# Developing a human mycobacterial challenge model

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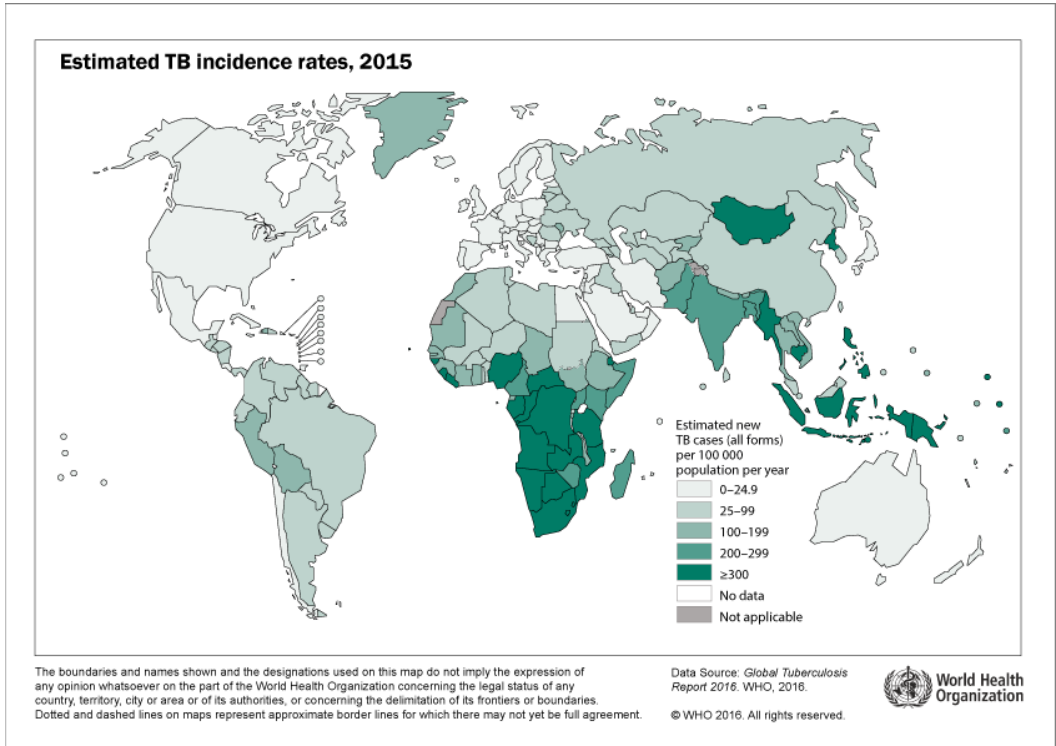
# Why do we need a TB challenge model?

- Uncertain predictive value of preclinical animal models
- Lack of validated immune correlate of protection
- Urgent need for an effective vaccine
  - 10.4m new cases and 1.8m deaths in 2015
- We need tools for vaccine selection

BUT

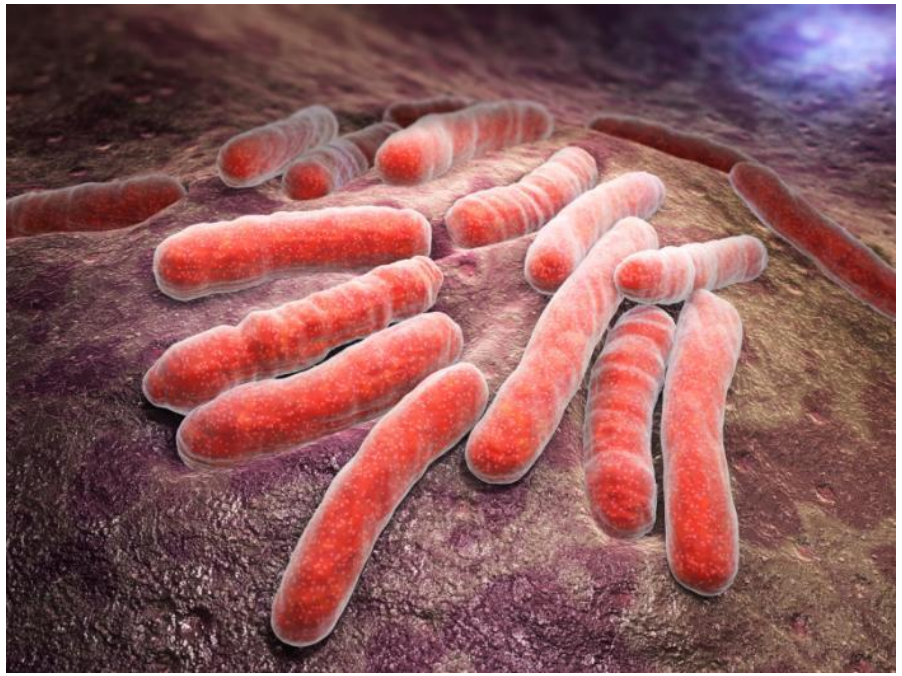
- TB Rx takes 6 months
- Drugs can be toxic
- 5% chance of relapse

**We can’t challenge with the virulent organism!**



# Elements of a *M. tuberculosis* Human Challenge Strain

- Control System for Bacterial Death
  - Survival for multiple generations
  - Eliminates **ALL** bacteria at the end of test
    - No lengthy antibiotic course
    - No relapse
- Detection System
  - Measures the levels of bacterial load in the lungs without having to do a CFU count on the lungs
  - Non-invasive or minimally invasive



Fortune, Rubin, Robertson

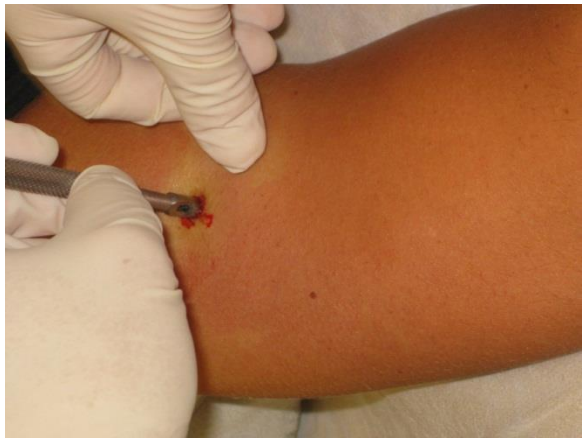
# Some questions

- How safe does a strain need to be?
- How long does a strain have to live?
- How sensitive does a reporter need to be?

- What kind of vaccines would this work for?
- Can we detect a vaccine effect?
- Would this be acceptable to the regulators?

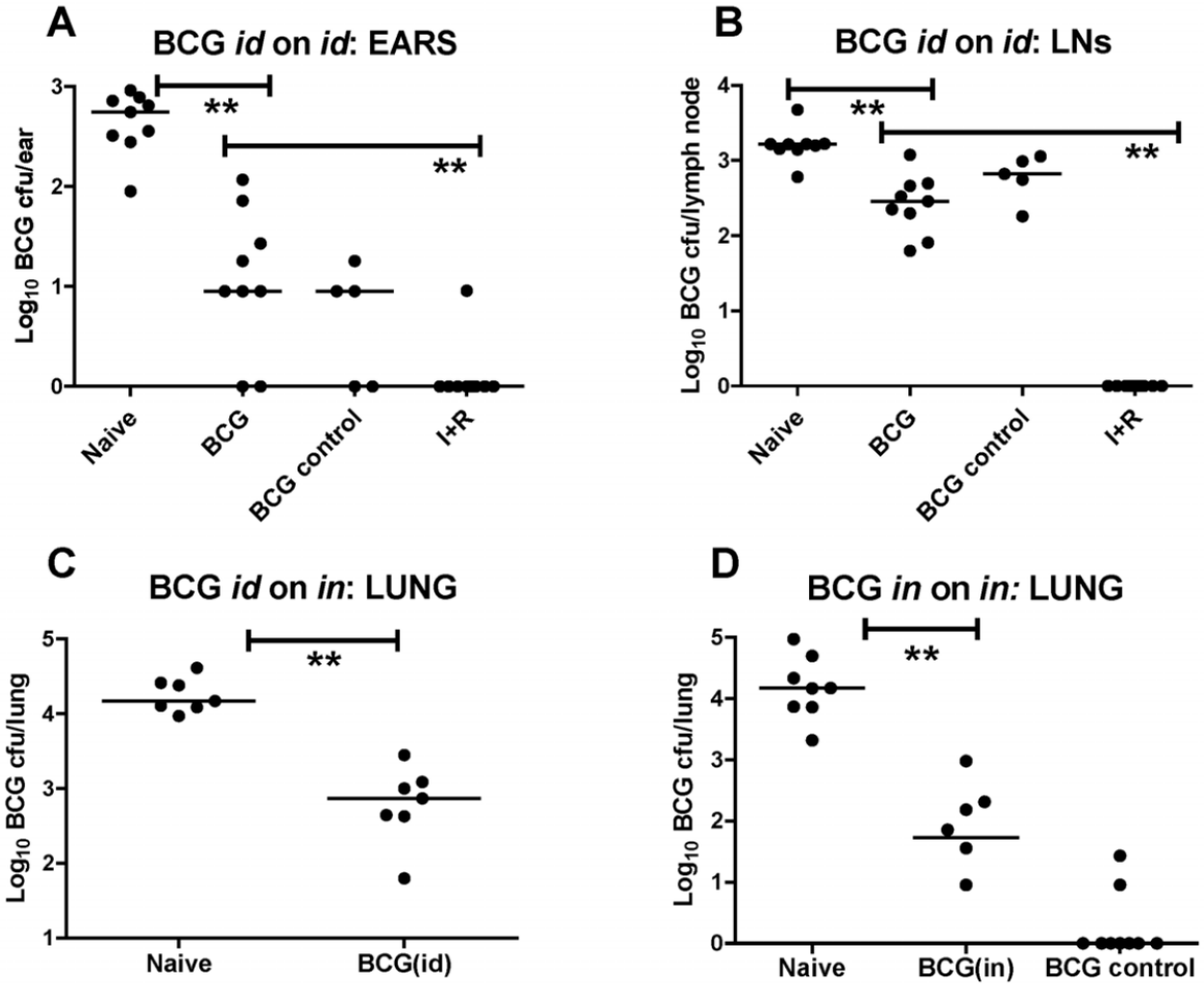
# A human intradermal BCG challenge model

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



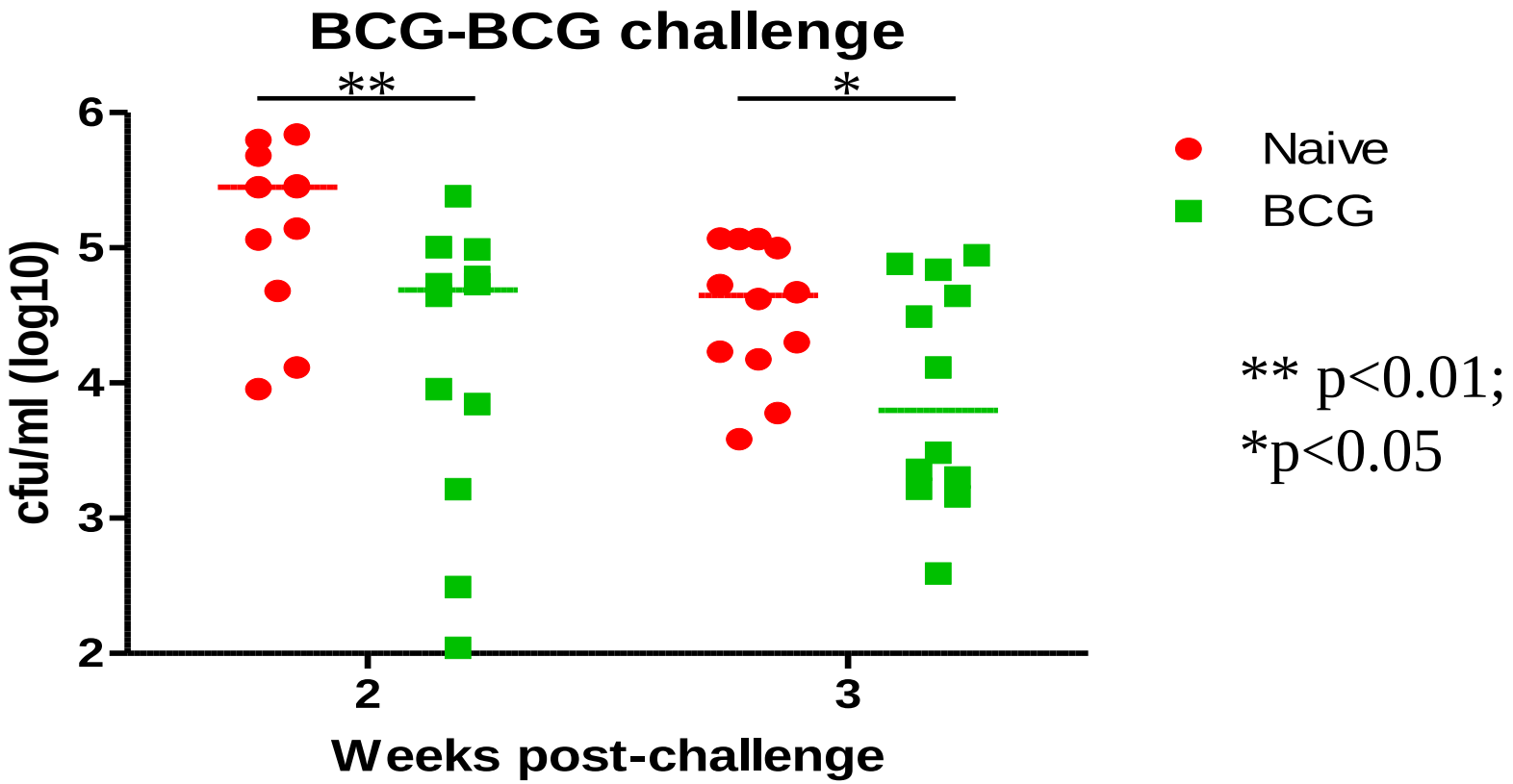
- Does intradermal BCG ‘challenge’ provide a good model for aerosol *M. tuberculosis* challenge?
  - Validation in preclinical animal models

# 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

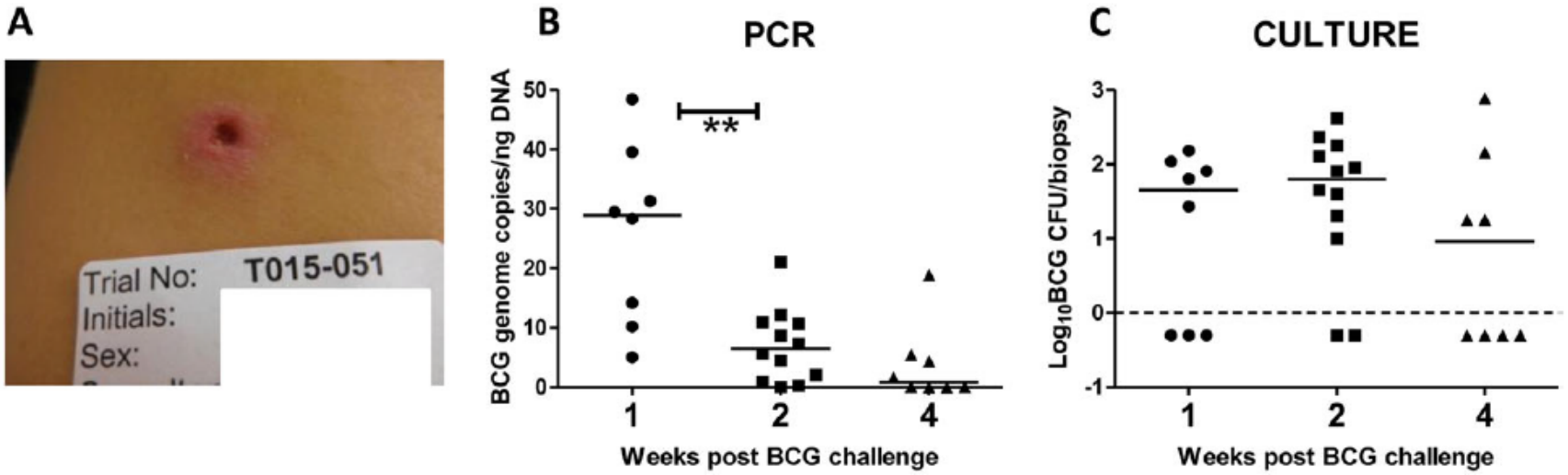



Animal Health & Veterinary Laboratories Agency

Villarreal-Ramos et al, Vaccine 2014

# Pilot BCG challenge study

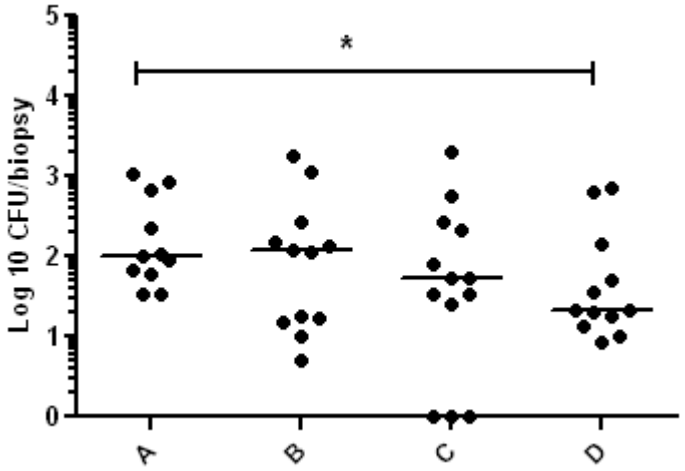
- BCG (SSI), 2-8 x $10^5$cfu/ 100ul
- Route i.d
- Sampling: 4mm punch biopsy
- Biopsy at 1, 2, or 4 weeks post BCG



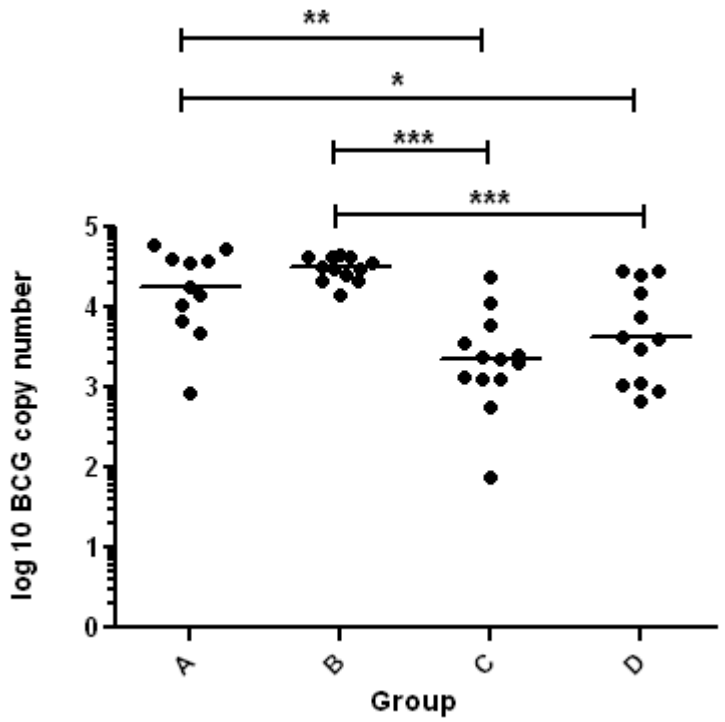

Minassian A et al, JID 2012

# Prior BCG vaccination protects against intradermal BCG challenge in humans

Culture




PCR

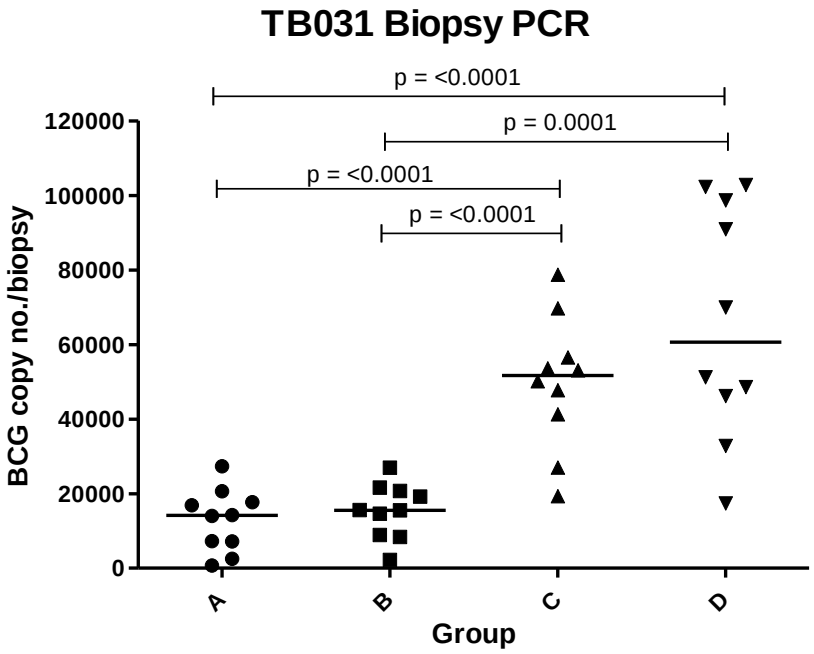


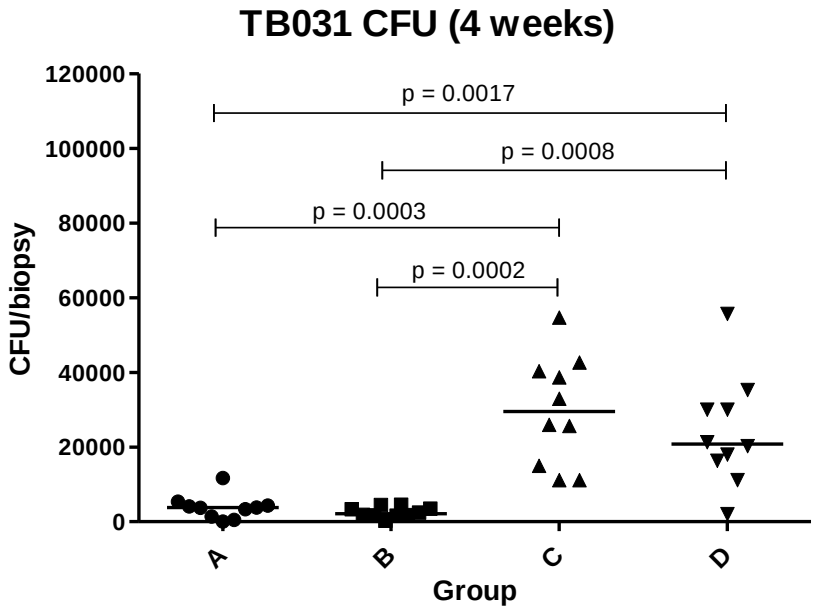

A = naïve
B = MVA85A
C = BCG
D = BCG-MVA85A

| | |
|---|---|
| * | $p < 0.05$ |
| ** | $p < 0.01$ |
| *** | $p < 0.001$ |

Harris S et al, JID 2013

# Comparing BCG yield by strain and dose




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

# Summary

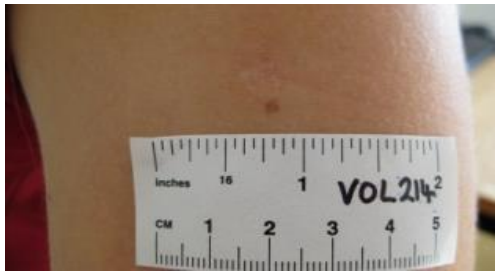
- Work ongoing to develop attenuated, labelled M.tb strain for use in a human challenge study
  - 3-5 years away from clinical use
  - Regulatory discussions ongoing
- BCG vaccination protects against intradermal BCG challenge in mice, cattle, NHPs and humans
- BCG delivered by aerosol is, to date, well tolerated
- BCG recovery rate from BAL/IS is low
  - May need to dose escalate
- A controlled human mycobacterial challenge model
  - is feasible
  - can be validated in preclinical animal models
  - Ultimately needs validation against field efficacy trials

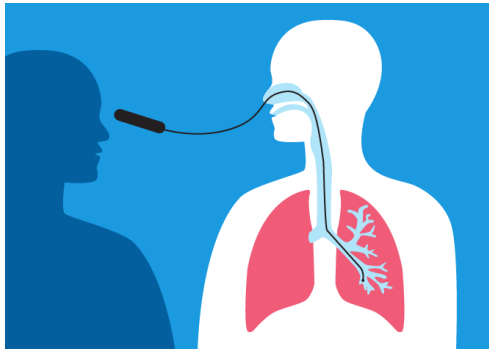
Animal models
- Toxicity
- Mechanisms
- Efficacy

Human safety & immunogenicity

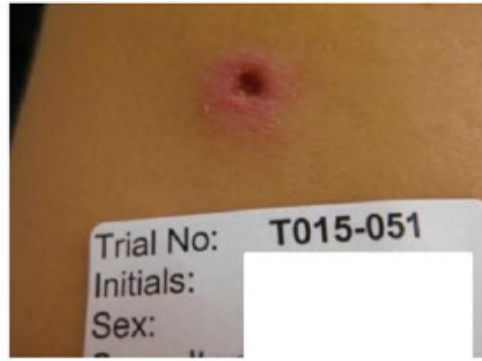
Human challenge model

Human field efficacy



A



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