Design and development of a vaccine against *Shigella*



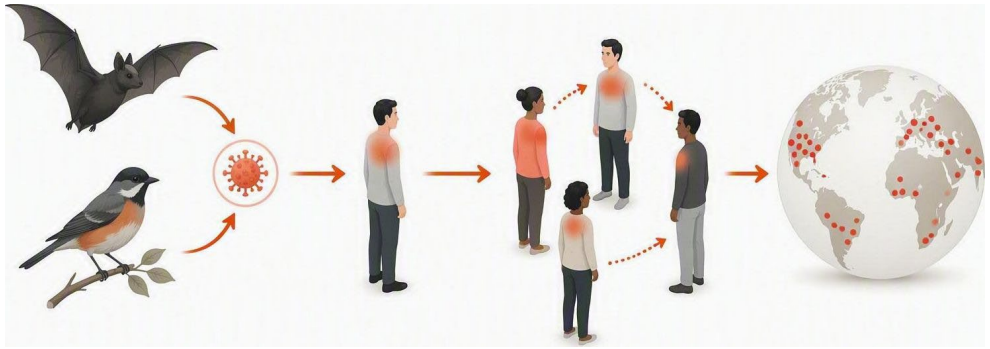
Francesca Micoli
Head of Chemistry and Molecular Biology, Discovery Technology, Vaccines Infectious Diseases Research Unit, GSK

IASOC
Ischia, 17-21 September 2026

Viral pathogens and pandemics

Pandemics are the result of a **new pathogen emerging and spreading** around the world that have occurred at infrequent and unpredictable intervals throughout human history.

New and emerging diseases can affect humans anywhere and at any time, with zoonotic diseases (diseases that can spread from animals to humans), such as **COVID-19, Ebola and avian influenza**, a major cause of epidemics and pandemics.



Antimicrobial resistance is a growing public-health threat

Drug-resistant infections are already eroding the effectiveness of modern medicine.

1.27M

deaths directly attributable to bacterial AMR in 2019

4.95M

deaths associated with bacterial AMR in 2019

39M

projected direct deaths from bacterial AMR, 2025–2050

The burden is global, but poverty and inequality amplify exposure and consequences — making AMR a health-security and equity issue.

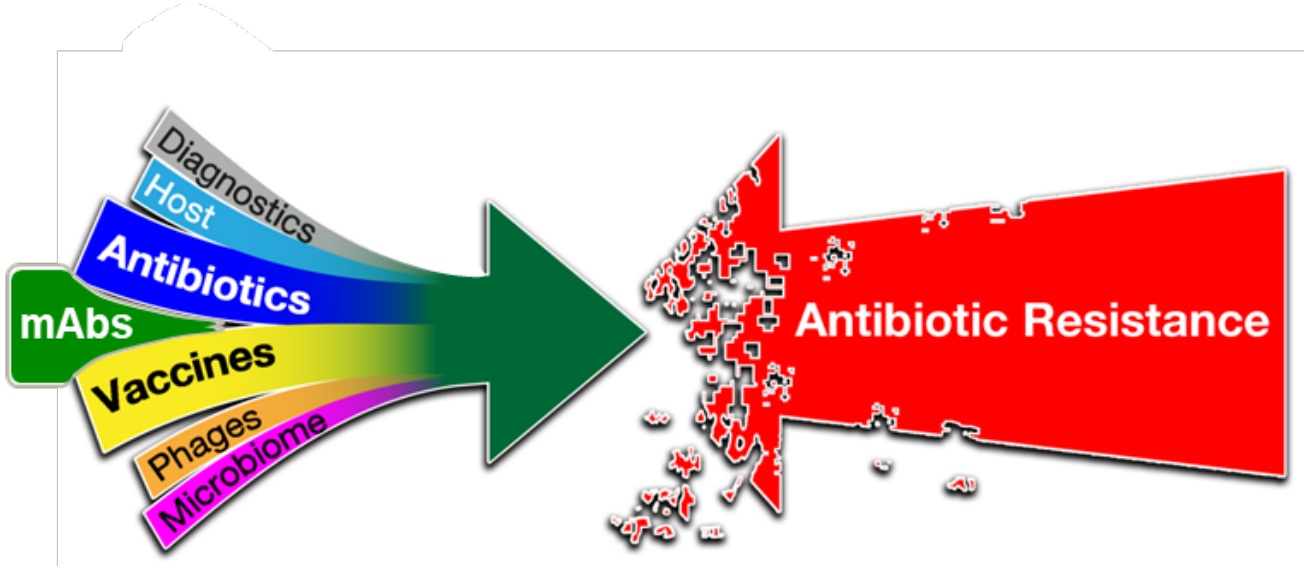
Prevention matters: fewer bacterial infections means less antibiotic use and less selection pressure for resistance.

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WHO AMR fact sheet (2023); GRAM Project / The Lancet (2024)

Approaches to contain AMR

The global challenge of antimicrobial resistance needs **an integrated strategy** to develop new interventions to fight multidrug-resistant bacterial pathogens effectively



Vaccines

- A **vaccine** is a biological preparation that provides active acquired immunity to a particular pathogen



- A vaccine typically contains an **agent that resembles a disease causing micro-organism** and is often made from **weakened** or **killed forms of the microbe**, **its toxins or one of its surface proteins**



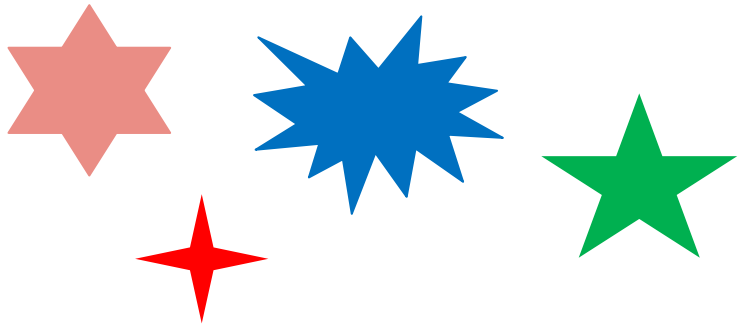
- The agent stimulates the body's immune system to recognize the agent as a threat, destroy it, and keep a record of it, so that the immune system can more easily recognize and destroy any of these micro-organisms that it later encounters

- Vaccines can be prophylactic (to prevent disease) or therapeutic (against existing pathology)

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Vaccines

Antigen(s)



- Needed for **specificity of the immune response**
- Depending on the vaccine platform, may be **directly administered** (e.g., subunit vaccines, inactivated or live attenuated vaccines) **or generated in the body after administration** (e.g., mRNA and viral vector vaccines)
- **Complex and multiple antigens** (with different structural features and doses) **may be combined** (e.g., some glycoconjugate/ protein subunit vaccines)

Adjuvants



- Depending on the vaccine platform, **adjuvants or delivery vehicles** may be needed
- **Aluminum salts or Adjuvant Systems** (combination of immunostimulatory molecules) may be a component. Needed **for most of the inactivated (whole or subunit) vaccines to enhance and modulate immunogenicity of the vaccine antigen**

Administered Vaccine



- All components in an **appropriate formulation**
- **May require reconstitution/ mixing of different components** before administration
- **Typically filled in vial or syringe, but other administration routes are/ will be possible** depending on the product characteristics and medical need (e.g., oral solutions, microneedles, inhalation)

Which steps to follow?

- Criteria for **pathogen selection**
- Requirements to support **vaccine development** against a certain pathogen
- Selection of **proper antigen(s) & optimal platform**
- **Preclinical data package** to support further development
- **Clinical pathway**

Shigellosis

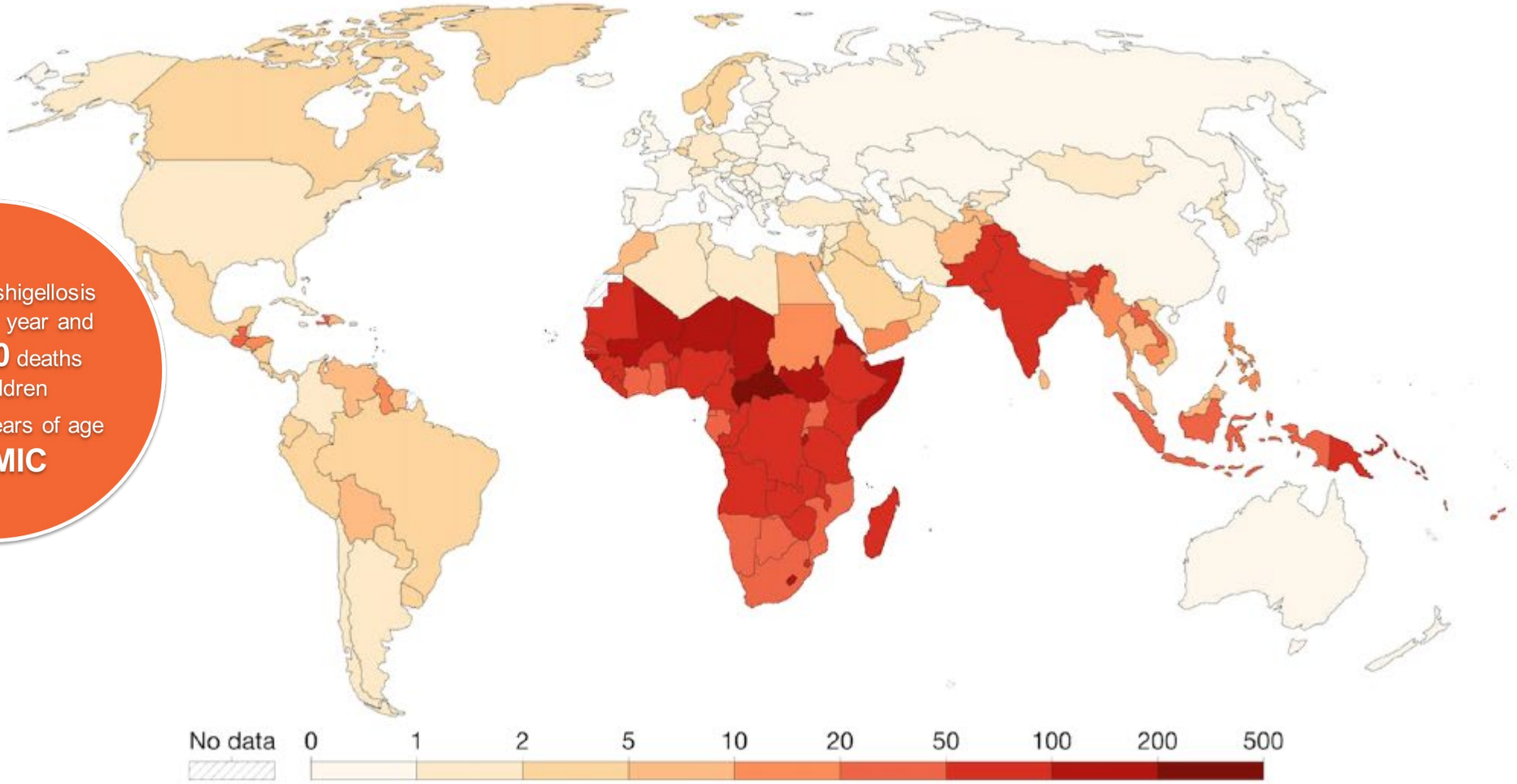
Leading bacterial cause of diarrheal mortality

Increasingly associated with **AMR**

Associated with **stunting**

270 M shigellosis cases per year and **64,000** deaths in children under **5** years of age in **LMIC**





Global burden *-Diarrheal diseases death rate, 2019 (per 100,000 people); WHO Global Health Estimates 2020*

Lancet Infect Dis 2018; Curr Opin Infect Dis. 2023 Oct 1;36(5):360-365; PLoS Negl Trop Dis. 2023 Sep 12;17(9):e0011475

Shigellosis, a disease in need for a vaccine

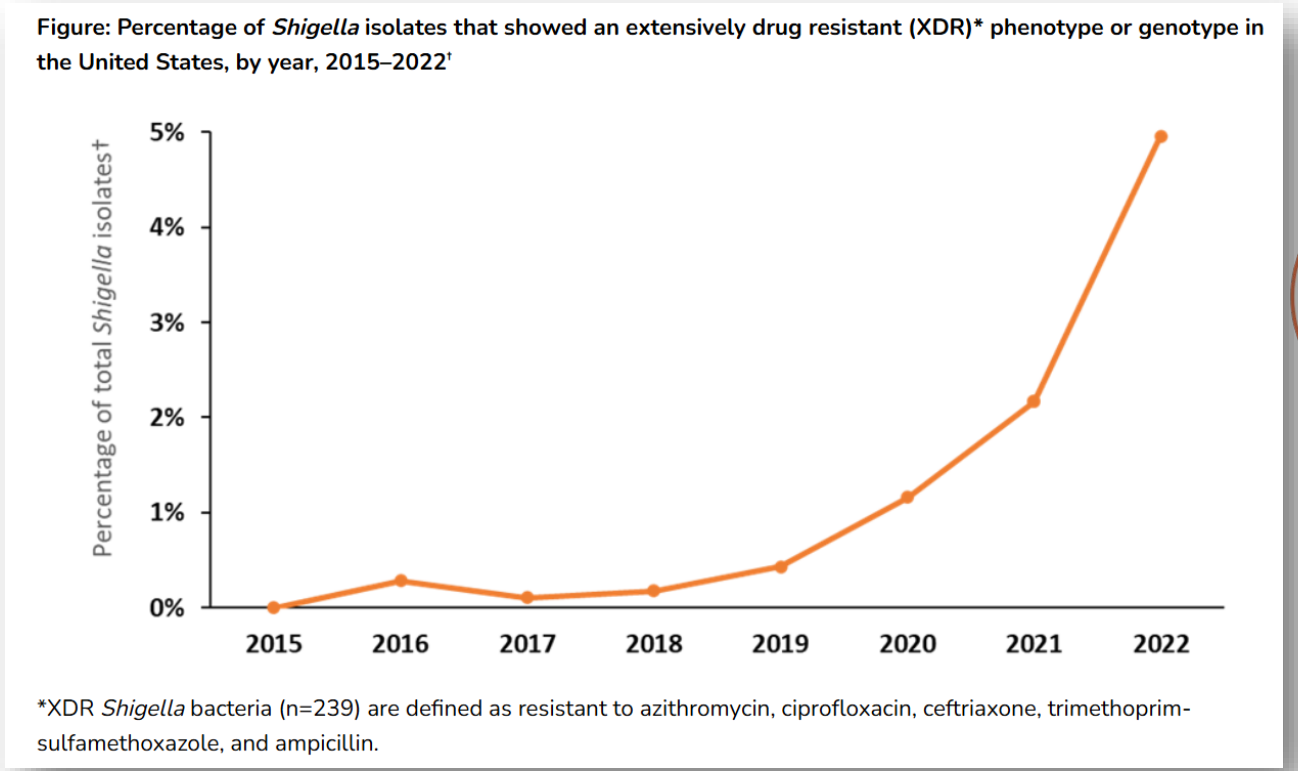
Leading cause of death for diarrhoeal diseases in children <5 years old

WHO Bacterial Priority Pathogens List, 2024

High group



Shigella spp.
fluoroquinolone-resistant



Increase in Extensively Drug-Resistant Shigellosis in the United States, CDC 2023

Increasingly associated with **AMR**

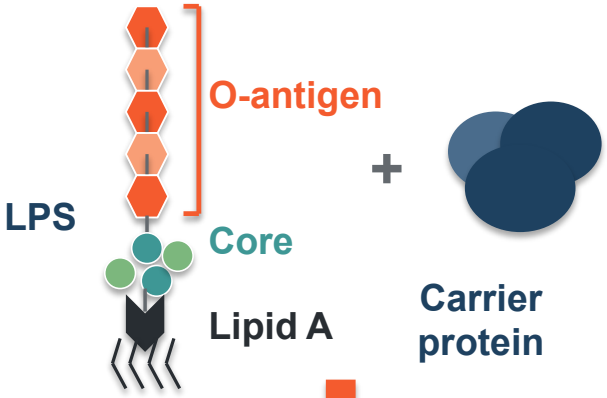
Associated with **stunting**

270 M shigellosis cases per year and **64,000** deaths in children under **5** years of age in **LMIC**



No licensed vaccine against shigellosis is currently available

Proof of concept that *Shigella* O-antigen based vaccines can be efficacious



O-antigen–carrier conjugate

- A 1st generation NIH ***S. sonnei* conjugate** vaccine gave **74% efficacy in Israeli adults**
- **Protection** was associated with serum **IgG antibody response to O-antigen**
- The vaccine failed to protect children < 3 years. Loss of protection was closely associated with decreased induction of O-antigen IgG

Efficacy of 2 doses of *Shigella* conjugate vaccines by age, per-protocol.

Age	Vaccine administered		Efficacy	(95% CI)
	S. sonnei			
	N	Cases		
a. *Shigella sonnei*				
1–2 years	516	18	3.8%	(101.1, 46.5)
>2–3 years	497	8	35.5%	(−56.4, 73.4)
>3–4 years	371	3	71.1%	(−4.43, 92.0)

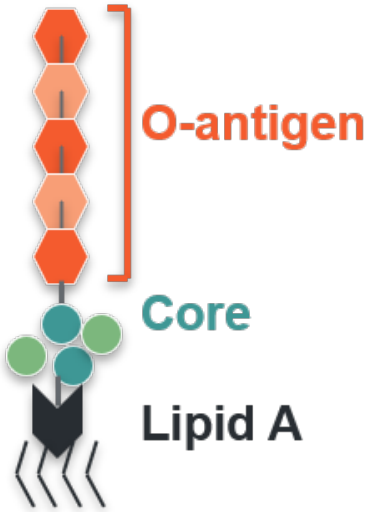
Age-related IgG anti-LPS levels of sera drawn randomly >2 weeks after the second vaccine dose.

G.M. IgG anti-LPS (EU)*			
Vaccine	Age (years)	*N*	*S. sonnei*
S. sonnei	1–2	38	1.40
	>2–3	44	3.71
	>3–4	29	6.38

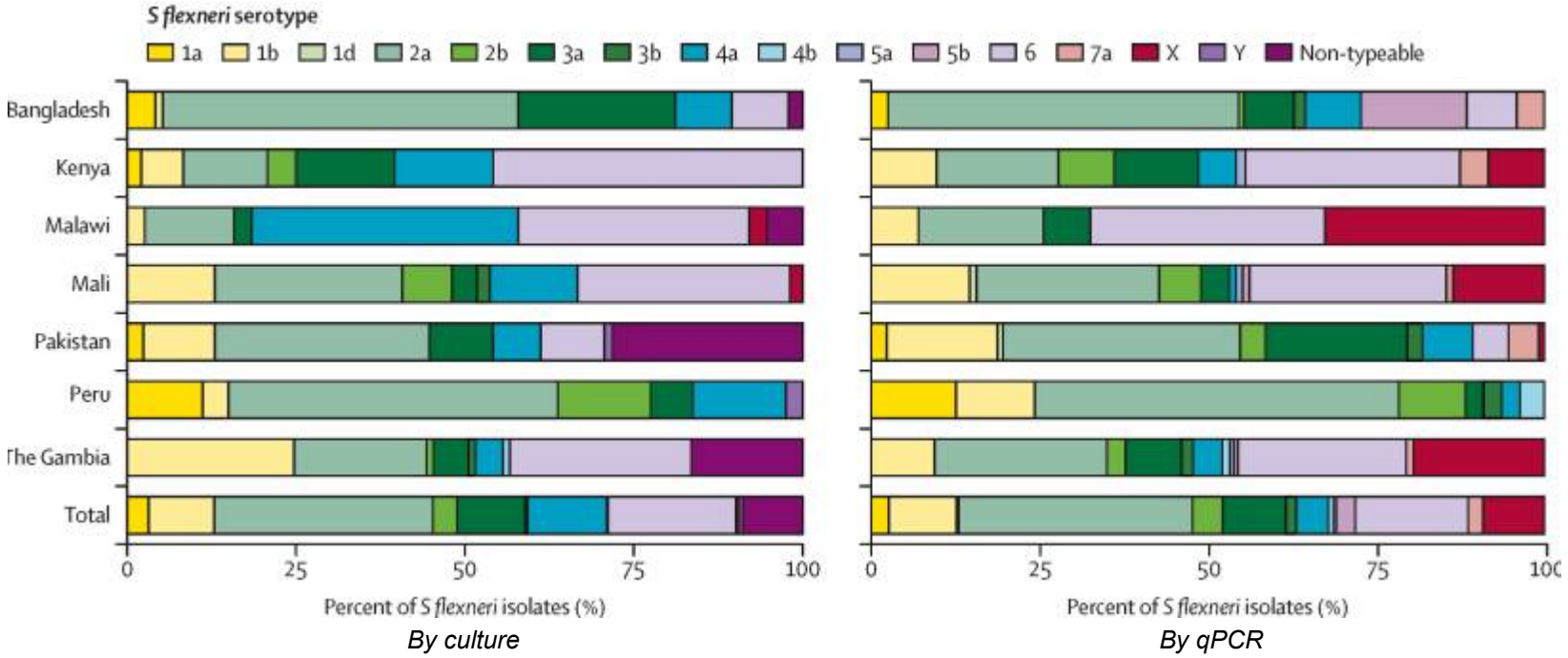
Passwell et al. Vaccine. 2010;28(10):2231; Cohen et al. Hum Vaccin Immunother. 2019;15(6):1401; Cohen et al. Clin Microbiol Infect. 2023;29(3):366

Most *Shigella* vaccines are combination vaccines

- **4 major *Shigella* species** and more than **50 different serotypes**
- **Immunity** to *Shigella* appears to be **serotype-specific** (driven by **O-antigen** diversity)



***Shigella* prevalence and serotype distribution by EFGH country site and laboratory method**



Yousafzai MT et al. Lancet Glob Health. 2026;14(5):e749

Vaccine serotypes:

Shigella sonnei

***Shigella flexneri* 2a**

Shigella flexneri 3a

Shigella flexneri 6/1b

Preferred product characteristics for vaccines against *Shigella*

Indication

Prevention of moderate to severe diarrhea caused by *Shigella*

Efficacy

≥ 60% efficacy against moderate to severe diarrhea episodes caused by *Shigella* strains in the vaccine

Route of administration

IM administration using standard volumes

Durability of protection

Duration of protection for 24 months following the last vaccine dose in the primary series, with protection up to 5 years desirable

Population

Children, 6 months to 5 years (the peak of incidence is between 12–24 months of age)

Safety & reactogenicity

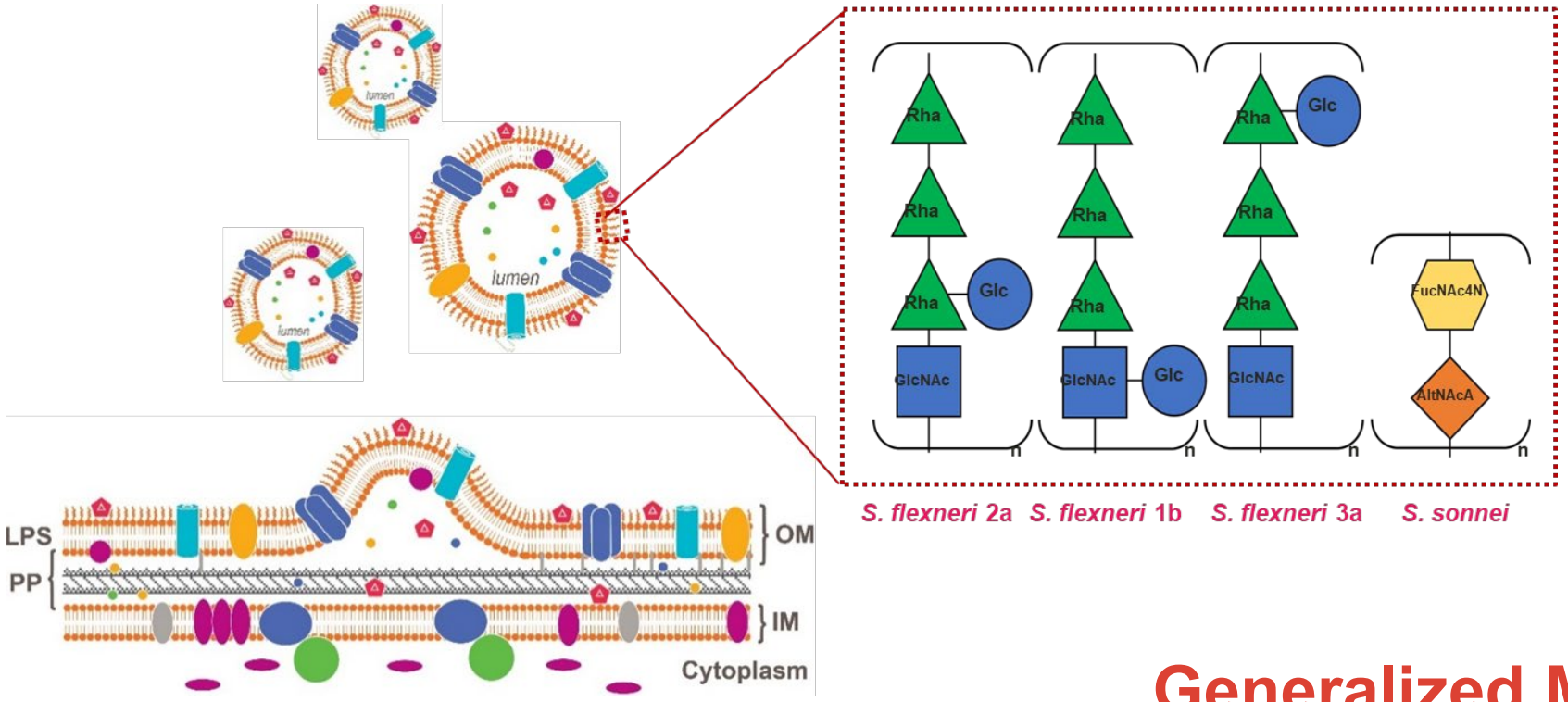
Similar to licensed vaccines for the given age group

Dose & schedule

1–2 doses for primary immunization, given during the first 12 months of life. An additional booster dose may be required to maintain effective, protective immunity through the first 5 years of life

WHO preferred product characteristics for vaccines against Shigella, 2021; ***WHO PPC is under revision as per latest PDVAC***

An innovative technology for a 4-valent O-antigen based vaccine with broad protection against most prevalent *Shigella* serotypes



altSonflex1-2-3

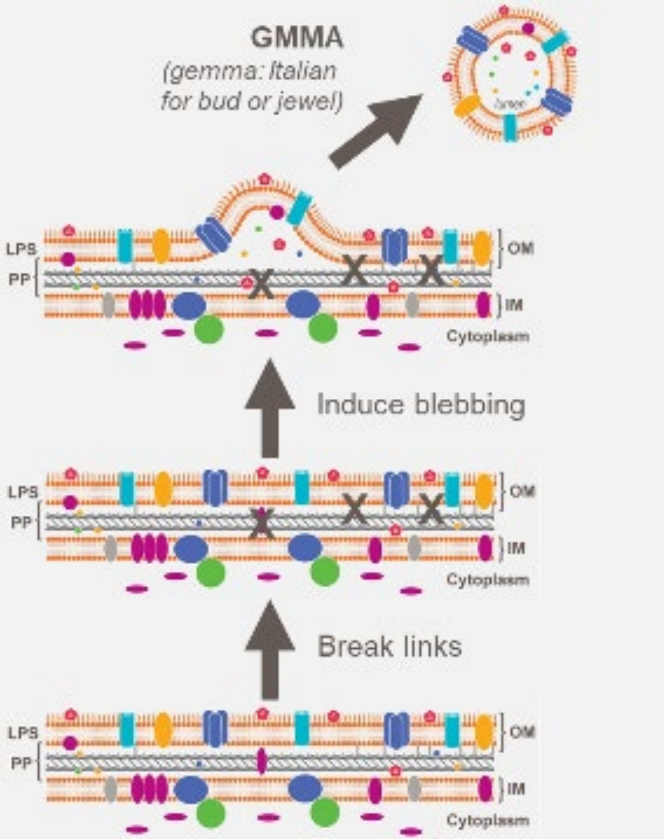
Micoli F et al. Vaccines (Basel). 2022;10(2):328

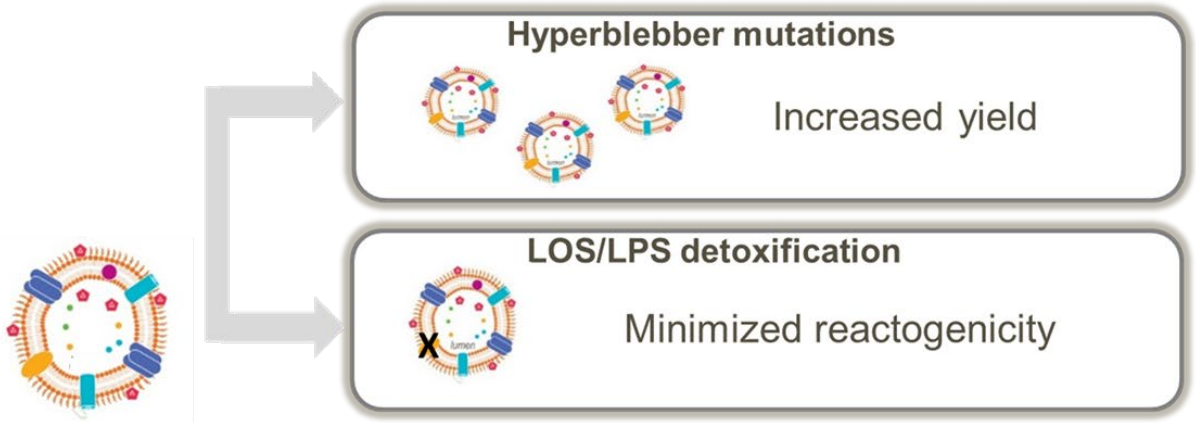
Generalized Modules for Membrane Antigens (GMMA)

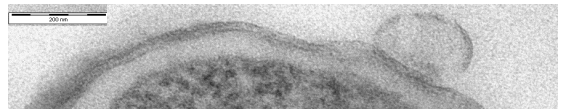
cost-effective and **generic** technology platform enabling our vaccine strategy

Generalized Modules for Membrane Antigens (GMMA)

GMMA represent an attractive platform for the development of effective vaccines against bacterial pathogens







targeting bacterial pathogens from which they derive

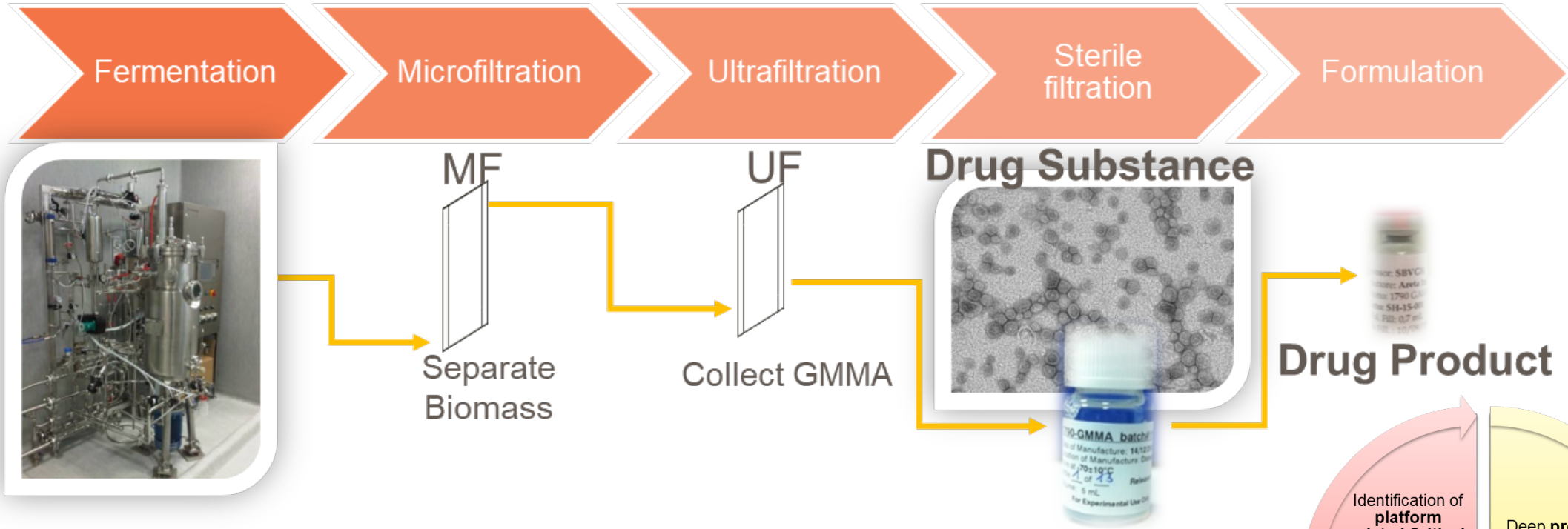
GMMA are released yielding pure source of outer membrane

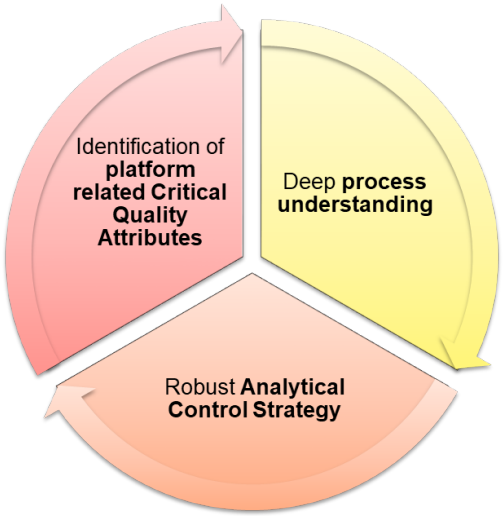
- Similar size to virus-like particles
- Contain Pathogen Associated Molecular Patterns: naturally adjuvanting
- Multiple antigens are presented in their natural environment and conformation

Micoli F et al. Vaccines (Basel). 2022;10(2):328

GMMA-based vaccine manufacturing process

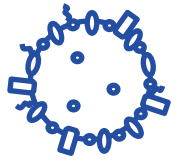
Generic, industrially scalable and economic process



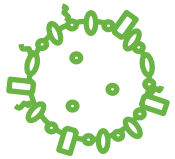


Kis Z et al. Biotechnol J 2019;14:e1800376; Berlanda Scorza F et al. PlosOne 20127;(6):e35616; Gerke C et al, PloS one 2015;10(8):e0134478; Giannelli C et al. AAPS J. 2024;26(2):32

altSonflex1-2-3: a 4-component GMMA based vaccine



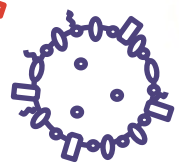
S. sonnei GMMA



S. flexneri 2a GMMA



S. flexneri 1b GMMA



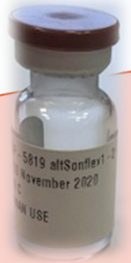
S. flexneri 3a GMMA



Development start in 2020

Scale up @ 3L scale

June 2020
Tox Lot produced



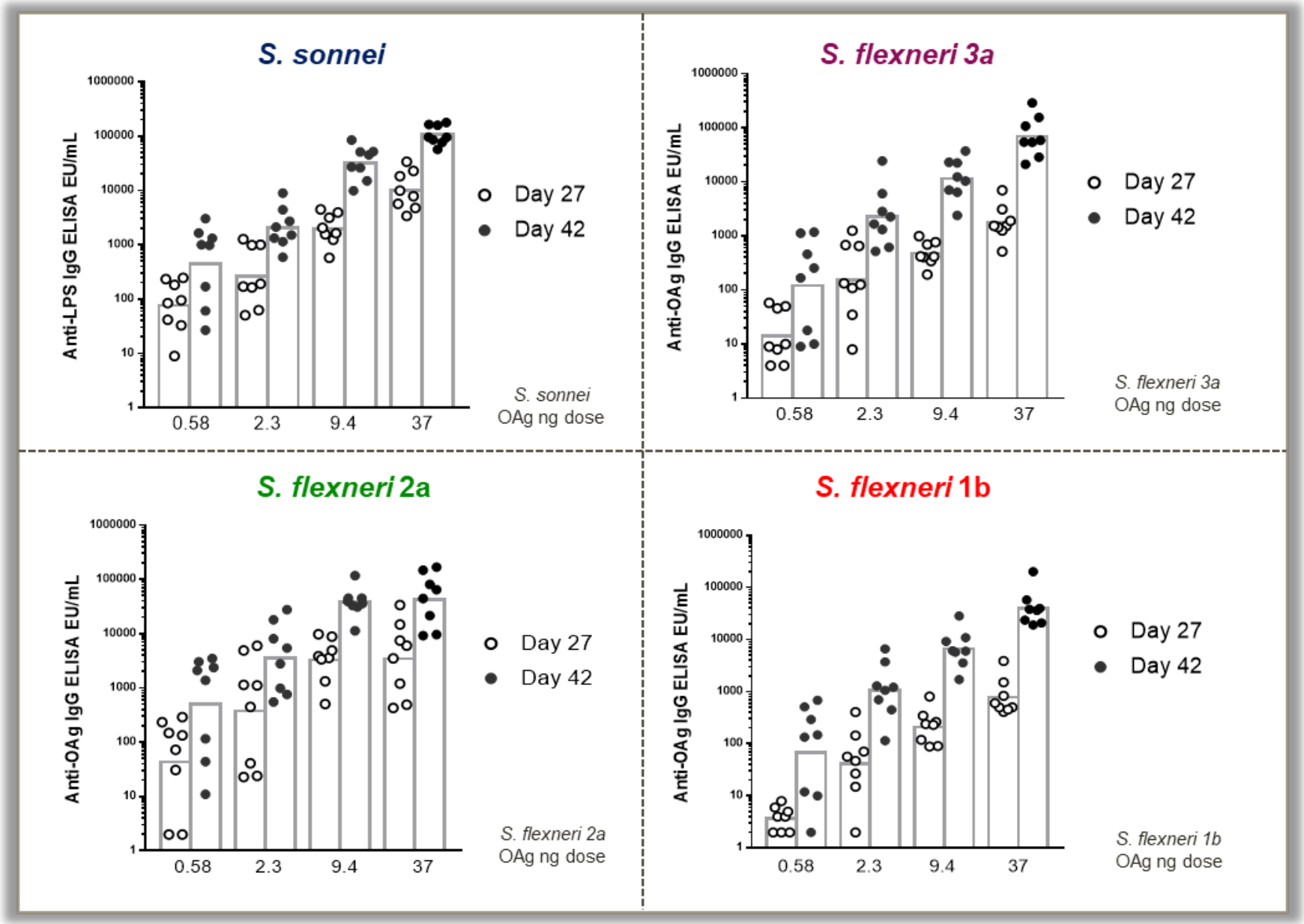
May 2021
1st GMP Lot produced

2021-2022
Phase 1 Europe

- Leveraging on the scientific-technical know how on **GMMA-platform**
- Real time stability data on **Tox Lot** to support the **shelf-life** of the GMP Lot (extended to **42 months**)
- **3 GMP Lots** produced

GMMA are highly immunogenic in animal models

Rossi O, Citiulo F et al. NPJ Vaccines. 2023;8(1):130



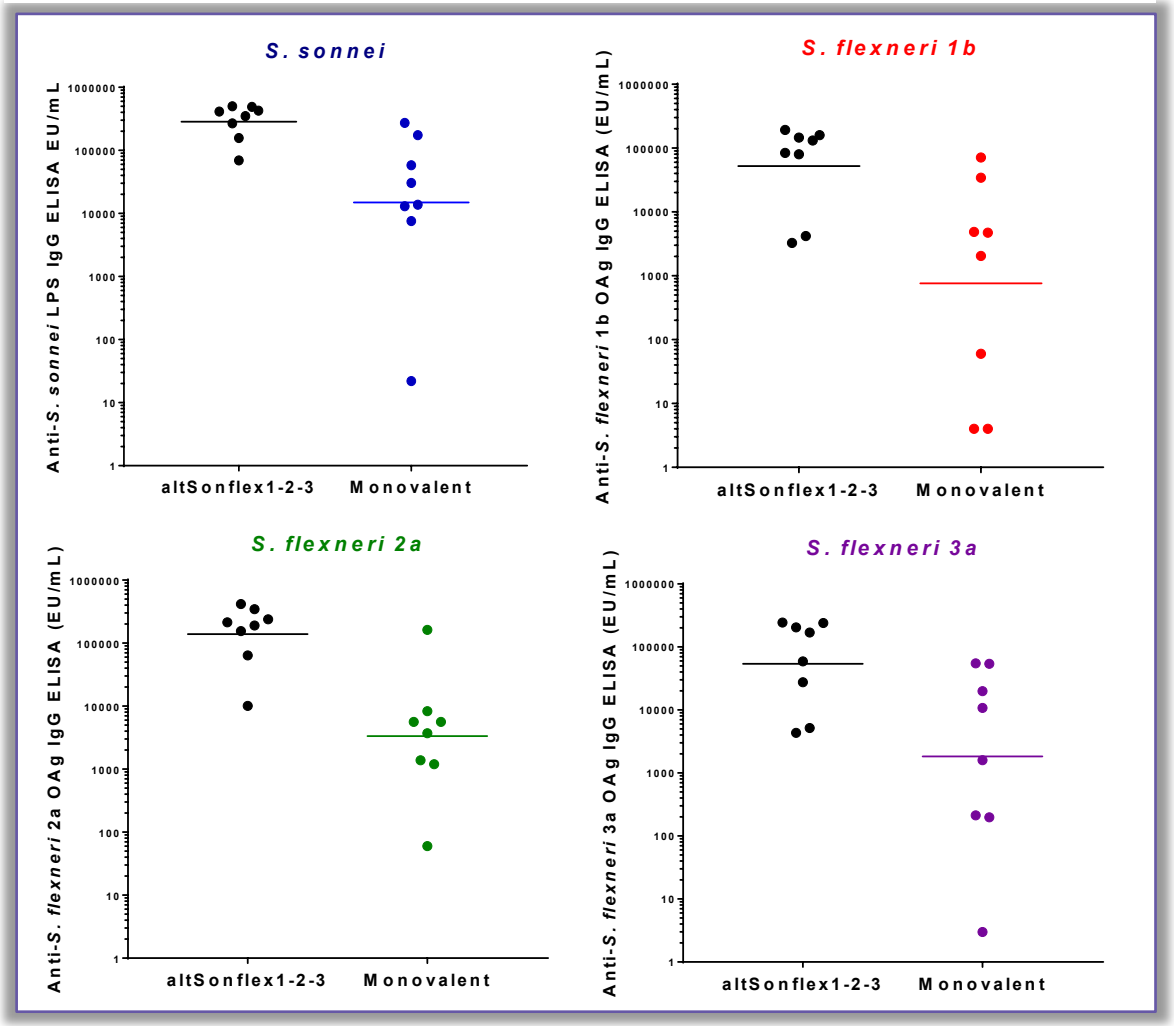
Mice
IP injections
at days 0 and 28

altSonflex1-2-3 elicits functional antibodies with no evidence of negative antigenic interference

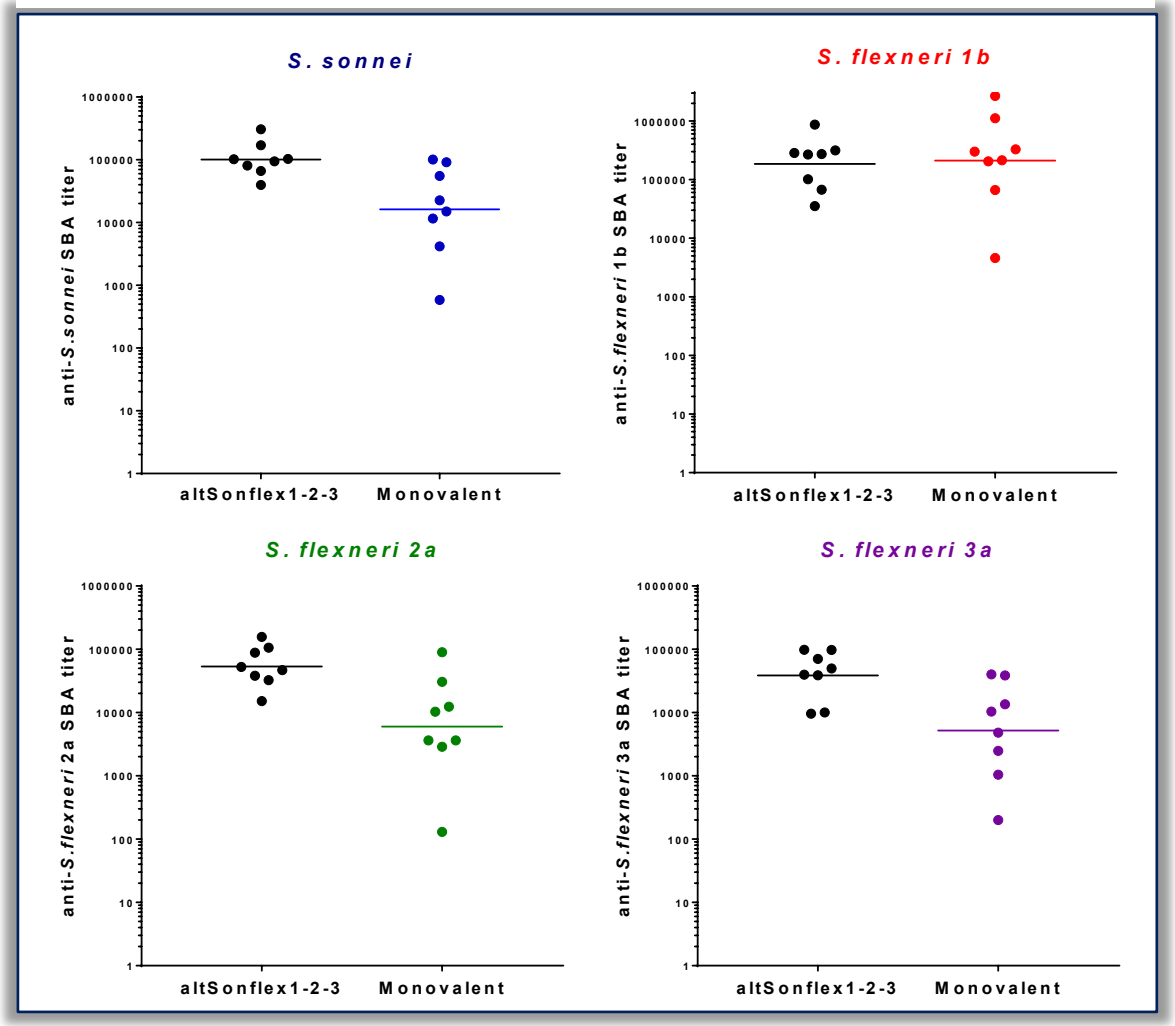
IP injections of mice at days 0 and 28

Day 42 sera

Immunogenicity (ELISA)



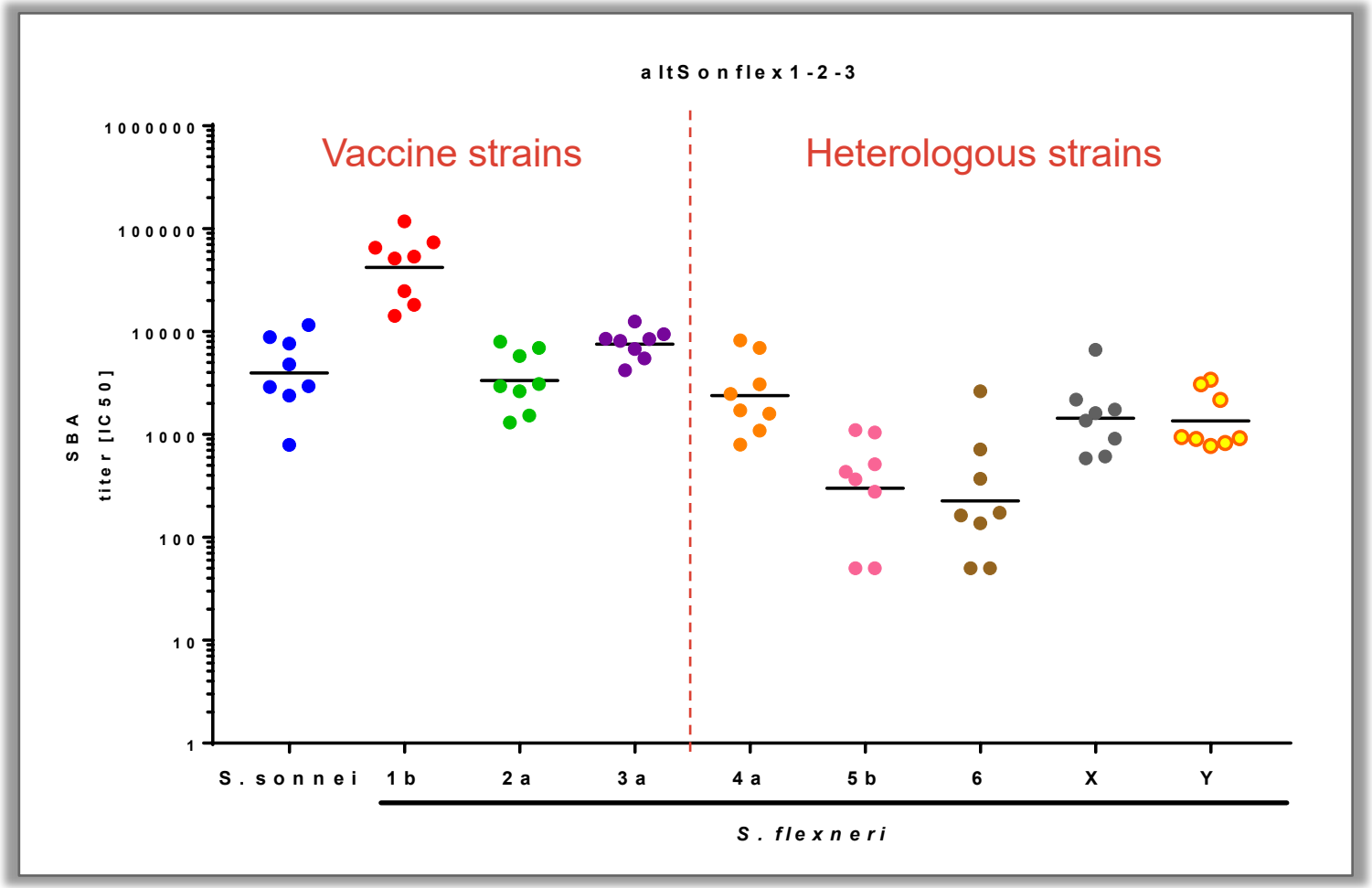
Functionality (SBA)



GSK With as little as 9 ng OAg dose (mice data, confirmed in rabbits)

Rossi O, Citiulo F et al. NPJ Vaccines. 2023;8(1):130

altSonflex1-2-3 induces antibodies cross-functional with serotypes not included in the vaccine

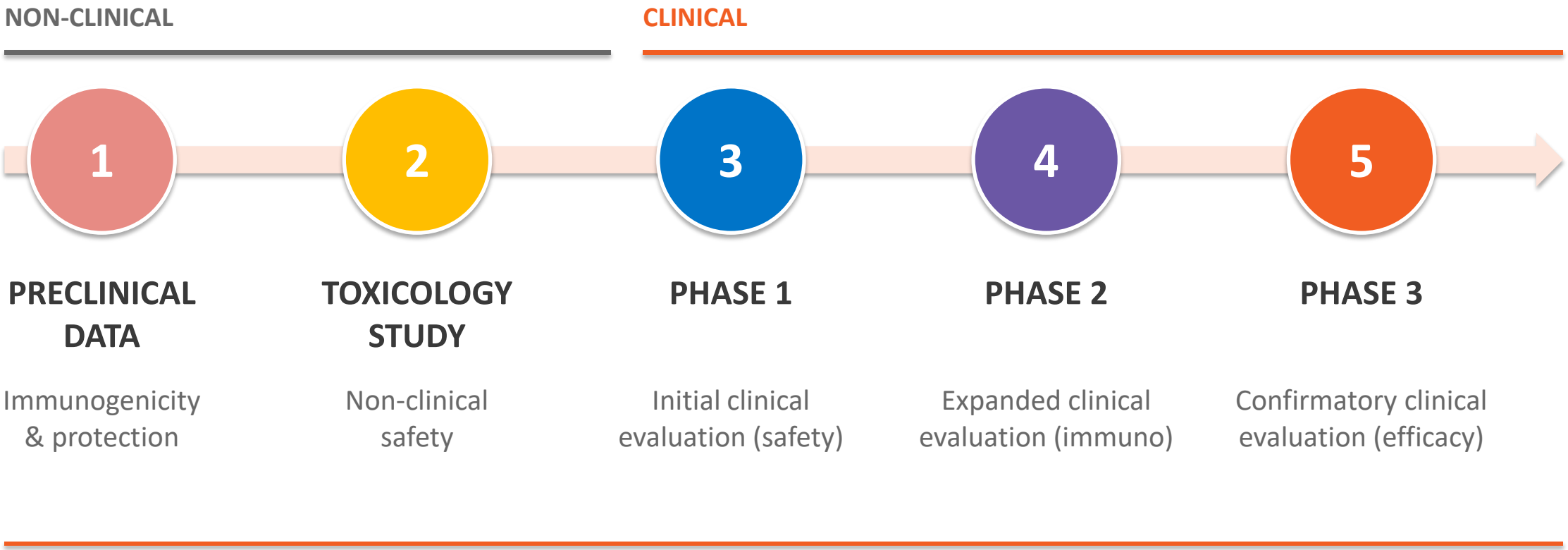


IM injections of rabbits
at days 0 and 28
1.5 µg each OAg/dose

Rossi O, Citiulo F et al. NPJ Vaccines. 2023;8(1):130

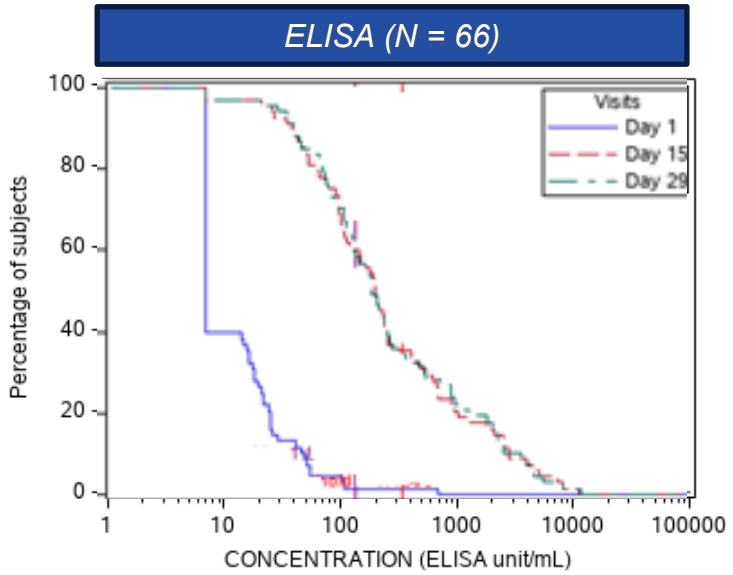
From preclinical evidence to Phase 3

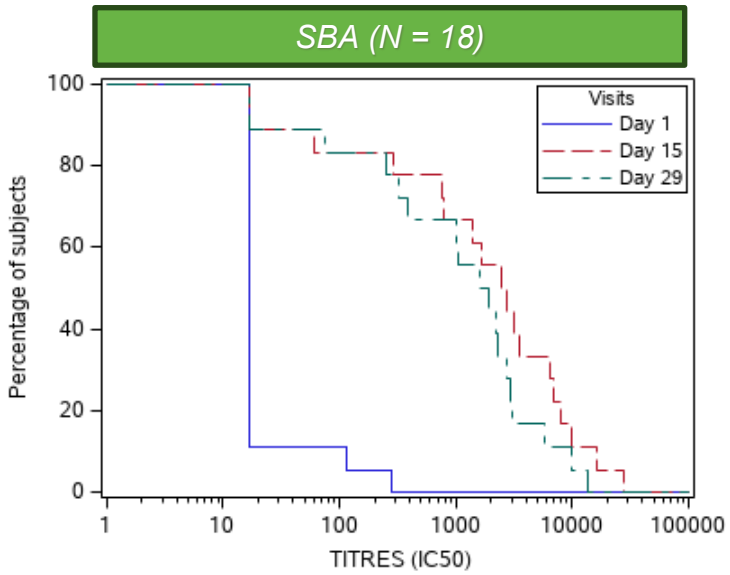
A staged pathway builds evidence from non-clinical assessment to confirmatory clinical evaluation.



Each stage informs the decision to progress to the next

Phase 1 in EU adults - High anti-OAg IgG response and increase in antibody functionality already post dose 1

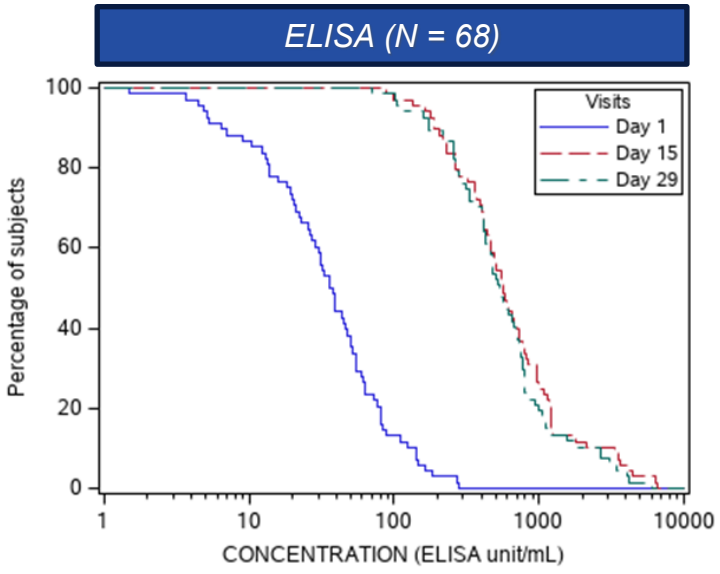


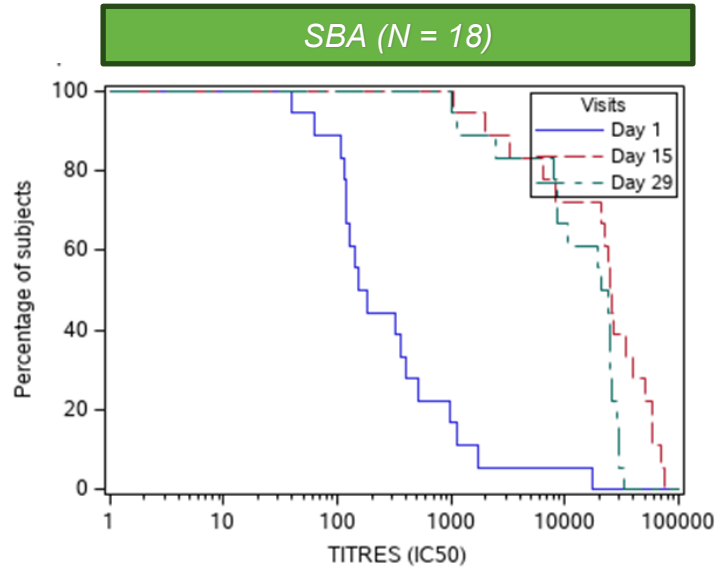


S. sonnei

77.3% 4-fold increase, **20.4** GMR

83% 4-fold increase, **42.4** GMR





***S. flexneri* 2a**

91% 4-fold increase, **16.8** GMR

94% 4-fold increase, **43.7** GMR

Leroux-Roels I et al. J Infect Dis. 2024;230(4):e971

The vaccine has been tested in Phase 2 trials

H06_01TP Stage 2 age de-escending trial (NCT05073003)



AGE-DE-ESCALATION

Africa • infants, 9 months of age

20 infants per group

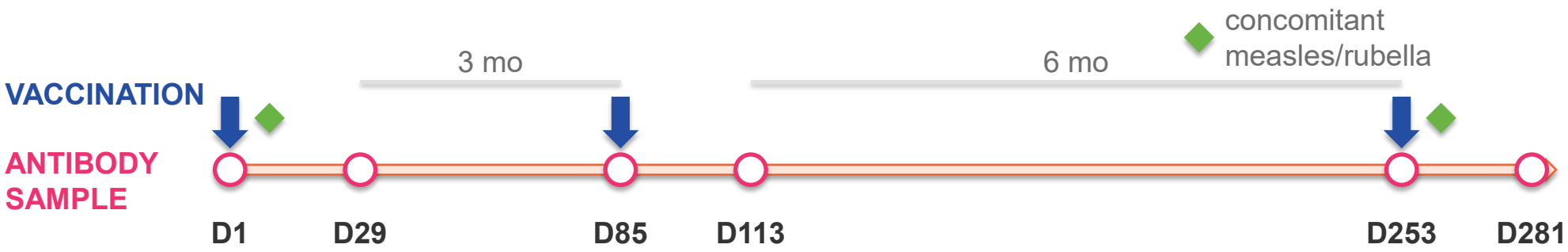
A	B	C
Dose A or control	Dose B or control	Dose C or control

SAFETY COHORTS

No safety concerns observed during planned safety reviews

The study has progressed to dose-finding in infants

DOSE-FINDING COHORT **329** **infants**



Dose A: ¼ full dose

Dose B: ½ full dose

Dose C: full dose –15 μg each OAg

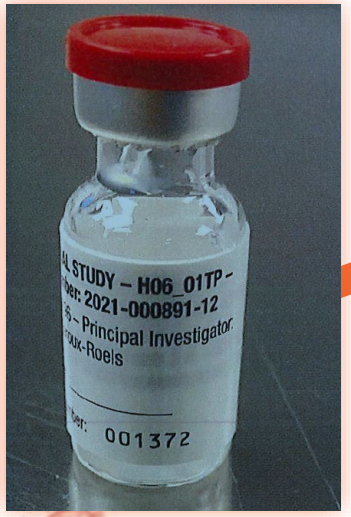
Control group: MENVEO for 1st and 2nd dose, INFANRIX HEXA for 3rd dose

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Abstract presented at EMBO Shigella Workshop, 20-24 April 2026, Paris

Shigella GMMA vaccine development

4-component GMP lot released



2021

Phase 1 in Europe

2023-2024

Two Phase 2 in Kenya

2025

29April Licensing agreement with Bharat Biotech fully executed

2026

Decision on dose and schedule for further development

Phase 3

Press release
For media and investors only

GSK

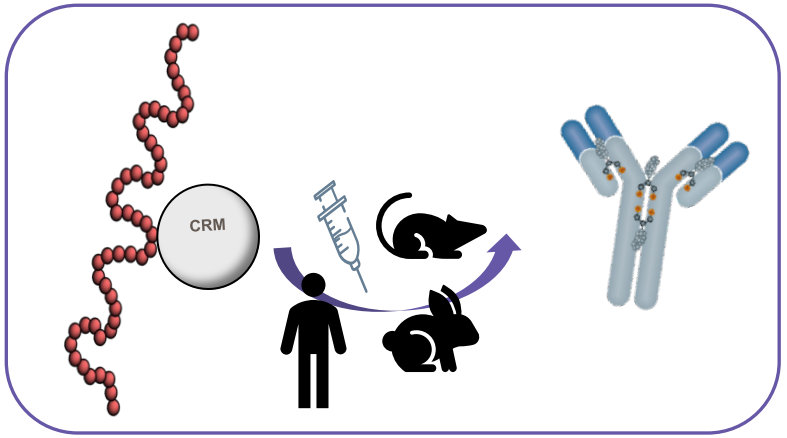
Issued: 12 June 2025, London UK

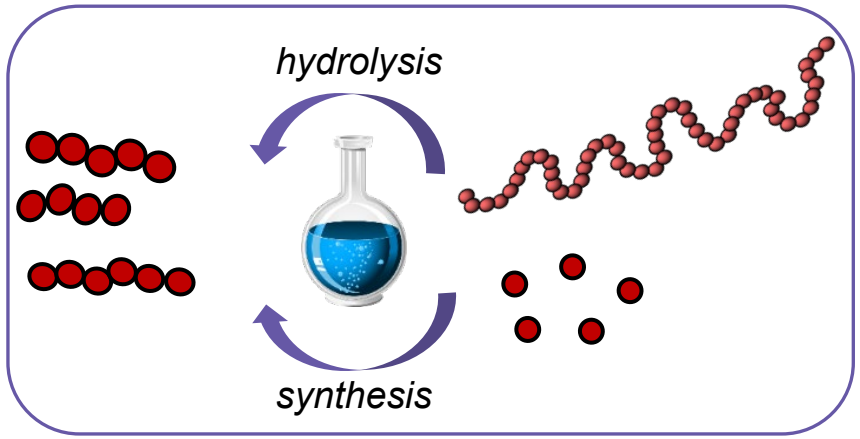
GSK licenses *Shigella* vaccine candidate to Bharat Biotech for continued development

- *Shigella* poses a significant health threat to children under five in low- and middle-income countries, where it is the leading bacterial cause of diarrhoea[1]
- Rise of antimicrobial-resistant bacteria like *Shigella* highlights critical need for a vaccine to prevent illness, help save lives, and tackle antimicrobial resistance (AMR)[1,2]
- Collaboration will accelerate GSK's innovation and investment in early development, advancing late-stage vaccine development with the aim of achieving maximum health impact in populations who need the vaccine

Structure-based vaccine optimization approach

Isolation of functional mAbs

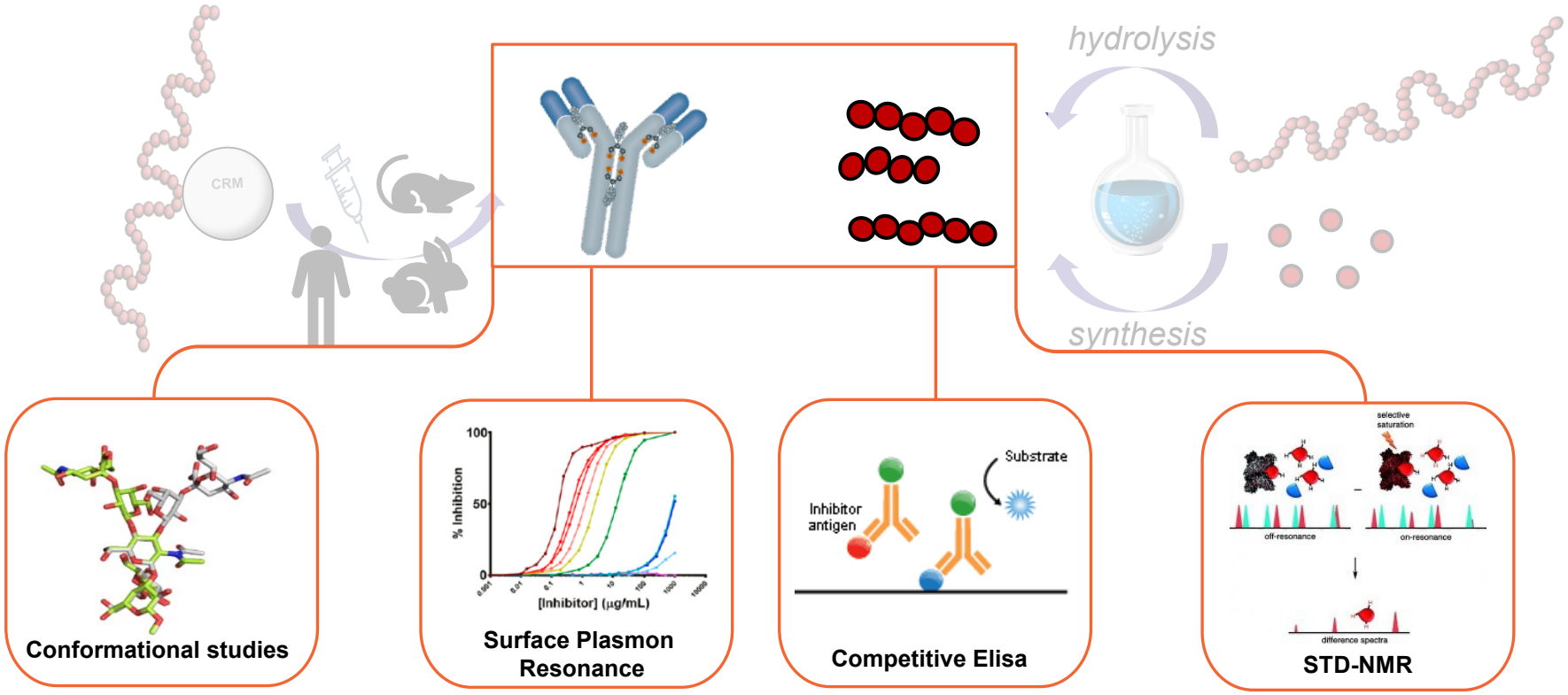




Well-defined oligosaccharides

Structure-based vaccine optimization approach

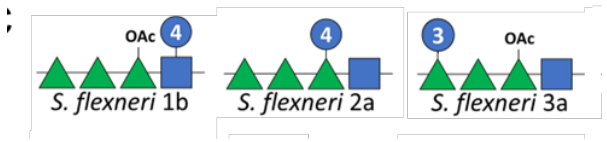
Isolation of functional mAbs



Well-defined oligosaccharides

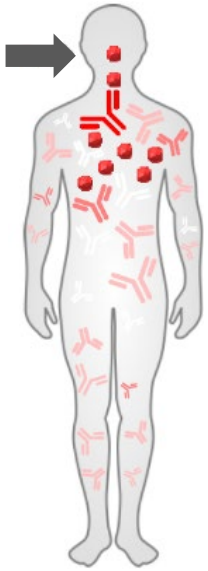
Structural analysis: definition of protective epitope

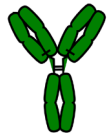
Monoclonal antibody driven design of a universal *Shigella flexneri* vaccine





altSonflex1-2-3





In vitro functional assays

Human Antibody Discovery

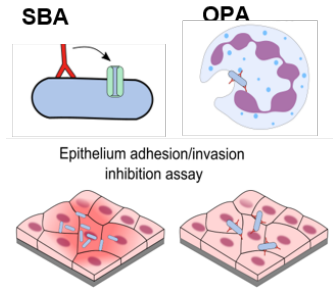
Structural studies & Antigen Design

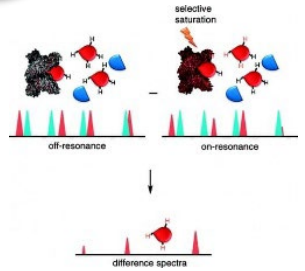
Vaccine Antigens

Early Formulation

New GMMA Production & Characterization

anti-LPS cross-reactive mAb









Acknowledgements

GVGH

Shigella Project Team



Thank you!

GSK Safety Evaluation and Risk Management

GSK Data Management

GSK Clinical Programming

GSK Science Writing

GSK procurement

GSK Intellectual Property

GSK TRD Drug Product development Unit I

Gates Foundation

NIBSC
Paul Stickings
Caroline Vipond

TLS Toscana Life Sciences
Claudia Sala
Rino Rappuoli

University of Maryland
Ushasi Bhaumik,
Girmay Tarekegn
Marcela Pasetti

Tel Aviv University
Israeli University in Tel Aviv
Dani Cohen

KEMRI | Wellcome Trust
Melissa Kapulu

Ragon Institute
MASS GENERAL | MIT | HARVARD
Ryan McNamara

WRAIR Walter Reed Army Institute of Research

ANTIGEN DISCOVERY INC
Angela Yee
Joe Campo

Isabel Leroux
UNIVERSITEIT GENT
KEMRI/WRAIR-A/HJFMRI
Deborah Langat
Fredrick Sawe

wellcome trust

GSK

FM is employed by the GSK group of companies and reports ownership of GSK shares. This work was performed at GSK Vaccines Institute for Global Health Srl (GVGH) - an affiliate of GlaxoSmithKline Biologicals SA. This work was undertaken at the request of and sponsored by GlaxoSmithKline Biologicals SA and partially funded by BMGF and WT. All animal studies are ethically reviewed and carried out in accordance with GSK Policy and local legislation.