



Update on recent development in tuberculosis clinical research in Africa

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Tuberculosis

“TB is out of control in the world and disproportionately affects people in developing countries in terms of morbidity and especially in terms of mortality”

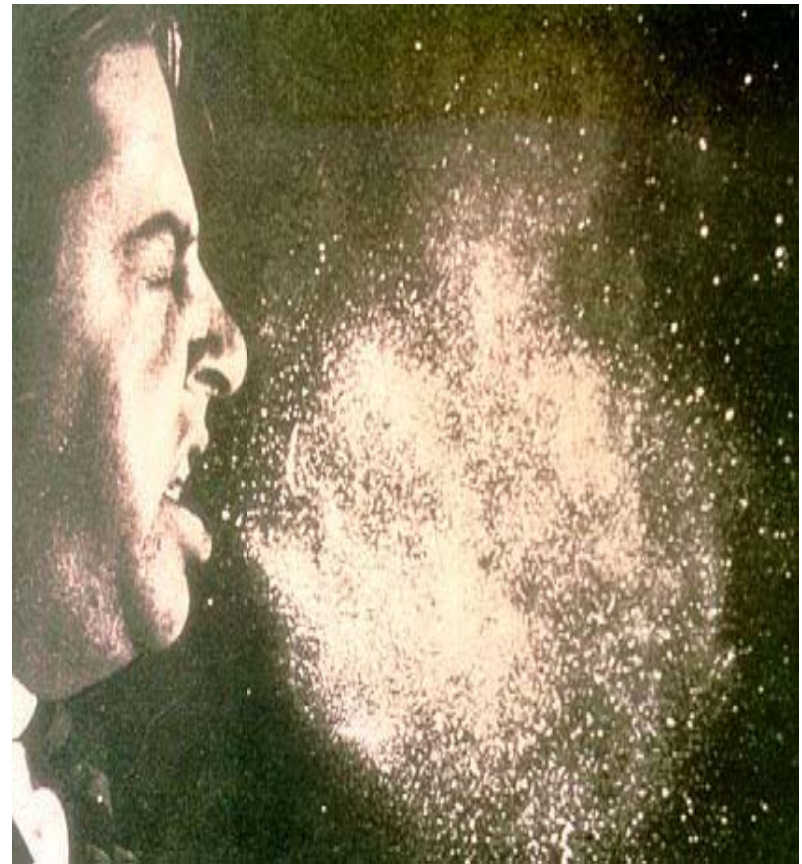


Outline

- Background
- Improving TB Diagnostics
- New TB treatment regimen
- Evaluation of a new TB vaccine

Tuberculosis

- Caused by *Mycobacterium tuberculosis* (M.tb)
- Aerosol, mouth
- Chronic infection: multiple organs
 - Lungs
 - Bones
 - Brain

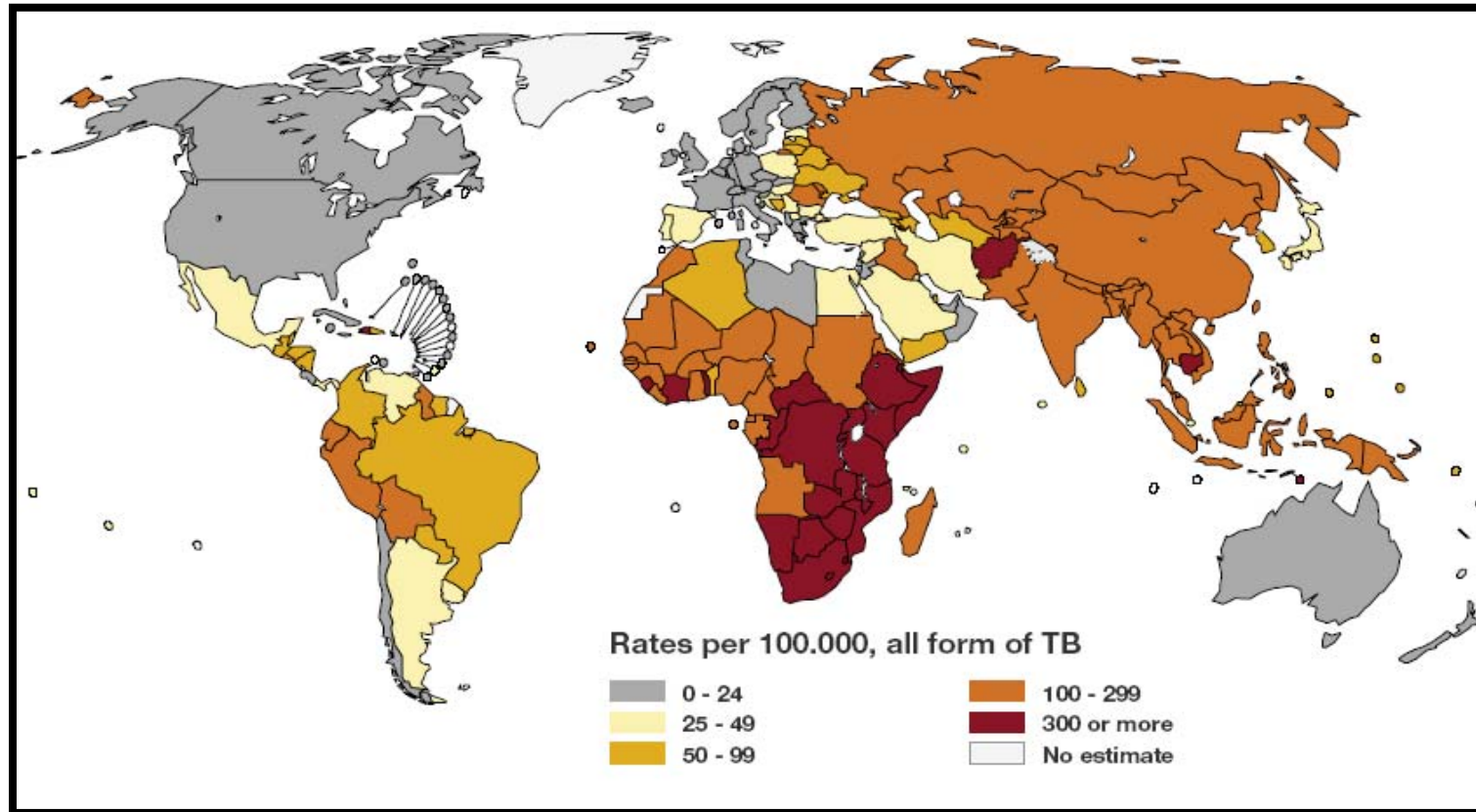




Epidemiology of TB

- Burden of latent infection, 1/3 of the world
- 10% progress to disease
- Overlap with HIV epidemic
- In 2003:
 - 8.8 million new cases
 - Total of 15.4 million cases
 - 1.7 million deaths
 - 500 000 cases of MDR-TB
- Global incidence rising by 1% pa
- Emergence of XDR-TB

Global Burden of Tuberculosis



Persons Infected
Estimated Cases
Estimated Deaths

2.0 Billion
8,800,000
1,700,000

WHO: The World
Health Report 2003

Global plan to stop TB: 2006-2015

● Targets

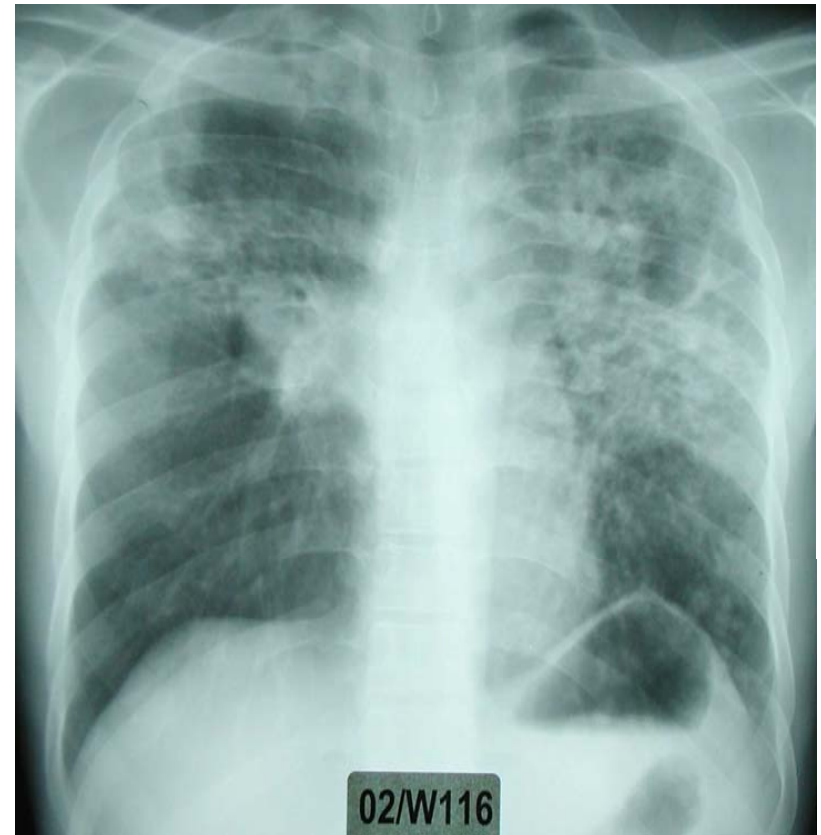
- > 70% of people with infectious TB will be diagnosed and >85% of those will be cured
- 50% reduction of 1990 levels of global prevalence of TB
- Global TB incidence <1/million population by 2050

● How?

- Use of current tools
 - DOTS; DOTS-plus; DOTS expansion
- New tools
 - New drugs
 - New diagnostics
 - New vaccines

Some Gaps in knowledge of TB

- Huge variability in BCG efficacy
- Why only 10% of *M.tb* infections progress to disease (Biomarkers)
- Improvement of TB diagnosis
- TB-HIV interaction
- Drug resistance
- Novel TB vaccines





Diagnosis of Tuberculosis

- History
- Chest Xray
- Sputum for AFB
- Tuberculin skin test (TST, Mantoux test)



New TB Diagnostics

- IFN- γ release assays
 - T-SPOT
 - Quantiferon
- Bactec
- MGIT
- Spoligotyping

The ELISPOT plate

1) CFP-10

2) **ESAT-6**

3) PLA-1

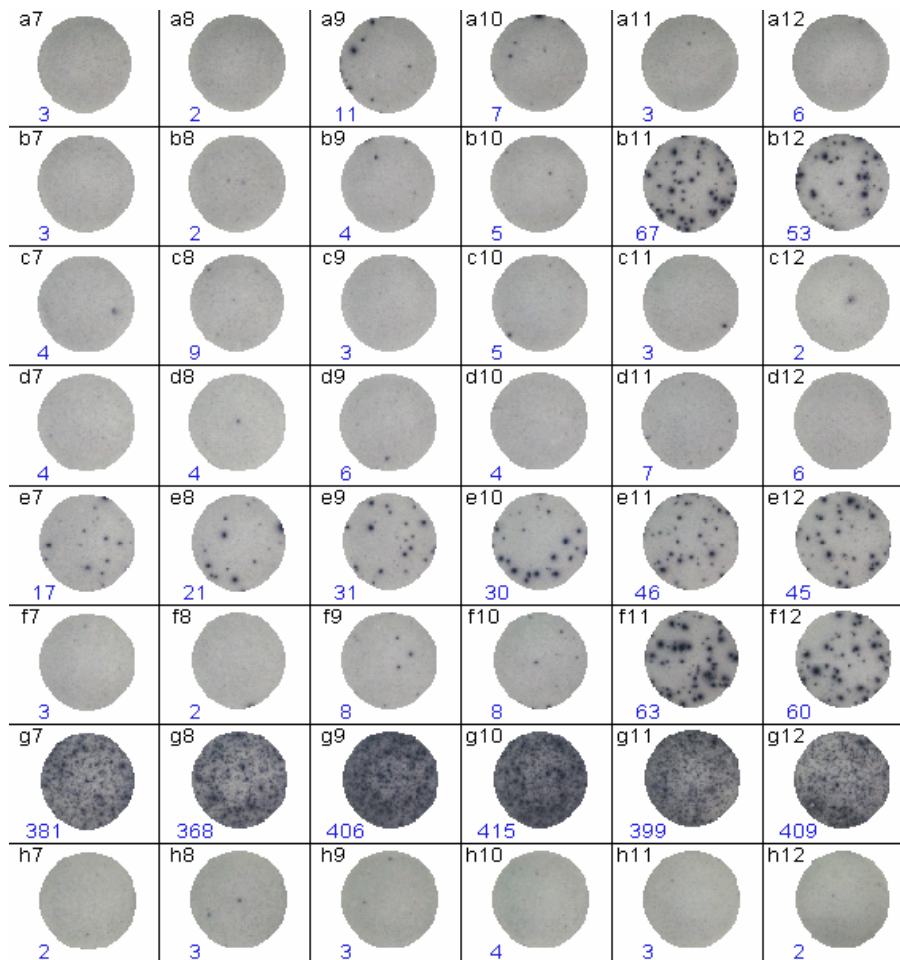
4) PLA-2

5) PPD

6) **ES/CF**

7) PHA

8) Medium



Peptide pools

Latency antigen
protein pools

ESAT-6 & CFP-10
proteins

1

2

3



New TB test brings tuberculosis care into 21st century

Oxford Immunotec launches revolutionary T SPOT-TB blood test

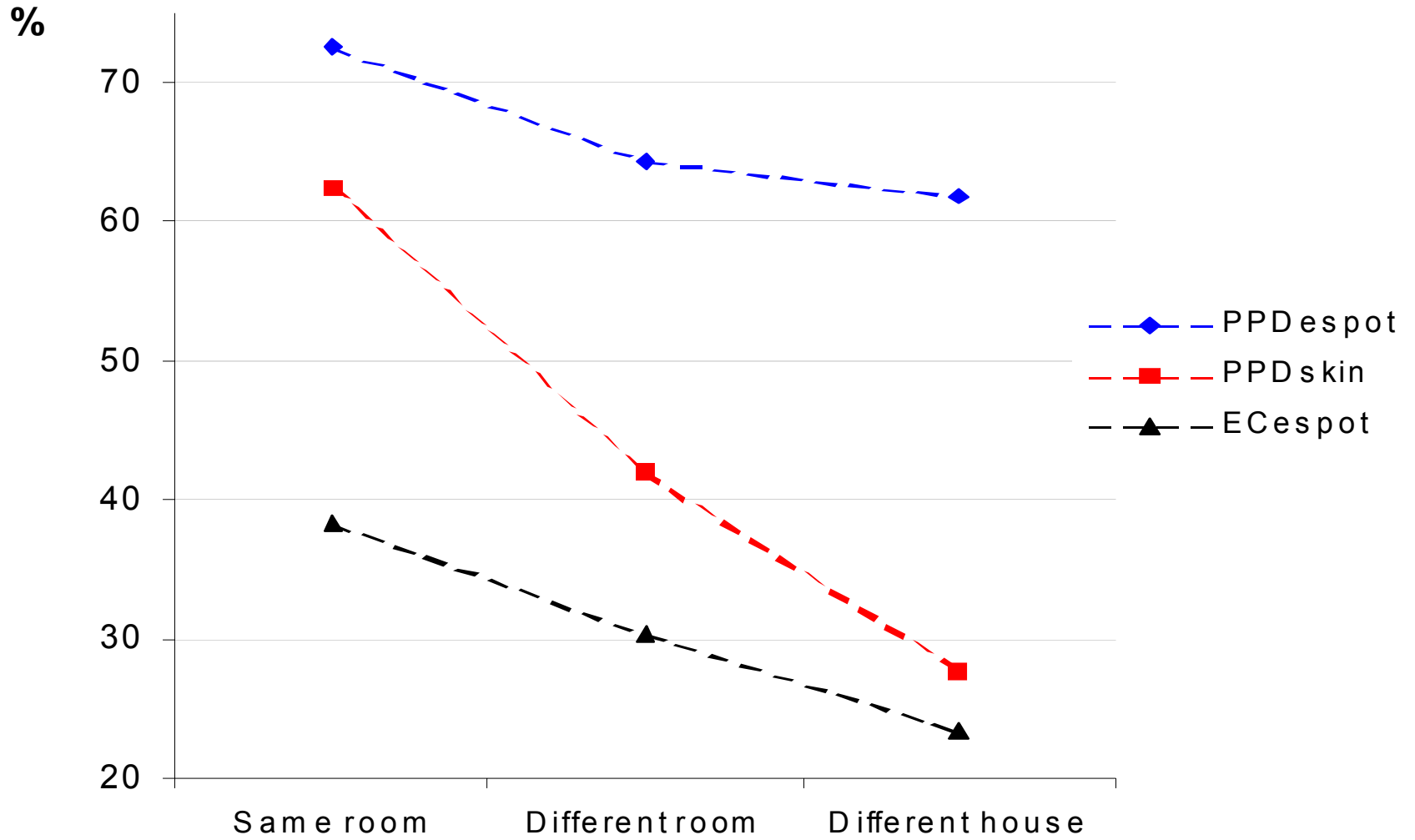
.... a revolutionary new blood test, T SPOT-TB, has been approved for use in Europe and gives real hope that the tide can be turned in the fight against the disease.

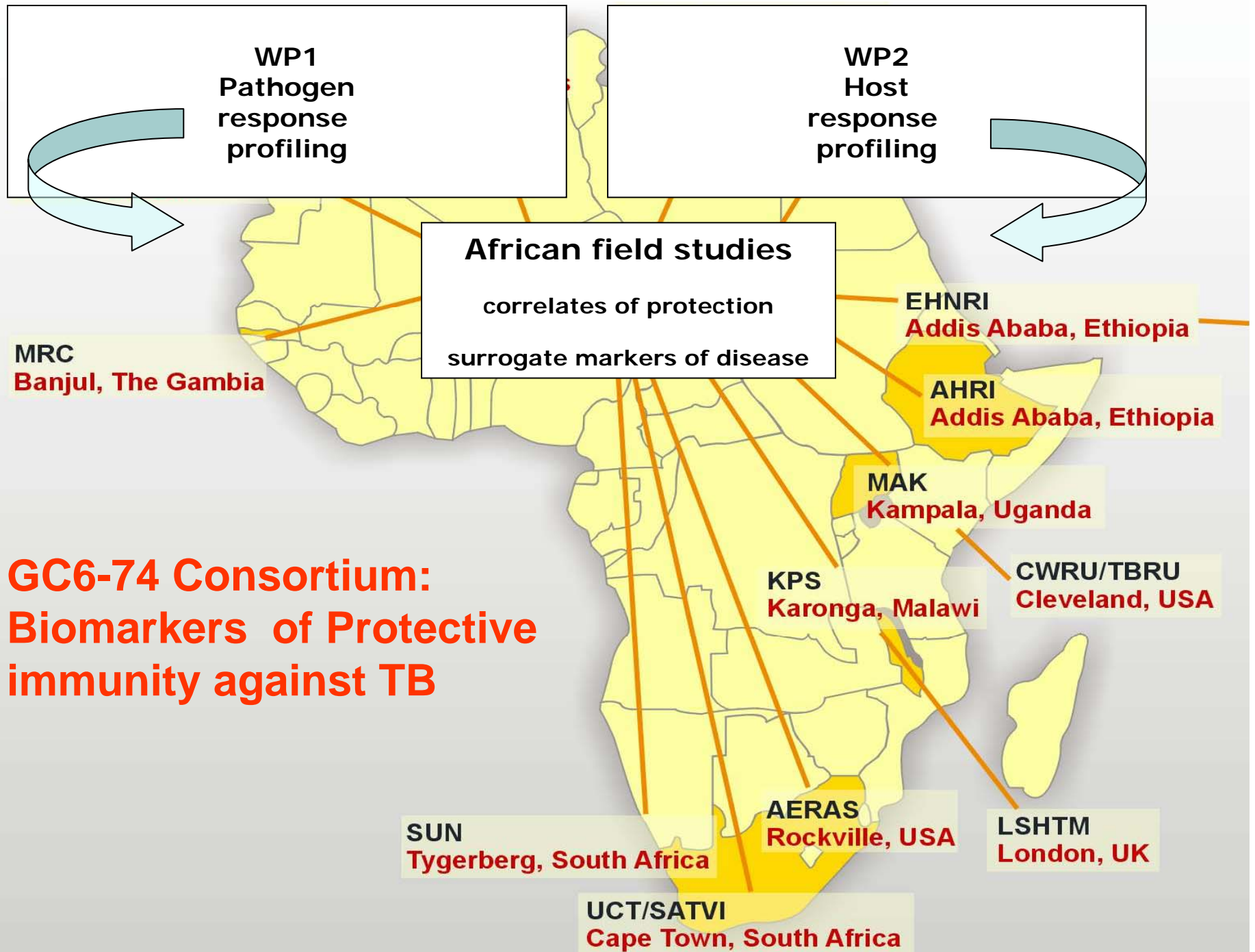
Oxford Immunotec's new test is set to replace the century old tuberculin skin test, the oldest diagnostic test still in use today. The launch of T SPOT-TB is a key milestone in mankind's fight against this ancient disease and will bring TB care out of the Victorian era and into the 21st century.

T SPOT-TB enables doctors to reliably screen people who have been in contact with a TB sufferer, allowing those who have been infected to be identified and treated long before they actually develop the disease and become infectious to others. (1,2) It provides an accurate and effective tool for controlling the spread of TB. (3)

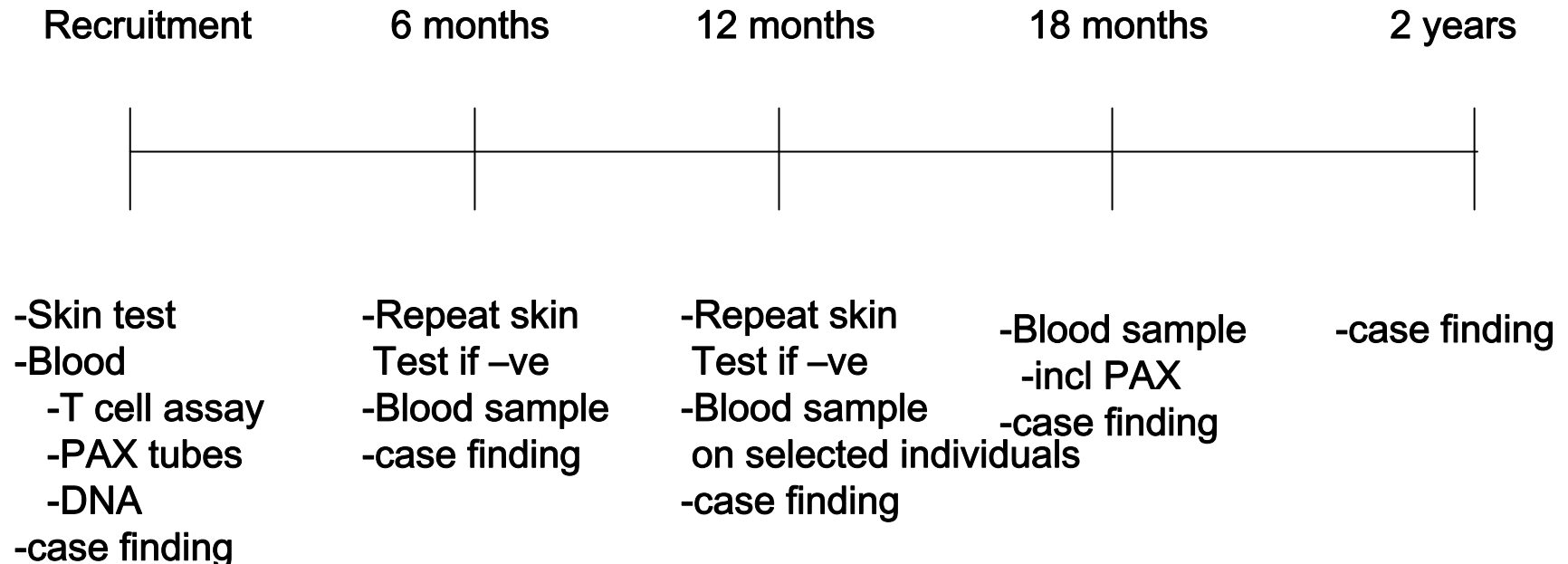
'The new gold standard for diagnosis of TB infection'







WP-3 Recruitment and follow-up framework



Define phenotypes after 2 years and retrospectively examine samples to identify biomarkers



Identification of Biomarkers using TB Case-Contact Study

**Host/
Environmental
effects**

**Immunological
markers**

**Diagnosis
Phenotyping**

Non-exposed

Exposure* → *Infection* → *Disease

Open PTB

**Prevention ±BCG
post-exposure vaccine**

**Prophylactic
vaccine ±BCG**

**Improving treatment
new drugs; adherence**



TB Drug Regimen evaluation

EU- funded Multi-site trial of
gatifloxacin containing
regimen in Africa



Rationale

- despite a treatment of proven efficacy, TB rates continue to increase in resource-poor countries
 - persistence of high treatment default rates
 - spread of multi-drug resistance
 - high impact of HIV infection
-
- improve access to and delivery of treatment
 - decrease duration of treatment
 - new drugs
 - new drug combinations

Pivotal “Proof of Concept” Phase III Trial

- *First Proof of Concept* trial on shortening treatment of pulmonary TB to 4 months with the inclusion of a fluoroquinolone
- Phase III Multicentre open-label Randomised Controlled Trial
- 4-month gatifloxacin-containing short-course regimen *versus* standard 6-month regimen
- Gatifloxacin substituted for Ethambutol



Methods

- Open-label Randomised Controlled Trial
- Non-inferiority
- Treatments:
 - test: 2 months GHRZ / 2 months GHR
 - control: 2 months EHRZ / 4 months RH
- Sample size: 1035 patients/arm
- Follow-up: 2 years after completion of treatment
- Trial sites: Benin, Guinea, Kenya, Senegal, South Africa

End-points

Efficacy:

- *Primary outcome:*
 - Percent unfavourable outcome (bacteriological failures and relapses) at 24 months following the end of treatment
- *Secondary outcome:*
 - percent relapses at 24 months
 - time to unfavourable outcome (failure/relapse)
 - percent culture conversion at 8 weeks
 - percent patients cured by the end of treatment

Status of trial > half the sample size recruited into the study



New Vaccines against TB

- About 80% of the world's population is vaccinated with BCG, the only licensed vaccine available against TB.
- Despite this wide coverage of BCG, TB epidemic is on the increase.
- There is an urgent need for a new vaccine.
- BCG has some non-target beneficial effects like it improves child's survival, improves responses to other EPI vaccines etc.
- A vaccination schedule that improves rather than replace BCG will be ideal.



Design of an improved TB vaccine

- Needs to induce cellular immune response
- Possible strategies:
 - ▣ Replace BCG or repair BCG
 - ▣ Boost BCG with a subunit vaccine



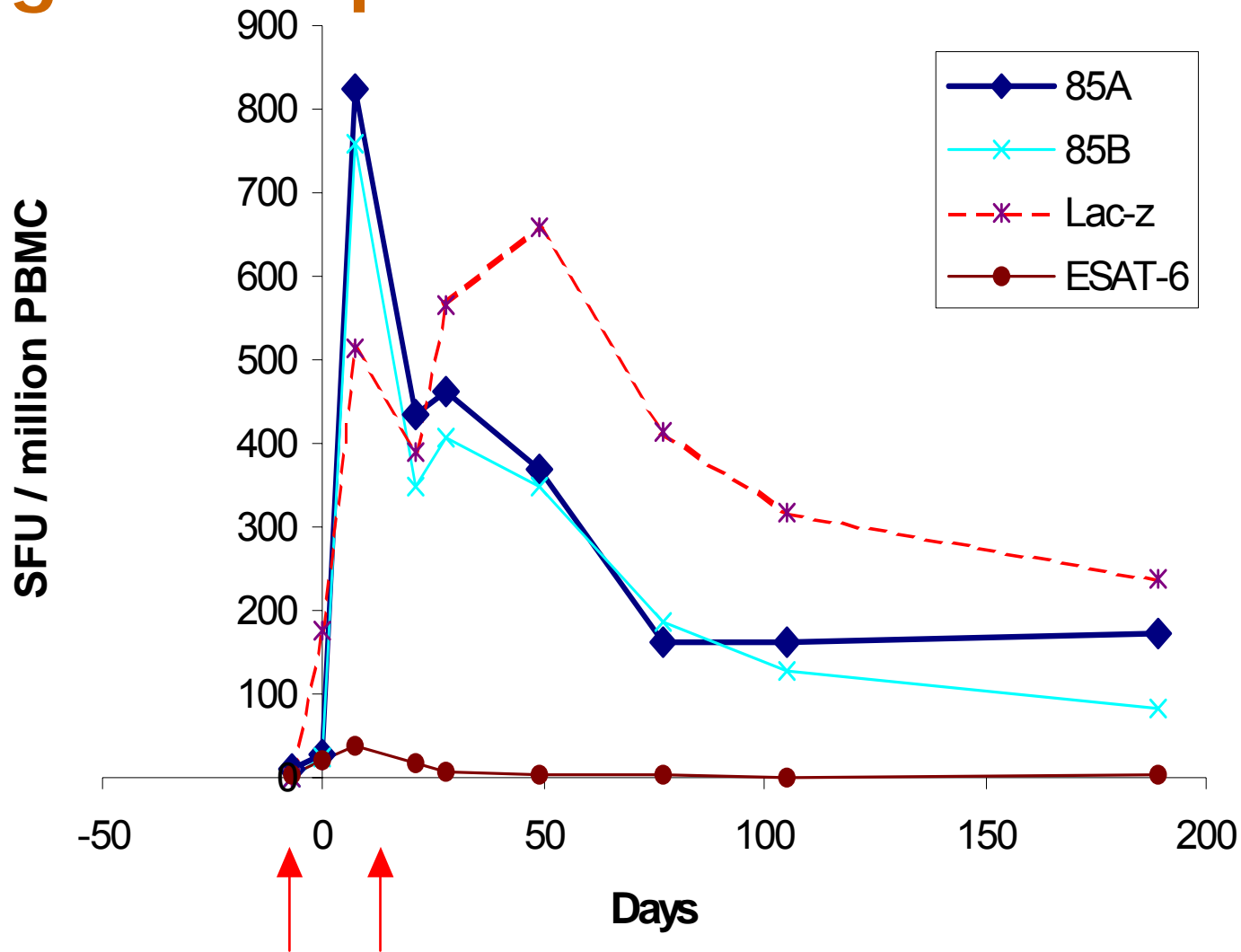
New TB vaccines in or on their way to the clinic

- rBCG30
 - ▣ Live, recombinant BCG overexpressing Ag 85B from MTB
- rBCG:: Δ ureC
 - ▣ Live, recombinant BCG, urease deficient expressing lysteriolysin
- Mtb72f
 - ▣ Recombinant protein
- MVA85A
 - ▣ Live, recombinant, replication-deficient vaccinia virus, expressing Ag85A from MTB

MVA85A vaccine

- Is promising as a heterologous prime-boost strategy to BCG during infancy.
- Ag85A is an immunodominant antigen in MTB. Also found in environmental mycobacterium and BCG.
- Protective in animal models.
- Safe and immunogenic in adults in the UK, South Africa and Gambia.

Ag85A responses in MVA-85A vaccinees



MVA85A vaccine trial in infants

- Ideal vaccine is that given as early as possible, and provides long protection.
- MVA85A in infants will coincide with when other EPI vaccines are administered
?Safety, ?Interaction, ?immunogenicity
- This study conducted in human infants for the first time aims to provide the necessary data required for large efficacy trial.

Objectives

- Dose selection, safety and immunogenicity of MVA85A in 4 month old healthy Gambian infants
- Impact of MVA85A on the immunogenicity of EPI vaccines (DTwPHib, and Hep B) and vice versa when administered simultaneously to children who have had BCG within the first month of life.

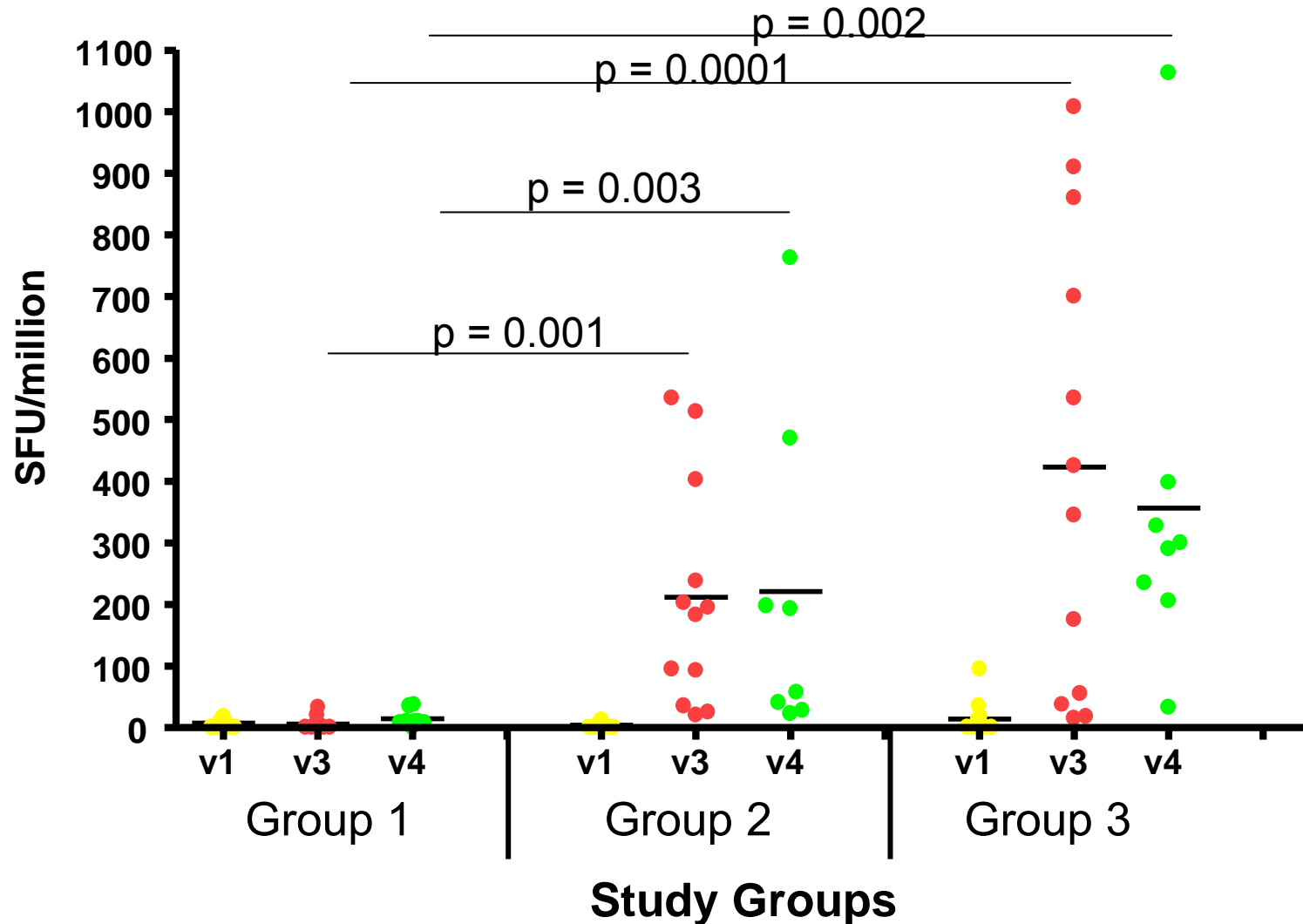
Study Design - 1

		EPI alone (Control) Group 1	MVA85A with EPI Group 2	MVA 85A with EPI deferred for 1 week Group 3
STAGE ONE	Low dose Stage 1a	Group 1(n=12)	Group 2(n=12)	Group 3(n=12)
	High dose Stage 1b	Group 1(n=12)	Group 2(n=12)	Group 3(n=12)
STAGE TWO	Using selected dose	Group 1(n=48)	Group 2(n=48)	Group 3(n=48)
STAGE THREE	Using selected dose	Group 1(n=85)	Group 2(n=85)	Group 3(n=85)

Study Design - 2

- Visit schedules
 - Pre-vaccination = visit 1
 - Vaccination day = visit 2
 - 1 week post vaccination = visit 3
 - 4 weeks post vaccination = visit 4
- Outcome parameters
 - Safety
 - Liver function tests, serum electrolytes, haematology, local and systemic reactogenicity
 - Immunogenicity of MVA85A
 - IFN- γ SFU following an overnight stimulation with single peptide pool of antigen 85A
 - Interference with EPI
 - Antibody levels of DPT-Hib and Hep B

Immune response to p85a after high dose of MVA85A



Phase IIa studies with MVA85A in South Africa

- Age de-escalation
 - Adults (n = 24) - completed
 - Adolescents (n = 12) – enrolment complete
 - Children (n = 24) – final approval pending
 - Infants (n = 108) – final approval pending
- High risk groups (adults) - ongoing
 - HIV infection (n = 12)
 - *M.tb* infection (n = 12)
 - HIV and *M.tb* co-infection (n = 12)



Findings to date in adults/adolescents

- Adverse event profile very similar to UK and Gambian studies
- Immunogenicity profile similar to UK/Gambian studies

Forward look

- Epidemiological studies on going in several countries
- Unprecedented global efforts involving private/public/academia aimed at combating the disease in Africa and attaining the MDG
- EDCTP is providing funding and support for capacity development, networking and preparation of clinical trial sites in Africa. WHO, BMGF, AERAS, FIND, etc.
- New diagnostic tests, drugs and vaccines which will require evaluation in large clinical trials.



Acknowledgements

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Thank you for your attention