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

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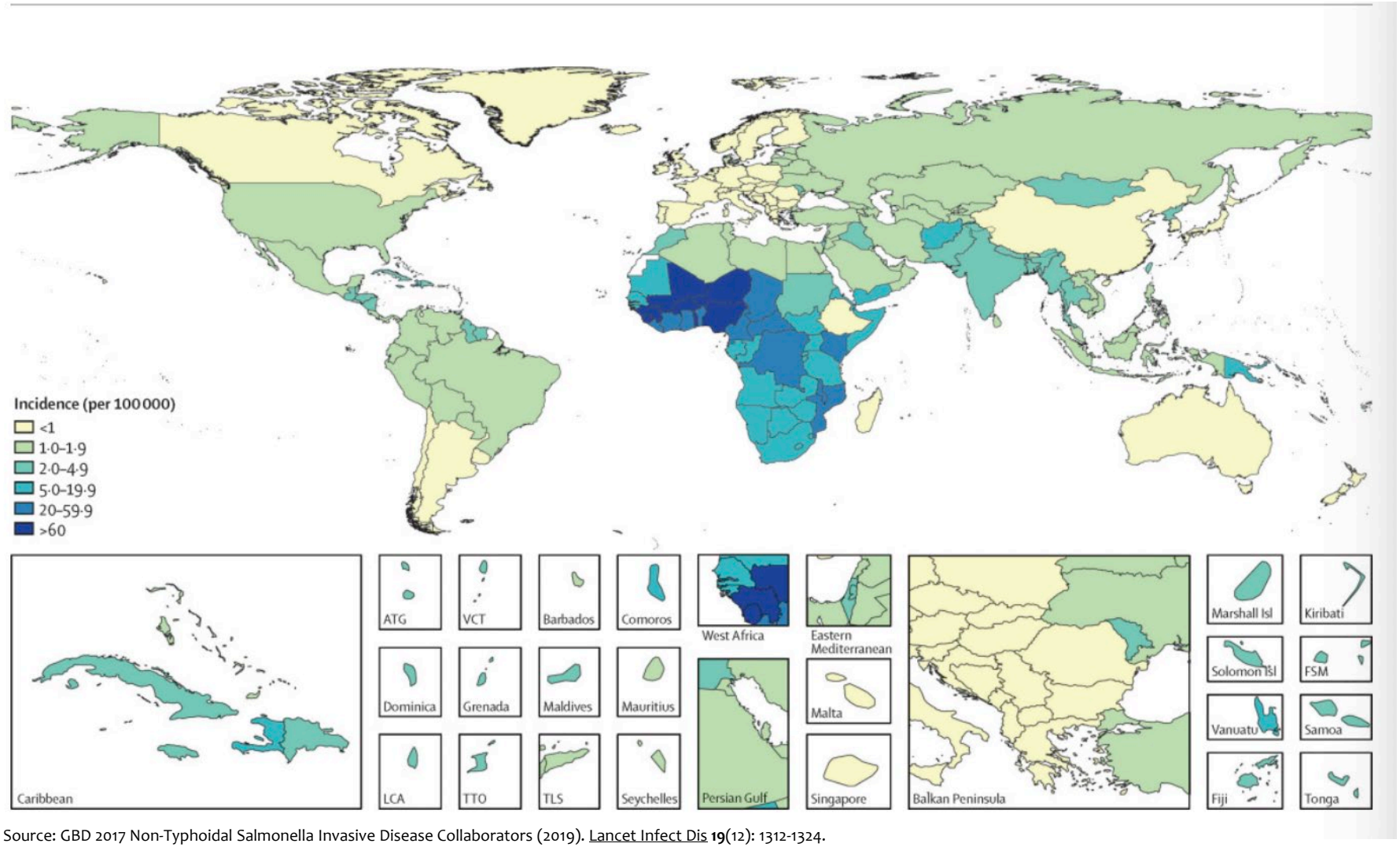
Overview

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

Conflicts of Interest PDS: No financial interest, no honoraria

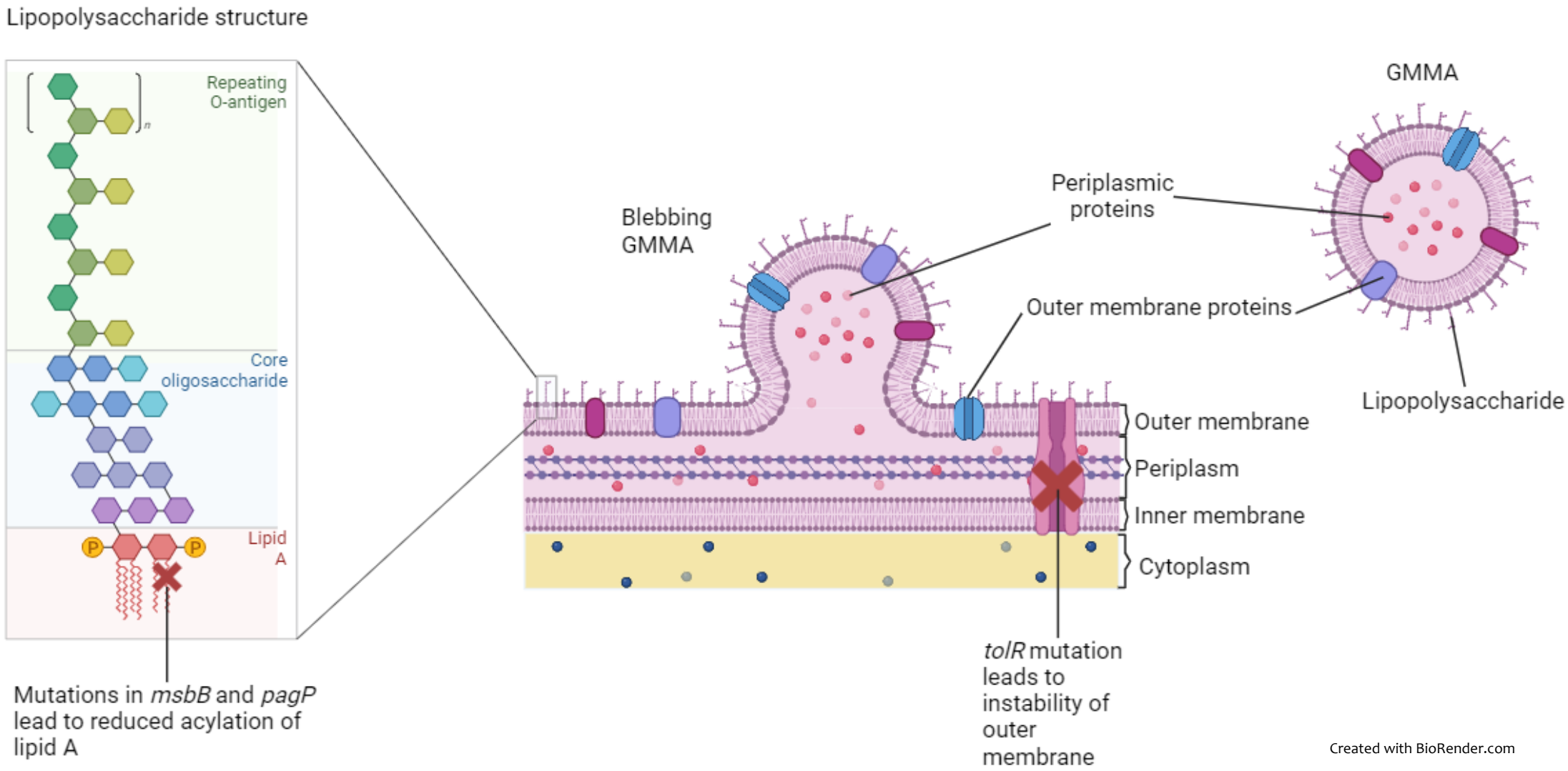
Global incidence of iNTS in 2017



Source: GBD 2017 Non-Typhoidal Salmonella Invasive Disease Collaborators (2019). Lancet Infect Dis **19**(12): 1312-1324.

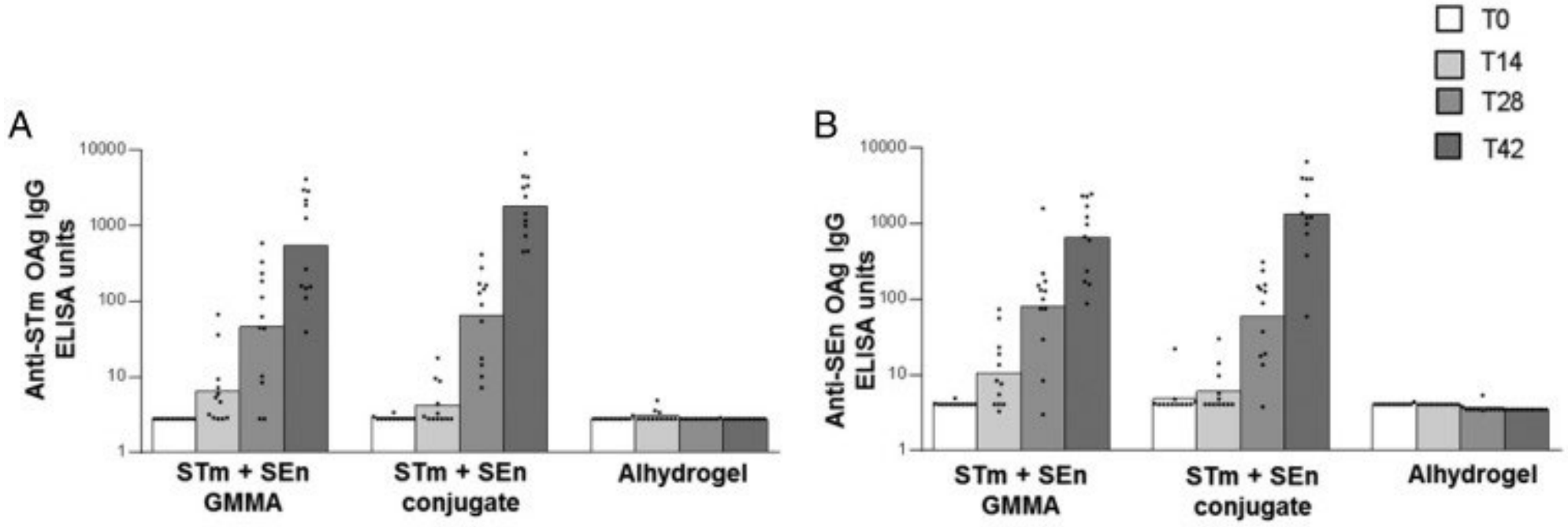
- 51/100,000 in SSA
- Bimodal distribution
- 90% caused by *S. enterica* serovars Typhimurium (STm) & Enteritidis (SEn)
- Case fatality rate 15%
- High rates of AMR
- No licensed vaccines

Generalised Modules for Membrane Antigens (GMMA)



iNTS-GMMA vaccine

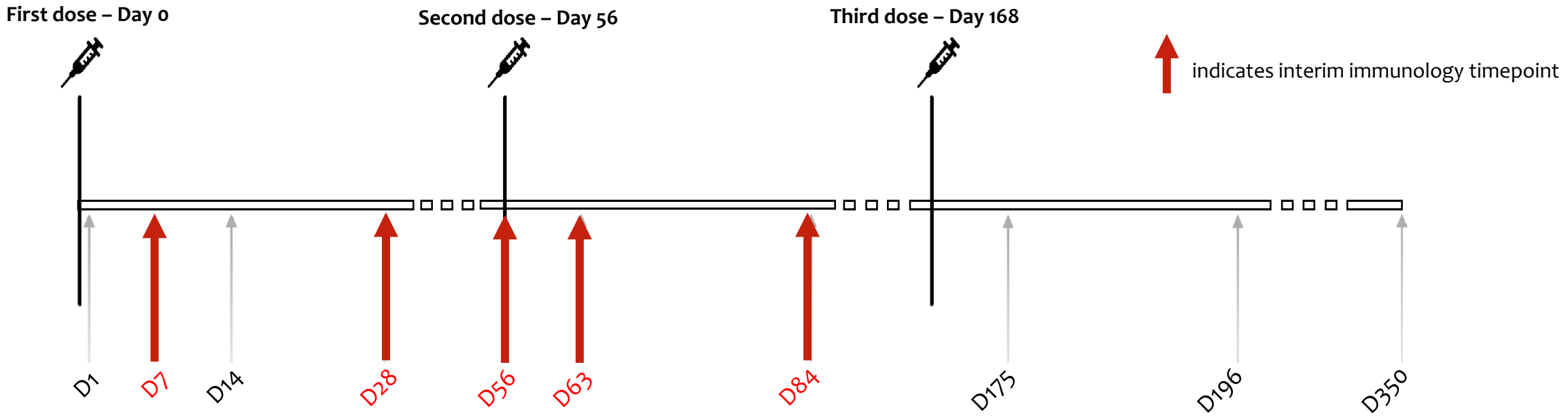
- Bivalent vaccine – GMMA from serovars *S.* Typhimurium and *S.* Enteritidis, formulated with Alhydrogel®
- Developed by GSK Vaccines for Global Health (GVGH)
- GMMA vaccine against *Shigella sonnei* (1790-GMMA) well-tolerated and immunogenic in healthy adults
- Pre-clinical data (mice):



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).
Data published in Micoli, F., et al. (2018). "Comparative immunogenicity and efficacy of equivalent outer membrane vesicle and glycoconjugate vaccines against nontyphoidal Salmonella." Proc Natl Acad Sci U S A 115**(41): 10428-10433**.

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

Placebo	Alhydrogel	n=12
Low dose	10.6 µg total OAg per dose	n=4
High dose	40 µg total OAg per dose	n=15

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

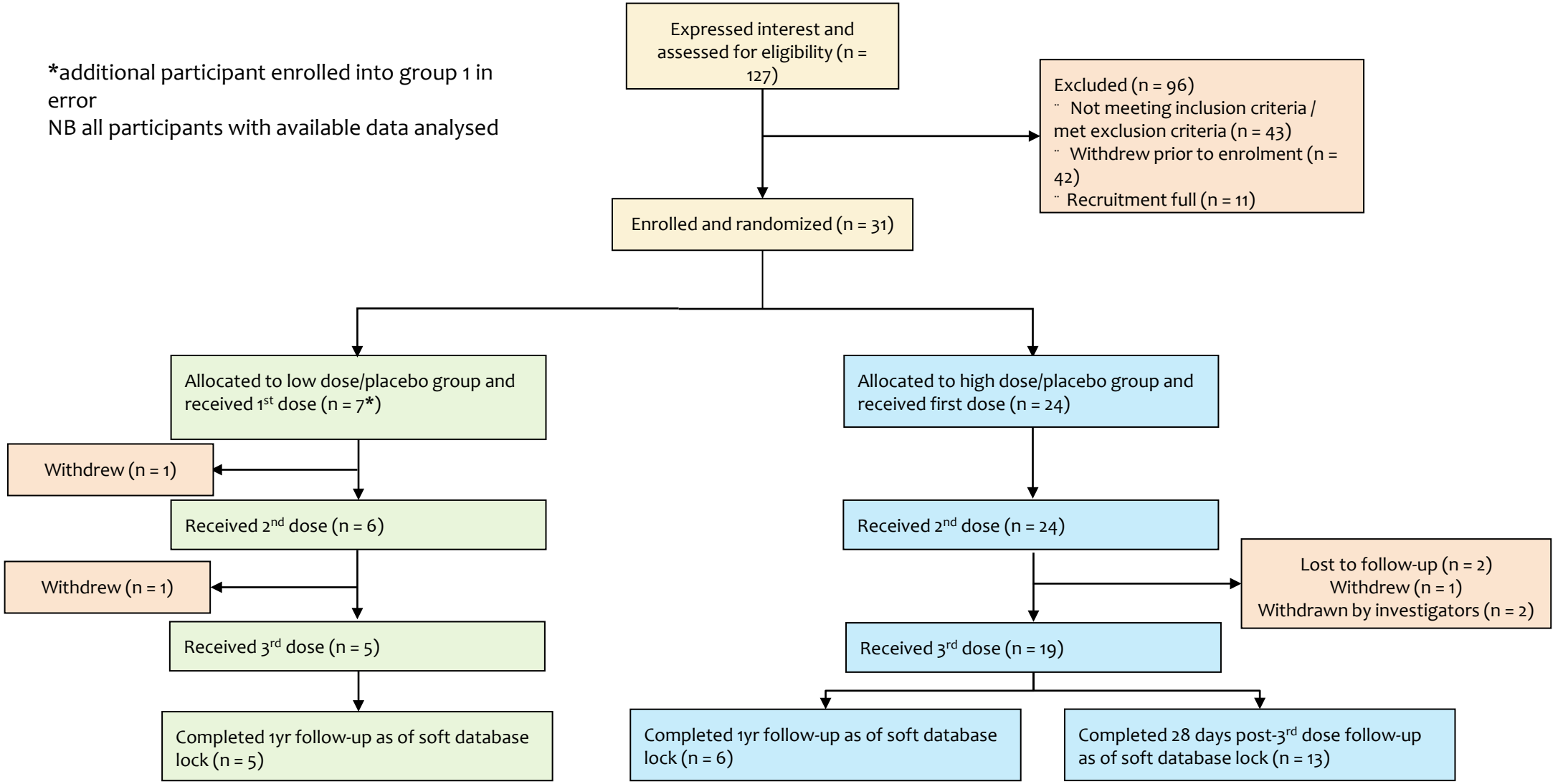
SALVO trial timeline and demographics

- First participant first visit 22nd June 2022
- Recruitment complete November 2022
- Last vaccination 15th May 2023
- Last participant last visit 16th October 2023

	Group 1 (low dose/placebo)	Groups 2+3 (high dose/placebo)	All participants
Sex (female)	28.6%	33.3%	32%
Median age at enrolment (years)	23.0	30.0	27.0
Ethnicity (white background)	71.4%	91.7%	87%

CONSORT flow diagram (blinded)

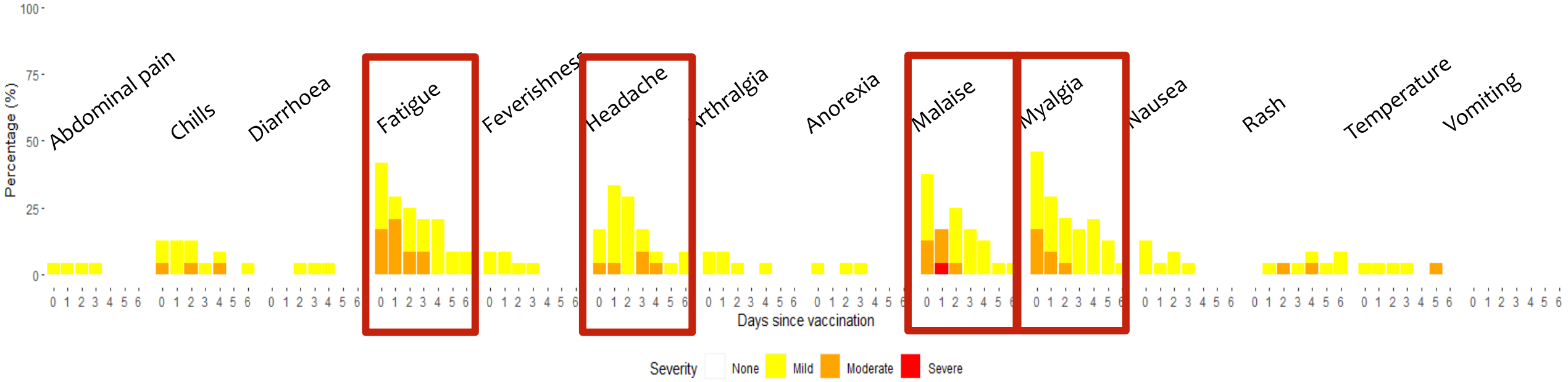
*additional participant enrolled into group 1 in error
NB all participants with available data analysed



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:



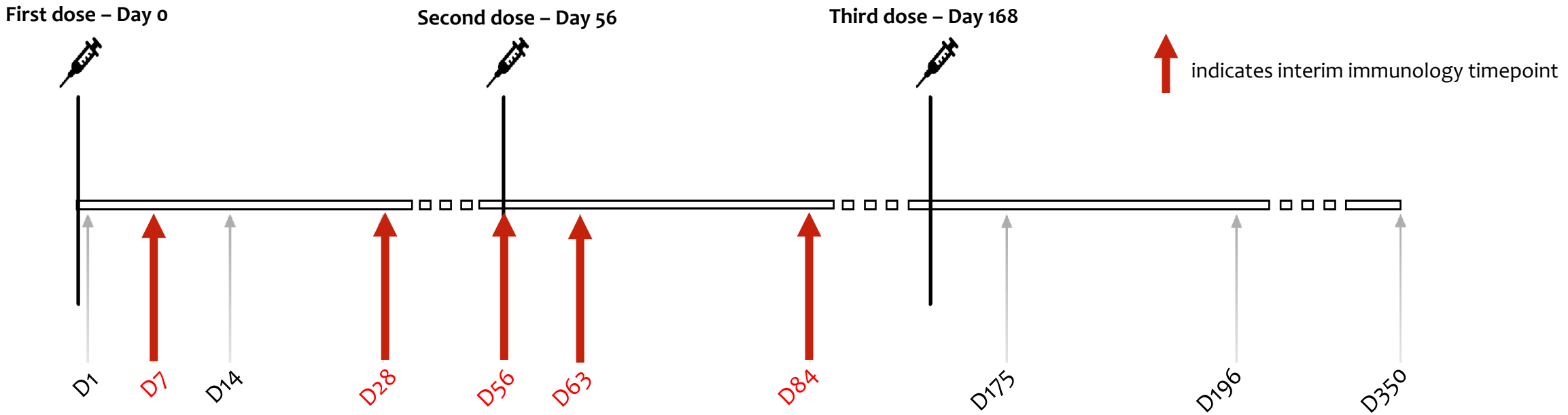
NB similar profile after 2nd and 3rd doses. Blinded data

AEs were mostly mild-moderate in severity at both dose levels

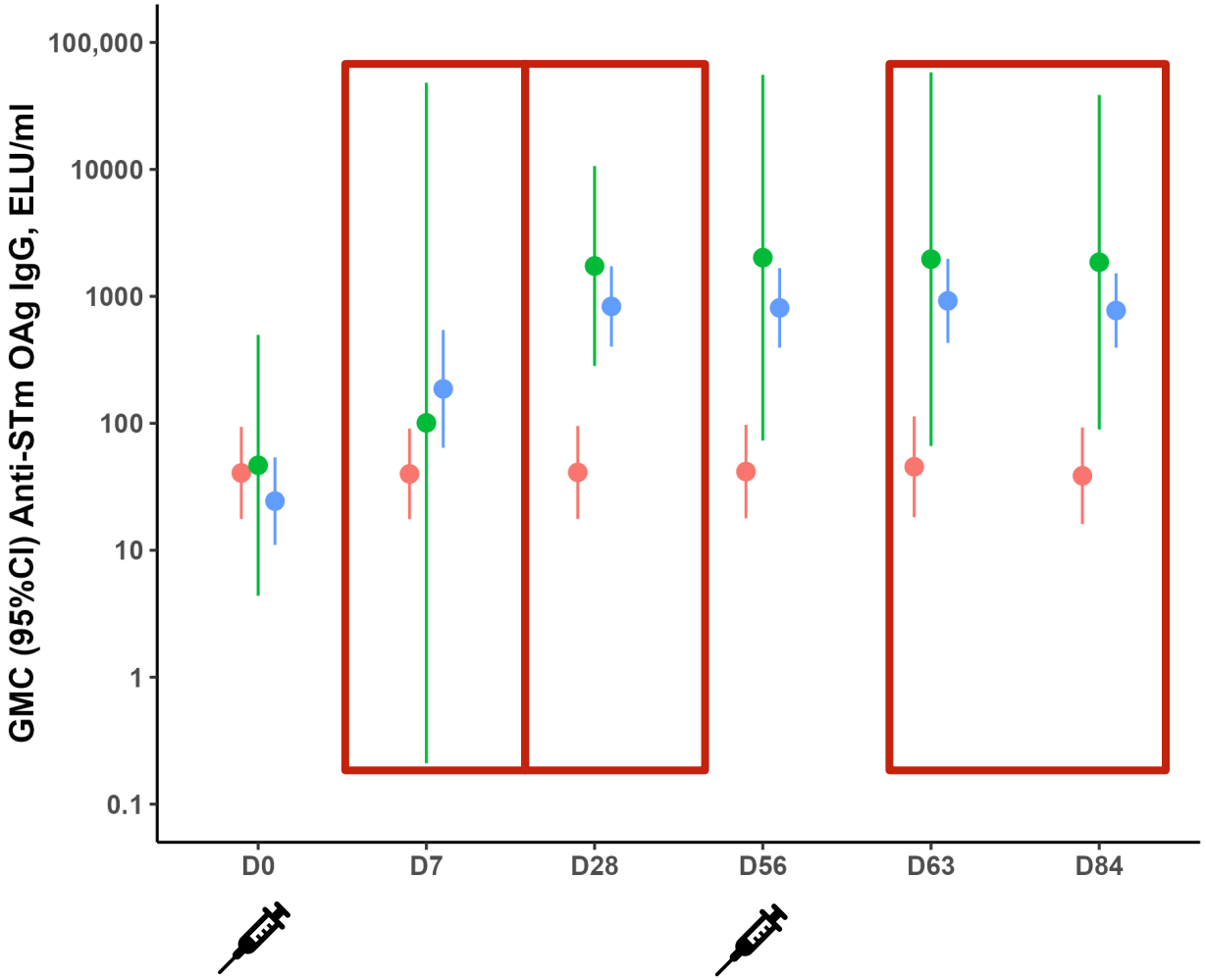
- Local pain and tenderness were mild-moderate and self-resolving
- Erythema, swelling and induration were mostly mild
  - 3/31 participants developed ≥ 100mm erythema after 1st dose, self-resolving
  - 1/31 participant developed 155mm area of swelling after 1st dose (subsequently withdrawn after similar 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 2nd 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



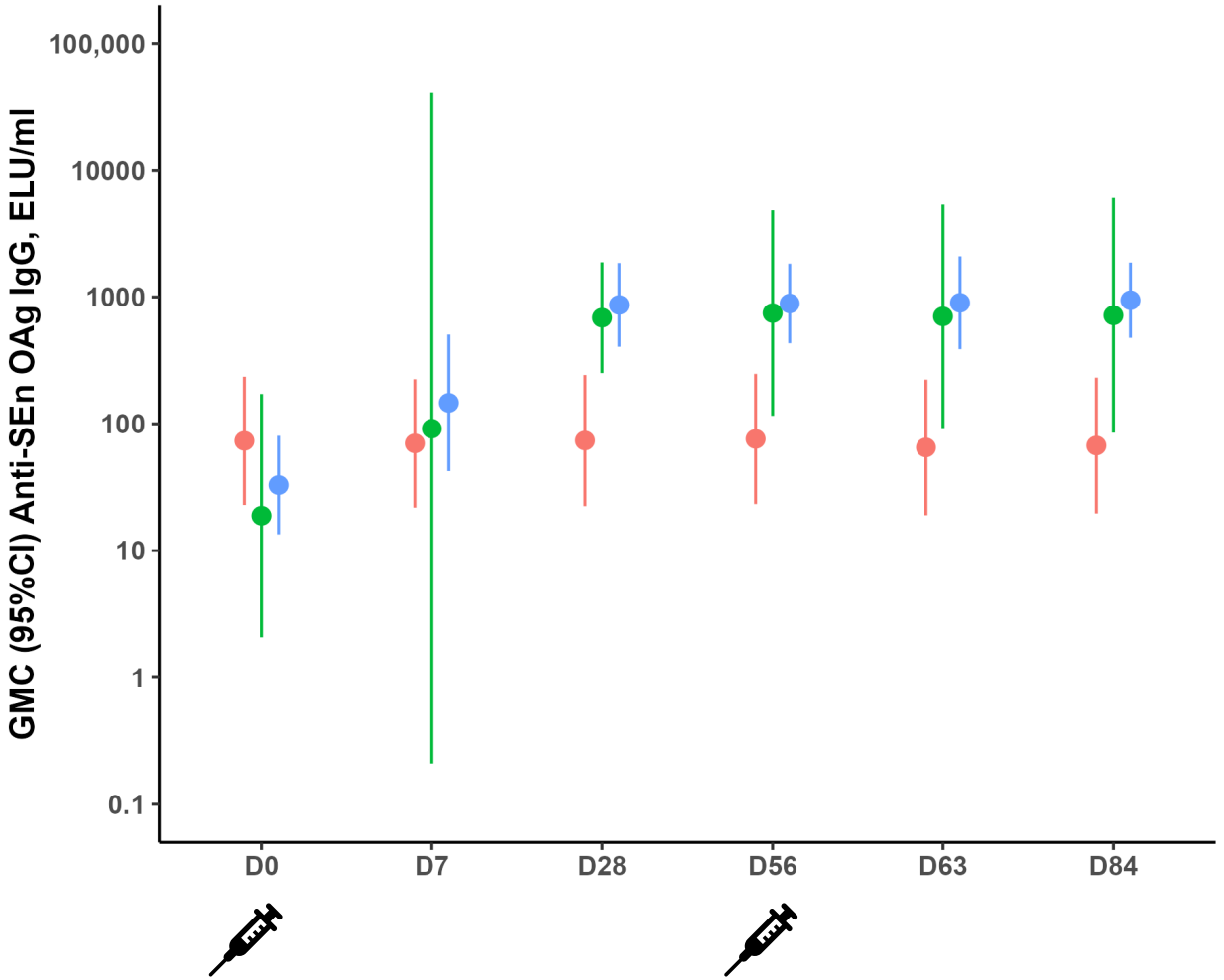
Both dose levels elicited robust anti-STm IgG responses



Placebo	Alhydrogel	n=12
Low dose	10.6 µg total OAg per dose	n=4
High dose	40 µg total OAg per dose	n=15

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.

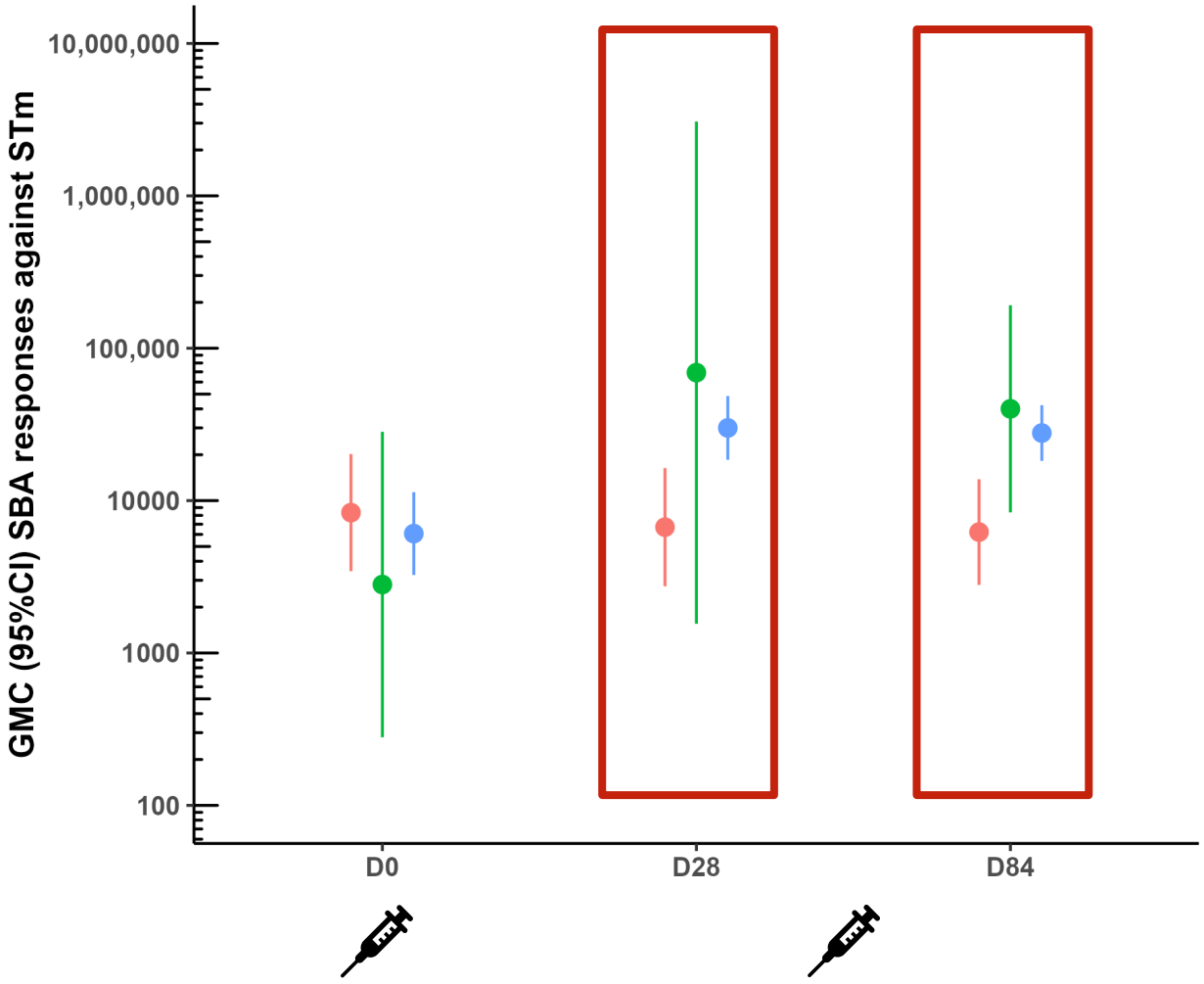
Both dose levels elicited robust anti-SEn IgG responses



Placebo	Alhydrogel	n=12
Low dose	10.6 µg total OAg per dose	n=4
High dose	40 µg total OAg per dose	n=15

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.

Full dose group demonstrated anti-STm SBA response



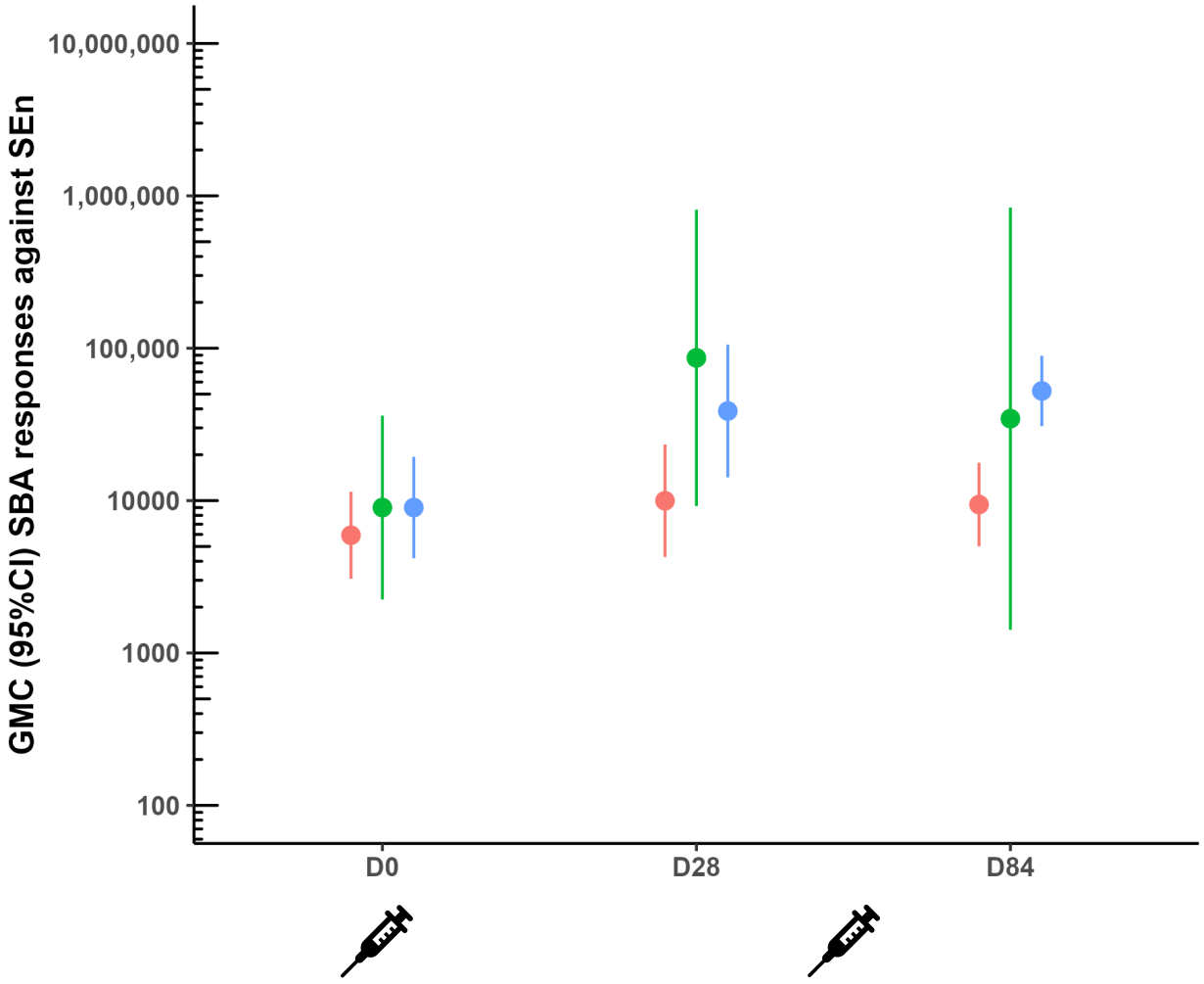
Study arm

- Placebo
- Low dose
- Full dose

Placebo	Alhydrogel	n=12
Low dose	10.6 µg total OAg per dose	n=4
High dose	40 µg total OAg per dose	n=15

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 Do and D56.

Full dose group demonstrated anti-SEn SBA response



Placebo	Alhydrogel	n=12
Low dose	10.6 µg total OAg per dose	n=4
High dose	40 µg total OAg per dose	n=15

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 Do and D56.

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.