The promise of new TB vaccines: The role of TBVAC2020

Stefan H.E. Kaufmann
Max Planck Institute for Infection Biology, Berlin
Chair TBVAC2020 Steering Committee

TBVI Symposium
Innovation in the TB vaccine field
TBVAC2020 kick-off meeting

10 February 2015
IJmuiden, The Netherlands
Agenda

• The problem
• The future
• The promise of new TB vaccines
• Potential complications & solutions
• European perspective: TBVI and TBVAC2020
• A broader picture: GTBVP
• Conclusions
Agenda

• The problem
• The future
• The promise of new TB vaccines
• Potential complications & solutions
• European perspective: TBVI and TBVAC2020
• A broader picture: GTBVP
• Conclusions
TB: the biggest killer ever

No. of deaths in the past 200 years (source: Nature)
125,000 infections / day

2,000,000,000 latently infected

25,000 new cases / day

9,000,000 new TB cases annually

4,000 / day

1,500,000 TB deaths annually

Kaufmann, Immunity, 2010
...and this all costs money

...a lot of money

...more than generally appreciated
### Direct treatment costs of TB (excluding hospital and additional costs) in Germany / NL:

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Cost (€)</th>
<th>Cost (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive TB</td>
<td>7,700</td>
<td>100 – 500</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>55,000</td>
<td>9,200</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>188,000</td>
<td>48,500 (WHO 2014)</td>
</tr>
</tbody>
</table>

### Costs of TB including hospitalization (30 days for sensitive TB; 85 days for MDR-TB; > 4 months for XDR-TB) and productivity much higher based on Diel et al, ERJ, 2013

### High TB burden countries:

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Cost (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive TB</td>
<td>100 – 500</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>9,200</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>48,500 (WHO 2014)</td>
</tr>
</tbody>
</table>
Recent cost analysis by TBVI:

The financial burden of TB in Europe (estimated):

- Germany: 50 million €
- EU: 550 million €
- European region of WHO: > 3 billion €

The 15 high-burden countries of the European region according to WHO (only Bulgaria and Estonia EU members): 2.1 billion €

Calculated total loss (based on estimated monetary value of DALYs): 5.9 billion €

(based on Diel et al, ERJ, 2013)
Agenda

• The problem
• The future
• The promise of new TB vaccines
• Potential complications & solutions
• European perspective: TBVI and TBVAC2020
• A broader picture: GTBVP
• Conclusions
The Future of TB Control

Millennium development goal 6:

• Hold and reverse TB incidence by 2015
  Achieved

Stop TB Partnership:

• Reduce by 50% TB mortality and prevalence between 1990 and 2015

Unlikely to be reached, notably in Europe and Africa
The Future of TB Control

Post 2015 targets by Stop TB Partnership (WHO)

Initial proposal:

• Eliminate TB by 2050
  (< 1/1 million new cases)

Realistic?

Revised (approved by World Health Assembly 2014):

• 95% reduction in TB deaths

• 90% reduction in TB disease incidences (between 2015 and 2035)

Ambitious.
Projected acceleration of TB incidence decline to target levels

Optimize current tools, pursue universal health coverage and social protection

Introduce new vaccine

Current global trend: -2%/year

Average -10%/year

Average -17%/year

Rate per 100,000/year
Agenda

• The problem
• The future
• The promise of new TB vaccines
• Potential complications & solutions
• European perspective: TBVI and TBVAC2020
• A broader picture: GTBVP
• Conclusions
Protection:
• Against tuberculous meningitis and miliary TB in infants

Coverage:
• High (> 80%); part of the expanded program on immunization (EPI) for infants
• Ca. 100 million children BCG-vaccinated per year
  Ca. 4 billion vaccinations thus far

Safety:
• Very safe but adverse reactions possible
• Risk for HIV+ newborn

Cost:
• 0.1 – 0.5 US $ total (BCG, needle & syringe)

But:
• No reliable protection against pulmonary tuberculosis & transmission in all age groups (variable efficacies)
## Global Clinical TB Vaccine Pipeline

<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>Crucell Ad35 / Aeras402 B</td>
<td>MVA85A /Aeras-485 B</td>
<td>B</td>
</tr>
<tr>
<td>McMaster University, Can Sino</td>
<td>Crucell, Aeras (formerly PhIIb)</td>
<td>UOXF, AERAS</td>
<td>M. Indicus pranii IT Dpt of Biotechn (Gvt of India), Cadila</td>
</tr>
<tr>
<td>ID93 + GLA-SE IDRI, Aeras</td>
<td>VPM1002 P MPIIB, VPM, TBVI, SII</td>
<td>M72 + ASO1E GSK, Aeras</td>
<td>B</td>
</tr>
<tr>
<td>MTBVAC UniZaragoza, Biofabri, TBVI</td>
<td>RUTI Archivel Pharma</td>
<td></td>
<td>M. vaccae An Hui Longcom IT</td>
</tr>
<tr>
<td>DAR-901 Dartmouth University, Aeras</td>
<td>H I + IC31 Valneva, TBVI, Intercell, EDCTP</td>
<td></td>
<td>16 candidates P priming vaccine B boosting vaccine IT therapeutic vaccines</td>
</tr>
<tr>
<td>ChAdOx1.85A UOXF</td>
<td>H56 : IC31 Valneva, Intercell, Aeras</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crucell Ad35 – MVA85A prime-boost UOXF, Aeras, Crucell</td>
<td>H4 : IC31 Valneva, SP, Aeras</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Global Clinical TB Vaccine Pipeline

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
<th>Phaselll</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad5 Ag85A</td>
<td>Cruvell Ad35 / Aeras402</td>
<td>MVA85A /Aeras-485</td>
<td>B</td>
</tr>
<tr>
<td>McMaster University, Can Sino</td>
<td>Cruvell, Aeras</td>
<td>UO XF, AERAS</td>
<td></td>
</tr>
<tr>
<td>Phase IIa</td>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
<td></td>
<td>M. Indicus pranii</td>
</tr>
<tr>
<td>ID93 + GLA-SE</td>
<td>VPM1002</td>
<td>M72 + ASO1E</td>
<td>B</td>
</tr>
<tr>
<td>IDRI, Aeras</td>
<td>MPIIB, VPM, TBVI, SII</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
<td>B</td>
<td>M. vaccae</td>
</tr>
<tr>
<td>MTBVAC</td>
<td>RUTI</td>
<td>IT</td>
<td>An Hui Longcom</td>
</tr>
<tr>
<td>UniZaragoza, Biofabri, TBVI</td>
<td>Archivel Pharma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
<td></td>
<td>IT</td>
</tr>
<tr>
<td>DAR-901</td>
<td>H I + IC31</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Dartmouth University, Aeras</td>
<td>Valneva, TBVI, Intercell, EDCTP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>ChAdOx1.85A</td>
<td>H56 : IC31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UO XF</td>
<td>Valneva, Intercell, Aeras</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Crucell Ad35 – MVA85A</td>
<td>H4 : IC31</td>
<td>16 candidates</td>
<td></td>
</tr>
<tr>
<td>prime-boost</td>
<td>Valneva, SP, Aeras</td>
<td>P priming vaccine</td>
<td></td>
</tr>
<tr>
<td>UO XF, Aeras, Crucell</td>
<td></td>
<td>B boosting vaccine</td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
<td>IT therapeutic vaccines</td>
<td></td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
<td>Half of them</td>
<td>current/former TBVI</td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
<td>involvement</td>
<td></td>
</tr>
</tbody>
</table>
Agenda

• The problem
• The future
• The promise of new TB vaccines
• Potential complications & solutions
• European perspective: TBVI and TBVAC2020
• A broader picture: GTBVP
• Conclusions
The promise of new TB vaccines
Financial constraints

Cost and time for TB vaccine trials:
• Phase I for safety and efficacy: 500,000 US$, >2 year
• Phase IIa in target population: 1 million US$, >2 years
• Phase IIb for first proof of efficacy: 20 million US$, >5 years
• Phase III for ultimate safety & efficacy: 100 million US$, >6 years

Global funding for TB vaccine R&D: 250 million US$

Conclusion: We need to be selective.

Stages of development of new vaccines and gates

<table>
<thead>
<tr>
<th>Gate</th>
<th>From</th>
<th>To</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Discovery</td>
<td>Preclinical</td>
</tr>
<tr>
<td>B</td>
<td>Preclinical</td>
<td>Phase 1 – 1&lt;sup&gt;st&lt;/sup&gt; in man</td>
</tr>
<tr>
<td>C</td>
<td>Phase 1</td>
<td>Phase 2</td>
</tr>
<tr>
<td>D</td>
<td>Phase 2</td>
<td>Phase 3</td>
</tr>
<tr>
<td>E</td>
<td>Phase 3</td>
<td>Market authorization</td>
</tr>
<tr>
<td>F</td>
<td>MA</td>
<td>Introduction</td>
</tr>
</tbody>
</table>
How can we select better candidates?

shifting the risk curve . . .

- discovery
- preclinical
- Phase I
- Phase II
- Phase III

prediction of likely efficacy in preclinical plus early human

assessment of efficacy in Phase IIB clinical trial

RISK → MONEY
Agenda

• The problem
• The future
• The promise of new TB vaccines
• Potential complications & solutions
• European perspective: TBVI and TBVAC2020
• A broader picture: GTBVP
• Conclusions
TBVAC2020

• Jan 2015 until Dec 2018
• 25 M Euro
  – EC contribution 18.2 M Euro
  – 6.7 M co-financing
• 40 Partners (7 partners outside EU)
• We will introduce innovation / diversity
  We can build on previous consortium
TBVAC2020
Steering Committee

Chair – Stefan H.E. Kaufmann

WP1 – Discovery – WPL: Olivier Neyrolles, Else-Marie Agger, Steffen Stenger

WP2 – Preclinical models – WPL: Frank Verreck

WP3 – Preclinical evaluation of TB vaccine candidates – WPL: Ann Rawkins, Mei Mei

WP4 – Early clinical evaluation of TB candidates – WPL: Helen McShane

WP5 – Correlates of protection – WPL: Tom Ottenhoff

WP6 – Portfolio management – WPL: TBVI

WP7 – Project coordination – WPL: TBVI
Overall aims of the project in a nutshell

• **Diversify** the TB vaccine pipeline by introducing innovative approaches

• **Select** the most promising candidates by portfolio management

• **Work in global partnership**
Creativity in Research and Discovery

• Identify mechanisms of protective immunity
• Introduce new vaccine mechanisms
• Facilitate translational research, comparative preclinical studies and animal models
Correlates of Protection Biomarkers for TB Vaccines

• Explore novel approaches to identify correlates of protection
• Introduce novel assays in efficacy trials to help establish correlates of protection.
• Identify signatures of vaccine efficacy
Clinical trials: harmonization & cooperation

- Select trial sites and choose target populations
- Design clinical trials to determine efficacy using better defined clinical endpoints
- Address regulatory, ethical and sustainability issues
TBVAC2020

• Jan 2015 until Dec 2018
• 25 M Euro
  – EC contribution 18.2 M Euro
  – 6.7 M co-financing
• 40 Partners (7 partners outside EU)
• We will introduce innovation / diversity
• We can build on previous consortium
The European TB Vaccine Community

Les Diablerets
History of TBVAC & TBVI

2000 – 2004
Tuberculosis Vaccine Cluster:
EU FP 5 Integrated Project

2004 – 2010
TBVAC:
EU FP 6 Integrated Project

2007
EU R&D Commission
Supports creation of a separate entity

As of 2008:
• 6 new EU FP7 projects
  • Notably NEWTBVAC (2010-2013)
• Other projects:
  • Bill & Melinda Gates Foundation
  • Calouste Gulbenkian Foundation
  • EDCTP
  • Norwegian Government
  • DFID

05-03-2008: TBVI established

Today:
Kick-off TBVAC2020:
EU H2020 project
TuBerculosis Vaccine Initiative

• **TBVI**: Consortium of (mainly European) TB Vaccine Research Organisations to speed up vaccine development harnessing synergies between various programs and information sharing

• **TBVI**: Non-profit foundation with operational office to ‘service’ the TBVI consortium through financial and technical support
TBVI / TBVAC portfolio

**Phase IIb**
- MVA85A, University Of Oxford
- M72/AS01E, GSK/Aeras

**Phase IIa**
- rBCG VPM1002, VPM/MPIIB/SII
- Hybrid I + IC31, SSI/Valneva/EDCTP
- H56 + IC31, SSI/Valneva/Aeras

**Phase I**
- MTBVAC , Uni Zaragoza/Biofabri
- ChAdV/Ag85a, University of Oxford

**Preclinical**
- rBCG::Ais1/zmp1, Uni of Zürich/Aeras
- Native and rHBHA, IP Lille/Aeras

**Discovery**
- LCMV-based candidates, Uni Geneva
- ChAdV-based candidates, Uni Oxford
- rBCG::hly::nuoG, MPIIB
- Att. Mtb Rv1503c, CNRS Toulouse
- Mtb SigE::Fad26, Uni of Padua
- Inactivated MTBVAC, Uni Zaragoza
- M. tuberculosis ΔESX5, IP, Paris
- MTBVAC 2\(^{nd}\) gen., Uni Zaragoza
- M. microti MP Praha (ATCC 35782)::ESX-1, IP, Paris
- Latency, in vivo expressed and reactivation antigens, LUMC
- Latency antigens, GSK Biologicals
TBVI – Partners in R&D

Australia
- University of Sydney

Belgium
- Université Libre de Bruxelles
- Scientific Institute of Public Health
- University of Ghent
- GSK-Biologicals

Denmark
- Statens Serum Institute

France
- Centre National de la Recherche Scientifique
- Institut National de la Santé et de la Recherche Médicale
- Institut Pasteur (Paris)
- Institut Pasteur de Lille
- Institut Mérieux
- PX’ therapeutics

Germany
- Max-Planck Institute for Infection Biology
- University of Ulm
- Vakzine Projekt Management GmbH
- Paul Ehrlich Institute

Italy
- University of Palermo
- Istituto Superiore Di Sanità
- University of Padua
- IRCCS Lazzaro Spallanzani

Ireland
- National University College Dublin

Netherlands
- Biomedical Primate Research Centre
- Leiden University Medical Centre
- Free University Medical Centre Amsterdam
- Intravacc

Norway
- Norwegian University of Life Sciences

Republic of Korea
- Educational Foundation Yonsei University
- Institute Tuberculosis Research Centre

Senegal
- Espoir Pour La Santé (EPLS)
- Centre Hospitalier Universitaire (CHU) Le Dantec

South Africa
- SATVI/University of Cape Town
- Stellenbosch University
- K-Rith Kwazulu-Natal Research Institute for Tuberculosis

Spain
- Universidad de Zaragoza
- Fundacio Institut De Investigado de Ciencies De La Salut
- Germans Trias I Pujol
- CZ Veterinaria/Biofabri

Switzerland
- University of Geneva
- University Hospital of Basel
- University of Basel
- University of Zürich
- Centre Hospitalier Universitaire Vaudois
- University of Lausanne

The Gambia
- Medical Research Council

United Kingdom
- University of Oxford
- London School of Hygiene and Tropical Medicine
- Veterinary Laboratory Agencies DEFRA
- Public Health England Porton Down
- National Institute for Biological Standards MHRA
- Aston University
- Imperial College of Science Technology and Medicine
- University of Bangor

United States of America
- Aeras
Agenda

- The problem
- The future
- The promise
- Potential complications & solutions
- European perspective: TBVI and TBVAC2020
- A broader picture: GTBVP
- Conclusions

From: ...think global, act local
To: ...think global, act global
The promise of new TB vaccines
Global portfolio management

- Tuberculosis Vaccine Initiative (TBVI)
- Aeras
- Bill & Melinda Gates Foundation (BMGF)
- European and Developing Countries Trials Partnership (EDCTP)
- European Commission (EC)
- European Investment Bank (EIB)

Formation of Global TB Vaccine Partnership (GTBVP)
Strong EU-US axis, also include South/BRICS

Rational selection of TB vaccine candidates

- Establish **global criteria** for selecting vaccine candidates for clinical studies
- Obtain **consensus** on criteria to advance new candidates
GTBVP well placed to shift the risk curve

- Prediction of likely efficacy in preclinical plus early human discovery
- Assessment of efficacy in Phase IIB clinical trial

Risk vs. Money diagram
Agenda

• The problem
• The future
• The promise of new TB vaccines
• Potential complications & solutions

• European perspective: TBVI and TBVAC2020
• A broader picture: GTBVP

Conclusions

Accelerate clinical trials
Adaptive trial design
Develop biosignatures
Do not ignore research
Be cooperative/iterative