Recent Advances in Tuberculosis

7th EDCTP Forum
30 June, 2014
Berlin, Germany

Ann M. Ginsberg, MD, PhD
Chief Medical Officer

AERAS | Advancing Tuberculosis Vaccines for the World
TB Is #1 Infectious Killer over the Centuries

- Airborne transmission
- 8.6 million new cases and 1.3 million deaths in 2012
- Kills 1 in 4 people infected with HIV; 13% of TB is in HIV+ individuals.
- 530,000 annual cases among children under 15 years old
- 410,000 women killed annually by the disease
- MDR/XDR-TB on the rise; XDR-TB identified in 92 countries

TB Will Not Be Eliminated by 2050

-2%/yr: Current rate of decline globally

-4%/yr: China, Cambodia (the best observed currently)

-10%/yr: W Europe after WWII (Historical example)

-20%/yr: Elimination target:<1/million/yr

Today TB incidence ~1000x higher than elimination target for 2050
Projected Acceleration of TB Incidence – the Road to Elimination

Optimize current tools, pursue universal health coverage and social protection

Introduce new vaccine, new latency prophylaxis

Current global trend: -2%/year

Average -17%/year

Average -10%/year

Average -5%/year
TB FORCES FAMILIES AND COMMUNITIES INTO THE CYCLE OF POVERTY

TB is unaffordable and causes severe economic challenges for families.

250,000 children develop TB each year, 100,000 die from it, a 40% mortality rate.
## Economic Impacts of TB

**FAMILY**

TB primarily strikes down working-age adults.

A study in Ghana, Vietnam and the Dominican Republic found that despite TB diagnosis and treatment being provided for free, the average total patient costs equal approximately one year of individual income.

**COUNTRIES**

TB costs the global economy an estimated $1B each day (World Bank report 2007).

The economic burden of TB between 2006 and 2015 for the 22 high-burden countries is estimated to be $3.4 trillion.

**BUSINESS SECTOR**

Annual cost to the South African mining sector is over $880 million.

Worldwide, TB is estimated to cost the global economy 0.52% of gross national income per year in lost productivity and wages.

**GROWING COST OF DRUG-RESISTANT TB**

Cost of treatment for MDR - $12,462 per patient in highest burden countries, £50,000-70,000 in the UK, and $250,000 in the U.S.

Hospitalization for one XDR patient: $500,000 - $1M in Australia or the U.S.
Controlling and Reducing TB Incidence Requires the Application of Transformational Interventions

- Prevent transmission and infection
- Block progression to infectious TB
- Diagnose, treat and/or sterilize active TB

Modified from Gilla Kaplan, Bill & Melinda Gates Foundation
## Current TB Tools and Unmet Needs

<table>
<thead>
<tr>
<th>Tool</th>
<th>Unmet Needs</th>
</tr>
</thead>
</table>
| **Diagnostics** | ✓ Estimated 1/3 new cases are missed each year  
• Rapid, accurate and affordable tests  
• Suitable for use at point-of-care  
• Able to rapidly identify all drug-resistant strains of TB |
| **Drugs**   | • Faster, simpler regimens  
• Effective against drug sensitive and drug resistant TB  
• Compatible with ARVs  
• Extra-short course therapy for latent TB infection suitable for mass campaigns  
• Pediatric formulations |
| **Vaccines** | • Effective, affordable  
• Protective against all forms of TB – pre and post-infection  
• Suitable for use in children, adolescents and adults  
• Safe for use in people infected with HIV |
Advances in TB Diagnostics

- Liquid culture and DST
- Rapid speciation
- LPA for MDR-TB
- Non-commercial culture and DST (MODS, NRA, CRI)
- LPA for XDR-TB
- LPA for MDR-TB second generation

Reference level laboratories
- New SS+ case definition
- Two-specimen approaches
- LED microscopy
- Same-day diagnosis
- Xpert MTB/RIF
- Manual NAAT
- Xpert second generation

Intermediate level laboratories
- VOC detection
- Enzymatic detection
- Ag and Ab detection
- NAAT second generation

Peripheral level laboratories
- Technologies or methods endorsed by WHO
- Technologies commercialised, not yet endorsed by WHO
- Technologies at feasibility stage
- Technologies at early stages of development

Crucial Next Generation TB Diagnostics

- Point of care diagnostic
- Drug susceptibility testing for 1\textsuperscript{st} and 2\textsuperscript{nd}-line drugs
  - Rapid
  - Affordable
  - Sensitive
  - Specific
Progress in Drug Development
Advances in TB Drug Development (Active TB)

- Recently approved, novel drugs for MDR-TB:
  - Bedaquiline (J&J; US FDA, 2012; Russia, 2013; EMA, 2014)
  - Delamanid (Otsuka; EMA; 2013)

- Recently completed Phase 3 trials:
  - Rifaquin: see presentation by A. Jindani
  - 4-month, fluoroquinolone-based, treatment-shortening regimens for DS-TB
    - Oflutub/gati (IRD, WHO, EC)
    - REMox-TB (TB Alliance, EDCTP, Bayer) – Results not yet announced

- Ongoing Phase 3 trials:
  - Delamanid (Otsuka) – added to MDR regimen
  - STREAM - 9 month MDR regimen [4KCMEHZP/5MEZC]
    [van Deun et al 2010, AJRCCM 182:684-92]; adding Bedaquiline-containing arm(s)?

- Phase 3 trials in planning: STAND; NExT (MDR); NiX-TB (XDR)
Global TB Drug Pipeline

Preclinical Development

Early Stage Development
- CPZEN-45
- BTZ043
- DC-159a
- SQ609
- SQ641
- TBI-166

GLP Tox.
- PBTZ169
- TBA-354
- Q203

Clinical Development

Phase I
- AZD5847
- Bedaquiline
- Linezolid
- PA-824
- Rifapentine
- SQ-109
- Sutezolid

Phase II
- Delamanid
- Gatifloxacin
- Moxifloxacin
- Rifapentine

Phase III

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

Details for projects listed can be found at [http://www.newtbdrugs.org/pipeline.php](http://www.newtbdrugs.org/pipeline.php) and ongoing projects without a lead compound series identified can be viewed at [http://www.newtbdrugs.org/pipeline-discovery.php](http://www.newtbdrugs.org/pipeline-discovery.php).

Drug candidate currently in combination regimen in clinical testing

Submitted for approval or approved by stringent regulatory authority (i.e., FDA, EMA, WHO Prequalification)

New chemical entity
Paradigm Change in TB Drug Development

**CURRENT REGIMEN DEVELOPMENT PARADIGM:**

- New Drug 1
- New Drug 2
- New Drug 3
- New Drug 4

**NOVEL COMBINATION TESTING PARADIGM:**

- New Drug 1
- New Drug 2
- New Drug 3
- New Drug 4

Existing regimen consists of four drugs

Fully novel regimen
Upcoming Phase 3 Trials of Novel Regimens
STAND: A Global Phase 3 Trial
Shortening Treatments by Advancing Novel Drugs

• The STAND trial will test PaMZ regimen
• PaMZ = PA-824, moxifloxacin, and pyrazinamide
• First Phase 3 trial to test a regimen in patients with drug-sensitive and drug-resistant TB (must be sensitive to drugs in the regimen)
• Holds potential to transform treatment of both drug-sensitive and especially drug-resistant TB
Phase 3: MDR-TB Treatment-shortening

6 months investigational regimen vs. 24 months conventional regimen
N=100 per arm

From Keertan Dheda, TB2014, Durban, SA; June 2014
**NiX-TB: Accelerating solutions for XDR-TB**

New Investigational Drugs for XDR-TB

- First clinical trial for a new XDR-TB treatment
- Tests “universal” regimens, with no pre-existing resistance
- Regimen includes bedaquiline, PA-824, and linezolid; may substitute a potentially safer oxazolidinone when it becomes available
- Potential to be a 6 month oral treatment option for XDR-TB
- NiX-TB will launch at 2-3 sites in South Africa by the end of 2014

Novel treatments to fight XDR-TB are urgently needed. A 2014 *Lancet* study found nearly half of XDR-TB patients died within a year of diagnosis, and an additional 30% failed treatment or defaulted.
Factors Influencing the Outcome of *M. tb* Infection

*New Approach to Host-directed Therapy?*

Mayer-Barber et al, Nature (June 2014)
Progress in Vaccine Development
New Vaccines Are Urgently Needed

![Vaccine Coverage Matrix]

- **Active Disease**
- **Latent**
- **Pre-Infection**

- **Infants**
- **Adolescents**
- **Adults**
- **HIV+ All Ages**

- **Covered by existing vaccine**
- **No coverage or impact from existing vaccine**
The Potential of New TB Vaccines

The goal is to deliver new TB vaccines that would:

- Be safer and more effective in preventing TB in children, adolescents and adults, including people with HIV
- 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
- Play a crucial role in global efforts to control TB
Potential World-wide Health Impact of New Adult and Infant TB Vaccines

Conservative estimate: >30M cases averted over 20 years

Immunization of infants, adolescents, adults with a 60% efficacious vaccine:
- 90% coverage rate for infants;
- 20% coverage rate for adolescents and adults
# TB Vaccines: Global Clinical Portfolio

<table>
<thead>
<tr>
<th>PHASE I</th>
<th>PHASE IIa</th>
<th>PHASE IIb</th>
<th>PHASE III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad5 Ag85A</td>
<td>VPM 1002</td>
<td>MVA85A/AERAS-485</td>
<td>M. Vaccae</td>
</tr>
<tr>
<td>McMaster CanSino</td>
<td>Max Planck, VPM, TBVI, SII</td>
<td>Oxford, Aeras</td>
<td>Anhui Zhifei Longcom, China</td>
</tr>
<tr>
<td>MTBVAC</td>
<td>H1 + IC31</td>
<td>M72 + AS01E</td>
<td></td>
</tr>
<tr>
<td>TBVI, Zaragoza, Biofabri</td>
<td>SSI, TBVI, EDCTP, Intercell</td>
<td>GSK, Aeras</td>
<td></td>
</tr>
<tr>
<td>ID93 + GLA-SE</td>
<td>RUTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDRI, Aeras</td>
<td>Archivel Farma, S.L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crucell Ad35/MVA85A</td>
<td>H4: IC31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crucell, Oxford, Aeras</td>
<td>SSI, Sanofi-Pasteur, Aeras, Intercell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAR-901</td>
<td>H56: IC31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dartmouth, Aeras</td>
<td>SSI, Aeras, Intercell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB/FLU-04L</td>
<td>Crucell Ad35/AERAS-402</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIBSP</td>
<td>Crucell, Aeras</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Therapeutic Categories:**
- **VIRAL VECTOR**
- **PROTEIN/ADJUVANT**
- **MYCOBACTERIAL – WHOLE CELL OR EXTRACT**
- **rBCG**
- **ATTENUATED M. Tb**
Clinical Trials – ‘Shift to the Left’

• **Phase I/IIa**: intensive immunologic studies to see if novel animal data can be reproduced in humans; answer key vaccinology questions
  – measure safety, assess immune response, generate human samples for investigation, head to head comparisons; compare different delivery routes, etc.

• **Phase II**: Proof of Biological Activity (‘PoC’)

  *In both Prevention of Infection and Prevention of Recurrence studies, samples collected for correlates of infection or correlates of risk*
Novel Approaches: exploring likelihood of success at lower cost

1. RCT: compare vaccines’ efficacy in preventing MtB infection

2. RCT: compare vaccines’ efficacy in preventing recurrent TB disease

Example:
1. BCG vs Hyvac4 vs placebo to start at SATVI; n=990 total
2. Ongoing adaptive trial setting, allowing future testing of other candidates

Examples:
1. H56 vs placebo planned at multiple sites by Aeras; n~800 total
2. ID-93 vs placebo planned at SATVI; n=800 total
Incidence of recurrent TB disease at least 5% in 1st year

• Consider prevention of TB disease trials in other high risk populations, e.g., prisoners, health care workers, household contacts of adults with lung TB

In both Prevention of Infection and Prevention of Recurrence studies, samples collected for correlates of risk and/or prevention
TB Vaccine Development: recent highlights

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

2014
>15 vaccines currently in clinical trials

• Phase 2b trial in 2800 infants successfully completed in 2013 - no efficacy seen/modest immune response generated in infants boosted at age 4-6 mo. using MVA85A
• Recent NHP studies have shown ability of novel constructs to protect in a highly stringent model that resembles human tuberculosis
• Increased diversity of candidates in pipeline
• Correlate of risk of TB disease/correlate of protection studies underway
• Development of a human challenge model initiated
• Capacity and infrastructure development for large-scale trials enhanced
• Epidemiological cohort studies for baseline incidence conducted in several countries
The Road to TB Elimination
Some Key Unanswered Questions

- What are the main factors driving differences in transmission and incidence among different locales?
- Where is transmission happening in each locale?
- How can we most cost-effectively improve the quality of the data globally?
- What enables 90% of infected individuals to contain the infection? What is the human protective immune response?
The Road to TB Elimination

- **Stop transmission**
  - Earlier point of care diagnosis
  - Safe, effective vaccine – hot spot strategy for delivery?

- **Neutralize latent infection – prevent reactivation**
  - Vaccine (or ultra-short drug regimen) delivered globally

- **Treat active TB appropriately**
  - Universal health care
  - DOTS until better regimens available
  - Rapid DST for all drugs
    - [9% MDR cases in 2011 were diagnosed and notified; Raviglione et al, Lancet 2012]
  - Shorter, simpler drug regimens

**Keys:**
- Strong basic science foundation
- Committed leadership
- Advocacy
- Resources
Special thanks to the sites and participants in our clinical trials!
And thanks to TB Alliance, WGND and Aeras colleagues for slides and input
Thank you.

aginsberg@aeras.org
www.aeras.org

TB anywhere is TB everywhere.