BILL & MELINDA GATES foundation

Status of *Shigella* vaccine pipeline and product development considerations

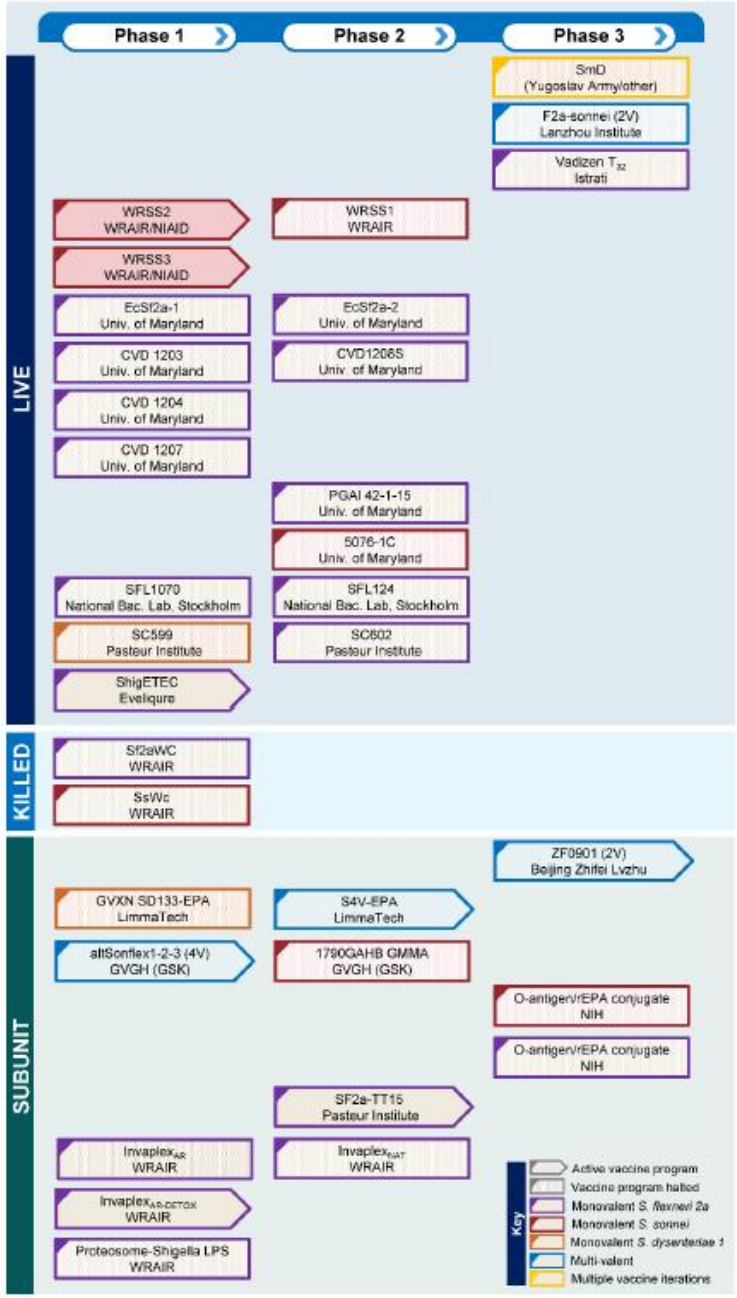
Cal MacLennan

WHO PDVAC Meeting

December 12, 2023

Shigella vaccine pipeline

- 100 years of Shigella vaccine development
- Proof of concept from NIH glycoconjugate vaccine in Israel 1997
- Graveyard of reactogenic/poorly immunogenic LAV candidates
- New emphasis on O-antigen-based parenteral vaccines



(The *Shigella* Vaccines Pipeline Vaccines 2022)

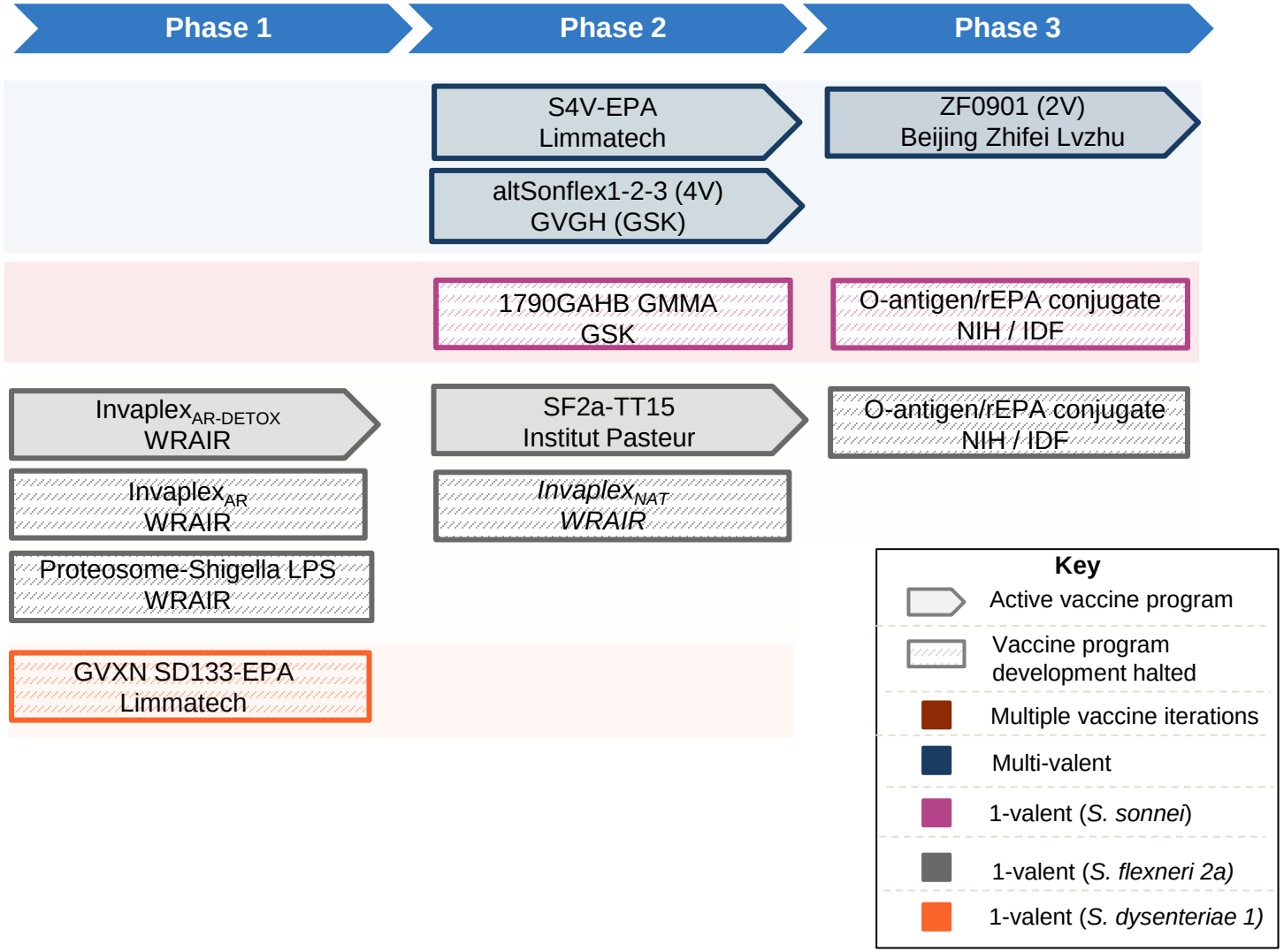
WHO preferred product characteristics (PPC)

- **Indication** Prevention of moderate-to-severe diarrhoea (MSD) due to *Shigella* infection
- **Target Population** Infants from 6 months and children up to 36 months of age
- **Schedule** 1–2 dose primary series during first 12 months of life +/- booster for protective immunity through to 5 years
- **Efficacy** 60% (point estimate) or more against moderate-to-severe *Shigella* diarrhoea caused by vaccine serotypes
- **Duration** For 24 months following last vaccine dose in the primary series. Protection up to 5 years desirable
- **Route** Oral or injectable (IM, ID or SC), using standard volumes of administration

(WHO, 2021)

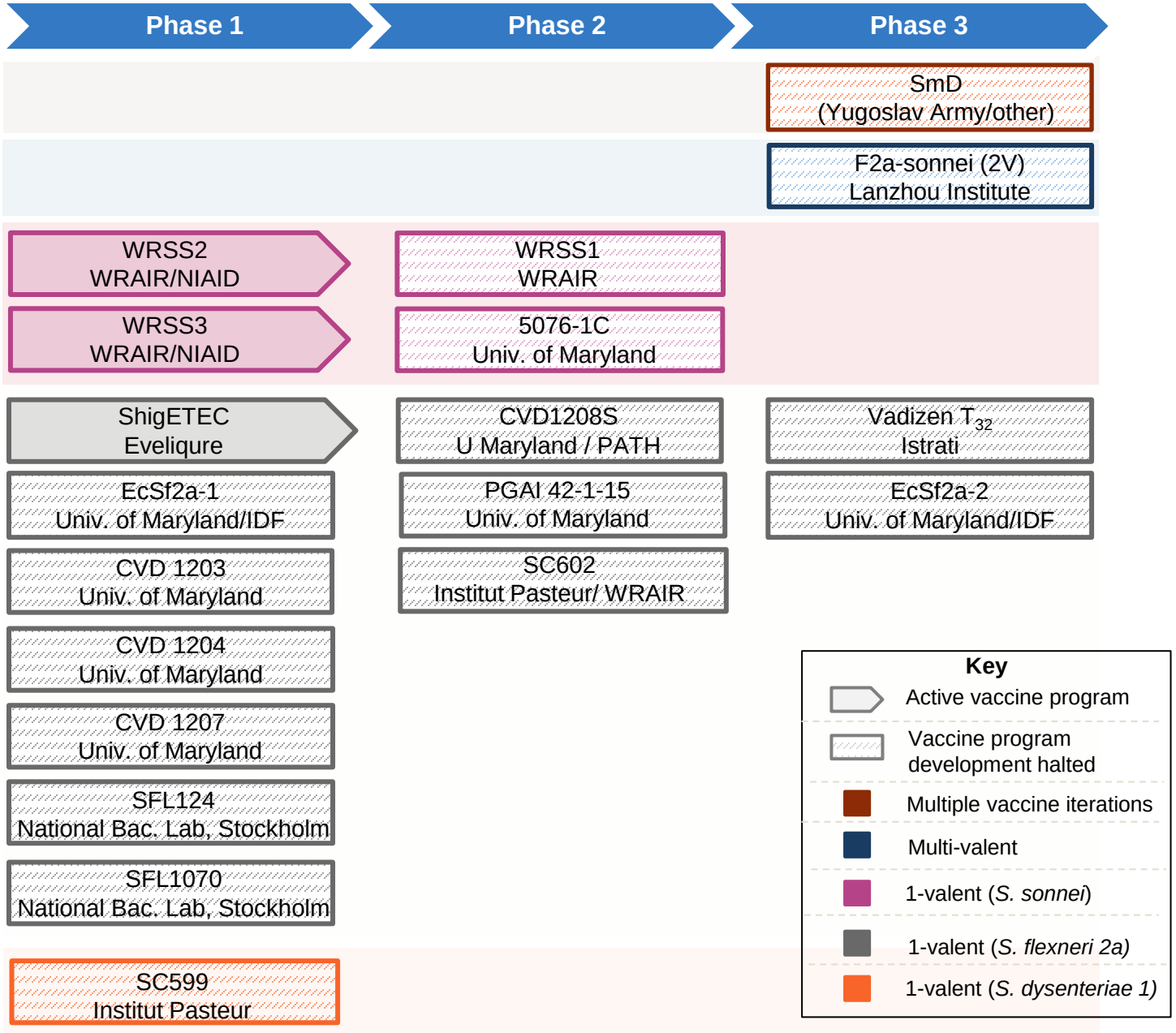
Subunit vaccines

- Proof of principle from NIH *S. sonnei* O-antigen/rEPA conjugate vaccine
- Limited progress over next 20 years
- Resurgence in subunit approach over past five years
- Multiple candidates in clinical trials



Live attenuated vaccines

- Builds on efficacy from historic but discontinued Yugoslav ‘SmD’ and Istrati ‘Vadizen T_{32}’ vaccines
- Perennial challenge of balancing acceptable reactogenicity with sufficient immunogenicity
- Additional challenge of poor response among children in low- and middle-income settings
- Development of most candidates halted



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Opportunity of Shigella-containing combination vaccines

Conference report

Challenges and opportunities in developing a *Shigella*-containing combination vaccine for children in low- and middle-income countries: Report of an expert convening

Mark S. Riddle [a,*], A. Louis Bourgeois [b], Allison Clifford [b], Suhi Jeon [c], Birgitte K. Giersing [d], Mark Jit [e], Marta Tufet Bayona [f], Jared Ovitt [a], William P. Hausdorff [b,g]

(Vaccine 2023; 41:2634-2644)

- to address increasing vaccine delivery challenges
- to bring additional vaccines into crowded schedules
- challenges of compatibility

- Measles + Shigella +/- adjuvant
- Meningococcal A + Shigella
- TCV + Shigella

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Controlled human infection models in *Shigella* clinical development

How can controlled human infection models accelerate clinical development and policy pathways for vaccines against *Shigella*?

Birgitte K. Giersing [a,*], Chad K. Porter [b], Karen Kotloff [c], Pieter Neels [d], Alejandro Cravioto [e], Calman A. MacLennan [f]

(Vaccine 2019; 37: 4778-4783)

- CHIM studies could have a role as a basis for, and/or supportive of licensure
- CHIM studies have a potential role in establishing correlates of protection
- CHIM studies are not conducted in the pediatric global health population
- Need to consider various product development scenarios

Clinical & regulatory development strategies

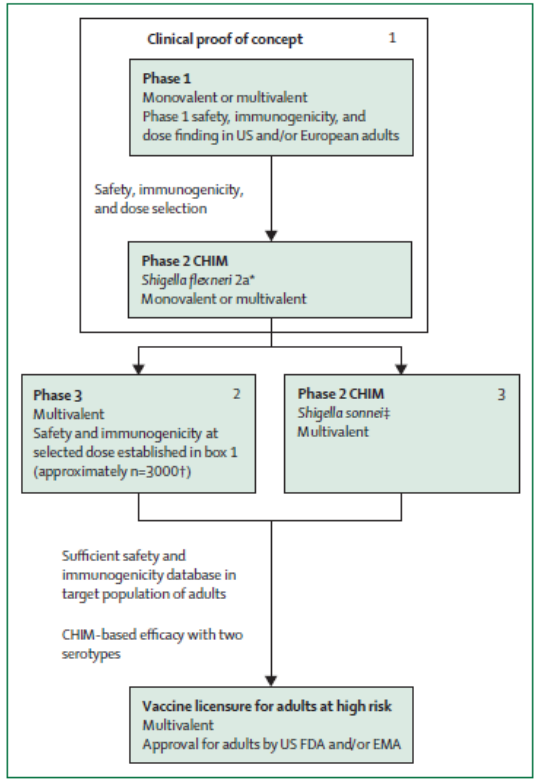


Figure 1: **Potential regulatory approval pathway for a *Shigella* vaccine intended for use in adult populations in high-income countries who are exposed to high-risk settings**
The CHIM studies are interchangeable and could be combined to assess efficacy in the same protocol. CHIM=controlled human infection model. FDA=Food and Drug Administration. EMA=European Medicines Agency. *The study might assess more than one dose. †Minimal safety database. ‡Assume proof of concept against both *S flexneri* 2a and *S sonnei* will be needed.

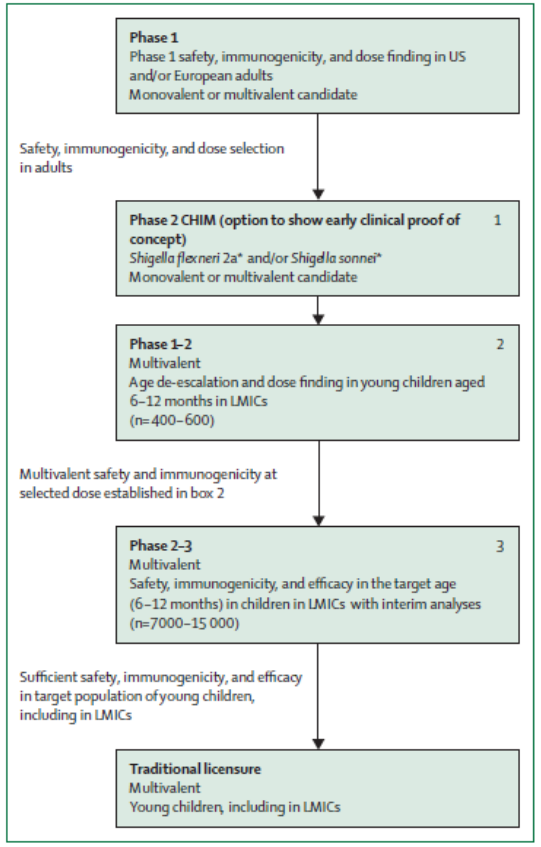


Figure 2: **Potential regulatory approval pathway based on a traditional efficacy-based pathway for a *Shigella* vaccine intended to support broad use (based on a global policy recommendation), in infants and children younger than 5 years in LMICs**
LMIC=low-income or middle-income country. *The study might assess more than one dose.

Clinical and regulatory development strategies for *Shigella* vaccines intended for children younger than 5 years in low-income and middle-income countries

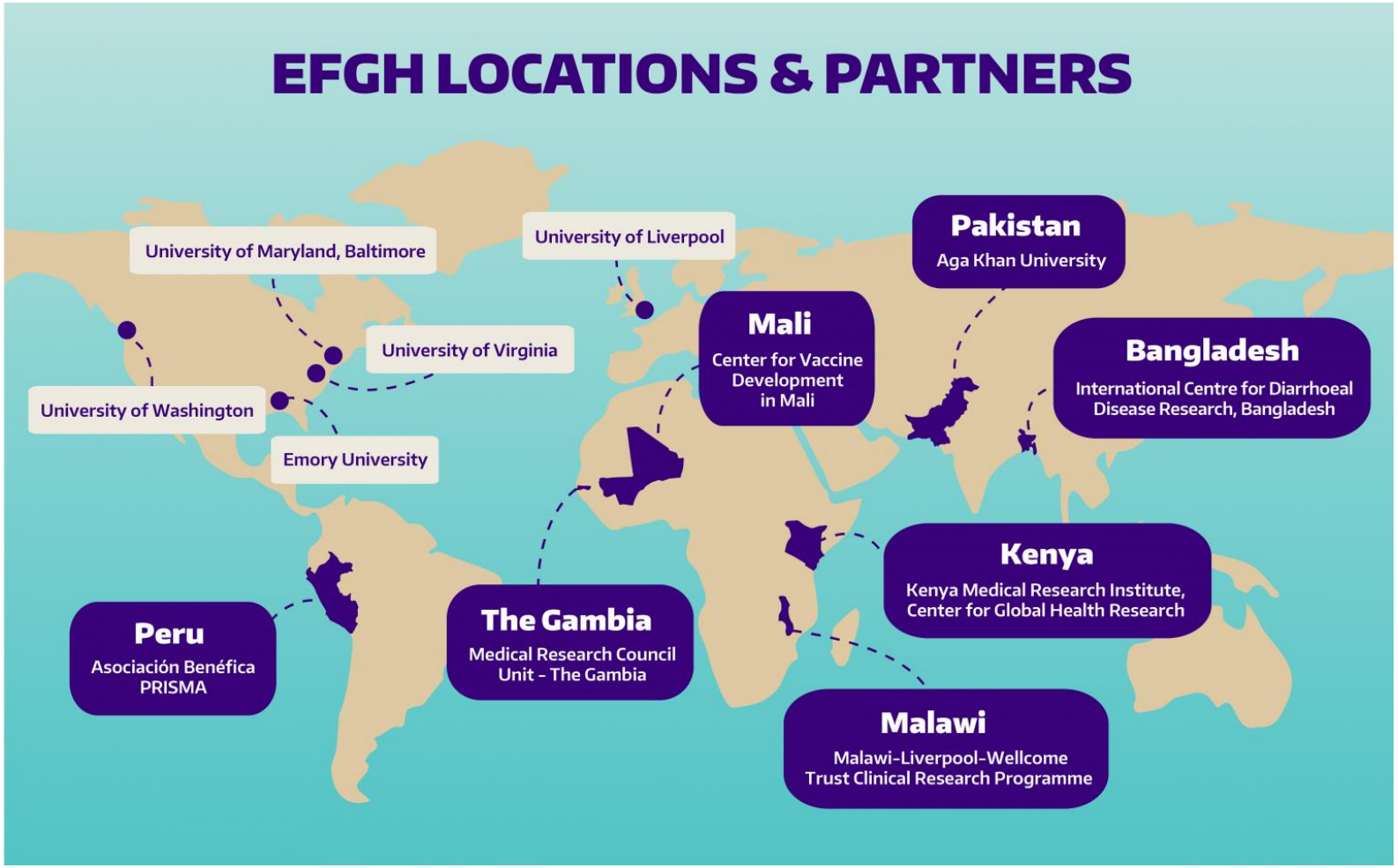
Birgitte K Giersing, Richard Isbrucker, David C Kaslow, Marco Cavaleri, Norman Baylor, Diadié Maiga, Patricia B Pavlinac, Mark S Riddle, Gagandeep Kang, Calman A MacLennan

(Lancet Global Health; 2023; 11: e1819 - 26)

Potential regulatory approval pathways for Shigella vaccines:

- CHIM-based regulatory approval strategy in adults, for travellers and military personnel
- Traditional efficacy-based regulatory approval route for use in infants and young children in LMICs
- **Fully integrated Shigella vaccine regulatory approval pathway**
- Conditional Marketing Authorisation to expedite the approval time of *Shigella* vaccines for use in infants and young children in non-Gavi countries

EFGH Consortium



Funded by
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EFGH Goals

1. Gather key data that will inform pivotal *Shigella* vaccine efficacy trial study design in representative target countries using a standardized methodology
2. Ready potential pediatric clinical trial sites to quickly implement *Shigella* vaccine efficacy trials, accelerating time to vaccine availability to children

https://depts.washington.edu/efgh/

EFGH Overview	
Study Design	Facility-based hybrid surveillance (for *Shigella* incidence estimation) & prospective cohort (for sequelae)
Case definition	Children aged 6-35 months with new & acute medically-attended diarrhea (MAD) / dysentery presenting to EFGH health facilities
Follow-up period	3 months (visits at 4 weeks & 3 months)
Outcomes	Etiology-specific incidence, diarrhea duration, diarrhea recurrence, hospitalization, anthropometry, death, cost
Surveillance period	24 months
Population enumeration	Random household sampling to estimate population denominator
Health-care utilization estimation	Health-care utilization surveys
Microbiologic confirmation	Culture + qPCR
Sample size	1400 children/ country site
Timeline	Planning: 2021, Recruitment: 2022-2024, Study completion/ reporting: 2024

Phase 3 efficacy with *Shigella sonnei* conjugate & correlates of protection

- **26 years ago** a 1st generation NIH 'lattice-type' *S. sonnei* conjugate vaccine gave 74% efficacy among Israeli military.
- Protection strongly associated with serum IgG antibody response to LPS O-antigen, supporting this modality as a correlate of protection…
- **Issue:** many years later, the vaccine failed to protect children <3 years. Loss of protection closely associated with decreased induction of LPS O-antigen IgG
- **Hypothesis** that a 2nd generation vaccine that induces higher levels of IgG to O-antigen will protect young children

THE LANCET

Double-blind vaccine-controlled randomised efficacy trial of an investigational *Shigella sonnei* conjugate vaccine in young adults

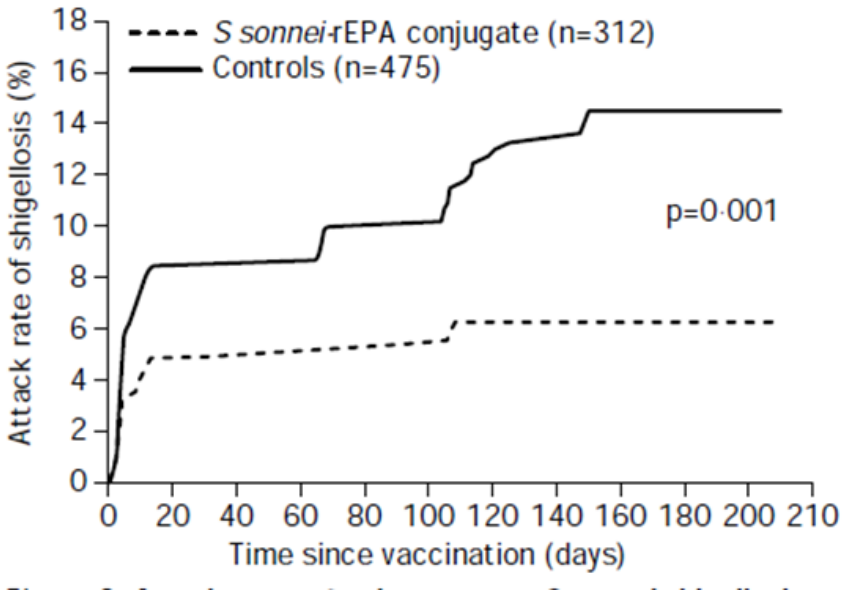
Dani Cohen, Shai Ashkenazi, Manfred S Green, Michael Gdalevich, Guy Robin, Raphael Slepon, Miri Yavzori, Nadav Orr, Colin Block, Isaac Ashkenazi, Joshua Shemer, David N Taylor, Thomas L Hale, Jerald C Sadoff, Danka Pavliakova, Rachel Schneerson, John B Robbins

(Lancet 1997; 349: 155-9)

Age-related efficacy of *Shigella* O-specific polysaccharide conjugates in 1–4-year-old Israeli children

Justen H. Passwell[a,1], Shai Ashkenzi[b], Yonit Banet-Levi[a], Reut Ramon-Saraf[a], Nahid Farzam[a], Liat Lerner-Geva[c], Hadas Even-Nir[a], Baruch Yerushalmi[d], Chiayung Chu[e], Joseph Shiloach[f], John B. Robbins[e], Rachel Schneerson[e,*], The Israeli Shigella Study Group[2]

(Vaccine 2010; 28: 2231-2235)



Confirmation of correlate of Protection against Shigellosis

- Serum IgG to O-antigen of *S. sonnei* subsequently confirmed as a correlate of protection in adults following analyses on historic clinical trial samples and better correlated with protection than SBA (Cohen et al, 2019)

- Evidence of serum IgG to *S. flexneri* 2a being a correlate of protection against shigellosis caused by *S. flexneri* 2a from human challenge study data, and better correlated with protection than SBA (Talaat et al, 2021)

- Threshold protective levels of serum IgG to *S. sonnei* O-antigen determined to be >1:1600 TAU (Tel Aviv University) ELISA Units (Cohen et al, 2022)

REVIEW

OPEN ACCESS Check for updates

Serum IgG antibodies to *Shigella* lipopolysaccharide antigens – a correlate of protection against shigellosis

Dani Cohen[a], Shiri Meron-Sudai[a], Anya Bialik[a], Valeria Asato[a], Sophy Goren[a], Ortal Ariel-Cohen[a], Arava Reizis[a], Amit Hochberg[b], and Shai Ashkenazi[c]

(Human Vacc Immunotherap 2019; 15: 1401-1408)

Research paper

Human challenge study with a Shigella bioconjugate vaccine: Analyses of clinical efficacy and correlate of protection

Kawsar R. Talaat[a,1,*], Cristina Alaimo[b,1], Patricia Martin[b], A. Louis Bourgeois[a,e], Anita M. Dreyer[b], Robert W. Kaminski[c], Chad K. Porter[d], Subhra Chakraborty[a], Kristen A. Clarkson[c], Jessica Brubaker[a], Daniel Elwood[a], Rahel Frölich[b], Barbara DeNearing[a], Hailey Weerts[c], Brittany L. Feijoo[a], Jane Halpern[a], David Sack[a], Mark S. Riddle[d], Veronica Gambillara Fonck[b]

(EBioMedicine 2021; 66: 103310)

Original article

Threshold protective levels of serum IgG to *Shigella* lipopolysaccharide: re-analysis of *Shigella* vaccine trials data

Dani Cohen [1,*], Shai Ashkenazi [2,3], Rachel Schneerson [4,†], Nahid Farzam [5], Anya Bialik [1], Shiri Meron-Sudai [1], Valeria Asato [1], Sophy Goren [1], Tomer Ziv Baran [1], Khitam Muhsen [1], Peter B. Gilbert [6,7], Calman A. MacLennan [8,9]

(Clin Microbiol & Infection 2022; 29: 366-71)

Correlate of Protection against Shigellosis - Utility

Critical Needs in Advancing *Shigella* Vaccines for Global Health

Calman A. MacLennan,[1] Kawsar R. Talaat,[2] Robert W. Kaminski,[3] Dani Cohen,[4] Mark S. Riddle,[5] and Birgitte K. Giersing[6]

[1]Bill & Melinda Gates Foundation, London, United Kingdom, [2]Center for Immunization Research, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, [3]Diarrheal Disease Research, Bacterial Diseases Branch, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA, [4]School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [5]University of Nevada, Reno School of Medicine, Reno, Nevada, USA, [6]World Health Organization, Geneva, Switzerland

(J Infect Dis 2021)

- Need for:
  - An international standard serum and harmonized enzyme-linked immunosorbent assay
    (Rob Kaminski presentation)
  - demonstration of field efficacy in young children in low- and middle-income countries
  - early engagement with regulators and policy makers.

- **If a Phase 3 efficacy study can confirm correlate of protection status of serum IgG to *S. sonnei* and *S. flexneri* 2a O-antigen, it might be possible to license further vaccines on the basis of IgG antibody levels without the need for additional long & expensive field trials**

Summary

- Multiple O-antigen-based subunit vaccines in clinical trials with different technological approaches
- Evaluation for immunogenicity in descending-age/dose-finding studies LMIC children
- Quadrivalent format appears necessary for sufficient serotype coverage

- Preparations for Phase 3 field efficacy studies
- Advanced assay harmonisation & standardisation work
- Subsequent vaccines could potentially be licensed on basis of immune non-inferiority
- Opportunity for combination vaccines

Question to PDVAC

If correlate of protection status can be established in the pediatric global health target population (LMIC infants) from a Phase 3 efficacy study of a first *Shigella* vaccine, could PDVAC opine on the broad concept of an accelerated pathway to licensure for subsequent *Shigella* vaccines based on immunobridging and safety?

Updates on:

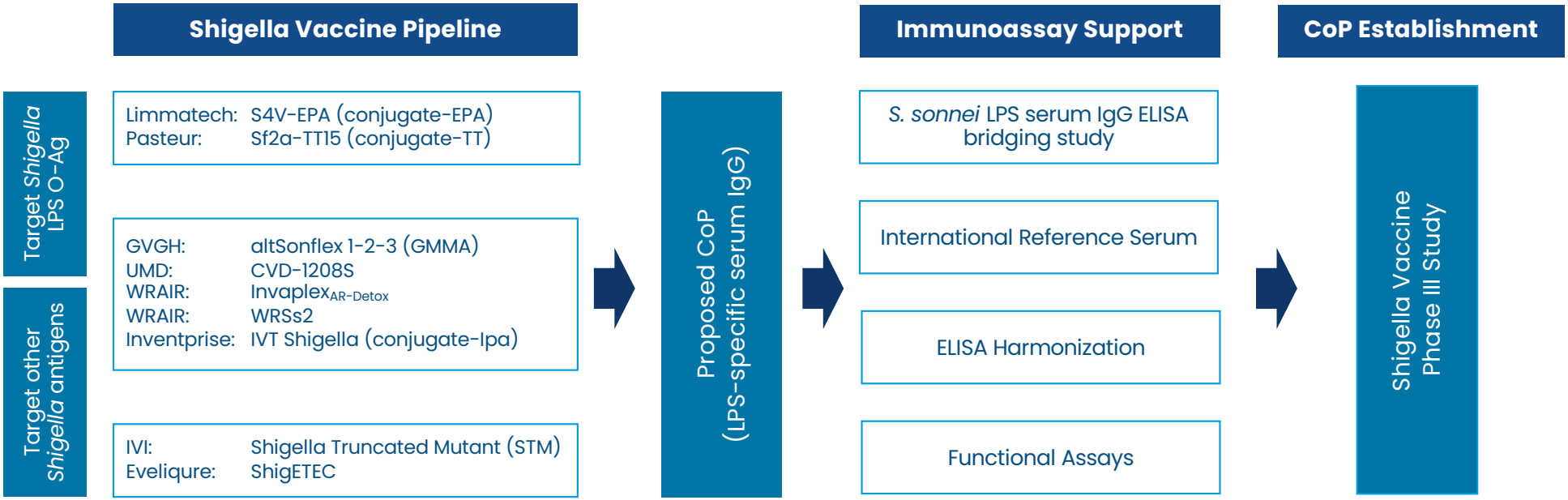
Shigella Immunoassay Activities

WHO Regulatory Workshop

Robert Kaminski, Ph.D.
WHO Consultant

IVB

Role of Immunoassays: Supporting Shigella Vaccine Licensure



Immunoassays: *Shigella sonnei* LPS Bridging Assays

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Threshold protective levels of serum IgG to *Shigella* lipopolysaccharide: re-analysis of *Shigella* vaccine trials data

Dani Cohen [1,*], Shai Ashkenazi [2,3], Rachel Schneerson [4,†], Nahid Farzam [5], Anya Bialik [1], Shiri Meron-Sudai [1], Valeria Asato [1], Sophy Goren [1], Tomer Ziv Baran [1], Khitam Muhsen [1], Peter B. Gilbert [6,7], Calman A. MacLennan [8,9]

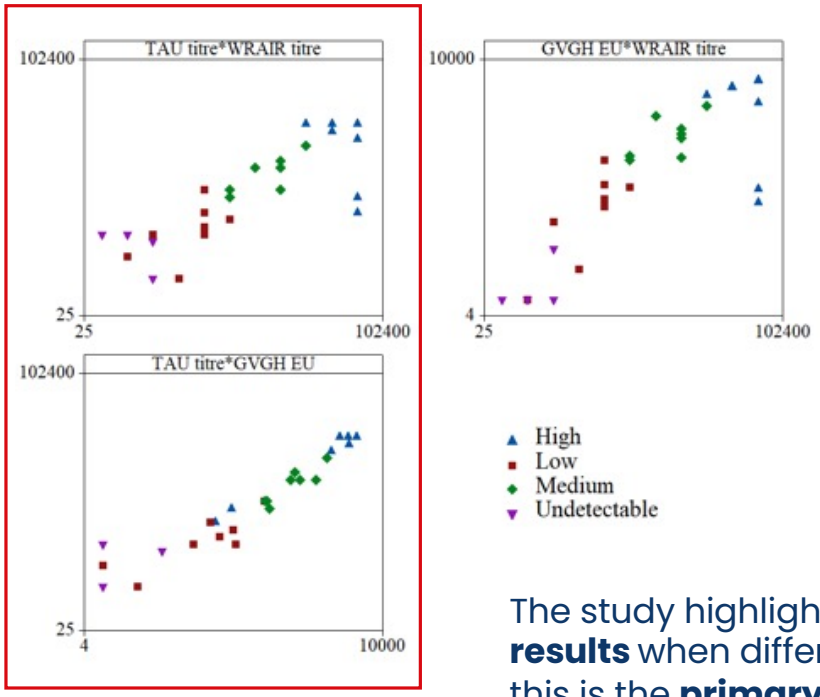
- Anti-Shigella LPS serum IgG is proposed to be a correlate of protection against shigellosis
- Threshold of 1600 expressed as an endpoint titre (using **TAU** ELISA protocol)

Objective: Use a panel of representative samples (n = 32) to determine the "1600 equivalent" in two other laboratories to facilitate analysis and interpretation of responses to vaccination in clinical trial samples analysed in other laboratories/methods

WRAIR – ELISA with results expressed as **endpoint titres**

GVGH – ELISA with results expressed in ELISA Units (**EU)** relative to an internal reference serum

Immunoassays: *Shigella sonnei* LPS Bridging Assays



Using the fitted equation from the regression analyses to convert a **TAU titre of 1600** (i.e. 3.204 $\log_{10}$ titre) to GVGH EU gives a result of **396 EU** (i.e. 2.597 $\log_{10}$ EU) and a 95% confidence interval for this estimate of **315 – 497 EU**.

Further values calculated using the fitted equations from the regression analyses are shown below:

TAU titre	Estimated GVGH EU (95% CI)	Estimated WRAIR titre (95% CI)
800	161 (124 – 211)	1053 (703 – 1577)
1600	396 (315 – 497)	2550 (1811 – 3590)

The study highlights the **existing challenges with comparing and interpreting results** when different ELISA methods and/or reporting measures are used **–** this is the **primary driver for developing an International Standard reference serum**

International Standard Serum for Shigella immunoassays

The development of a well characterised, stable reference serum is intended for standardisation of shigella immunoassays

Within laboratories	Between laboratories
Standard is used for calibration of assay Helps control for variation between plates / operators / days / studies etc.	Standard is used for calibration of different assays Provided the standard is **commutable** with patient samples, it will **improve agreement** in measurement obtained across different labs/methods

- Ultimate objective is to **harmonise the measurement** of anti-Shigella antibody responses across studies and laboratories.
- Well harmonised assays will facilitate **comparison of data from vaccine trials where the analysis is done in different labs/methods**, helping to identify common criteria/thresholds that are **predictive of protection** against disease

Shigella LPS ELISA Harmonization Activities

The overall project goal is to **harmonize an ELISA procedure** to measure **anti-*Shigella* LPS serum antibody** responses across global laboratories to support Shigella vaccine development

Project Objectives:

- Identify Key Assay Reagents
- Identify Key Assay Steps
- Investigate robustness and ruggedness of the ELISA
- Establish a Standard Operating Procedure (SOP) for use by the global community

Assay Step	Test Parameter	Conditions with acceptable outcomes
Plate Coating	Plate Type	Immulon 1B round Immulon 2 flat
	Coating Buffer pH	pH 9.8 pH 7.4
	Temperature Incubation Time	4˚C-overnight 4˚C – 3 hrs 37˚C – 1 hr Stable for 7 days at 4˚C
Blocking & Primary Antibody	Buffer Type	2% Casein
Secondary Antibody	Incubation Time	60 ± 5 min
	Plate Washing	5 automated washes (375 ul each @ 418 ul/sec)
Substrate	pNPP Format Stop Solution Incubation Time	Powder pNPP – 30 ± 2 min - no stop Powder pNPP – 30 ± 2 min - stopping with 3M NaOH

- **ELISA protocol is transferable** between laboratories supporting future tech transfer efforts**,** and, together with use of a well characterised reference serum, can help **support harmonisation** of the measurement of *S. flexneri* 2a IgG responses
- **Work continues** for LPS ELISAs from other *Shigella* serotypes (*S. sonnei*, *S. flexneri* 3a, 6 and 1b)

Functional Immunoassays

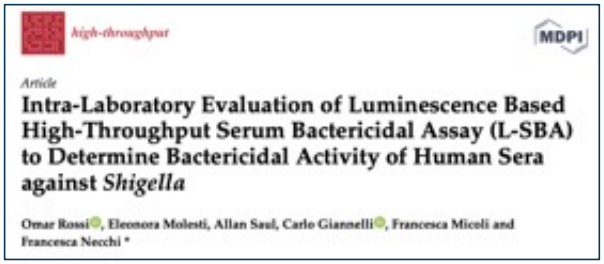
Functional assays can improve our understanding of the role of **protective antibodies** in blocking infection and disease

Several functional assays have been developed:

- Serum bactericidal assays (**SBA**)
- Opsonophagocytic Killing Assays (**OPKA**)
- Adhesion/Invasion inhibition assays

Serum bactericidal antibody titers have been associated with **protection from shigellosis** in controlled human infection models (CHIMs) and phase IIb vaccination/challenge studies.

SunFire Biotechnologies



VISMEDERI
ANALYSES FOR LIFE IMPROVEMENT

Two SBA protocols have been **successfully transferred** to commercial research organizations to potentially **support future clinical studies**.

WHO Regulatory Workshop on Clinical Pathways for Shigella vaccines

WHO Regulatory Workshop on Clinical Pathways for Shigella vaccines intended for use in children in low- and middle-income countries

WHO: Regulators, Clinicians, Policy makers, Laboratory SMEs, Donors, Vaccine manufacturers

WHAT: Two-day WHO Regulatory Workshop focused on clinical pathways for Shigella vaccines

WHERE: Nairobi, Kenya

WHEN: 20-21 March 2024

Workshop Objectives

- **Raise awareness** of Shigella burden and vaccine development status with regulators, particularly those from countries in which the phase III study is expected to be conducted
- Review the current thinking, **study design considerations** and preparations for **phase III** field efficacy studies in **high burden countries**, and discuss with **regulators** through a series of round tables
- **Identify** aspects of **consensus** and areas that require **additional discussion/alignment** to inform phase III study design in line with regulatory expectations.

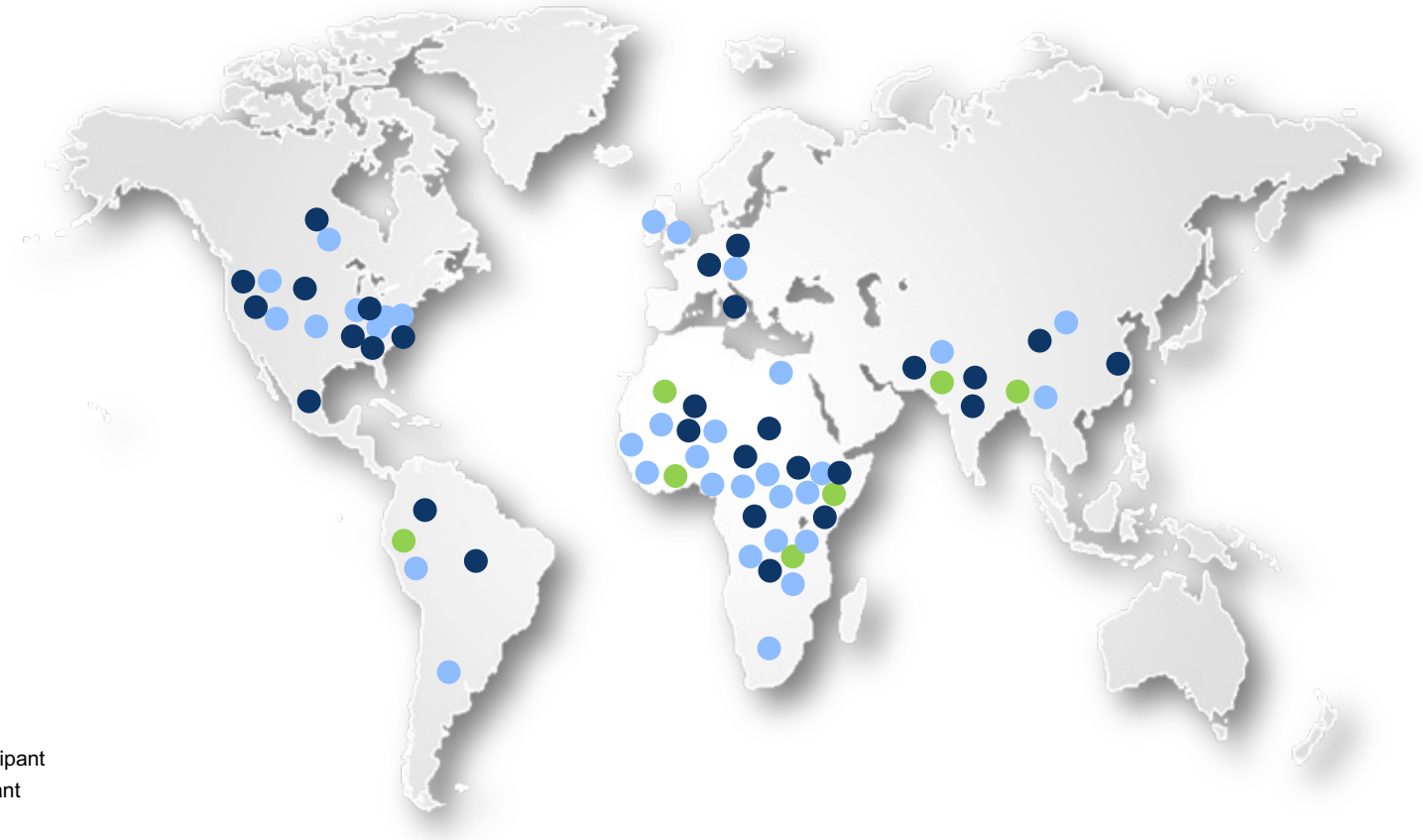
Key questions to address and build consensus

- Do the primary endpoints presented meet regulatory expectations?
- What is the anticipated lower bound required to demonstrate a vaccine efficacy of 50% against prevention of disease?
- Do the case ascertainment methods and proposed severity scoring system align with regulatory expectations?
- Do the secondary endpoints (LSD, Hospitalization, Time to Treat) meet regulatory expectations?
- Are the safety endpoints sufficient to support market authorization?
- Value of exploratory/research endpoints (vaccine impact on AMR reduction and growth faltering/stunting) to the regulatory community? To the policy community?
- How can efficacy data from traveler populations obtained in CHIM studies support market authorization for an indication in infant populations?

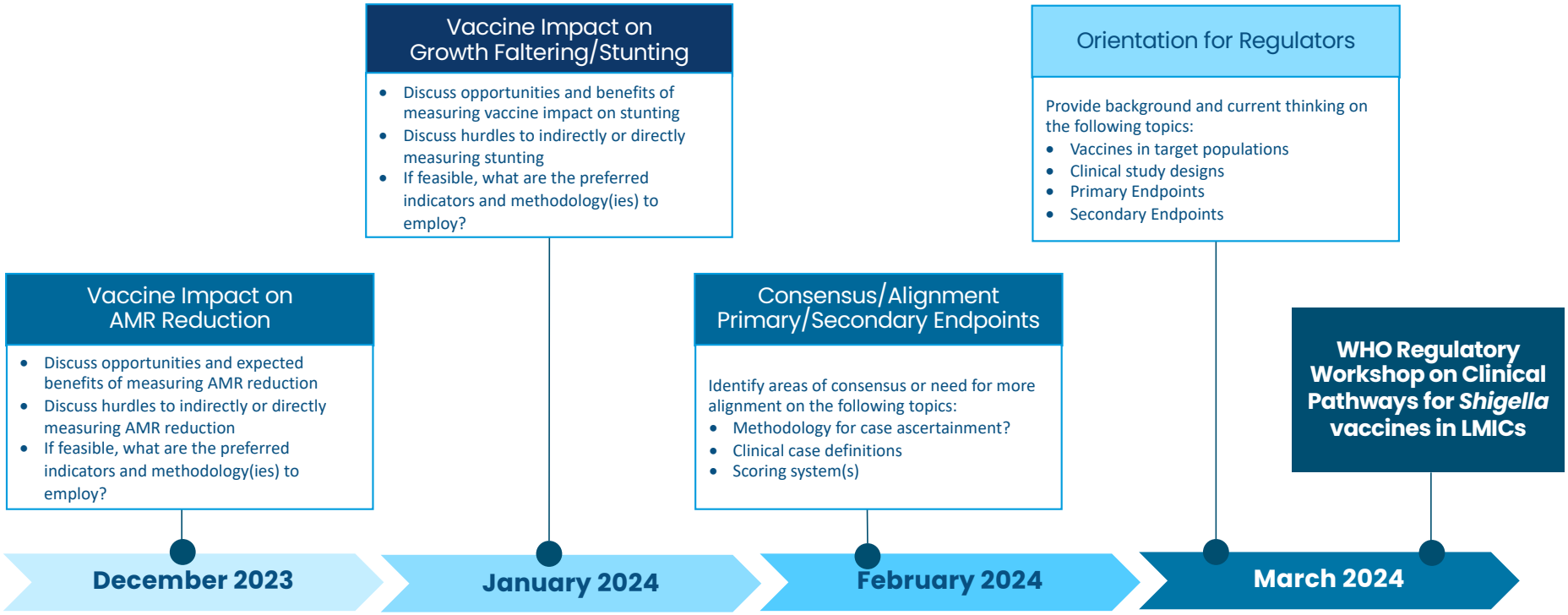
Workshop Expected Outcomes

- **Improved engagement** from **regulators** on Shigella **vaccines**, based on **awareness of burden** and public health **need for a vaccine**
- Clarity on **areas of alignment** regarding phase III study design and aspects that need further discussion with regulators
- **Meeting report** summarizing deliberations and **recommendations** for next steps

Global Distribution of Participants



Preparation for Regulatory Meeting: Virtual Engagements



PDVAC Questions

- Does PDVAC consider the scope of the regulatory meeting and its objectives / intended outcomes to be sufficiently comprehensive? (please note: the draft meeting agenda is loaded in the background material)
- Can PDVAC opine on the importance of a Shigella vaccine demand assessment at this stage of development, particularly with the potential for a future combination vaccine?
- Would PDVAC support a separate, related WHO Workshop to engage regulators and policy makers on combination vaccine strategies, perhaps in the context of “Shigella + X” vaccines?