Tackling iNTS disease

Allan Saul
Sclavo Behring Vaccines Institute for Global Health
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Tackling iNTS diseases

Prevention AND treatment

- Treatment
  - Diagnosis remains a challenge
  - Awareness of population at risk and risk factors
  - Changing patterns of drug resistance
- Environmental intervention
  - Mode of transmission?
  - What is the reservoir?
    - Human to human or animal (bird) to human?
    - Environmental persistence?
- Vaccines
  - Burden of disease estimates
  - Identification of target populations
  - Identification of trial sites and endpoints

All three depend on epidemiological research
Why a vaccine for iNTS?

– Difficult to diagnose
– Rapid onset
– Widespread drug resistance
– Other vaccines (Hib, pneumococcal) work well in the African context

- iNTS vaccine attractive
- Likely be feasible to develop and efficacious
### iNTS vaccines

<table>
<thead>
<tr>
<th>Candidate Name/Identifier</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>POC</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attenuated oral vaccine: CVD 1931<em>Typhimurium</em> $\Delta$guaBA, $\Delta$clipX and CVD 1944 (S. Enteritidis $\Delta$guaBA, $\Delta$clipX) [UMB]</td>
<td>X</td>
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<tr>
<td>Attenuated oral vaccine: WTO5S. (S. Typhimurium $\Delta$aroC, $\Delta$ssaV) [Microscience Limited]</td>
<td>X</td>
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<tr>
<td>O:4,5-TT [NIH]</td>
<td>X</td>
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<tr>
<td>O antigen-flagellin conjugates. O:4,5 : FliCi and O:9 : FliCg,m. [UMB; Bharat Biotech; Wellcome Trust]</td>
<td>X</td>
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<tr>
<td>Bivalent conjugate (O:4,5-CRM$<em>{197}$ and O:9-CRM$</em>{197}$) [SBVGH]</td>
<td>X</td>
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<tr>
<td>O:4,5-GMMA and O:9-GMMA [SBVGH]</td>
<td>X</td>
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<tr>
<td>OmpD [University of Birmingham, SBVGH]</td>
<td>X</td>
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</table>

See discussion paper for WHO vaccine priority meeting

[http://who.int/entity/immunization/research/meetings_workshops/NonTyphoidalSalmonella_VaccineRD_Sept2014.pdf?ua=1](http://who.int/entity/immunization/research/meetings_workshops/NonTyphoidalSalmonella_VaccineRD_Sept2014.pdf?ua=1)
Timelines for iNTS vaccine 2015 - 2026

- Best case scenario for development
  - Assumes no delays (almost never happens)
  - Minimizes future predictions for burden of disease
- Worst case scenario for resources
  - Potential bottleneck in obtaining epidemiological input
  - Requires major early investment in trials and manufacturing
## Timeline and epidemiological implications

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<th>2015: Preclinical</th>
<th>2016-2017: Phase 1</th>
<th>2019: Phase 2 &amp; cPoC</th>
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<td>Production of pilot scale GMP vaccine</td>
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<td>Trials in healthy adult volunteers</td>
<td>Phase 3 manufacturer engaged</td>
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<td>Epidemiology to support case for deployment</td>
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<td>Target groups identified</td>
<td>cPoC criteria identified</td>
<td>Phase 3 trial sites ready</td>
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<th>2023: Phase 3 Efficacy</th>
<th>2025: Registration</th>
<th>2026+ deployment</th>
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<td>Manufacture scaled up</td>
<td>National registration</td>
<td>Phase 4 studies</td>
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<tr>
<td>Consistency lots</td>
<td></td>
<td>WHO prequalification</td>
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<tr>
<td>Trials in HIV infected adults</td>
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<td>allowing UNICEF/GAVI involvement</td>
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<td>Phase 3 studies complete</td>
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<td></td>
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<tr>
<td>Efficacy estimates</td>
<td></td>
<td></td>
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<tr>
<td>Update of burden of disease figures</td>
<td></td>
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<tr>
<td></td>
<td>Preparation for deployment</td>
<td>Vaccine effectiveness studies</td>
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Target Product Profile (TPP)

- Target populations (infants, HIV all ages, high incidence areas?)
- Minimum usable efficacy
  - This strongly impacts Phase 3 trial design
- Minimum usable longevity of protection
- A lot of technical stuff re dose, production, formulation etc.,

First 3 require substantial epidemiological input
The impact of the vaccine over period 2025 -2035?

– Need to know how many are infected now
– Predict changes that will happen in next 20 years and impact on iNTS incidence
– Need to predict impact of vaccine on burden of disease
  – Likely vaccine uptake
  – Likely efficacy
  – Other factors
– Burden of disease and impact need credible range estimates
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By 2017: cPoC criteria identified

- cPoC is NOT an estimation of efficacy for registration
- Existing animal models and *in vitro* killing activity (SBA, OP assay) but no surrogate for protection in humans
- For Infants
  - *S. Typhimurium* infection – inverse correlation with antibody
    - Loss of passive maternal antibody and low actively induced antibody
    - cPoC may be based on antibody levels
  - *S. Enteritidis* infection – no published data
- For HIV infections – not clear.
- Sero-epidemiology would be useful at least in infants
By 2017: Phase 3 / efficacy sites identified
By 2020 sites ready

- Infants only, HIV adults only, both?
- *S.* Typhimurium, *S.* Enteritidis, or both (and others)?
- Needs stable infection rates
- Needs infrastructure to identify and diagnose cases.
  - *c.f.* RTS,S trials for a disease with much higher incidence.
- Probably needs multiple sites
Efficacy studies – Trial design

– Assumptions
  – Testing a bivalent vaccine in Infants
  – Age distribution similar to that seen in Malawi (MacLennan et al, J Clin Invest. 2008)
  – Vaccination at EPI schedule and followed until 18 months old
  – Vaccine is 80% efficacious
  – Power of the trial is equal to 80%
  – Lower Limit of 95% CI for efficacy rate is ≥10%
  – Vaccine and placebo group ratio is 1:1
– Expect 15 cases in each group in absence of vaccination

10-20,000 subjects needed
assuming similar incidence to that seen in the RTS,S trials
Conclusions

- Vaccines for iNTS are feasible
- Development will require a strong epidemiological basis
  - Burden of disease estimates
  - Identification of target populations
  - Identification of trial sites and endpoints
- Timeline is critical – Delays add to development costs and uncertainties