Vaccine strategies to address drug-resistant tuberculosis

GJ Churchyard
20th February 2018
Overview

- MDR TB epidemiology
- AMR & MDR TB
- TB vaccines for MDR TB
  - Pipeline
  - Therapeutic vaccines
    - Pre clinical
    - Clinical
    - Trial design considerations
- Vaccination strategies
- Conclusion
MDR TB epidemiology
Percentage of new TB cases with MDR/RR TB (2016)

Percentage of new TB cases with MDR/RR TB (2016)

Estimated treatment coverage for MDR/RR-TB in 2016

(% Treatment coverage)

Treatment outcomes for RR TB cases started on treatment in 2014

Transmission of XDR TB in SA

- 404 XDR TB patients b/w 2011-2014
- 311 (77%) were HIV-infected
- 280 (69%) classified as transmitted resistance
- 323 (84%) in one of 33 clusters
- 30% had person-to-person/hospital-based links

(Shah. NEJM. 2017)
XDR TB: infectiousness & transmission dynamics

- 273 XDR TB patients
- 203 (74%) with programmatically incurable TB discharged home
- 23% had expectorated infectious cough aerosols in the respirable range (<5 μm)
- WGS provided evidence of transmission in the community

(Dheda, Lancet Resp Med, 2017)
Estimated cost / patient treated for MDR TB: 2016

Median cost /patient treated for DS TB: US$ 1253
Median cost /patient treated for DR TB: US$: 9529

AMR & MDR TB
TB the leading cause of AMR

TB accounts for more than 1 in 4 AMR fatalities per year

(Source: https://www.tballiance.org/why-new-tb-drugs/antimicrobial-resistance)
WHO priority pathogens list for R&D of new antibiotics (February 2017)

Priority 1: CRITICAL
1. Acinetobacter baumannii, carbapenem-resistant
2. Pseudomonas aeruginosa, carbapenem-resistant
3. Enterobacteriaceae, carbapenem-resistant, ESBL-producing

Priority 2: HIGH
1. Enterococcus faecium, vancomycin-resistant
2. Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant
3. Helicobacter pylori, clarithromycin-resistant
4. Campylobacter spp., fluoroquinolone-resistant
5. Salmonella, fluoroquinolone-resistant
6. Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM
1. Streptococcus pneumoniae, penicillin-non-susceptible
2. Haemophilus influenzae, ampicillin-resistant
3. Shigella spp., fluoroquinolone-resistant
Gearing up to end TB: a model for tackling antimicrobial resistance?

- Unless MDR-TB is confronted head on as part of the global efforts to contain AMR, we risk having an uncontrollable spread of MDR-TB and not reaching the SDGs of ending TB by 2030  
  (Raviglione, AMR Control. 2016)
- Strong political commitment and increased funding for research and universal diagnosis, effective treatment & vaccines for MDR/RR-TB are direly needed.
  (Weyer, AMR Control. 2017)
TB vaccines for MDR TB
TB vaccine pipeline

Efficacy of TB vaccines on DR vs DS TB

- The molecular changes resulting in drug resistance are unlikely to result in changes to antigenic proteins included in candidate vaccines.
- Vaccines capable of preventing DS-TB disease or infection are likely to have similar activity against DR TB.
Mechanisms of action

TB vaccines are essential to ending the MDR TB epidemic by:

- POI
- POD
- Therapeutic
  - Reducing treatment failure
  - POR
  - Treatment shortening
Mechanisms of action

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Priority setting for novel MDR TB regimens

<table>
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<tr>
<th>Regimen characteristic</th>
<th>Definition of characteristic</th>
<th>Values modeled for novel RR TB regimen</th>
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<tbody>
<tr>
<td>Efficacy</td>
<td>Probability that a patient who completes the specified novel regimen duration and whose infection is and remains susceptible to the regimen will be cured without relapse**</td>
<td>• Minimal: 76%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intermediate: 88%</td>
</tr>
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<td></td>
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<td>• Optimistic: 94%</td>
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<tr>
<td>Barrier to resistance</td>
<td>Probability that a patient treated with the novel regimen acquires and relapses with resistance to one or more components of the regimen</td>
<td>• Minimal: 10%</td>
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<td></td>
<td></td>
<td>• Intermediate: 5%</td>
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<tr>
<td></td>
<td></td>
<td>• Optimistic: 0.8%</td>
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<td>Preexisting novel-regimen resistance</td>
<td>Proportion of patients in the novel regimen’s targeted population (RS or RR TB) with resistance to one or more components of the novel regimen at baseline</td>
<td>• Minimal: 15%</td>
</tr>
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<td></td>
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<td>• Intermediate: 5%</td>
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<td></td>
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<td>• Optimistic: 0%</td>
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<tr>
<td>Medical contraindications</td>
<td>Proportion of target population excluded from novel regimen treatment due to patient characteristics or adverse reactions necessitating a change of regimen***</td>
<td>• Minimal: 11%</td>
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<td>• Minimal: 20 mo</td>
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<td></td>
<td></td>
<td>• Intermediate: 9 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Optimistic: 6 mo</td>
</tr>
<tr>
<td>Tolerability/ease of adherence</td>
<td>Reduction in monthly nonadherence with novel regimen compared to standard regimen (due to, e.g., dosing schedule, pill burden, or route of administration)</td>
<td>• Minimal: 0%</td>
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<td></td>
<td></td>
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Priority setting for novel MDR TB regimens

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Priority setting for novel MDR TB regimens

TB vaccines for MDR TB

- Pre Clinical
- Clinical
ID93/GLA-SE is an effective adjunct to TB treatment in mice

(Coler, JID, 2013)
HVJ-Envelope/HSP65 DNA + IL-12 DNA vaccine therapeutic in mice with MDR TB

- HVJ-Envelope/HSP65 DNA + IL-12 DNA vaccine showed therapeutic efficacy against MDR-TB
- Improved survival in XDR-TB infected mice
- Synergistic effect with INH treatment in mice infected with DS TB

(Kita. Human Vaccines & Immunotherapeutics. 2013)
Ag85A DNA vaccine with or without treatment in mice with MDR TB

- Ag85A DNA vaccine alone or in combination with RFP or PZA reduced the pulmonary and splenic bacterial loads by 1.03–1.38 logs, respectively

(Liang. Basic Immunology. 2011)
TB vaccines for MDR TB

- Pre Clinical
- Clinical
## Therapeutic MDR TB vaccines

<table>
<thead>
<tr>
<th>Product name</th>
<th>Basic data</th>
<th>Route of administration</th>
<th>Immune response</th>
<th>Safety</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. vaccae</em></td>
<td>Immodulon, London, Anhui Longcom, China</td>
<td>Intradermal, Oral, Intramuscular, Oral</td>
<td>Promotes Th1 response, Suppresses Th2 response</td>
<td>Only mild local reactions were observed</td>
<td>Multiple doses required</td>
</tr>
<tr>
<td>RUTI</td>
<td>Archivel, Barcelona</td>
<td>Subcutaneous</td>
<td>Mixed Th1/Th2/Th3 response towards latency antigen, Two-way immune modulation function</td>
<td>No hypersensitivity observed</td>
<td>Further study to ensure safety is required</td>
</tr>
<tr>
<td><em>M. smegmatis</em></td>
<td>Wuhan Institute of Biological Product, China</td>
<td>Subcutaneous</td>
<td>Promotes Th1 response</td>
<td>Only mild local reactions were observed</td>
<td>Further larger studies required</td>
</tr>
<tr>
<td><em>M. indicus-pranii</em></td>
<td>Immuvac, Cadila Pharmaceuticals, India</td>
<td>Subcutaneous, Aerosol</td>
<td></td>
<td>No human infection has ever been reported</td>
<td>Aerosol administration may increase compliance</td>
</tr>
<tr>
<td>V5</td>
<td>Immunitor, Canada</td>
<td>Oral</td>
<td>Improved clinical parameters, attenuates TB-associated inflammation</td>
<td>No exacerbated immune response reported</td>
<td>The exact content remains to be further investigated</td>
</tr>
</tbody>
</table>

Gröschel. Vaccine. 2014)
Adjunctive *M. Vaccae* with MDR TB treatment: systematic review & meta-analysis

- 25 studies involving 2281 patients with MDR TB
- Effectiveness (pooled OR)
  - Smear conversion: 3.84 (95% CI: 3.8-4.7)
  - Absorption of TB foci: 4.08 (95% CI: 3.1-5.5)
  - Cavity closure: 3.42 (95% CI: 2.7-4.4)
- Studies were small and of poor quality

(Weng. Biomedical Reports. 2016)
Percentage converting sputum smear to negative

- Total: V5 78.3%
- 1st DX: V5 61.5%
- RTB: 100%
- MDR: V5 87.5%

V5 administered orally daily for 30 days

(Butov. Journal of Immune Based Therapies and Vaccines 2011)
Trial design considerations
Trial design considerations

- Recurrent disease is the main adverse outcome in DS-TB, particularly as the duration of treatment is shortened.

- Treatment failure (the inability to convert sputum cultures to negative) and death are the main adverse outcomes in MDR-TB.
Sputum culture conversion in relation to clinical outcome in MDR-TB

(Kurbatova. Lancet Respir Med)
Trial design considerations

MDR-TB patients are ideal for evaluating therapeutic vaccines

- Sputum culture conversion with standard or WHO short course treatment is delayed compared to treatment for DS-TB
- MDR TB patients have the most favorable benefit-risk balance
  - Benefit: Improved bacteriological outcomes
  - Risk: worse clinical outcomes due to Koch’s phenomenon
Trial design considerations

Potential trial designs

- A phase 2b trial examining acceleration of sputum culture conversion in MDR-TB
  - And treatment failure rate
- A phase 3 treatment shortening trial comparing
  - 6-month TB treatment with vaccination to WHO 9-months MDR TB regimen
  - 4 months NIX or equivalent regimen + vaccine to 6 months NIX or equivalent regimen alone
MDR TB therapeutic vaccine trials

- Searched: Clinicaltrials.gov, ICTRP
- Safety trial of
  - H56:IC31
  - Cyclooxygenase-inhibitors (etoricoxib)
  - Enrolling
- RUTI
  - Safety trial: Netherlands
  - Phase 2B: India
  - Enrolment pending
- ID93-GLA-SE
  - Safety & efficacy (biomarker endpoints)
  - Planned
TB vaccines for MDR TB

Vaccination strategies
Modelled impact of novel TB vaccines

- All-age or adolescent/adult targeted prevention of disease vaccines achieve greater and more rapid impact than neonatal vaccines
- TB vaccines are overwhelmingly cost-effective
  - CE likely to be greater if preventing DR TB factored in
- Novel TB vaccines could be important in tackling MDR TB through prevention of infection or disease

(Harris. Human Vaccines & immunotherapeutics. 2016)
The role of hotspots in propagating TB epidemics

Achieving TB control targets in a hotspot containing 6% of a city’s population can have similar impact on citywide TB incidence as achieving the same targets throughout the remaining community.

(Dowdy. PNAS. 2012)
Potential impact of spatially targeted TB vaccine in Gujarat, India

(Shrestha. The Royal Society Publishing. 2016)
Modelled impact of untargeted (UTV) and spatially targeted (STV) TB vaccine campaigns

(Shrestha. The Royal Society Publishing. 2016)
MDR TB Hotspot: Lima, Peru

(Zelner. JID. 2016)
Conclusion

• MDR TB remains a global health threat & is the leading cause of AMR
• TB vaccines will be essential to ending the MDR TB epidemic
• Therapeutic TB vaccines should be evaluated in MDR TB Patients
• Vaccination strategies should include targeting adolescents and adults, particularly in hotspots
• Additional research and funding is required to develop TB vaccines that may benefit MDR TB
“Today we are calling on the world to recognize that we can’t fight AIDS unless we do much more to fight [MDR] TB as well”