# Developing a human challenge model for TB

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# A TB controlled human infection model: Why, what for and how?

WHY:

- Uncertain predictive value of preclinical animal models
- Lack of validated immune correlate of protection
- Signal detection in the host species

WHAT FOR:

- Vaccine selection
- Immunobiology studies to inform basic science knowledge gaps

HOW:

- Not with virulent *Mycobacterium tuberculosis*!
- Can we develop safe, attenuated organisms with a kill switch?
- Can we use BCG as a model agent
  - At least to do clinical model development
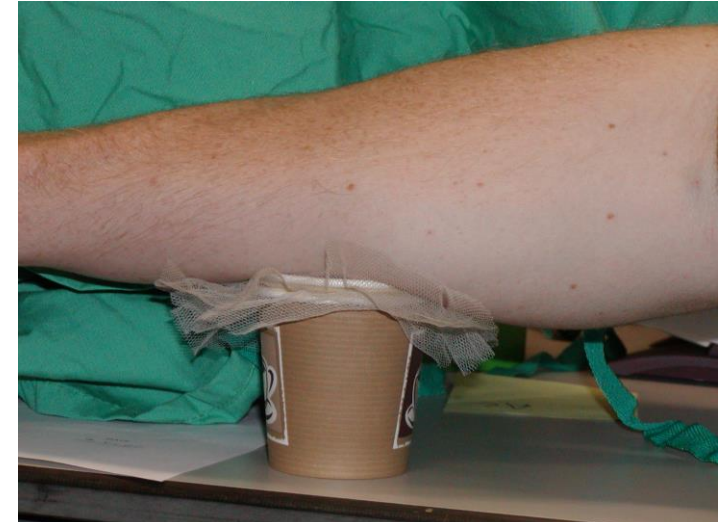
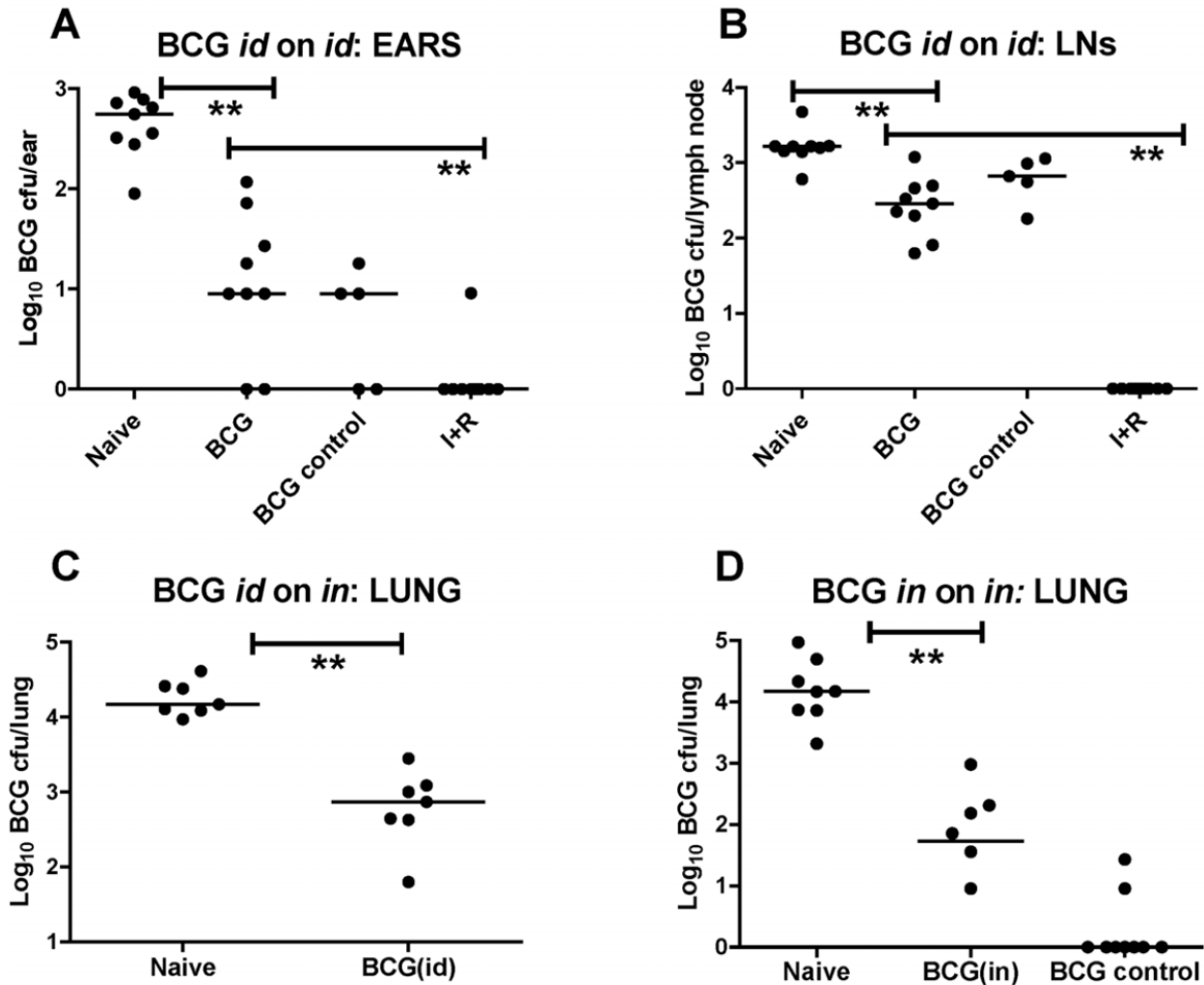# A human intradermal BCG challenge model



- An effective vaccine against BCG should also protect against *M. tuberculosis*

- Does intradermal BCG 'challenge' provide a good model for aerosol *M. tuberculosis* challenge?
  - Validation of a known vaccine effect in preclinical animal models

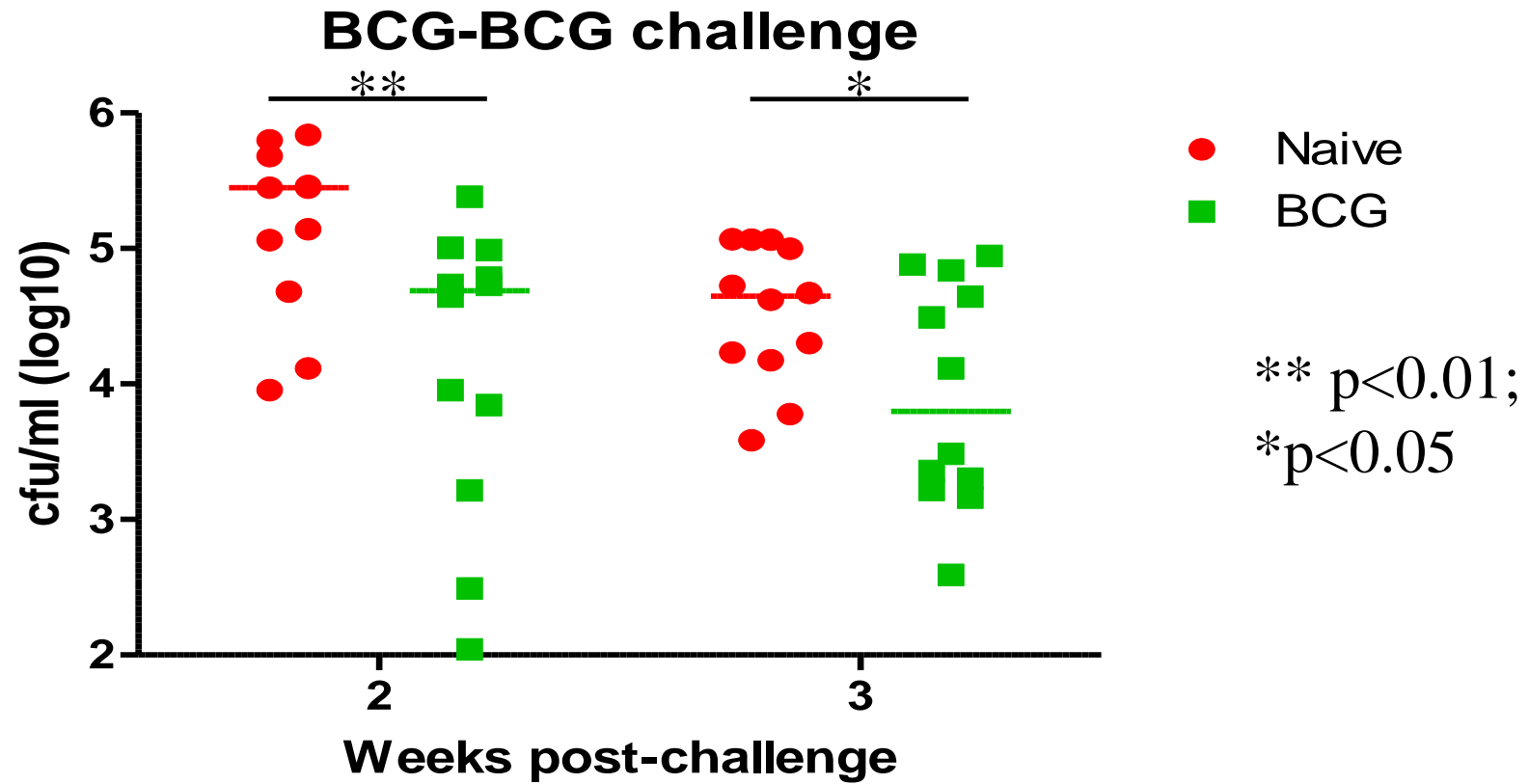BIOLOGICAL VALIDATION IS CRITICAL ISSUE IN CHIM DEVELOPMENT

# BCG vaccination protects against intradermal and intranasal BCG challenge in mice
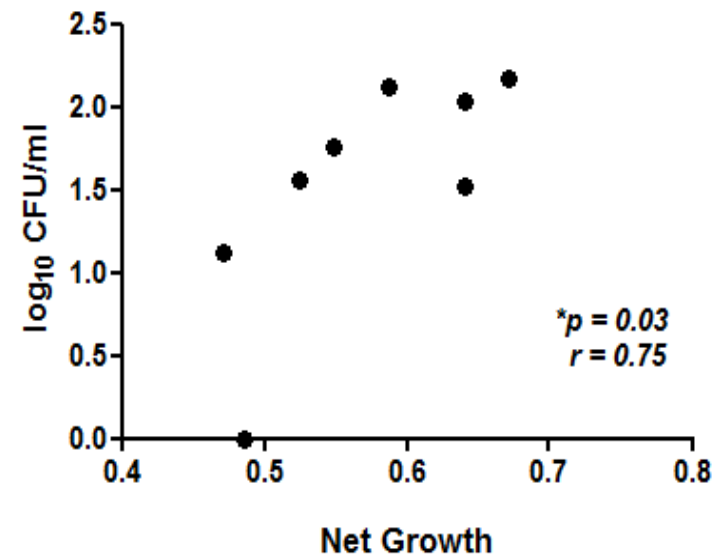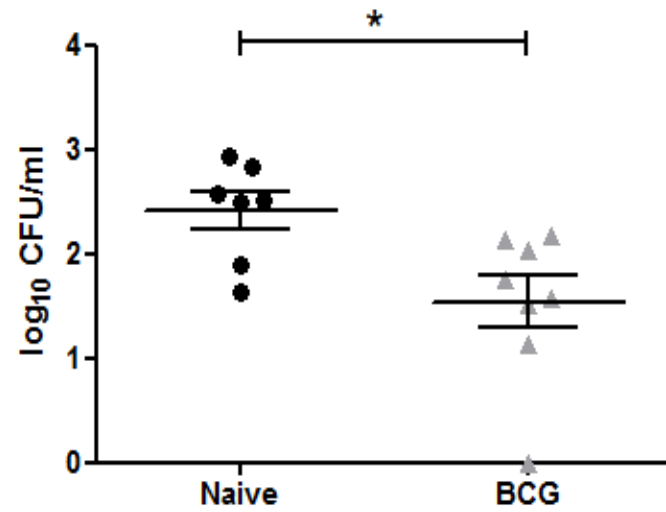


Minassian et al, PLoS One 2011

# BCG vaccination protects against intranodal BCG challenge in cattle



Villarreal-Ramos et al, Vaccine 2014

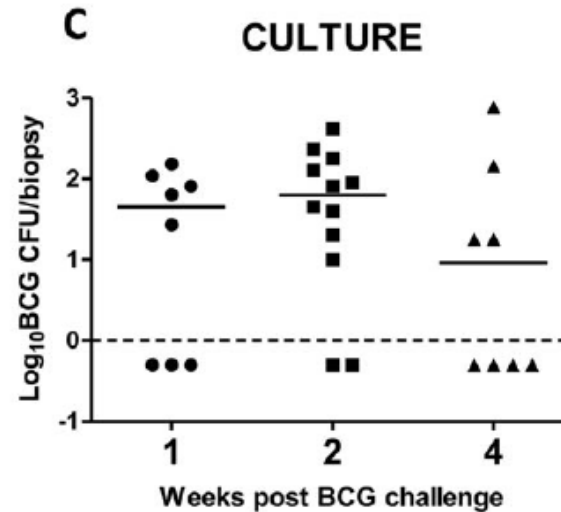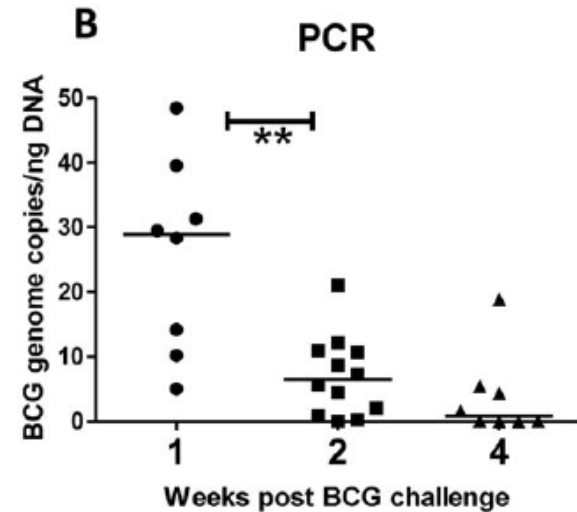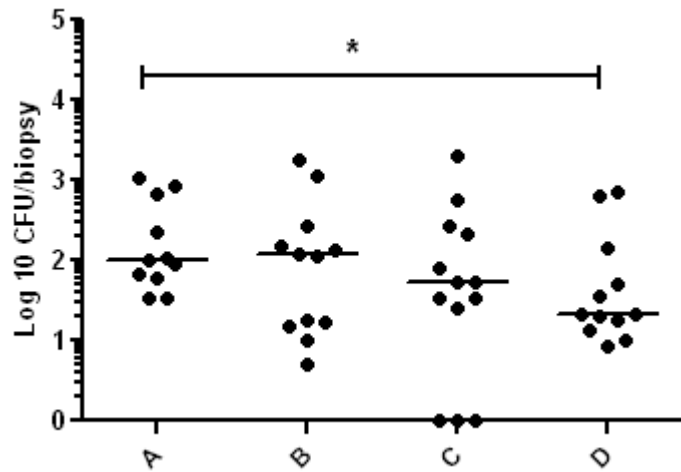# BCG vaccination protects against intradermal BCG challenge in NHPs

# Pilot BCG challenge study

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

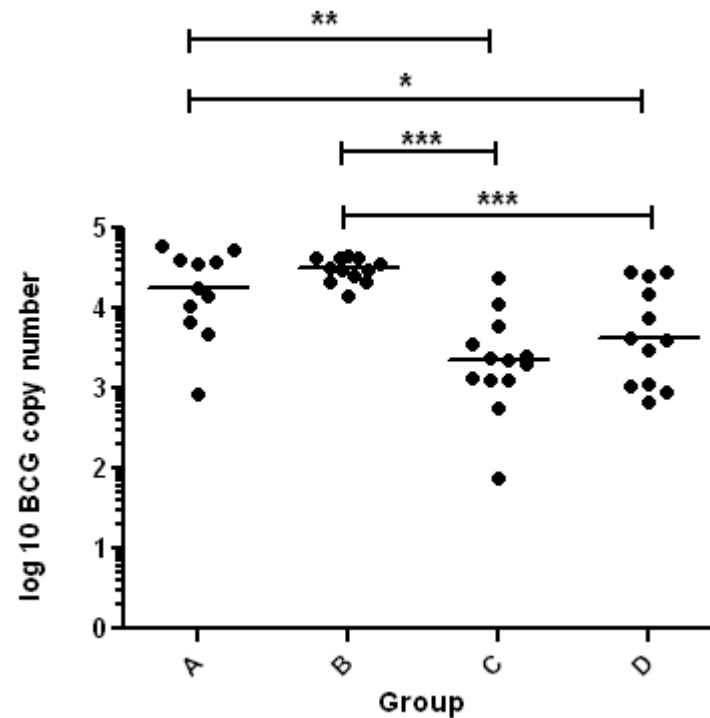

Minassian A et al, JID 2012

# BCG vaccination protects against intradermal BCG challenge in humans



Culture

PCR

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

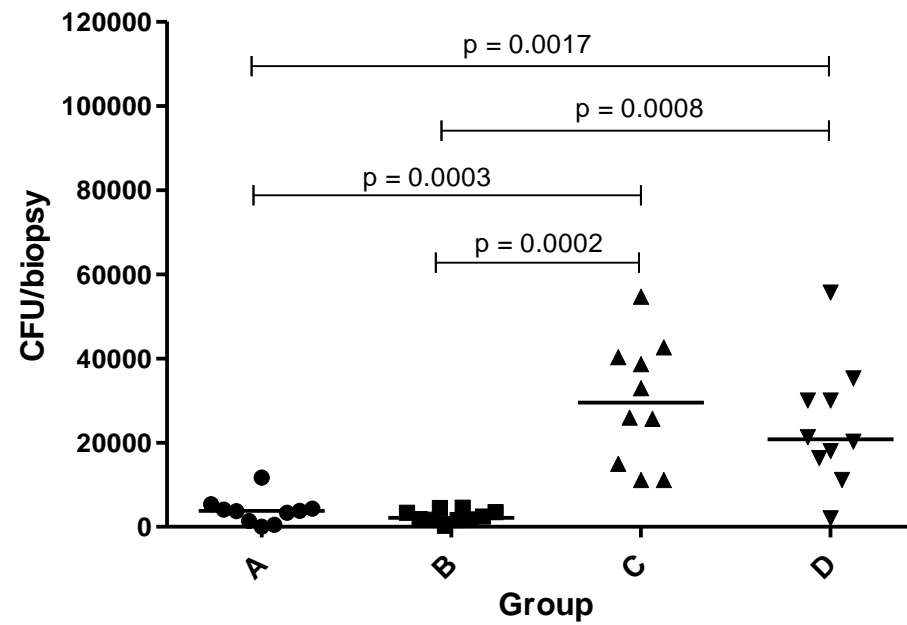| *   | p < 0.05 |
| **  | p < 0.01 |
| *** | p < 0.001 |

Harris S et al, JID 2013

# Comparing BCG yield by strain and dose

**TB031 Biopsy PCR**
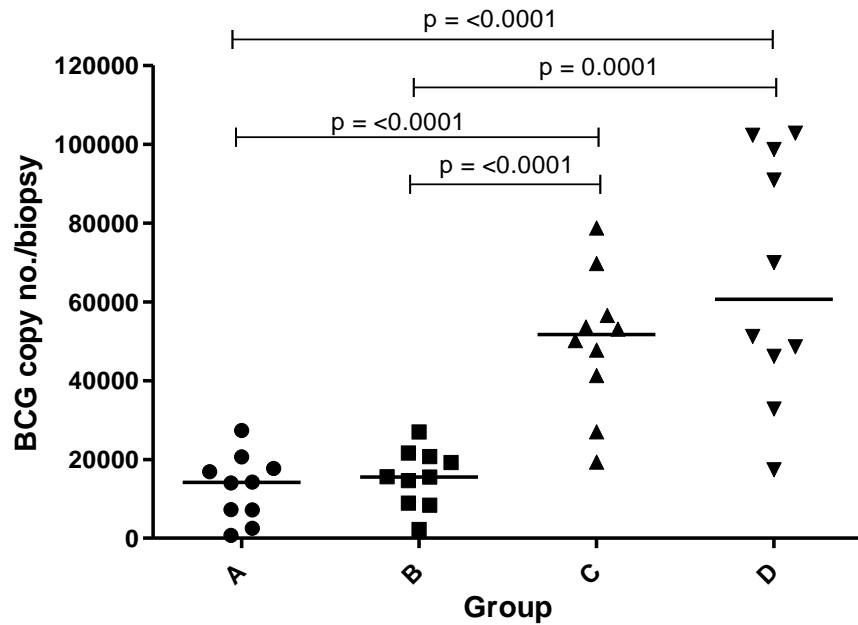
**TB031 CFU (4 weeks)**



Group A – low dose SSI
Group B – low dose TICE
Group C – high dose SSI
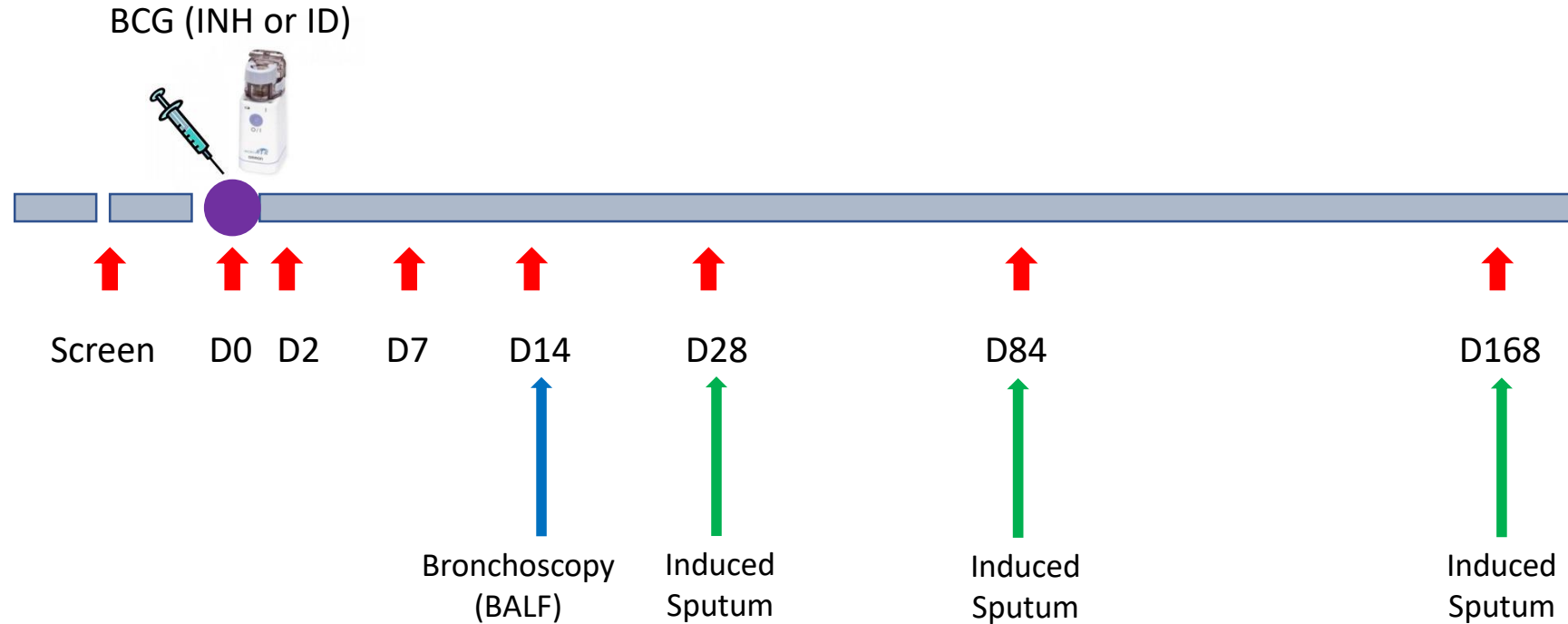Group D – high dose TICE

Minhinnick A et al, JID 2015

# 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

# TB041 - Trial Schedule

BCG (INH or ID)

Screen | D0 D2 | D7 | D14 | D28 | D84 | D168

Bronchoscopy (BALF)

Induced Sputum

Induced Sputum

Induced Sputum

PPD ELISpot @ D0, 7, 14, 28, 84, 168

WB ICS @ D0, 14, 168

BAL fluid – detection of BCG by MGIT/PCR, ICS

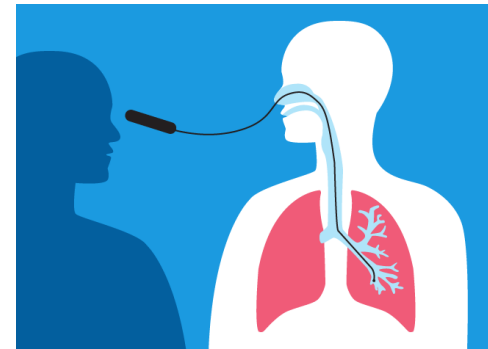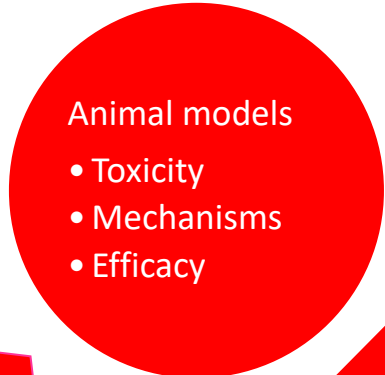Induced sputum - detection of BCG by MGIT/PCR

# Summary

- Development of an attenuated, labelled *M.tb* strain underway
  - 3-5 years away from clinical use
  - Regulatory discussions ongoing
- Validation of a BCG vaccine effect against intradermal BCG challenge in mice, cattle, NHPs and humans
- BCG delivered by aerosol is, to date, well tolerated
- Possible to detect BCG in BALF after aerosol BCG
  - How to quantitate?
- A controlled human mycobacterial challenge model
  - Is feasible
  - Can be validated using a known vaccine effect in preclinical animal models
  - Ultimately needs validation against field efficacy trials

# Approvals for a mycobacterial challenge model

- Need for regulatory approval
  - Not for ID BCG
  - Yes for aerosol BCG
  - Yes for attenuated r*Mtb* strain
  - Yes if candidate vaccine

- H&S assessment
  - Particularly for aerosol BCG

- GMO
  - Not needed for BCG
  - Would be for a r*Mtb* strain

- Ethics

Animal models
- Toxicity
- Mechanisms
- Efficacy

Human field efficacy

Human safety & immunogenicity

Human challenge model

# Acknowledgements



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# Study participants

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