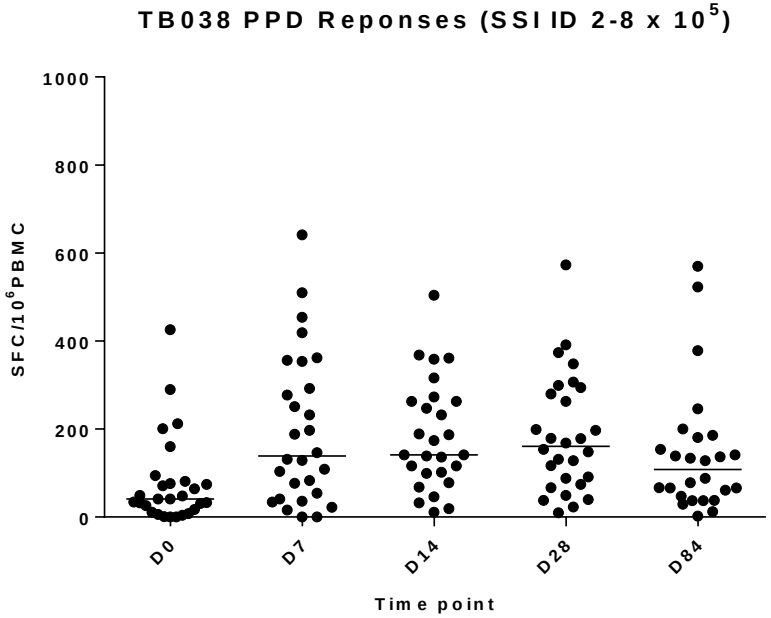
Sharpe et al, unpublished

Human ELISpot data

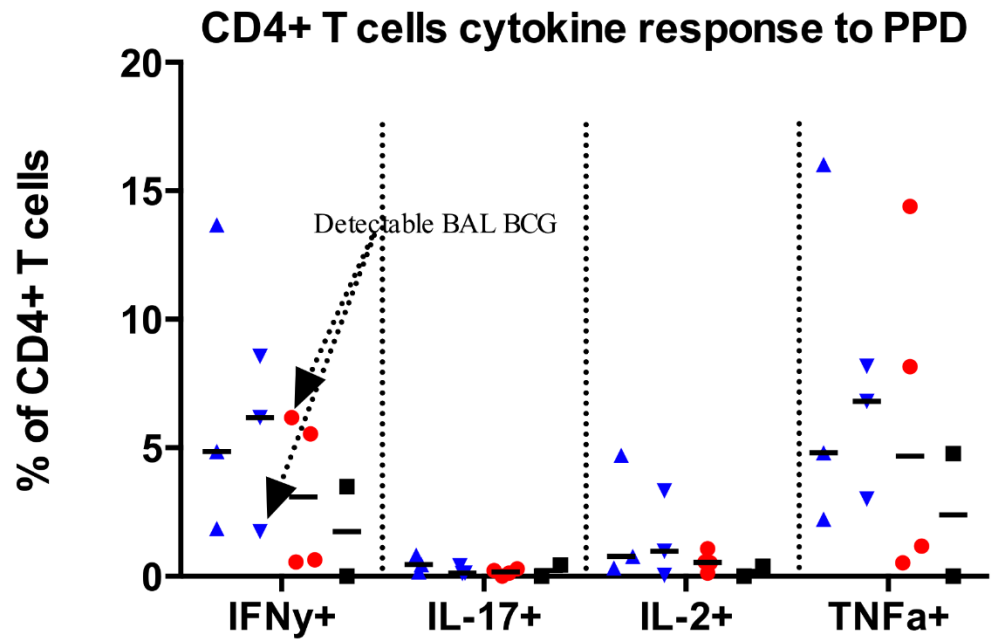


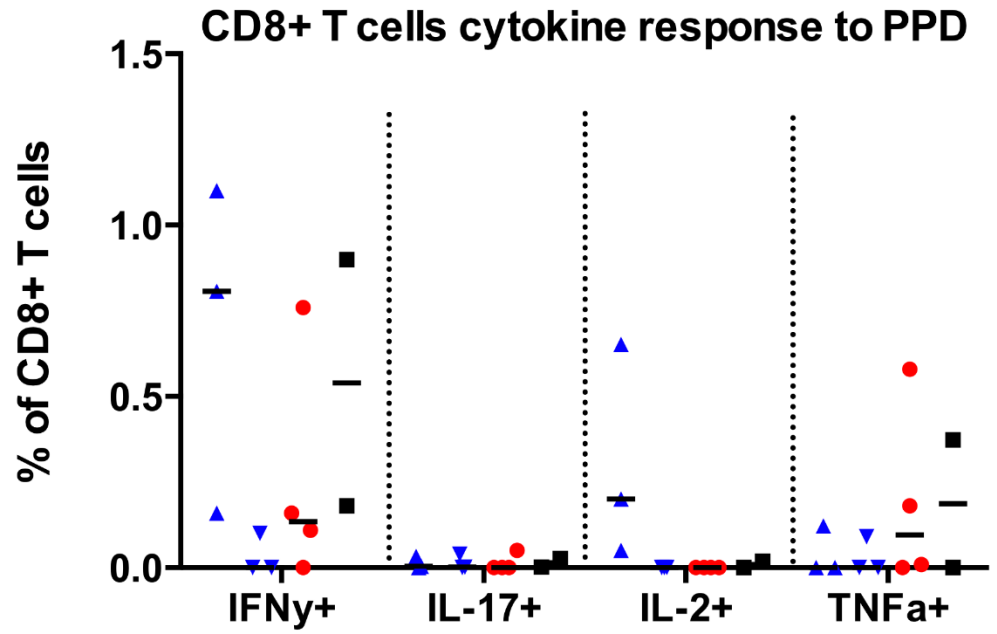






BAL ICS responses (SSI)





Summary

- We can learn a lot from well designed efficacy trials
  - Regardless of the efficacy outcome
- We need better tools for vaccine selection
  - *In vitro* MGIA
  - Controlled human challenge models
- Aerosol vaccination may be a more effective route of delivery
  - More data needed
  - Parallel human and NHP studies
- Validated animal models and immune correlates would be transformative
- There is currently no substitute for human efficacy testing

Acknowledgements

- **Oxford Centre for Respiratory Medicine**
  - Henry Bettinson
- **Jenner Transcriptomic Core Facility**
  - Julius Muller

Animal & Plant Health Agency

Martin Vordermeier
Bernardo Villarreal-Ramos

Public Health England

Sally Sharpe
Andrew White
Ann Williams

London School of Hygiene & Tropical Medicine

Helen Fletcher

Iman Satti
Rachel Tanner
Stephanie Harris
Lisa Stockdale
Matt O'Shea
Rachel Kandt
Magali Matsumiya
Zita Manjaly-Thomas
Sharon Sheehan
Jonny Peter
Ian Poulton
Mary Smith
Raquel Ramon-Lopez
Alison Lawrie
Alice Minhinnick
Paulo Bettencourt
Morven Wilkie
Sam Vermaak
Elena Stylianou
Ilaria Pepponi

Bill & Melinda Gates foundation

Lynda Stewart
Anne Kasmar
Willem Hanekom

wellcome trust

satvi South African Tuberculosis Vaccine Initiative

Tom Scriba
Michele Tameris
Willem Hanekom
Mark Hatherill & 020 Study team

AERAS

Peggy Snowden
Bruce McClain
Bernard Landry
Tom Evans

Study participants

CHUV, Lausanne
Francois Spertini
Regine Autran

VALIDATE

"**VA**ccine deve**L**opment for complex **I**ntracellular neglecte**D** p**AT**hog**E**ns"

VALIDATE is an international network of researchers working together to accelerate the development of vaccines for:

- **TB**
- **Leishmaniasis**
- **Melioidosis**
- **Leprosy**

VALIDATE provides pump-priming grants, training grants, workshops, a mentoring scheme, seminars, & a website featuring news & opportunities.

Becoming a member is free – for details on how to join visit our website.

Find out more at www.validate-network.org

@NetworkValidate

or email Samantha.Vermaak@ndm.ox.ac.uk

MRC Medical Research Council

GCRF Global Challenges Research Fund

BBSRC bioscience for the future