INVASIVE NON-TYPHOID SALMONELLA VACCINES

WHO Product Development for Vaccines Advisory Committee
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Confidential and proprietary data
INTRODUCTION AND OBJECTIVES

Background

• WHO SAGE recommendation for use of typhoid conjugate vaccines (October 2017)
• WHO pre-qualification of the Typbar TCV vaccine (Bharat Biotech) (December 2017)
• GAVI-supported implementation of TCV
• Increasing global interest in the development of broadly-protective vaccines against Salmonella disease, particularly invasive Salmonella disease

Co-interest from

• Wellcome Innovations and Vaccines
• BMGF Enteric and Diarrheal Disease
• National Institute of Allergy and Infectious Diseases
• Initiative for Vaccine Research, WHO
SCIENTIFIC CONSULTATION ON PAN-SALMONELLA APPROACHES, LONDON. MAY 2019

Broad aims of a scientific consultation hosted by Wellcome Trust and BMGF

• Examine the case to support the development of broadly-protective *Salmonella* vaccines
• Review the current status of *paratyphoid A* and *iNTS* vaccine development
• Discuss how to advance broadly-protective *Salmonella* vaccines, including identification of knowledge gaps and potential pathways towards licensure

• Disease burden
  *Discussion - strength of case for vaccine need, data gaps, plan to address*

• Vaccines in development
  *Discussion - comparison of approaches, clinical trials considerations*

• Pathway to licensure, value proposition, CHIM, assays & standards, regulatory considerations
  *Discussion - pathway feasibility, data gaps, regulatory engagement*
INTRODUCTION AND OBJECTIVES

Two potential combination *Salmonella* vaccines

1. ‘Enteric fever vaccine’
   - To include coverage of S. Paratyphoid A
   - Potentially most plausible in combination with Typhoid Conjugate Vaccine as a bivalent vaccine
   - Coverage South/South-East Asia

2. ‘Invasive non-typhoidal Salmonella’ (iNTS) disease
   - S. Typhimurium and S. Enteritidis
   - Coverage Sub-Saharan Africa
   - Is a trivalent combination vaccine plausible including TCV and S. Typhimurium and S. Enteritidis?
THE CASE

Jeff Stanaway, UW IHME. Pan-Salmonella Meeting, London 2019
The burden of iNTS disease, caused by *Salmonella* Typhimurium and *Salmonella* Enteritidis, is a serious public health concern in Sub-Saharan Africa.

- 600,000 to 3.4M cases of iNTS disease occurred globally in 2010*. >50% of cases of iNTS disease occur in Sub-Saharan Africa. Case-fatality rates commonly reported at ~15-20%
- ~622,000 cases estimated in 2017 (490,000 – 800,000). ~68,000 deaths in 2017**
- High prevalence of iNTS disease seen in children under 3 years of age
- Clinical presentation is most commonly with fever alone: diagnosis not usually possible
- Diagnosis requires blood culture facilities that are uncommon in Sub-Saharan Africa
- Antimicrobial drug resistance to iNTS isolates, including MDR, is common. Emergence of fluoroquinolone and ceftriaxone resistance makes treatment increasingly difficult
- Effective methods for disease control as improvement to water supply and sanitation is lagging and cost prohibitive in endemic countries

*Ao et al, 2015; **GBD, 2017
RESULTS: COMPARING GBD AND OTHER PUBLISHED ESTIMATES

- Two previous studies reported iNTS burden estimates, and both produced estimates for the year 2010:

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimated cases, 2010</th>
<th>Estimated deaths (thousands), 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ao et al, 2015</td>
<td>3.4 million (2.1 to 6.5)</td>
<td>681.3 (415.2 – 1,302)</td>
</tr>
<tr>
<td>GBD 2017</td>
<td>622 thousand (490 to 800)</td>
<td>67.6 (39.2 – 110.0)</td>
</tr>
<tr>
<td>Kirk et al, 2015 (WHO FERG)</td>
<td>597 thousand (?)</td>
<td>63.2 (39.0 – 94.2)</td>
</tr>
</tbody>
</table>

Ao et al include deaths for which HIV is underlying cause
Kirk et al exclude such deaths
NON-TYPHOIDAL SALMONELLA INVASIVE DISEASE DALYS AND DEATHS BY AGE, WORLDWIDE, GLOBAL BURDEN OF DISEASE 2017

Disability Adjusted Life Years

Deaths

http://vizhub.healthdata.org/gbd-compare/
A ROLE FOR ANTIBODIES IN IMMUNITY TO iNTS DISEASE IN AFRICAN CHILDREN

Acquisition of bactericidal antibodies inversely corresponds to age at which African children are susceptible to iNTS disease.


IMMUNOLOGY
Antibiotic antibodies

The discovery of functional antibodies against strains of Salmonella that do not cause typhoid raises hopes that a vaccine can be developed. In Africa, such strains kill up to 24% of infected children in communities in which appropriate antibiotics and blood-culture facilities are available.
...AND THE ARGUMENTS AGAINST

- iNTS disease incidence appears to be falling in some settings
- Complexity due to co-dependence of iNTS disease on co-morbidities - that are potentially preventable (malaria) and treatable (HIV infection)
- Complexity due to co-dependence of iNTS disease on co-morbidities - disparity in key mechanisms of immunity with different co-morbidities (malaria, HIV infection, malnutrition)
- Crowded EPI schedule at point where the vaccine is most likely needed (infants at 6/10/14 weeks)
- Lack of commercial incentive – diseases of the most vulnerable populations
- Large financial/time commitment required before efficacy read out – phase 3 field study required, as there is no CHIM available
VARIATION IN INVASIVE NON-TYPHOIDAL SALMONELLA DISEASE INCIDENCE IN AFRICA OVER TIME
HIV AND NTS DISEASE

Figure 1. Changing susceptibility to NTS bacteraemia with ART among HIV-Infected Africans

A. Estimated minimum incidence of NTS bacteraemia in Malawi in relation to time on ART*

*figure kindly prepared by Dr Nick Feasey, collaborator

*based on data from Feasey NA et al, PLoS One 2014, assuming a 50% blood culture sensitivity rate to detect NTS bacteraemia

Gordon MA et al, AIDS 2002
## THE VACCINE CANDIDATES

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Developer</th>
<th>Stage of development</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>O:4,12-TT</td>
<td>O:4-TT Conjugate</td>
<td>NIH</td>
<td>Preclinical</td>
<td>51</td>
</tr>
<tr>
<td>Os-po</td>
<td>O:4-porin Conjugate</td>
<td>National Bacteriology Laboratory, Stockholm</td>
<td>Preclinical</td>
<td>146</td>
</tr>
<tr>
<td>WT05</td>
<td>Live attenuated</td>
<td>Microscience, Wokingham Berkshire</td>
<td>Phase 1</td>
<td>147</td>
</tr>
<tr>
<td>CVD 1921 and CVD 1941</td>
<td>Live attenuated</td>
<td>University of Maryland</td>
<td>Preclinical</td>
<td>148</td>
</tr>
<tr>
<td>S. Typhimurium ruv8 mutant</td>
<td>Live attenuated</td>
<td>Seoul National University</td>
<td>Preclinical</td>
<td>149</td>
</tr>
<tr>
<td>Salmonella hfg deletion mutant</td>
<td>Live attenuated</td>
<td>Indian Institute of Science Bangalore</td>
<td>Preclinical</td>
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<tr>
<td>SA186</td>
<td>Live attenuated</td>
<td>Istituto Superiore di Sanità Roma</td>
<td>Preclinical</td>
<td>151</td>
</tr>
<tr>
<td>MT13</td>
<td>Live attenuated</td>
<td>KIIT University Odisha</td>
<td>Preclinical</td>
<td>152</td>
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<tr>
<td>Various</td>
<td>Live attenuated, DNA adenine methylase mutants</td>
<td>University of California, Santa Barbara</td>
<td>Preclinical</td>
<td>153,154</td>
</tr>
<tr>
<td>Various</td>
<td>Live attenuated, regulated delayed attenuation</td>
<td>Arizona State University</td>
<td>Preclinical</td>
<td>155-157</td>
</tr>
<tr>
<td>Porins</td>
<td>S. Typhimurium porins</td>
<td>National Bacteriology Laboratory, Stockholm</td>
<td>Preclinical</td>
<td>146</td>
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<tr>
<td>OmpD</td>
<td>Outer membrane protein</td>
<td>University of Birmingham, UK</td>
<td>Preclinical</td>
<td>73</td>
</tr>
<tr>
<td>S. Typhimurium and S. Enteritidis GMMA</td>
<td>Generalized Modules for Membrane Antigens</td>
<td>NVGH</td>
<td>Preclinical</td>
<td>65,158,159</td>
</tr>
</tbody>
</table>

*an exhaustive list, particularly of all candidate vaccines in preclinical studies, is beyond the scope of this review*
LIPOPOLYSACCHARIDE (LPS) & FLAGELLA

**LPS**
- Surface polysaccharide of un-encapsulated bacteria
- Conserved core PS (species)
- OPS structure defines serotype:
  - *S. Typhimurium* (serogroup B)
  - *S. Enteritidis* (serogroup D)
- Anti-OPS antibodies bactericidal, protect in animal models

**Flagella**
- Filament comprised by multimer of single flagellin protein
- Multiple types -- variable epitopes define serovar
- Anti-flagellin antibodies have functional bactericidal activity, protect mice against invasive infection [Ramachandran et al., PLoS One 2016]

- **CVD iNTS vaccine: Core-OPS conjugate with phase 1 flagellin protein (FliC)**
A VACCINE TO PREVENT INVASIVE SALMONELLA DISEASE INCLUDING NTS AND TYPHOID FEVER IN SUB-SAHARAN AFRICA

• **Need a single combination vaccine** to cover main NTS serovars: S. Typhimurium and variants (I:4,[5],12:i), S. Enteritidis & S. Dublin

• **Vaccine must be compatible with the Expanded Programme on Immunization (EPI) schedule** for sub-Saharan Africa

**Attenuated engineered *Salmonella* mutants:**
- Increase the **occupational safety** of large-scale fermentation in the industrial setting
- **Increase the yield** of COPS (hapten) and flagellin subunits (carrier protein)
- Conjugates made this way have a **lower cost of goods**

• **Tri-valent** parenteral conjugate vaccine to prevent invasive Salmonella disease in Sub-Saharan Africa with the pre-qualified Typbar TCV.
PROTECTION AGAINST FATAL INFECTION WITH MALIAN S. ENTERITIDIS (R11) OR S. TYPHIMURIUM (D65) BLOOD ISOLATES IN MICE IMMUNIZED WITH THE HOMOLOGOUS PATHOGEN MONOVALENT COPS:FLIC VACCINES

**S. Enteritidis**

Immunization: D0, D14, D28 with 2.5 µg conjugate polysaccharide or PBS

Challenge: IP infection at D56 with 1 x 10^6 CFU S. Enteritidis R11 (IP LD50 = 2 x 10^5) or 5 x 10^5 CFU S. Typhimurium D65 (IP LD50 = 2 x 10^4); *P<0.0001 (log-rank)

**S. Typhimurium**

(Slide courtesy of Rafi Simon)
PROPOSED CLINICAL DEVELOPMENT

- **Phase 1 safety** and immunogenicity study of bivalent and trivalent vaccines and placebo 4-fold increases in serum anti-COPS, anti-Vi and homologous anti-FliC IgG antibody

- Step-wise **age-descending (down to infants 6 weeks of age) Phase 2 study** of Trivalent Conjugate Vaccine in 2 field sites in sub-Saharan Africa with iNTS burden and pre-licensure vaccine trial experience

- **Non-inferiority trial** with EPI vaccines used in Africa in relevant target age groups

- Phase 2 safety/immunogenicity in HIV-positive children

- **3-lot consistency trial** (for reactogenicity and immunogenicity) of vaccine versus placebo (3 vaccinees:1 placebo)

- **Large-scale randomized, controlled efficacy trial** of the Trivalent Conjugate Vaccine to be performed at multiple sites in Africa with iNTS burden and pre-licensure trial experience
GVGH’S INTS VACCINE APPROACH

GMMA (Generalized Modules for Membrane Antigens) Technology

- Source of outer membrane
- Compartment containing immunogenic antigens
- Avoid side effects of whole cell bacteria vaccines
- Antigens presented in their natural environment and conformation, mimicking surface of the bacterium
- No additional chemical treatment needed
- Naturally adjuvanting

Genetic modification to break links between outer and inner membrane and peptidoglycan to induce continuous **over-blebbing**

(Slide courtesy of Oliver Koeberling)
2-COMPONENT iNTS-GMMA VACCINE
GMMA from S. Typhimurium (STm) and S. Enteritidis (SEn)

iNTS-GMMA vaccine approach

- 2-component vaccine containing GMMA from S. Typhimurium and S. Enteritidis formulated on Alhydrogel

(Slide courtesy of Oliver Koeberling)
- A comprehensive preclinical data package for the iNTS-GMMA vaccine in place demonstrating iNTS-GMMA
  - Immunogenicity in mice and rabbits
  - Manufacturability
  - Stability
- iNTS-GMMA project is at the stage to proceed with early clinical development
WHAT IS THE PATH FORWARD FOR UPTAKE OF AN INTS VACCINE...AND GAPS

(Slide courtesy of Birgitte Giersing WHO)
CONCLUSIONS FROM SALMONELLA CONVENING: iNTS

- Early stage with more questions and several unknowns
- Value proposition will need to evaluate iNTS/NTS, HIV-/HIV+, mortality, DALYs
- Epidemiology gap – incidence, shedding; is there an opportunity to explore in the RTS,S malaria vaccine pilot introductions in Africa
- Risk factor attribution needs further evaluation
- Reservoirs, sources, and modes of transmission need to be elucidated
- Clinical trials to target population are key next step
- Trial design and endpoints – carriage/shedding, immune indices
- iTPP - age of administration, combination – TCV (others)
- COPs examination of existing data & sero-epidemiology
WHAT COULD ACCELERATE THE PATHWAY FORWARD?

• Early proven immunogenicity in the target population
• Availability of a Correlate of Protection
• Availability of a Controlled Human Infection Model (CHIM)
• Potential tethering to Typhoid Conjugate Vaccine – this seems unlikely given the differences in epidemiology and likely immunization schedules
• Value proposition
• Impact on carriage/shedding of NTS

• Early engagement with regulators
IMMUNOGENICITY STUDIES IN TARGET POPULATION

Are candidates sufficiently immunogenic to confer protection in LMIC children?

- No iNTS vaccine has been tested to date in the target population: young infants in LMICs
- Must evaluate immunogenicity in this target population, as soon as safety has been established in naive adults
- Requires a safety and immunogenicity study in descending age groups (to 6 weeks old) in LMICs.
- For a first iNTS vaccine: need for field data for safety and efficacy
SUMMARY

• A strong case for iNTS vaccine development, but community needs to be aware of detractors in addition to lack of a commercial driver
• No candidates currently in clinical development, but promise of two:
  • UMD/Bharat Biotech bivalent O-antigen/flagellin conjugate, and
  • GVGH/GSK bivalent vesicle vaccine First-in-Human studies in coming year
• Pathway potentially long without a clear Correlate of Protection to link immunogenicity to efficacy, or a Controlled Human Infection Model to give an early indication of efficacy
THE WORK IS COMPLICATED.

WHY WE DO IT IS NOT.