WorldMEDSchool GLOBAL EDUCATION

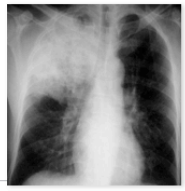
Where are we with TB vaccine development?

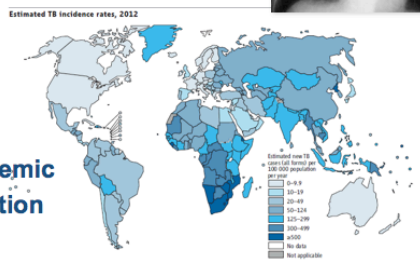
Helen McShane
The Jenner Institute
University of Oxford

UNIVERSITY OF OXFORD

Epidemiology of human TB in 21st Century

- 8.6 million new cases in 2012
- 1.3 million deaths in 2012
- Resistance:
  - MDR-TB
  - XDR-TB
  - TDR-TB
- Overlap with HIV epidemic
- Burden of latent infection





UNIVERSITY OF OXFORD

TB Control

- Active treatment
  - Need new drugs
- Rapid and accurate diagnosis
  - Need better diagnostic tests
- Prevention:
  - Need a more effective vaccine than BCG

UNIVERSITY OF OXFORD

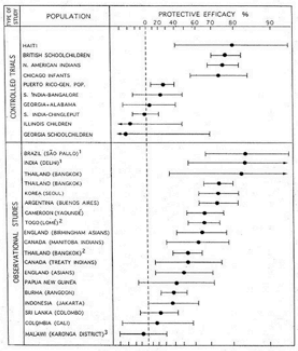
BCG

- **Live attenuated *M. bovis***
- **First used in 1921 (per os)**
- **Efficacy:**
  - Good
    - Disseminated TB and TB meningitis
    - Leprosy
  - Bad
    - Lung disease – at any age
    - Boosting (Rodrigues et al, Lancet 2005)

UNIVERSITY OF OXFORD

BCG Protective Efficacy – Meta analysis

- **70 trials; spanning 46 years**
- **Efficacy of 0% - 80%**
- **Average reduction in incidence of 50%**
- **Latitude has major influence on efficacy**



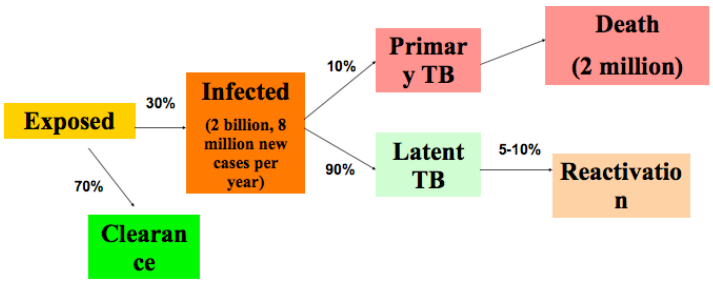
UNIVERSITY OF OXFORD

Why doesn't BCG work?

- **Different strains of BCG**
- **Nutrition**
- **Exposure to environmental mycobacteria**
  - Masking (Black et al, 2002)
  - Blocking (Brandt et al, 2002)

UNIVERSITY OF OXFORD

Tuberculosis in humans



UNIVERSITY OF OXFORD

What do we know about protective immunity

- **Essential:**
  - CD4+ T cells
  - IFN γ
  - TNF
- **Probably important:**
  - CD8+ T cells
  - γδ T cells
  - CD-1 restricted T cells
  - IL-17
  - Il-2
- **May be relevant**
  - B cells and antibodies

UNIVERSITY OF OXFORD

Potential vaccine types

- **Whole organism**
  - Improved BCG
  - Attenuated M.tb
- **Subunit – choice of vector and antigen**
  - DNA
  - Protein/adjuvant
  - Recombinant virus/bacteria

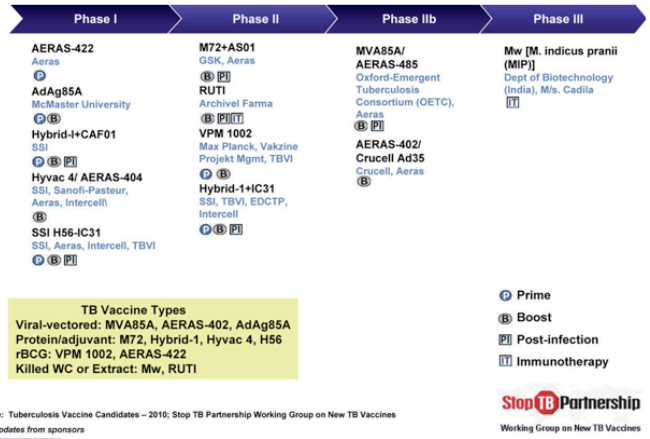
UNIVERSITY OF OXFORD

Design of an improved vaccine against TB

- **Include BCG in new regime**
- **Needs to induce cellular immune response**
- **3 possible strategies:**
  - Enhance BCG with a subunit vaccine
    - Protein + adjuvant
    - Viral vector
- **Replace BCG with improved BCG / attenuated *M. tb***
- **Enhance an improved BCG**

UNIVERSITY OF OXFORD

Global TB Vaccine Pipeline



UNIVERSITY OF OXFORD

Brennan and Thole, Tuberculosis 2012

MVA85A

Modified vaccinia Ankara (MVA)

Poxvirus
No replication in mammalian tissues
Good T cell boosting vector
Excellent safety record

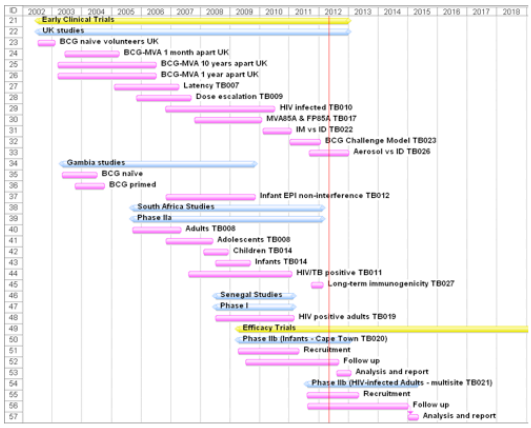
***M.tb* antigen 85A**

Mycolyl transferase
Major target antigen
Protective in small animals
In all environmental mycobacteria
Doesn't interfere with new diagnostic tests

BCG - MVA85A regimen

UNIVERSITY OF OXFORD

Summary of clinical trials with MVA85A since 2002



UNIVERSITY OF OXFORD

Bibliography

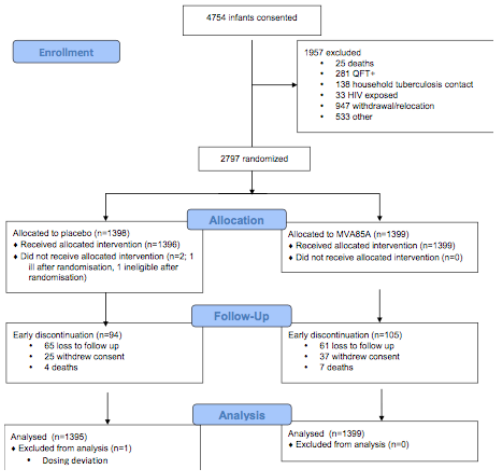
Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

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

UNIVERSITY OF OXFORD

Figure 1



UNIVERSITY OF OXFORD

Primary and secondary efficacy endpoints

Parameter	Placebo (n=1395)	MVA85A (n=1399)	Vaccine Efficacy % (95% CI)
Endpoint #1 (Primary Efficacy Endpoint)	39 (2·8)	32 (2·3)	17·3% (-31·9 to 48·2)
Endpoint #2 (Exploratory Efficacy Endpoint)	52 (3·7)	55 (3·9)	-6.9% (-56·1 to 26·9)
Endpoint #3 (Exploratory Efficacy Endpoint)	177 (12·7)	196 (14·0)	-12.1% (-37·4 to 8·5)
QFT conversion:	171	178	-3.8% (-28.1 to 15.9)

UNIVERSITY OF OXFORD

Tameris M et al, Lancet 2013

Summary

- Enormous progress has been made in the last decade
- Challenges for the next decade are very clear
- There is an urgent need for better models to evaluate vaccines
- We should use every opportunity to identify potential correlates
- We need to use human efficacy data to review and refine models
- We need to design more potent vaccines
- Currently no substitute for human efficacy testing

UNIVERSITY OF OXFORD

WorldMEDSchool
GLOBAL EDUCATION

Where are we with TB vaccine

UNIVERSITY OF OXFORD