Initial immunogenicity and safety data from a first-in-human randomised controlled trial of an invasive non-typhoidal *Salmonella* GMMA vaccine: The SALVO trial

**Peter D Skidmore**¹, Melanie Greenland¹, Kiarash Tanha¹, Brama Hanumunthadu¹, Tesfaye Demissie¹, Nelly Owino¹, Gareth Plested¹, Carla Ferreira Da Silva¹, Usman Nakakana², Daniele De Simone², Antonella Silvia Scire², Marta Benincasa², Chiara Crispino², Maria Grazia Aruta², Giulia Luna Cilio³, Valentino Conti², Omar Rossi², Elizabeth A Clutterbuck¹, Rocio Canals², Maheshi N Ramasamy¹ and the Vacc-iNTS Consortium

1. Oxford Vaccine Group, NIHR Oxford Biomedical Research Centre, Department of Paediatrics, University of Oxford, Oxford, UK
2. GSK Vaccines for Global Health (GVGH), Siena, Italy
3. GSK Biologicals SRL, Siena, Italy
Overview

- Introduction - iNTS incidence and iNTS-GMMA vaccine
- Methods – trial design, CONSORT diagram
- Results -
  - Interim safety data
  - Immunogenicity data up to 28 days following 2\textsuperscript{nd} dose administration
- Conclusions

Conflicts of Interest PDS: No financial interest, no honoraria
Global incidence of iNTS in 2017

- 51/100,000 in SSA
- Bimodal distribution
- 90% caused by *S. enterica* serovars Typhimurium (STm) & Enteritidis (SEn)
- Case fatality rate 15%
- High rates of AMR
- No licensed vaccines

Generalised Modules for Membrane Antigens (GMMA)

Lipoplysaccharide structure

Repeating O-antigen
Core oligosaccharide
Lipid A

Mutations in \textit{msbB} and \textit{pagP} lead to reduced acylation of lipid A

Blebbing GMMA

Periplasmic proteins

Outer membrane proteins

Lipoplysaccharide

GMMA

Outer membrane
Periplasm
Inner membrane
Cytoplasm

\textit{tolR} mutation leads to instability of outer membrane

Created with BioRender.com
iNTS-GMMA vaccine

- Bivalent vaccine – GMMA from serovars S. Typhimurium and S. Enteritidis, formulated with Alhydrogel®
- Developed by GSK Vaccines for Global Health (GVGH)
- GMMA vaccine against *Shigella sonnei* (1790-GMMA) well-tolerated and immunogenic in healthy adults
- Pre-clinical data (mice):

In vivo infection study in mice immunized with GMMA and conjugate in bivalent formulation. Twelve C57Bl/6 mice per group were s.c. immunized at days 0 and 28 at 1 μg OAg/dose per each antigen with Alhydrogel. (A and B) Summary graphs of anti-OAg IgG geometric mean units (bars) and individual antibody levels (dots).

Methods – SALVO trial design

• First-in-human, double-blind, single-centre, randomised, placebo-controlled clinical trial conducted at the University of Oxford, UK

• Healthy UK adults aged 18-55.

• n = 30-42

• 3 doses of iNTS GMMA or placebo (0, 2 and 6 months). 1 year total follow-up.

Clinical Trial Registration: ISRCTN51750695
Methods – SALVO trial design

• Allocated to one of 3 groups
  • Group 1 (n=7) – randomised 1:1 to receive low dose iNTS GMMA or placebo
  • Group 2 (n=6) – randomised 1:1 to receive high dose iNTS GMMA or placebo
  • Group 3 (n=18) – randomised 2:1 to receive high dose iNTS GMMA or placebo

• NB study remains blinded. For purposes of analysis Groups 2 and 3 combined into single high-dose group

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Alhydrogel</th>
<th>n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>10.6 µg total OAg per dose</td>
<td>n=4</td>
</tr>
<tr>
<td>High dose</td>
<td>40 µg total OAg per dose</td>
<td>n=15</td>
</tr>
</tbody>
</table>
Methods – SALVO trial objectives

• Primary – safety and tolerability of iNTS GMMA at two dose levels
  • Solicited and unsolicited adverse events (AEs)
  • Laboratory parameters

• Secondary – immunogenicity of iNTS GMMA at two dose levels
  • IgG responses to serovar-specific O-antigens using ELISA

• Exploratory immunology, including:
  • Serum bactericidal assays, functional antibody assays, B and T cell responses
SALVO trial timeline and demographics

• First participant first visit 22\textsuperscript{nd} June 2022
• Recruitment complete November 2022
• Last vaccination 15\textsuperscript{th} May 2023
• Last participant last visit 16\textsuperscript{th} October 2023

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (low dose/placebo)</th>
<th>Groups 2+3 (high dose/placebo)</th>
<th>All participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>28.6%</td>
<td>33.3%</td>
<td>32%</td>
</tr>
<tr>
<td>Median age at enrolment (years)</td>
<td>23.0</td>
<td>30.0</td>
<td>27.0</td>
</tr>
<tr>
<td>Ethnicity (white background)</td>
<td>71.4%</td>
<td>91.7%</td>
<td>87%</td>
</tr>
</tbody>
</table>
CONSORT flow diagram (blinded)

Expressed interest and assessed for eligibility (n = 127)

Excluded (n = 96)
- Not meeting inclusion criteria / met exclusion criteria (n = 43)
- Withdrew prior to enrolment (n = 42)
- Recruitment full (n = 11)

Enrolled and randomized (n = 31)

Allocated to low dose/placebo group and received 1st dose (n = 7*)

Withdrew (n = 1)

Received 2nd dose (n = 6)

Withdrew (n = 1)

Received 3rd dose (n = 5)

Completed 1yr follow-up as of soft database lock (n = 5)

Allocated to high dose/placebo group and received first dose (n = 24)

Received 2nd dose (n = 24)

Lost to follow-up (n = 2)
- Withdrew (n = 1)
- Withdrawn by investigators (n = 2)

Received 3rd dose (n = 19)

Completed 1yr follow-up as of soft database lock (n = 6)

Completed 28 days post-3rd dose follow-up as of soft database lock (n = 13)

*additional participant enrolled into group 1 in error
NB all participants with available data analysed

INTERIM IMMUNOGENICITY DATA

INTERIM SAFETY DATA

Completed 1yr follow-up as of soft database lock (n = 5)

Completed 1yr follow-up as of soft database lock (n = 6)

Completed 28 days post-3rd dose follow-up as of soft database lock (n = 13)
Solicited AEs were mostly mild-moderate and transient
Systemic AEs in full-dose group – daily severity across 0-6 days following first vaccination

Full dose group:

NB similar profile after 2\textsuperscript{nd} and 3\textsuperscript{rd} doses. **Blinded data**
AEs were mostly mild-moderate in severity at both dose levels

- Local pain and tenderness were mild-moderate and self-resolving
- Erythema, swelling and induration were mostly mild
  - 3/31 participants developed ≥ 100mm erythema after 1st dose, self-resolving
  - 1/31 participant developed 155mm area of swelling after 1st dose (subsequently withdrawn after similar reaction to 2nd dose)
- Laboratory AEs were mild-moderate
  - 1/31 participant withdrawn after 2nd dose due to moderate neutropenia (resolved)
- 59 unsolicited AEs – 81% considered unrelated to vaccine
- No serious AEs reported
Interim immunogenicity data

- Up to 28 days following 2\textsuperscript{nd} dose
- Study remains blinded – GMCs and 95% CI, not individual data points or range
- NB low dose vaccine group small (n=4) so wide confidence intervals
Both dose levels elicited robust anti-STm IgG responses

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Placebo</th>
<th>Low dose</th>
<th>High dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Hashtag</td>
<td>Hashtag</td>
<td>Hashtag</td>
</tr>
<tr>
<td>Placebo</td>
<td>Hashtag</td>
<td>Hashtag</td>
<td>Hashtag</td>
</tr>
<tr>
<td>Low dose</td>
<td>Hashtag</td>
<td>Hashtag</td>
<td>Hashtag</td>
</tr>
<tr>
<td>High dose</td>
<td>Hashtag</td>
<td>Hashtag</td>
<td>Hashtag</td>
</tr>
</tbody>
</table>

IgG specific to Salmonella Typhimurium O-antigen, measured by ELISA and expressed as geometric mean concentrations (GMCs) with 95% confidence intervals. Doses of iNTS GMMA or placebo were administered at D0 and D56.
Both dose levels elicited robust anti-SEn IgG responses

IgG specific to Salmonella Enteritidis O-antigen, measured by ELISA and expressed as geometric mean concentrations (GMCs) with 95% confidence intervals. Doses of iNTS GMMA or placebo were administered at D0 and D56.

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Dose Details</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Low dose</td>
<td>10.6 µg total OAg per dose</td>
<td>4</td>
</tr>
<tr>
<td>High dose</td>
<td>40 µg total OAg per dose</td>
<td>15</td>
</tr>
</tbody>
</table>
Full dose group demonstrated anti-STm SBA response

Serum bactericidal activity against Salmonella Typhimurium, expressed as geometric mean concentrations (GMCs) with 95% confidence intervals. Doses of iNTS GMMA or placebo were administered at D0 and D56.
Full dose group demonstrated anti-SEn SBA response

Serum bactericidal activity against Salmonella Enteritidis, expressed as geometric mean concentrations (GMCs) with 95% confidence intervals. Doses of iNTS GMMA or placebo were administered at D0 and D56.

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Alhydrogel</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Low dose</td>
<td>10.6 µg total OAg per dose</td>
<td>4</td>
</tr>
<tr>
<td>High dose</td>
<td>40 µg total OAg per dose</td>
<td>15</td>
</tr>
</tbody>
</table>
Discussion & conclusions

• iNTS-GMMA was well-tolerated in adults with no safety signals or concerns after 3 doses
  • AEs largely mild to moderate, and self-resolving

• iNTS-GMMA elicits robust antibody and functional responses to targeted serovars

• What next?
  • Complete safety data, with unblinding to further clarify safety profile
  • Immunogenicity data up to 1 year following first dose, antibody persistence
  • Exploratory immunology
    • Cell-mediated immunity
    • Mucosal immunity
  • Phase 1 stage 2 trial in KEMRI, Kenya
Acknowledgements & disclosures

**SALVO study participants**

**SALVO study team at Oxford Vaccine Group**

The Vacc-iNTS Consortium

Sclavo Vaccines Institute, Italy  
GSK Vaccines Institute for Global Health, Italy  
University of Oxford, UK  
Kenya Medical Research Institute, Kenya  
University of Cambridge, UK  
University of Siena, Italy  
Institute of Tropical Medicine in Antwerp, Belgium  
University of Liverpool, UK  
University of Otago, New Zealand  
University of Ouagadougou, Burkina Faso  
Kwame Nkrumah University of Science and Technology Kumasi, Ghana  
MMGH Consulting GMBH, Switzerland

**Disclosure statement**

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement no. 815439.

CC, MB, DDS, OR, RC, VC, UNN, ASS, MGA and GLC are employees of GSK and OR, VC, UNN, RC and GLC hold GSK shares.

RC reports that the iNTS-GMMA vaccine program is also supported by funding from the EDCTP2 programme supported by the European Union under the project PEDVAC-iNTS (RIA2019AMR-2658). Additionally, a combination of this vaccine with TCV, known as iNTS-TCV, is currently supported by a CARB-X grant. RC is a member of the Steering Committees of the Horizon 2020 and the EDCTP grants awarded to the iNTS-GMMA project.