New Tuberculosis Vaccines
Developmental Strategies

Michael Brennan, Ph.D.
Aeras

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The Potential of New TB Vaccines

A new, more effective TB vaccine could:

• Be safer and more effective in preventing TB in children, adolescents and adults, including people with HIV (for whom BCG is unsafe)

• Protect against all forms of TB – including MDR and XDR

• Reduce the cost and burden of TB on patients, health care systems and national economies

• Contribute significantly to global efforts to eliminate TB
Better TB Vaccines

Reasons for Optimism

• Most people (80-90%) do not get disease when infected with Mtb = natural resistance

• Evidence of limited BCG vaccine efficacy in children

• New TB vaccine candidates provide some protection in animals

• New TB vaccines boost immune responses in early human clinical studies
TB Vaccine Development
A Decade of Progress but much more to do!

2000
No new preventive TB vaccines in clinical trials

2002
1st preventive vaccine enters clinical trials (MVA85A)

2009
1st Phase IIb proof-of-concept of preventive vaccine initiated

2011
15 vaccines have entered clinical trials, 12 currently in clinical trials

FUTURE

2012-15
Efficacy data from phase IIb studies

Goal – A new, more effective vaccine available by the end of the decade
Accomplishments of the TB Vaccine Community over the Past Decade

- Epidemiologic studies in endemic countries – incidence of disease
- Vaccine safety in Target populations: infants, HIV+, PPD+, QFN+
- Endpoints developed for adults, infants and HIV+ phase IIB & III trials
- Incorporate Immunoassays in trials: T cell assays
- Boost BCG vaccinees in trials w new vaccines
- Regulatory/ethics approval of trials in endemic countries
- Community acceptance & participation
Key Questions and Critical Activities

- Why are certain Mtb infected individuals resistant to TB disease?
- Can vaccines prevent infection and provide sterilizing immunity?
- Is it possible to develop a useful human challenge model for TB?
Correlates of Immunity and Biomarkers for TB Vaccines

Identify mechanisms of protective immunity for tuberculosis
- need Correlate of Immunity
- need to define a Surrogate in vaccine trial
- need Biomarkers as readouts in vaccine trials
- define T cell pathways
- role of Antibodies in TB protection?
A Blueprint for TB Vaccine Development

Key Questions and Critical Activities

Next Generation Vaccines & Target Populations

- Develop a pipeline of 2nd generation candidates, novel vaccine constructs and new delivery platforms
- Define realistic target product profiles for individual candidates
- Prepare for population-based trials in adolescents and adults that impact transmission in populations
- Engage emerging countries in research, development, and production of new TB vaccines
### Meeting the Public Health Need

**Active Disease**

- Infants
- Adolescents
- Adults
- HIV+ All Ages

**Latently Infected**

- Infants
- Adolescents
- Adults
- HIV+ All Ages

**Pre-infection**

- Infants
- Adolescents
- Adults
- HIV+ All Ages

- Covered by existing vaccine
- No coverage or impact from existing vaccine

- Target vast, unmet need for new, more effective TB prevention in multiple populations
- Potential replacement and/or boost for widely used BCG:
  - 180 countries recommend BCG
  - 100M+ doses per year
A Blueprint for TB Vaccine Development

Key Questions and Critical Activities

Advocacy, Resource Mobilization & Regulatory Strategies

• Expand on efforts to raise awareness of TB and role of new TB vaccines as part of a comprehensive response – build support at all levels

• Broaden the base of advocates for TB and vaccines R & D

• Expand financing to provide sufficient resources to advance and sustain the field of TB vaccine development

• Identify creative new regulatory approaches to clinical trial approval and vaccine licensure
Traditional Approach to Vaccine Approvals

R & D
Manufacturing
Clinical Testing
Regulatory Approval

TB Vaccines: New Paradigm- Approval in TB Endemic Countries
<table>
<thead>
<tr>
<th>TB Vaccine</th>
<th>Clinical Site</th>
<th>Clinical Trial</th>
<th>Regulatory Authority</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA85A/AERAS-485</td>
<td>South Africa, Senegal</td>
<td>Phase IIb, Phase IIb</td>
<td>MCC, CNERS</td>
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<td>AERAS-402/Crucell Ad35</td>
<td>US, India, South Africa, Kenya, Mozambique, Botswana, Uganda</td>
<td>Phase I, Phase I, Phase I; Phase IIb, Phase IIb, Phase IIb</td>
<td>FDA, DCGI, MCC, KEMRI, MoH, DRU, NDA</td>
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<tr>
<td>SSI/SP H4-IC31</td>
<td>India, Sweden, Finland, South Africa, Switzerland</td>
<td>Phase I, Phase I, Phase I</td>
<td>DCGI, MCA, FICORA, MCC, CHUV</td>
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<tr>
<td>AERAS-422</td>
<td>US, South Africa</td>
<td>Phase I, Phase I</td>
<td>FDA, MCC / DAFF</td>
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<tr>
<td>SSI H56-IC31</td>
<td>South Africa</td>
<td>Phase 1</td>
<td>MCC</td>
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Regulatory Strategies for TB Vaccines

- Reviews by Stringent Regulatory Authorities (EMA, FDA)
- Work with National Regulatory Authorities (NRAs) in Emerging and Developing countries
- Use WHO programs:
  - Prequalification
  - SAGE Recommendations and Guidelines
  - Joint Review Initiatives (DCVRN, AVAREF)
WHO Recommendations for TB Vaccine use via SAGE

Critical Path for Vaccines: clinical trials and RA approval
New TB vaccines could have a significant impact on the global TB epidemic

Tremendous progress is being made in the field of TB vaccine development, with two preventive vaccine candidates now in Phase IIb trials

Manufacturing capacity being developed and manufacturing agreements are being explored with particular emphasis on emerging country manufacturers

Regulatory pathways and market and economic impact research being conducted now to lay the groundwork to accelerate adoption and uptake of new TB vaccines

Scientific, infrastructure and financial challenges remain; solutions will require global partnership and commitment

With sufficient resources and positive results for current clinical trials, a new TB vaccine could be available by the end of the decade