TB Vaccine Development

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Aeras Global TB Vaccine Foundation
Paris, France
October 21st 2009
Latest Global TB Estimates - 2007

All forms of TB
Greatest number of cases in Asia; greatest rates per capita in Africa

Estimated number of cases

- 9.27 million (139 per 100,000)
- 511,000
- ~50,000
- 1.4 million (15%)

Estimated number of deaths

- 1.77 million (27 per 100,000)
- ~150,000
- ~30,000
- 456,000

(Updated March 2009)
HIV Prevalence Among TB Cases, 2007

Global estimate: about 1.4 million TB/HIV cases and 450,000 TB/HIV deaths a year

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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Invention of BCG – The World’s Most Widely Used Childhood Vaccine (> 100 million doses/year)

By Calmette & Guérin
1906-1921
No new TB Vaccine in 88 years
The vaccine against tuberculosis that is routinely given to 75 percent of the world’s infants is too risky to give to those born infected with the AIDS virus, says a new study published by the World Health Organization. It recommended that vaccination be delayed until babies can be tested.
WHO 2007 Recommendations on BCG

- Children with HIV infection regardless of symptoms should not be BCG vaccinated
  - BCG immunized asymptomatic HIV infected children at later risk of disseminated BCG

- All high risk infants need HIV screening
  - Maternal antibody masks antibody tests
  - Detection of virus required
  - Very difficult to implement in many places

- Disseminated BCG in HIV infected infants recently (2009) estimated by Hesseling et al to be 992 per 100,000 (95% CI: 567–1495).

### Variable Efficacy of BCG vs. Pulmonary TB

#### Vaccine Efficacy (%)

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<thead>
<tr>
<th>Population</th>
<th>Vaccine Efficacy (%)</th>
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<td>British School Children</td>
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<td>N. American Indians</td>
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<td>USA (Chicago Infants)</td>
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<td>Puerto Rico (Gen. Pop.)</td>
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<td>S. India (Madanapalle)</td>
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<td>Colombia (Cali)</td>
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<td>Argentina (Santa Fe).</td>
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<td>Togo (Lome)</td>
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<td>Thailand</td>
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**Legend:**
- Controlled Trials
- Case-Control Studies
- Contact Studies
Results of SATVI/Aeras trial in over 10,000 infants in Worcester S.A. of BCG given at birth

18 month TB incidence = 4.5%
A new, safer and more effective TB vaccine regimen against Drug sensitive, MDR & XDR TB For HIV (+) and HIV (-) Infants, Adolescents and Adults Is required
Potential Uses of a TB Vaccine

Block Initial Infection

Prevent Early Disease

Prevent Latent Infection

Prevent Reactivation Disease
TB (all types) Mortality

- Neonatal pre-exposure
- Neonate pre-exposure + add effects
- Post-exposure
- Mass pre-exposure
- Mass pre-exposure + post-exposure

Abu-Raddad, Sabatelli, Achterberg, Sugimoto, Longini, Dye and Halloran
A New TB Vaccine is required to Eliminate of TB by blocking transmission

Cumulative Cases and Deaths Prevented by 2050 in Asian Region (millions)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
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<tbody>
<tr>
<td>Neonatal pre-exposure</td>
<td>18.2 (14%)</td>
<td>3.0 (13%)</td>
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<tr>
<td>Post-exposure</td>
<td>30.1 (23%)</td>
<td>5.0 (22%)</td>
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<tr>
<td>Mass pre-exposure</td>
<td>68.2. (52%)</td>
<td>11.5 (49%)</td>
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<tr>
<td>Mass pre-exposure + post-exposure</td>
<td>80.2 (61%)</td>
<td>13.5 (59%)</td>
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</table>

Abu-Raddad, Sabatelli, Achterberg, Sugimoto, Longini, Dye and Halloran
Prime –Boost Regimen for Infants

Recombinant BCG

IM or as an aerosol

Capsids in bacteria orally or as an aerosol

14- 24 Weeks

10 -14 Weeks
Regimens for Adolescents and Adults Previously Immunized with BCG

- rProtein + Adjuvant
- Viral Vector IM or as Aerosol
- Viral Vector 1
- Capsids in bacteria or as Aerosol
- rProtein + Adjuvant
- Viral Vector IM or as Aerosol
- Viral Vector 2
- Capsids in bacteria or as Aerosol
## Current TB Vaccine Pipeline

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<tr>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase IIB</th>
<th>Phase III</th>
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<tr>
<td>Other rBCG rMtb</td>
<td>AERAS rBCG</td>
<td>VPM 1002</td>
<td>Recombinant BCGs for priming infants</td>
<td>AERAS 402/ Crucell (2009)</td>
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<tr>
<td>AERAS Other Virus</td>
<td>AERAS 405 Capsid</td>
<td>AdAg85A</td>
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<td>MVA85A/AERAS 485</td>
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<tr>
<td>Other Protein PSS</td>
<td>HyVac4/AERAS 404</td>
<td>Hybrid 1 SSI</td>
<td></td>
<td>Recombinant fusion proteins for boosting infants, adolescents, young adults, HIV positive</td>
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<tr>
<td>AERAS PSS</td>
<td></td>
<td></td>
<td>GSK M72</td>
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*Replication-deficient viral vectored vaccines for boosting infants, young adults & HIV positive
Recombinant fusion proteins for boosting infants, adolescents, young adults, HIV positive*

April 2009
**AERAS GLOBAL TB VACCINE FOUNDATION**

*Ag85*-specific IFN-γ Producing CD8+ T cells (Hanekom Assay)

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**Point:** Median; Box: 25%-75%; Whisker: Non-Outlier Range

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Tice rBCG30 Group

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Day 0
Day 56
Day 112
Day 252

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* rBCG30 is more immunogenic than its TICE BCG parent for induction of antigen specific CD8+ T cells in humans by over-expression of Ag85B

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* *p=0.05 by Wilcoxon matched pairs test*
AERAS GLOBAL TB VACCINE FOUNDATION

SSI Danish BCG

AERAS-401 (Perfringolysin)

AFRO-1

Parent BCG Strain

Endosome Perturbation:
- Increased Safety
- Increased Immunogenicity

Research Vaccine strain
Endosome Perturbation:
- Increased Safety
- Increased Immunogenicity
Over-expression Ag85A, Ag85B, Ag10.4 from Kanamycin containing Plasmid
Enhanced Expression of Ag85A and Ag85B in Culture Supernatant of AFRO-1

1. Mr standard
2. Purified Ag85 complex
3. BCG Danish 1331
4. rBCG-AFR-01
5. Mr standard
Increased Safety of rBCG with endosome pertubation in Immunocompromised SCID Mice

Experiment #225: SCID data (wk 65)
Immune Response (IFN-γ expression) in Guinea Pigs Vaccinated with BCG or rBCG (AFRO-1) (assayed at Colorado State Univ)

**Ag85A**

Mean mRNA Fold Induction (sd)

- BCG (SSI)
- BCG (Liquid 10^4 CFU)
- BCG (Liquid 10^5 CFU)
- AFRO-1 (10^4 CFU)
- AFRO-1 (10^5 CFU)

**Ag85B**

Mean mRNA Fold Induction (sd)

**Mtb10.4**

Mean mRNA Fold Induction (sd)
AERAS-rBCG AFRO-1 provides a better prime than BCG in NHP for boosting with AERAS-402 Ad35 Crucell

![Ag85B Stimulation of whole blood graph](image-url)
AERAS-rBCG vaccines being compared for Clinical Trials Q2 2010

- **AERAS-422**
  - Endosome perturbation for increased safety
  - Plasmid expression of Ag85A, Ag85B, Rv3407

- **AERAS-418**
  - Endosome perturbation for increased safety
  - Chromosomal expression Ag85A, Ag85B, Rv3407, RpfA, C, D, DosR regulon (>50 Ag)

- **AERAS-440**
  - Non-replicating PanCD mutant for further safety
  - Same endosome perturbation and Ag over-expression as AERAS-418
rBCG with plasmid over expression of antigens without antibiotic resistance markers – AERAS-422

SSI Danish BCG
AERAS-401 (Perfringolysin)
AERAS-413
Pan CD
AERAS-422

Parent Strain
Endosome Perturbation:
Increased Safety
Increased Immunogenicity
Auxotrophic Mutation
Cannot Grow in absence of Pantothenic Acid
Multicopy Plasmid with Ag85A, Ag85B and Rv3407 Complements panCD
No antibiotic resistance
Over Expression of Transgenes from AERAS-422 (Similar to AFRO-1)
Construction of AERAS-418

SSI Danish BCG

AERAS-401 (Perfringolysin)

AERAS-418

ΔnuoG

Parent Strain

Endosome Perturbation:
Increased Safety
Increased Immunogenicity

Pro-apototic- ΔnuoG
Chromosomal Over Expression of 50 antigens
OsR Regulon Expression
AERAS-418 v BCG 1331
### Scoring of Antigens Over-expressed/Up-regulated in AERAS-418 – From List of Top 45

<table>
<thead>
<tr>
<th>Antigen 1</th>
<th>Antigen 2</th>
<th>Antigen 3</th>
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<tbody>
<tr>
<td>Rv1738</td>
<td>Rv1733c</td>
<td>Rv2029c</td>
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<td>Rv2450c</td>
<td>Rv1996</td>
<td>Rv2627c</td>
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<td>Rv2623</td>
<td>Rv2389c</td>
<td>Rv2780</td>
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<td>Rv1009</td>
<td>Rv0685</td>
<td>Rv1884c</td>
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<td>Rv0867c</td>
<td>Rv2628</td>
<td>Rv2620c</td>
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<tr>
<td>Rv2031c</td>
<td>Rv1980c</td>
<td>Rv2744c</td>
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<td>Rv1886c</td>
<td>Rv3804c</td>
<td>Rv3875</td>
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<td>Rv0288</td>
<td>Rv0079</td>
<td>Rv1926c</td>
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<tr>
<td>Rv2032</td>
<td>Rv3130c</td>
<td>Rv2030c</td>
</tr>
<tr>
<td>Rv2626c</td>
<td>Rv3131</td>
<td>Rv3132c</td>
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<tr>
<td>Rv3873</td>
<td>Rv0824c</td>
<td>Rv3347c</td>
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<tr>
<td>Rv2005c</td>
<td>Rv1908c</td>
<td>Rv0467</td>
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<td>Rv3127</td>
<td>Rv1174c</td>
<td>Rv1130</td>
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<td>Rv1349</td>
<td>Rv1169c</td>
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<td></td>
<td>Rv1813c</td>
<td>Rv1793</td>
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<td></td>
<td>Rv2006</td>
<td>Rv2629</td>
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</tbody>
</table>

32/45 top scoring antigens by bioinformatics analysis directly over-expressed or up-regulated in AERAS-418
Construction of non-replicating AERAS-440

SSI Danish BCG

AERAS-401 (Perfringolysin)

AERAS-413
Pan CD

AERAS-440

Parent Strain:
Endosome Perturbation:
Increased Safety
Increased Immunogenicity

Auxotrophic Mutation
Cannot Grow in absence
of Pantothenic Acid

Chromosomal over-
expression of 50 antigens
Boost Regimens

- **Recombinant BCG**
  - Newborn
  - 10 - 14 Weeks
  - Capsids in bacteria orally or as an aerosol

- **Protein with Adjuvant**
  - IM or as an aerosol
  - 14 - 24 Weeks
  - 10 - 14 Weeks

- **Viral Vector**
  - Capsids in bacteria

- **Capsids in Bacteria**
  - 14 - 24 Weeks
GSK Mtb72F in ASO-1E Adjuvant

Skeiky et al (2004); J. Immunol

Corixa/ GSK/Aeras
NHP Challenge Study with M72 vaccine

Reed et al
PNAS 2009
GSK M72 fusion protein induces CD4+ T cells in naïve and BCG vaccinated humans

CD4 only
Safety of M72/AS01E in 37 HIV positive adults with CD4>200 on ARV

- Well tolerated and no vaccine-related serious AEs were reported.
- Causally related AEs were mainly local, transient and lasted usually between 1-3 days and resolved without sequelae in all groups.
- Mild and moderate injection site pain, fatigue and headache were the most frequently reported solicited AEs.
- The M72/AS01E vaccine had no clinically relevant adverse effect on biological safety tests, HIV viral load and CD4 count and on individual HAART regimens.

1Gambillara, E. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention. Cape Town, SA, 2009
Frequency of M72-specific CD4+ T-cells expressing at least two markers among CD40-L, IL-2, IFN-γ and TNF-α (ICS)

- Robust induction of M72-specific CD4+ T cells after vaccination.
- No immune response with AS01E or saline
  - Increase of response from dose 1 to dose 2
Functional characterisation of M72-specific CD4+ T cells expressing at least two immunological markers on Day 60

Profile: CD40-L = IL-2 > TNF-α > IFN-γ
Targets CD46 on Human Dendritic Cells
Low African seroprevalence (<2% with neut >200)
E1 & Part of E3 deleted
• Makes room for TB antigens (85A, 85B, 10.4)
• Can’t replicate in humans
Grows to high titer in PerC6 cells
• Ad5 E1 in PerC6 chromosome
• Ad5 E4 Orf6, 6/7 put in Ad35
• Ad35 pIX put back
Longitudinal Polyfunctional CD4 response

AERAS GLOBAL TB VACCINE FOUNDATION
Longitudinal Ag85-specific CD4 T cell subset analysis (Group 3)
Aeras Study C-008-402
DSMO subtracted Ag85A/b CD8 Response
BCG/AERAS-402 (3x10^{10} vp)
### % Responders* DMSO-subtracted ICS response C-008-402

<table>
<thead>
<tr>
<th>Cytokine Response</th>
<th>Antigen</th>
<th>14-Days Post 1st Boost (Day 98)</th>
<th>28-Days Post 1st Boost (Day 112)</th>
<th>14-Days Post 2nd Boost (Day 126)</th>
<th>28-Day Post 2nd Boost (Day 140)</th>
<th>98-Day Post 1st Boost (Day 182)</th>
</tr>
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<tr>
<td></td>
<td>Ag85A/b</td>
<td>42.9% (3/7)</td>
<td>62.5% (5/8)</td>
<td>50% (4/8)</td>
<td>71.4% (5/7)</td>
<td>37.5% (3/8)</td>
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<td>TB 10.4</td>
<td>57.1% (4/7)</td>
<td>50% (4/8)</td>
<td>25% (2/8)</td>
<td>42.9% (3/7)</td>
<td>71.4% (5/7)</td>
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<tr>
<td></td>
<td>Ag85A/b</td>
<td>85.7% (6/7)</td>
<td>87.5% (7/8)</td>
<td>50% (4/8)</td>
<td>85.7% (6/7)</td>
<td>87.5% (7/8)</td>
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<tr>
<td></td>
<td>TB 10.4</td>
<td>42.9% (3/7)</td>
<td>50% (4/8)</td>
<td>25% (2/8)</td>
<td>14.3% (1/7)</td>
<td>85.7% (6/7)</td>
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</table>
Aeras Study C-022-402
Ag85A/b - CD8
BCG/AERAS-402 (1x10^{11} vp)
N=11

DMSO-Subtracted %CD8 T cell Response

Study Day

0 84 98 112 126 140 182
Aeras Study C-003-402
DMSO subtracted Ag85A/b CD8 Response
Planned Treatment: AERAS-402 3x10^10 vp 2 doses (N=8)

BCG Experienced S. African Adults
Longitudinal Ag85-specific CD8 T cell subset analysis (Group 3)
BAL Responses to Ag85A post rAd35

4 Animals per group. Animals were immunized with AERAS rAd35 at three doses by Aerosol (4 μm) or at one dose IM. Animals were immunized at week zero and again at week 8.

Studies with NIH VRC
Bob Seder, Mario Roederer, & Gary Nabel
### Clinical Trials

#### UK studies
- BCG naive volunteers UK
- BCG-MVA 1 month apart UK
- BCG-MVA 10 years apart UK
- BCG-MVA 1 year apart UK
- Latency TB007
- Dose escalation TB009
- HIV infected TB010

#### Gambia studies
- BCG naive
- BCG primed
- Infant EPI non-interference TB012

#### South Africa Studies
- **Phase Ila**
  - Adults TB008
  - Adolescents TB008
  - Children TB014
  - Infants TB014
  - HIV/TB positive TB011

#### Senegal Studies
- **Phase I**
  - HIV positive adults TB019

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BCG priming enhances immune responses
[CD4] to Oxford MVA85A/ AERAS-485 TB vaccine

* p<0.05
** p<0.01
MVA85A/AERAS-485 induced antigen specific CD4+ T cells are highly polyfunctional

Beveridge N et al, EJI 2007
Studies with MVA85A in 61 HIV+ subjects

- CD4 > 350, no anti-retrovirals
  - UK: 18 +/- TB infection
  - S. Africa: 12 + TB infection
    7 - TB infection
  - Senegal 12 +/- TB infection
- CD4 > 350 on ARV
  - S. Africa 12
- Safety profile excellent
  - No effect on viral load or CD4 count
Immunogenicity of MVA85A in HIV infected subjects UK (n = 8)
Aeras Partnerships in Clinical Development

- St John’s Research Institute, India
- KEMRI/CDC, Kenya
- Makerere University, Uganda
- Aurum Institute, Johannesburg, South Africa
- Cambodian Health Committee, Cambodia
- Manhiça Health Research Center, Mozambique
- SATVI/University of Cape Town, South Africa
SATVI Research Site

- Tulbagh
- And
- Wolseley
- Rawsonville
- Ceres
- De Doorns
- Worcester
- Breede River
- Cape Town 110 km
Vaccine Efficacy Trials in Infants

- **MVA85A/AERAS-485**
  - First efficacy trial of a new TB vaccine in infants in more than 80 years (proof of principle)
  - 2,800 infants – 90% power for 60% efficacy compared to BCG
  - In collaboration with SATVI, Oxford-Emergent Tuberculosis Consortium (OETC) and Wellcome Trust

- **AERAS-402/Crucell Ad35**
  - Planned multicenter study including SATVI (South Africa), Makerere University (Uganda), KEMRI/CDC (Kenya), Manhiça Health Research Centre (Mozambique)
  - In collaboration with EDCTP and Crucell

- **GSK M72** to be tested late 2010

- **AERAS-rBCG** to be tested in infant Phase III non-inferiority trial vs BCG in 2012
MVA85A/AERAS-485 Phase IIb Proof of Concept Efficacy Trial
First infant vaccinated 15 July, 2009, by the South African Tuberculosis Vaccine Initiative (SATVI)
MVA85A/AERAS-485 Phase IIb Proof of concept efficacy Trial
Safety & Proof of Principle in HIV+ subjects with Latent TB infection not on HART with CD4>350 given prophylactic INH

- AERAS-402/Cruccell Ad35 to begin Nov 2009 S. Africa in collaboration with Aurum Institute (Gavin Churchyard) Adaptive design 1200-2000 subjects
- MVA85A/AERAS-485 in HIV + subjects in 2010 (Aeras & EDCTP sponsorship)
Summary

• Four Aeras sponsored Vaccines in clinical trials in Africa with two more to enter in 2010

• Recombinant protein + adjuvant and non-replicating viral vectored TB vaccines thus far appear safe and immunogenic as boosters in HIV + individuals

• Proof of concept studies underway in infants and about to start in HIV+ adults

• New TB vaccines for infants & adults (regardless of HIV status) in 2014-16
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