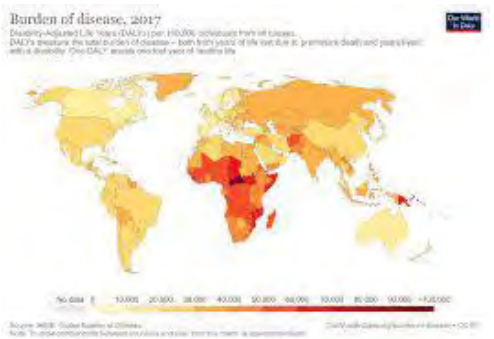
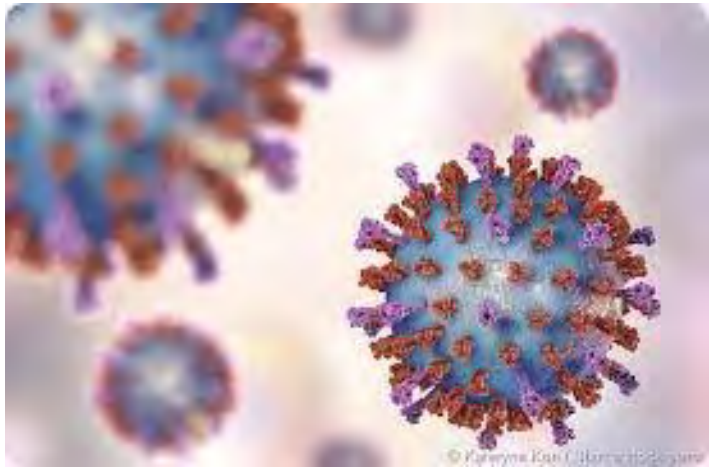
Overview of the PDVAC and vaccine product delivery research (PDR) unit scope and prioritization activities





WHO PDVAC meeting

5 December 2022

IVB

Presentation outline

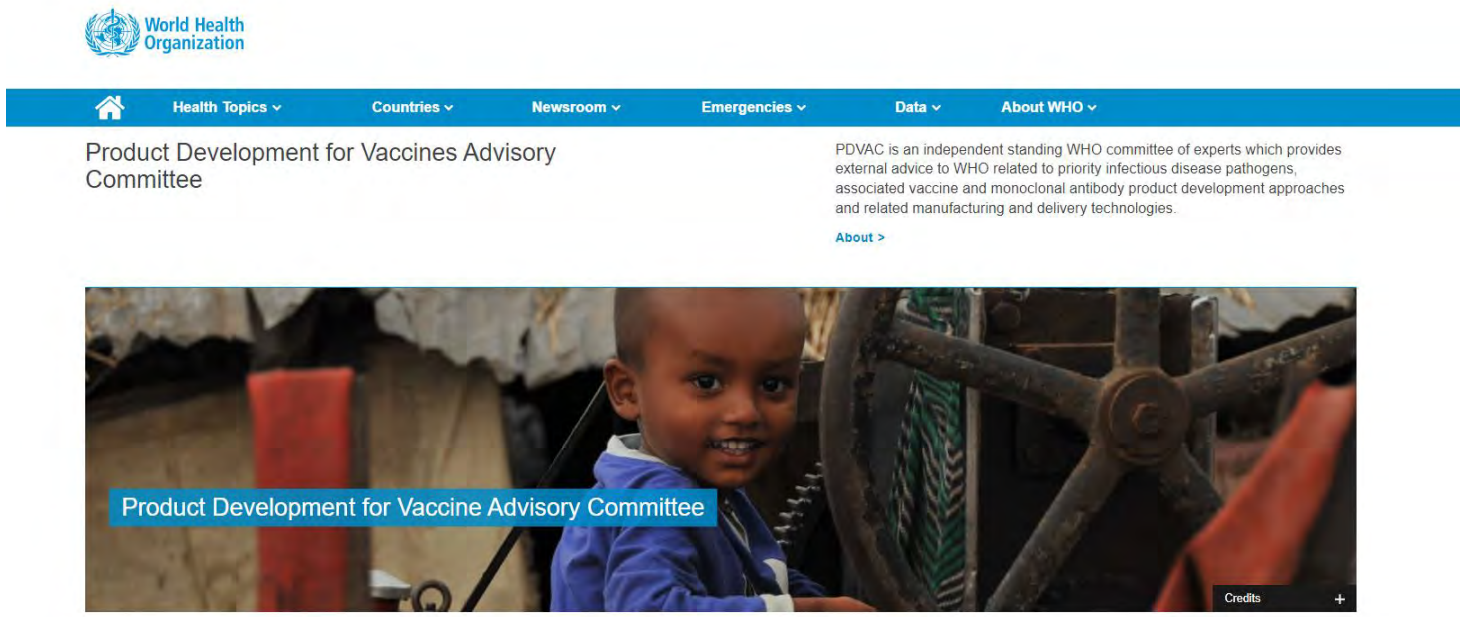
- Remit of PDVAC
- Types of and relationship between various technical documents
- Assessing full value of vaccines
  - Mortality and morbidity burden
- Pathogen/platform specific updates:
  - New TB vaccines
  - Dengue
  - HIV
  - mRNA hub and spokes
  - Group A streptococcus*
  - Non-typhoidal salmonella*
- Goals of this PDVAC meeting

*reviewed at PDVAC in 2022

Remit of WHO's Product Development for Vaccines Advisory Committee - PDVAC

An independent, standing committee of experts which provides external advice to WHO related to **vaccine and monoclonal antibody candidates for priority infectious disease pathogens**

...where there is, or may be, substantial disease burden in **low- and middle-income countries (LMICs),** where none of these products currently exist, but where there is some ongoing product development activity which may benefit from WHO guidance.



*reviewed at PDVAC in 2022

The Evolution of PDVAC since 2014

2014

Several vaccine PPCs and R&D Roadmaps developed

PDVAC formed; 12 members

Focus on pathogens for which:
- Public health need;
- Candidates in the clinic;
- A need for additional WHO engagement

2016

Profiles of vaccines against 24 pathogens published in Vaccine

2018

Full Value of Vaccines concept presented to SAGE; broadening of PDVAC scope

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

PDVAC expanded to include innovative delivery technologies

Formation of the Vaccine Innovation Prioritisation Strategy

2019

IVB (PDR's) CAPACITI framework developed to engage with countries on product choice

PDVAC's remit broadened to assess monoclonal antibodies

2021

Concept of earlier (pre-SAGE) policy framework proposed – now the ECVP

COVAX

CEPI Gavi

OPS unicef World Health Organization

ACTaccelerator

PDVAC expanded to include novel vaccine manufacturing technologies to support COVAX

2022

First regional mRNA hub selected in Cape Town, SA

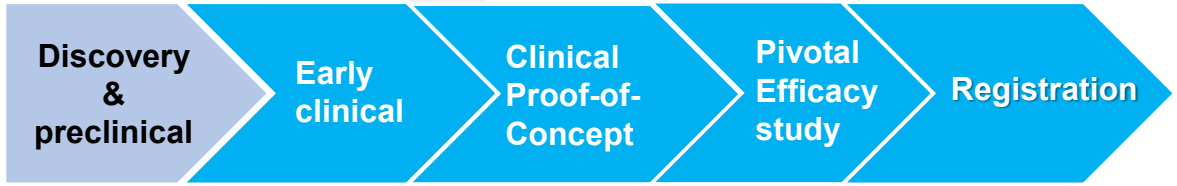
Several mRNA spokes selected in multiple regions

Development of a mechanism to partner with regions and countries to identify priority pathogens for vaccines

IA2030

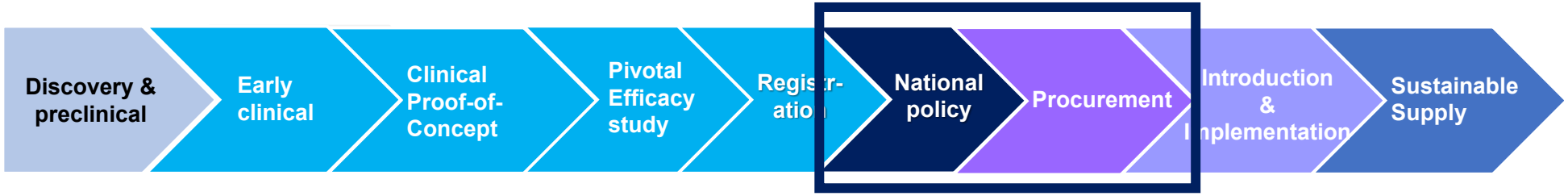
PDVAC expanded to include early policy considerations; end-to-end product development and **prioritization in partnership with countries**

Driven by an appreciation that evidence needs for vaccines differ by intended outcome, i.e. regulatory approval, national or global policy



Safety, quality and efficaccy
established with an endpoint defined by one or more clinical outcomes (or correlate of protection) that can be measured objectively to determine whether the intervention being studied has a favorable benefit-risk profile.

National regulatory approval and implementation pathway:



What data should be collected to **inform policy?**

Global regulatory approval and implementation pathway:

PAHO Pan American Health Organization World Health Organization
World Health Organization
unicef
Gavi The Vaccine Alliance

How do we begin to align and prepare for **access** and impact?

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  - Group A streptococcus*
  - Non-typhoidal salmonella*
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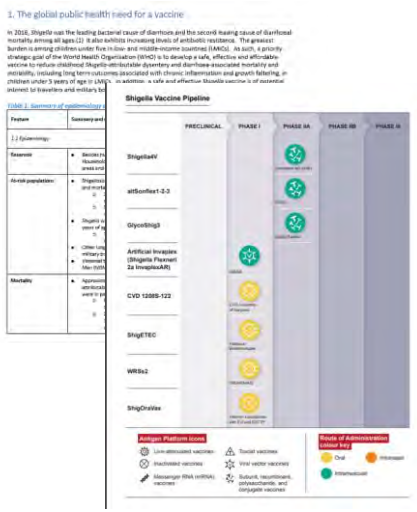
*reviewed at PDVAC in 2022

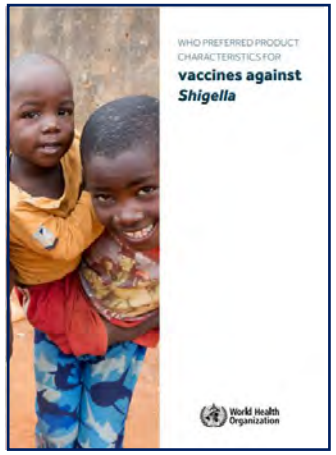
Types of technical documents – acronyms!



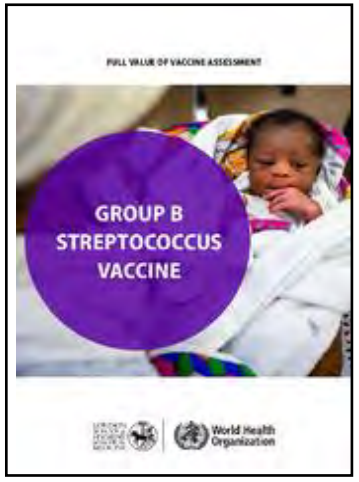
Vaccine Value Profiles (VVPs): provide a high-level, holistic assessment of the elements that are currently available to inform vaccine value for pipeline vaccines and highlights gaps in knowledge / research needs

Roadmaps highlight priority activities for vaccine researchers, funders and product developers, with the goal to accelerate the pathway to availability and access in LMICs.

Can be R&D focused, or vaccine introduction focused.



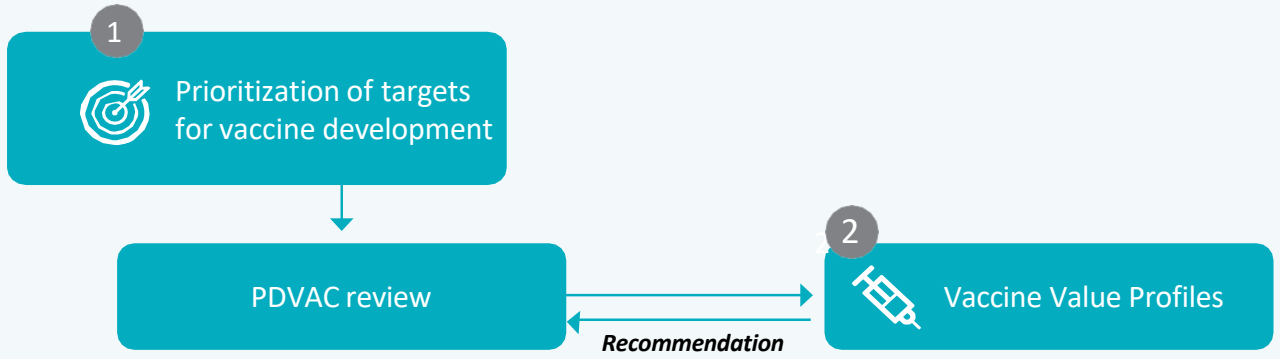
Preferred Product Characteristics (PPCs): define preferential attributes for vaccines to be used in LMICs



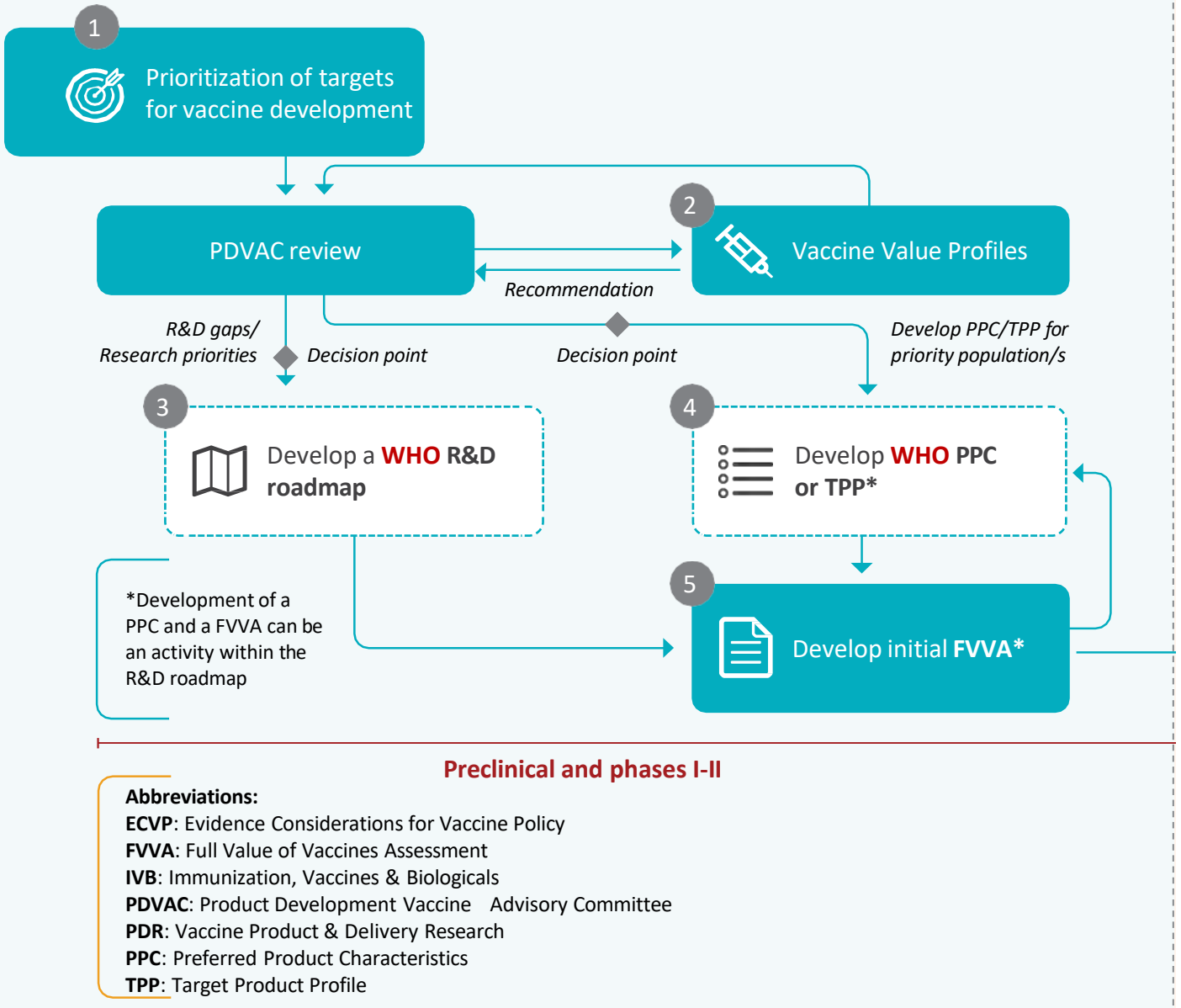
Full Value of Vaccines Assessment (FVVA): Health, economic, and societal value of vaccines for specific pathogens, considering direct (individual) and indirect (population) effects;

Evidence Considerations for Vaccine Policy (ECVP): Anticipates evidence needed from clinical trials and observational studies to guide policy decisions

Overview of PDR/PDVAC guidance to facilitate vaccine development to regulatory approval, policy and use

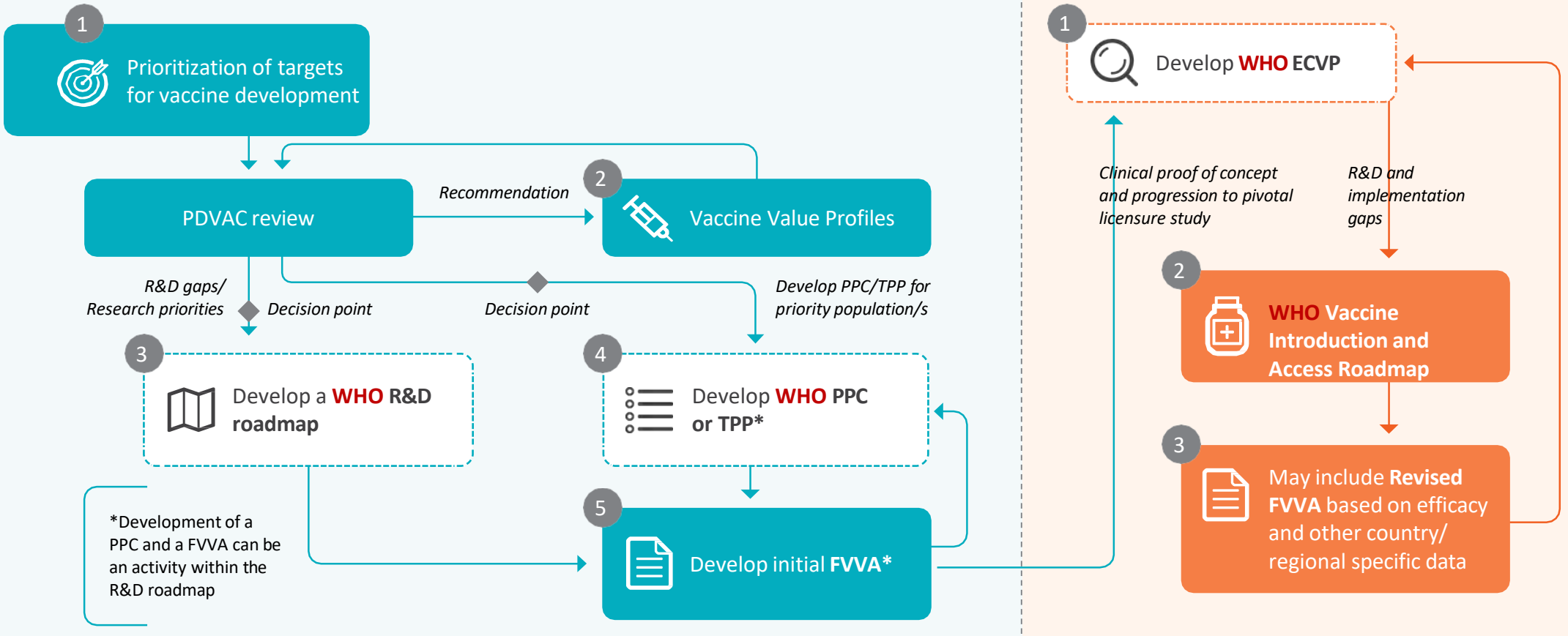


Overview of PDR/PDVAC guidance to facilitate vaccine development to regulatory approval, policy and use



Abbreviations:
ECVP: Evidence Considerations for Vaccine Policy
FVVA: Full Value of Vaccines Assessment
IVB: Immunization, Vaccines & Biologicals
PDVAC: Product Development Vaccine Advisory Committee
PDR: Vaccine Product & Delivery Research
PPC: Preferred Product Characteristics
TPP: Target Product Profile

Overview of PDR/PDVAC guidance to facilitate vaccine development to regulatory approval, policy and use



Abbreviations:
ECVP: Evidence Considerations for Vaccine Policy
FVVA: Full Value of Vaccines Assessment **IVB**: Immunization, Vaccines & Biologicals
IVIRAC: Immunization and vaccines related implementation research advisory committee
PDVAC: Product Development Vaccine Advisory Committee
PDR: Vaccine Product & Delivery Research
PPC: Preferred Product Characteristics
TPP: Target Product Profile

Evidence considerations for Vaccine Policy (ECVP)

EVIDENCE CONSIDERATIONs FOR VACCINE POLICY: evidence anticipated to facilitate global policy recommendations **before** phase III clinical studies

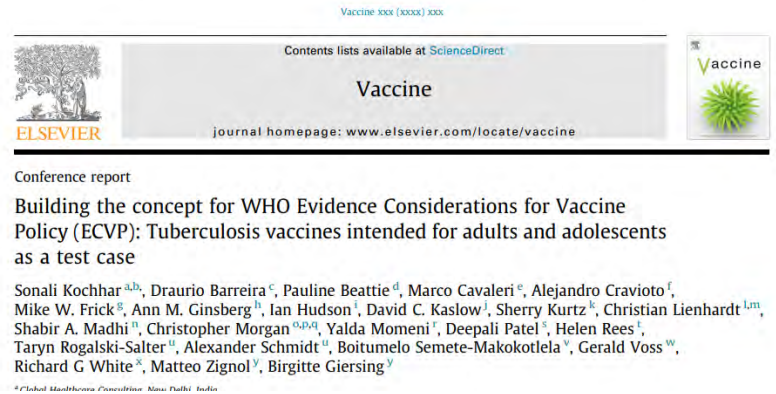
Preferred Product Characteristics: (PPC): defines product attributes for LMIC use

Scientific advice meetings: Data on **safety, quality and efficacy** for licensure

SAGE Evidence to Recommendation framework

WHO Position paper

WHO PQ



Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Conference report

Building the concept for WHO Evidence Considerations for Vaccine Policy (ECVP): Tuberculosis vaccines intended for adults and adolescents as a test case

Sonali Kochhar [a,b], Draurio Barreira [c], Pauline Beattie [d], Marco Cavaleri [e], Alejandro Cravioto [f], Mike W. Frick [g], Ann M. Ginsberg [h], Ian Hudson [i], David C. Kaslow [j], Sherry Kurtz [k], Christian Lienhardt [l,m], Shabir A. Madhi [n], Christopher Morgan [o,p,q], Yalda Momeni [r], Deepali Patel [s], Helen Rees [t], Taryn Rogalski-Salter [u], Alexander Schmidt [u], Boitumelo Semete-Makokotlela [v], Gerald Voss [w], Richard G White [x], Matteo Zignol [y], Birgitte Giersing [y]

Generic WHO ECVP framework has been developed and is available

WHO *Evidence Considerations* for *Vaccine Policy* Development
generic framework for vaccines/monoclonal antibodies
development

1. The concept and strategic intent of the WHO Evidence Considerations
Vaccine Policy (ECVP) framework.

1.1 Purpose and intended audience of the WHO ECVP guidance

There are frequently significant delays between vaccine licensure and introduction in lo countries [1], sometimes requiring the generation of data post-licensure to support defi and/or introduction decisions [2]. The WHO Evidence Considerations for Vaccine Policy (ECVP is a new approach to facilitate the early engagement and consequent alignment between the s involved in vaccine development and those that are responsible for regulatory, policy and i decisions, on the intended use cases and aspirations for policy recommendations. It aims outline the clinical trial and observational data or evidence anticipated to be needed for poli for new vaccine classes, and thereby to minimise delays between vaccine licensure and policy adoption and introduction, particularly in lower income countries.

The promotion and accelerated development of vaccines with optimal suitability and effective in LMICs is a major objective of the World Health Organisation (WHO), as elucidated in the Im Agenda 2030 (IA2030) [3]. Under the auspices of its Product Development for Vaccin Committee (PDVAC) [4]), WHO develops Preferred Product Characteristics (PPCs) for new WHO priority disease areas, early in clinical development. PPCs articulate preferent characteristics for programmatic use and impact, and whilst some policy, implementation, a components are alluded to, the data and evidence needs for policy consideration are addressed. Enhanced clarity on what is required for establishing global policy recommendatio bottlenecks and shorten time to introduction and use if the data needs can be anticipated an during development programmes. However, no formal mechanisms or systematic approach exist to align stakeholders on the essential evidence anticipated to facilitate gl recommendations and country introduction decision-making for pipeline vaccines, and to cc this to vaccine developers.

The ECVP is intended to engage and align the multiple stakeholders who have an interest in policy and introduction pathway. For example, while regulators review the safety, quality [illegible], data to approve a vaccine, licensure alone is insufficient for policy and deployment; national and global policymakers need to consider additional aspects such as cost-effectiveness, programmatic fit and performance against other outcomes that may not have been definitely quantified during clinical trials for regulatory approval, such as those that might impact vaccine transmission on a population level; vaccine developers/manufacturers/funders need clarity on what data is needed to position a vaccine for policy consideration to ensure vaccine use and return on investment; immunization partners seek to ensure the vaccine is acceptable to and effective in end-users who both deliver and receive the vaccine. The ECVP also seeks to catalyse early discussion with the various WHO advisory committees beyond PDVAC,

Table 1: Vaccine Product Related Parameters

	Critical parameters Beneficial parameters	Preferential vaccine product attributes	Initial Policy	Expanded Policy	Supportive data required	Rationale
1.1	Disease indication *(effect expected of the vaccine e.g. prevention of disease, severe disease, infection, transmission, recurrence)*					
1.2	Priority Target Population/s *(the populations who are most at risk of disease and will be the primary recipients of the vaccine following licensure)*					
1.3	Target countries *(countries where the vaccine is intended to be introduced soon after vaccine licensure)*					
1.4	Duration of protection for the disease indication					
1.5	Schedule *(dosing regimen for the primary series)*					

Table 5. Implementation Considerations

Please note: this table provides information on the type of data that could inform policy, financing and introduction decisions by multiple actors, including policy-makers at the national, regional and global levels, as well as global financing agencies such as Gavi, civil society organisations and implementation partners such as Medicines sans Frontiers or the International Committee of the Red Cross and non-governmental organizations, who often fund studies to generate this data and evidence. It represents an initial view of the evidence that is believed will be important to support decision-making, and **is intended to serve as a starting point to catalyse dialogue with regard to refining the data needs and expectations from different stakeholders depending on their specific contexts and policy scenarios.** For this reason, the information in this table is not stratified by initial and expanded policy; data on many parameters will be necessary for initial policy making but needs further discussion within the specific vaccine introduction context, i.e., the precise evidence needs for a self-procuring middle-income country may be distinct from a lower-income, Gavi supported country, and this needs to be further elucidated. The parameters that are believed to be most important are shown in red (critical parameters).

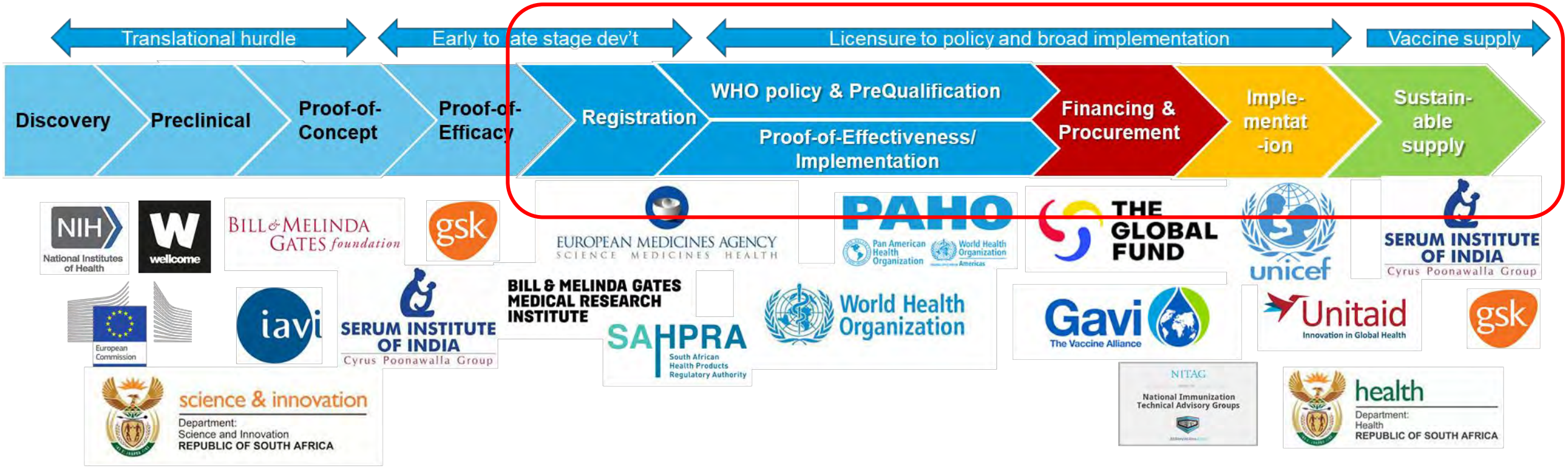
It is anticipated that the studies and data described below will be generated by multiple stakeholders, potentially working in collaboration. Several parameters will form part of the Gavi vaccine investment strategy (VIS) and likely needed for Gavi financing and initial policy introduction in Gavi-supported countries. Some of this evidence generation will be commissioned directly by Gavi. If available, this information may also be helpful for countries who are not Gavi-supported or when making initial or expanded policy decisions.

The tables below may not be exhaustive; global, regional and national implementation partners may have unique data/evidence requirements to facilitate delivery in fragile and/or conflict settings. These partners should be consulted if they are intended to be engaged in the vaccine implementation strategy. This section may be particularly helpful for vaccine developers, as it offers improved granularity on the types of data that will likely inform policy decisions. To rationalise investment in late-stage vaccine development, and to facilitate initial policy and procurement decisions, it is intended that many of these activities will be initiated during clinical development and will likely be based on modelling estimates in early iterations. These estimates will be refined as data on the vaccine characteristics become available, for example related to efficacy and duration of protection, and modelling estimates are supplemented with (pre-)implementation and operational research data.

Overarching activities related to implementation should include development of **communication strategies** to facilitate vaccine acceptability, build awareness, and generate demand. This requires generation of a **robust communications and community engagement plan/program**, vaccine-related events (VRE) response plan, and supporting materials which are updated throughout the development process. Issues and myths on the disease and vaccination need to be identified and addressed, prior to and during vaccination campaigns.

https://www.who.int/publications/m/item/who-evidence-considerations-for-vaccine-policy-development-(ecvp)#:~:text=WHO's%20IVB%20department%20has%20developed,to%20support%20WHO%20policy%20recommendations.

Global vaccine introduction and access roadmap



For late-stage vaccines in development, co-ordination and alignment of stakeholders is crucial to achieving access and impact

Presentation outline

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  - Group A streptococcus*
  - Non-typhoidal salmonella*
- Goals of this PDVAC meeting

*reviewed at PDVAC in 2022

We need a ‘better’ prioritization strategy for new vaccines

Immunization Agenda 2030 – grounded in regional partnership

- A robust priority-setting process will build awareness of disease burden, risks and threats, and potential interventions.

- We are seeking to **collectively** develop an approach to identify **regional and country priorities for vaccine R&D**, and a mechanism to drive progress at the country, regional and global levels

Vaccine Value Profiles

Publication of a **two volume special issue of Vaccine Value Profiles in the journal 'Vaccine'** is anticipated to occur in early 2023. Each profile contains a comprehensive summary of vaccine value-related information for 18 pathogens.

Monoclonal antibodies are also being considered where appropriate.

Intended to support the **regional pathogen prioritization deliberations**

Special Issue Vol. 1

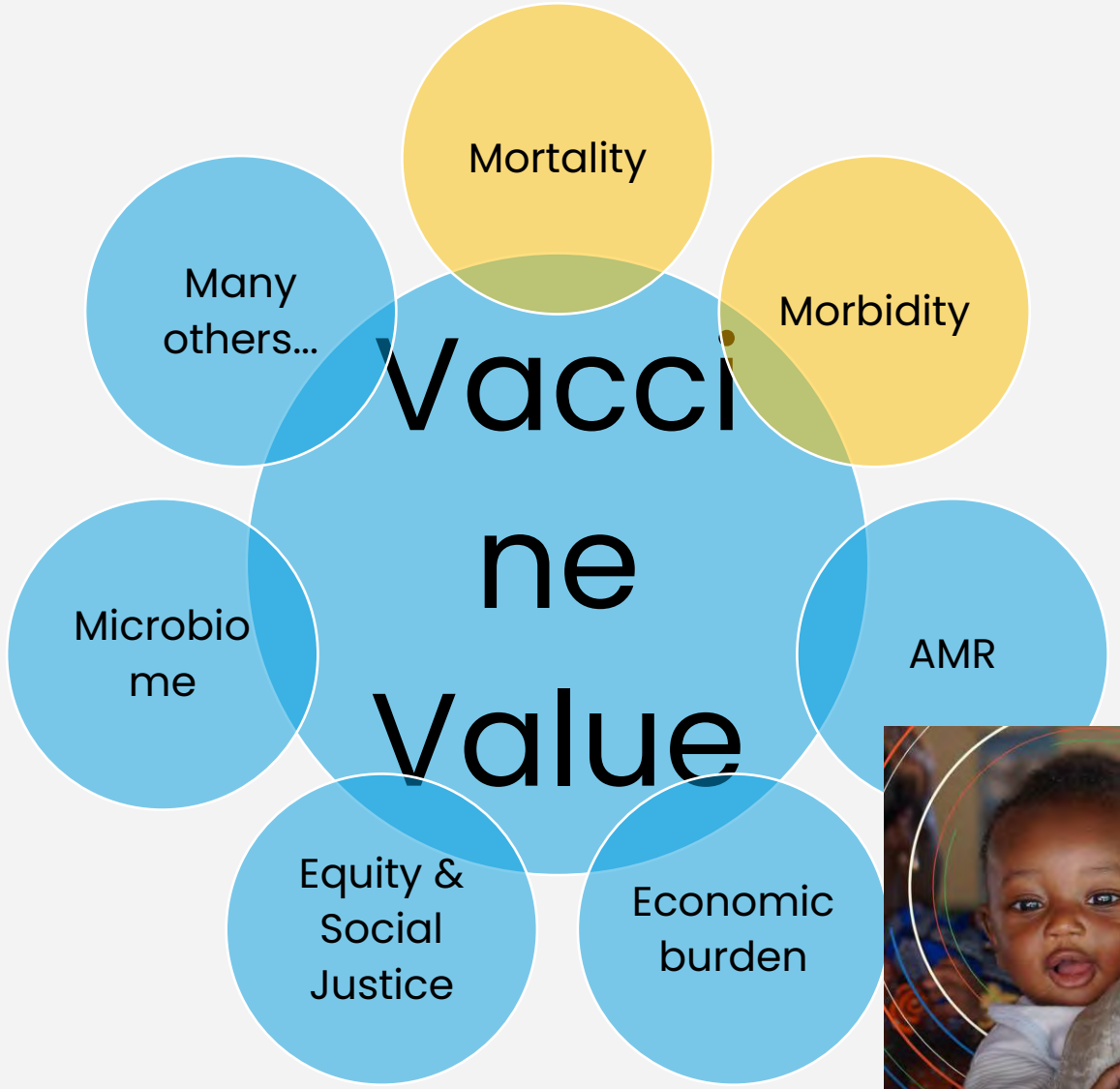
- Foreword
- Neglected Tropical Disease Vaccines: Hookworm, Leishmaniasis, and Schistosomiasis (commentary)
- Profiles:
  - Respiratory syncytial virus
  - *Shigella*
  - ETEC
  - iNTS
  - Paratyphi A
  - Hookworm
  - Leishmaniasis
  - GBS
  - Norovirus

Special Issue Vol. 2

- Advances in monoclonal antibodies
- Advances in mRNA vaccine technology
- The role of vaccines in reducing AMR
- Profiles:
  - Chikungunya
  - Gonococcal vaccines
  - Cytomegalovirus
  - Schistosomiasis
  - HSV
  - Malaria
  - New TB vaccines
  - HIV (vaccines)
  - HIV (monoclonal antibodies)
  - Influenza*

The need to measure broad impact of vaccines

- Vaccines have public health value in low- and middle-income countries but **limited commercial incentive**
- To prioritise vaccine development, introduction and use, we need to **articulate the value of vaccines** across a range of determinants;
- The value of vaccines can be measured across **numerous criteria;**
- **Mortality and Morbidity** remain critical drivers of the value of vaccines.



Mortality assessment of enteric pathogens

1. Increased transparency and better understanding of models, data and studies used to calculate mortality estimates in U5 for enteric pathogens;
2. Incorporation of revised modelling adjustments into future modelling estimates;
3. Incorporation of revised ORs into future modelling estimates;
4. Alignment on data and studies to be included in future mortality estimates;
5. Close collaboration and good working relationship with the two modelling groups MCEE and IHME.


Conference report

Meeting Report: WHO Workshop on modelling global mortality and aetiology estimates of enteric pathogens in children under five. Cape Town, 28–29th November 2018

H.J. Prudden [a], M. Hasso-Agopsowicz [a], R.E. Black [b], C. Troeger [c], R.C. Reiner [c], R.F. Breiman [d], M. Jit [e, f, g], G. Kang [h], L. Lamberti [i], C.F. Lanata [j, k], B.A. Lopman [d], W. Ndifon [l], V.E. Pitzer [m], J.A. Platts-Mills [n], M.S. Riddle [o], P.G. Smith


Case fatality risk of diarrhoeal pathogens: a systematic review and meta-analysis

Ernest O Asare ✉, Dianna Hergott, Jessica Seiler, Brooks Morgan, Helena Archer, Alison B Wiyeh, Boya Guo, Matt Driver, Birgitte Giersing, Mateusz Hasso-Agopsowicz, Jairam Lingappa, Benjamin A Lopman, Virginia E Pitzer

International Journal of Epidemiology, Volume 51, Issue 5, October 2022, Pages 1469–


Association of enteropathogen detection with diarrhoea by age and high versus low child mortality settings: a systematic review and meta-analysis

Julia M Baker, PhD • Mateusz Hasso-Agopsowicz, PhD • Virginia E Pitzer, ScD • James A Platts-Mills, MD • Andre Peralta-Santos, MD • Catherine Troja, MPH • et al. Show all authors

Global diarrhoea-associated mortality estimates and models in children: Recommendations for dataset and study selection

Egle Butkeviciute [1], Holly J Prudden [2], Mark Jit [3], Peter G Smith [3], Gagandeep Kang [4], Mark S Riddle [5], Benjamin A Lopman [6], Virginia E Pitzer [7], Claudio F Lanata [8], James A Platts-Mills [9], Robert F Breiman [10], Birgitte K Giersing [2], Mateusz Hasso-Agopsowicz [11]

The approach to assess the impact of enteric pathogens on morbidity

Workstream 1: identification and analysis of individual-level data from historical datasets to understand the impact of enteric infections and confounders on long-term morbidity, including growth faltering and cognitive impairment in children.

Workstream 2: a systematic review of evidence on the association of aetiology-specific diarrhoea with short- and long-term impact on growth, including stunting, and possibly cognitive impairment in children, while accounting for potential confounders.

Timeline 2021-2023

World Health Organization Expert Working Group Recommendations for assessing morbidity associated with enteric pathogens

Mateusz Hasso-Agopsowicz [1], Benjamin A Lopman [2], Claudio F Lanata [3], Elizabeth T Rogawski McQuade [2], Gagandeep Kang [4], Holly J Prudden [5], Ibrahim Khalil [6], James A Platts-Mills [7], Karen Kotloff [8], Mark Jit [9], Mark S Riddle [10], Patricia B Pavlinac [6], Paula M Luz [11], Virginia E Pitzer [12], Robert F Breiman [2], Birgitte K Giersing [13]

Pathogens prioritised for the assessment of morbidity:

1) *Shigella (dysenteraie, flexneri, sonnei)*
2) Norovirus (GI or GII)
3) ETEC (ST or LT)
4) *Campylobacter jejuni*

Criteria used to prioritise:

- Active vaccine candidates in the clinical pipeline;
- Feasibility of developing a vaccine;
- Evidence of association between symptomatic infections and morbidity;
- Evidence of association between asymptomativ infections and morbidity.

Morbidity systematic review results

1. Studies predominantly originated from few countries in South-East Asia, Africa, and South America and were conducted in the past decade.
2. Studies showed that *Campylobacter*, ETEC, and Norovirus infections impact linear growth across time and geographical locations.
3. There are limited studies assessing the long-term sequalae of *Campylobacter*, ETEC, and Norovirus on development of the nervous system in under 5 children.
4. Variations in outcome reporting and the observed findings make deriving conclusions challenging, limiting their usefulness in decision-making.
5. RCTs of highly effective, pathogen-specific treatments or vaccines with long follow-up may help inform the impact of the pathogens on the outcomes in question.

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*reviewed at PDVAC in 2022

*reviewed at PDVAC in 2022

The global clinical development pipeline for new TB vaccines, September 2022

Phase I	Phase IIa	Phase IIb	Phase III
AdHu5Ag85A[b] McMaster, CanSino	ChAdOx185A-MVA85A[b,i] University of Oxford	BCG revaccination to prevent infection[d,j] Gates MRI	GamTBvac[e] Ministry of Health, Russian Federation
TB/FLU-01L[b] TB/FLU-04L[b] RIBSP	ID93 + GLA-SE(QTP101)[e] Quratis U.S. NIH/NIAID	DAR-901 booster[f,j] Dartmouth	MIP/Immuvac[f,i,j] ICMR, Cadila Pharmaceuticals
BNT164[c] BioNTech SE	AEC/BC02[e] Anhui Zhifei Longcom	H56: IC31[e] SSI, Valneva, IAVI	MTBVAC[d,h] Biofabri, University of Zaragoza, IAVI, TBVI
		M72/AS01E[e,j] GSK, Gates MRI	VPM1002[d,g,i,j] SIIPL, VPM
		RUTI®[f] Archivel Farma, S.L.	BCG vaccination to prevent infection (TIPI)[d] HJF
			BCG revaccination in children and adolescents (BRiC)[d,i,j] ICMR

Source: WHO Global TB report, 2022

The TB vaccine ECVP is being finalized for publication

World Health Organization

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Home / Publications / Overview / Public consultation of ECVP for TB vaccines intended for adults and adolescents

Public consultation of ECVP for TB vaccines intended for adults and adolescents

25 September 2022 | Technical document

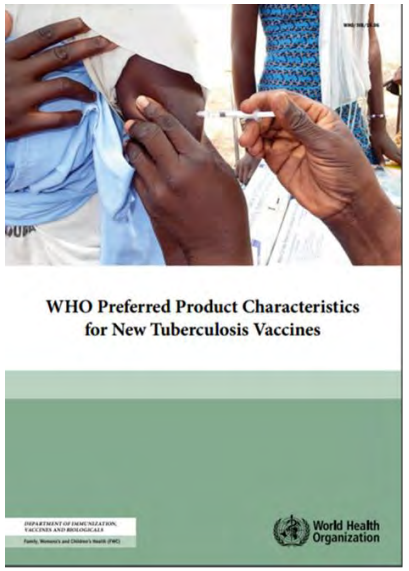
Download (1.2 MB)

Overview

WHO's IVB department has developed a novel kind of guidance for vaccine development stakeholders, referred to as Evidence Considerations for Vaccine Policy, or ECVP. The ECVP document aims to provide early information on the data and evidence that is likely to be required to support WHO policy recommendations. The first ECVP exemplar has been drafted for new Tuberculosis (TB) vaccines intended for adults and adolescents, in collaboration with a global expert technical advisory group.

The primary audience for this TB vaccine ECVP includes all stakeholders intending to support the product development, regulatory approval, introduction and widespread use of new TB vaccines intended for adults and adolescents, in low- and middle-income countries, with the aim of reducing delays between vaccine regulatory approval and vaccine introduction.

We invite all those interested in the ECVP for new Tuberculosis (TB) vaccines intended for adults and adolescents to review this draft document and provide comments on both the general utility of the document, and the specific guidance developed for new TB vaccine. Please use the comment form to capture your comments and return to: vaccines@who.int. **Please use the term "TB vaccine ECVP" in the subject line, otherwise your comments will not be received.** The document will be posted until the **28th October 2022** for comment.

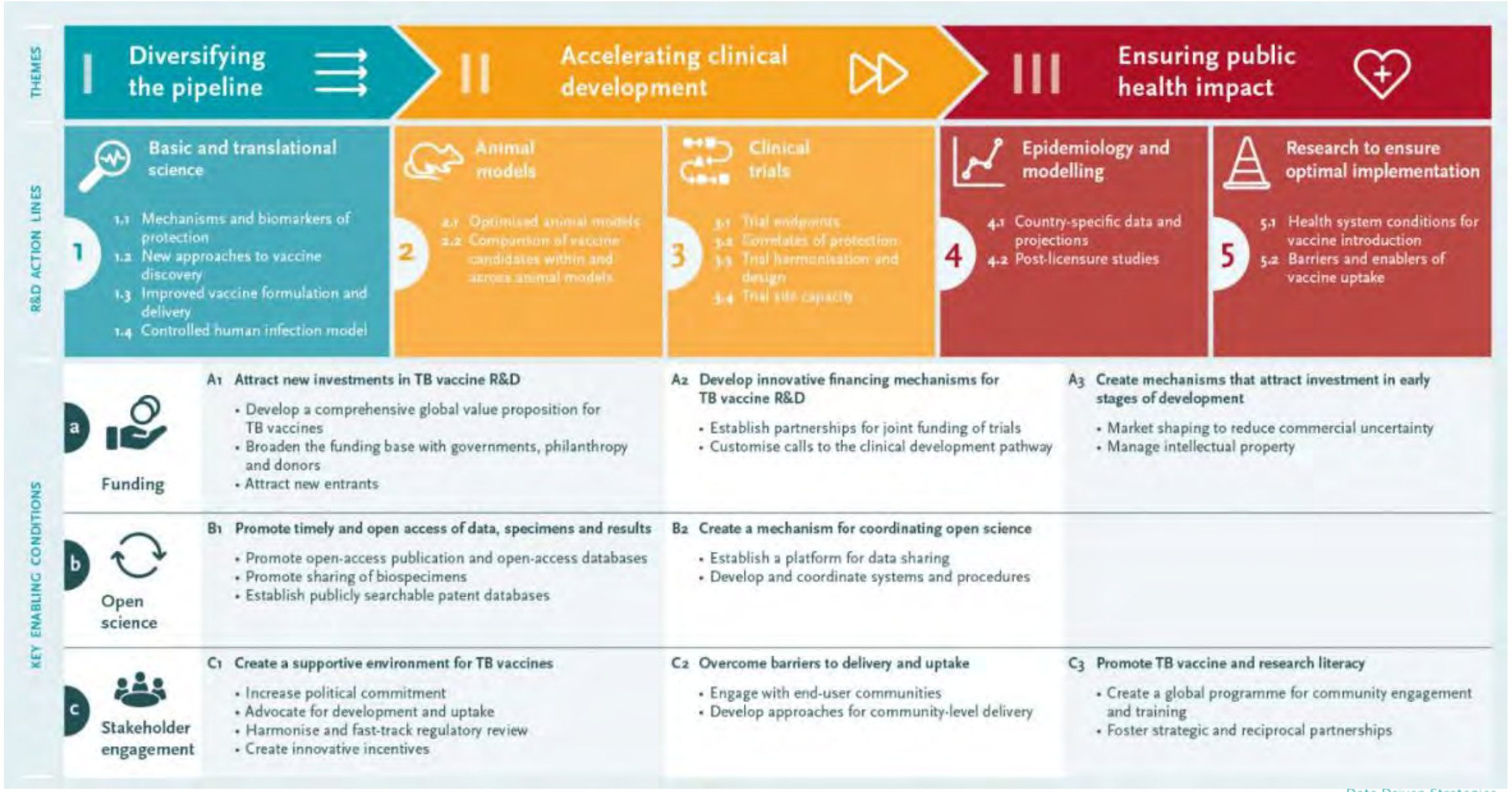


ECVP specific for new TB vaccines: Public consultation CLOSED 28th October

Aim to finalise and publish by early 2023

Public consultation of ECVP for TB vaccines intended for adults and adolescents (who.int)

TB Vaccine R&D Roadmap



Data Driven Strategies

Source: https://www.edctp.org/news/edctp-and-aighd-launched-a-global-roadmap-for-tuberculosis-vaccine-development/#

Draft strategic pillars of TB Access Vaccine Roadmap

3. National/Global Policy Making
evaluates the potential vaccine impact and cost-effectiveness , based on anticipated use case

WHO PQ

5. Financing, Supply, & Access
considers the potential financing and procurement mechanisms to sure access to LMICs

Country, regional and global implementation of new TB Vaccines

countries

2.Regulatory Strategy
outlines the proposed licensure pathway for first licensure and subsequent regulatory approvals including in additonal key populations

1. Pul
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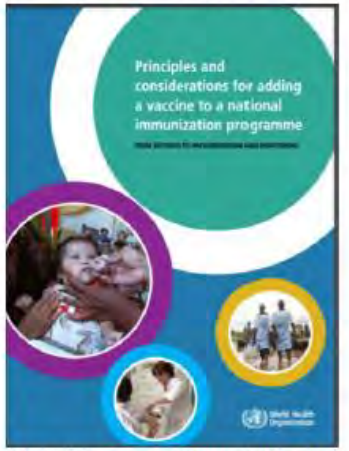


Source:
https://apps.who.int/iris/bitstream/handle/10665/111548/9789241506892_eng.pdf;sequence=1

DRAFT

Meeting 7 and 8th Dec

Source: Giersing B. Development of WHO Roadmap for Global Introduction of New TB Vaccines intended for adults and adolescents. PPT 29 Junee 2022

HIV vaccine and mAb pipeline - update

- **Imbokodo results** in 2021: ph2b efficacy trial of a 4 dose prime-boost candidate (J&J) in cisgender women in SSA, showed a non-significant 25% HIV risk reduction (will not advance further).

- **Mosaico ph3 trial ongoing** (completion in 2024). Similar 4 dose prime-boost regimen (J&J) in MSM in Europe & the Americas (slightly altered booster, diff pop, & larger sample size). Uncertain if it will achieve protective efficacy sufficient for licensure.

- 2 vaccines in ph2 & ~ 20 vaccine candidates in ph 1 (including DNA, mRNA, heterologous prime boost etc)

- Several HIV mAb candidates in ph1 (further discussed in the mAbs session). Results from AMP trial demonstrated proof of concept.

Update on Dengue Vaccines

CYD-TDV dengue vaccine was licensed in 2016 but its use is restricted to seropositive persons only. As a pre-vaccination screening is needed, uptake in dengue endemic countries has been low.

TAK-003: Phase 3 trial completed and interim efficacy and safety results have been published.

TAK-003 was licensed in Indonesia in 2022. EMA approval likely by Q2 2023

TV-003/005: First results of Phase 3 trials in Brazil will be released in Q1 2023.

A SAGE Working Group on dengue vaccines was established in November 2022 to assess the evidence of TAK-003, review updates needed for CYD-TDV, and review emerging data for TV 003.

Source: Annelies Wilder-Smith

PDVAC reviewed the applicants for the mRNA technology transfer hub, now established in Cape Town, South Africa

South African Consortium:

Afrigen Biologics & Vaccines — An Avacare Health & IDC Company

Private pilot facility with extensive lipid nanoparticle production experience

BIOVAC — science of protecting life

Public-private vaccine manufacturer with available production facilities and mRNA fill-finish experience

saMRC advancinglife

South African Medical Research Council with network of high-quality academic centres providing know-how on mRNA, preclinical and clinical studies etc.

Ecosystem includes regulatory agency, government investment and significant international investment in this project ($100 million)

Status:

- mRNA Covid vaccine produced at lab scale, scale-up underway.
- Training of 'spokes' initiated.
- R&D of second generation mRNA underway – more suitable for LMIC use.

… and selection of the Spokes: the technology recipients who will establish mRNA vaccine production capacity in their country

Announced so far:

- Africa region: South Africa, Senegal, Nigeria, Kenya
- Eastern Mediterranean region: Tunisia, Egypt, Pakistan
- South-east Asia region: Bangladesh, Indonesia, India
- Americas region: Brazil, Argentina
- Western-Pacific region: Vietnam
- European region: Serbia, Ukraine

Challenge: significant diversity of maturity levels

- existing manufacturers with numerous approved products
- manufacturers with infrastructure but no products approved yet
- nascent manufacturers with no infrastructure yet, and immature regulatory agency…

mRNA Tech Transfer Programme
F2F meeting, Cape Town, 17-21 April 2023

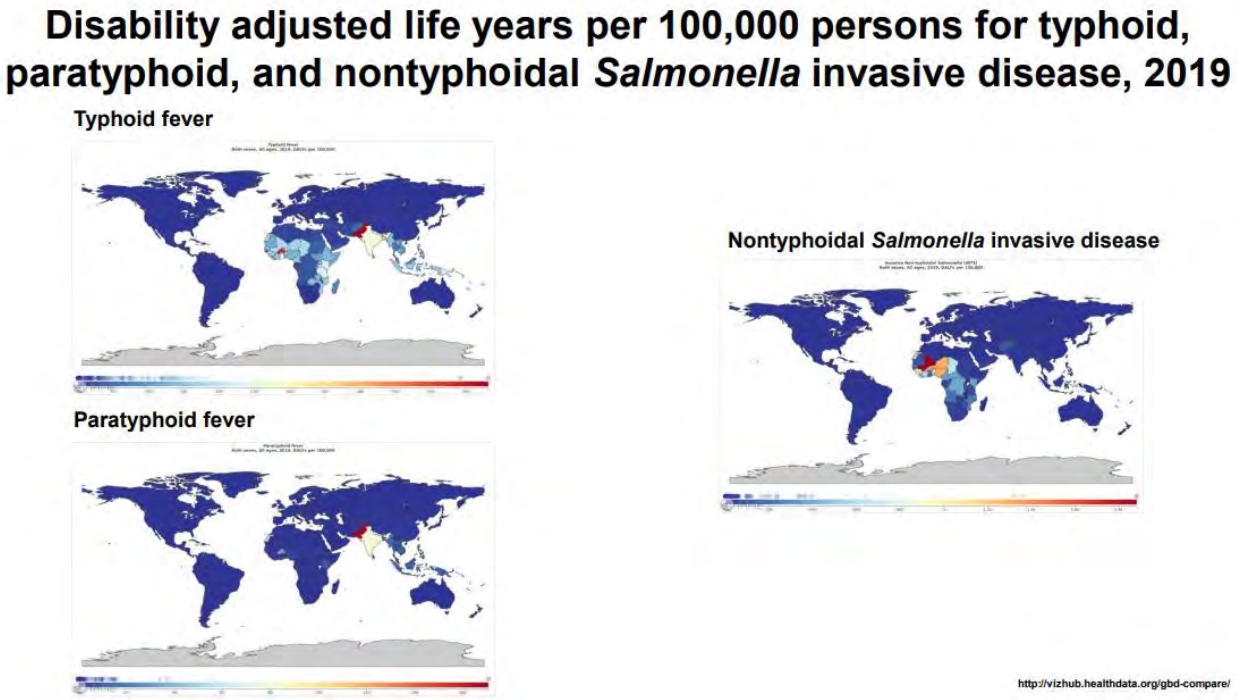
Meeting Objectives

- Review the progress of the mRNA technology transfer Programme
- Share experience among hub and spokes of the Programme
- Review business models, intellectual property issues and regulatory aspects relevant to mRNA vaccines.
- Review the science of mRNA technologies and discuss key applications relevant to LMICs
- Strengthen the mRNA R&D network and build communities among hub and spokes by R&D interests.
- Highlight the role of technology transfer and establishment of manufacturing and R&D on national and regional economic development.

Discuss whether developing a mRNA candidate vaccines for specific diseases of interests make sense from a scientific, regulatory, policy and market perspectives.

PDVAC meeting on non-typhoidal salmonella (NTS) vaccines

Objectives



1. Summarize learnings from the recent WHO global stakeholder consultations on NTS and broadly protective Salmonella vaccines;
2. Review status of the NTS and combination Salmonella vaccine development pipeline;
3. Communicate areas of consensus and uncertainty in the strategy towards development of an NTS-containing vaccine;
4. Report on the consultation with LMIC stakeholders on the perceived public health need for an NTS vaccine.

For full set of materials please see: https://www.who.int/news-room/events/detail/2022/02/07/default-calendar/pdvac-(virtual)-meeting-on-invasive-non-typhoidal-salmonella-(ints)-vaccines

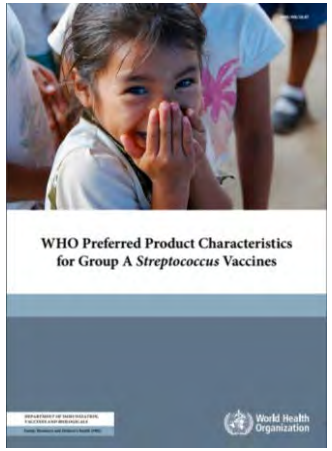
PDVAC meeting on non-typhoidal salmonella vaccines
Outcomes

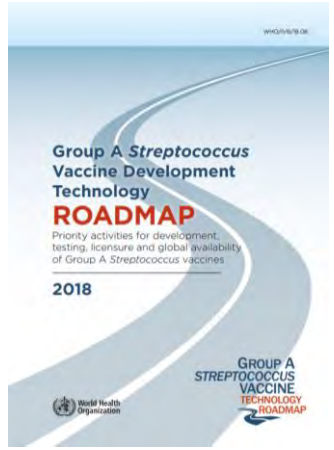
1. The bivalent iNTS and trivalent iNTS+TCV vaccine combinations are all steps along the pathway to a potential global quadrivalent iNTS+PTA+TCV combination;
2. Full vaccine of value assessments (FVVAs) will be necessary to evaluate each of these scenarios (iNTS alone, trivalent permutations, and quadrivalent) to assess multiple trade-offs;
3. There is considerable risk in signaling to vaccine manufacturers that any of these combinations is the preference today, without being informed by a) the relative health, social, and economic value, and b) better understanding the preferences of country and regional level stakeholders, including NITAGs and RITAGs, respectively;
4. The epidemiology, and associated need/demand for these iNTS containing vaccines may shift during the course of product development, particularly in the context of emerging data/shifting prevalence of malaria, people living with HIV, awareness of antimicrobial resistance and the potential impact that a vaccine could have; this may warrant revision of the PPC or development of a PPC for an alternate combination.

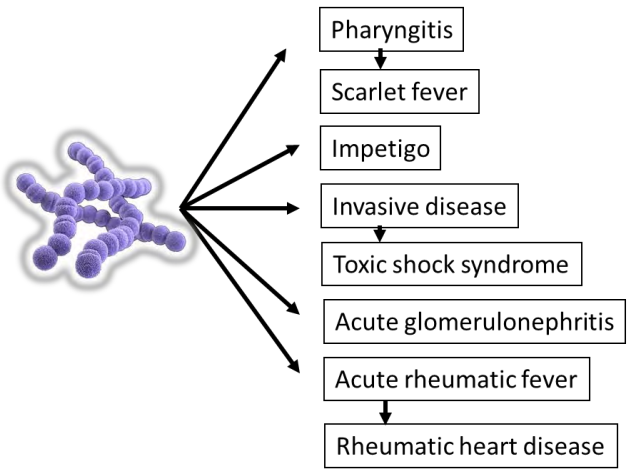
- WHO/IVI are in the process of developing a PPC and roadmap for iNTS+TCV vaccines in the first instance, as part of a FVVA for iNTS+TCV

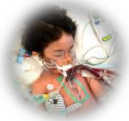
Joint PDVAC/IVIRAC meeting – Group A Streptococcus

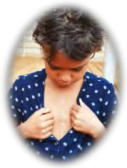
Objectives





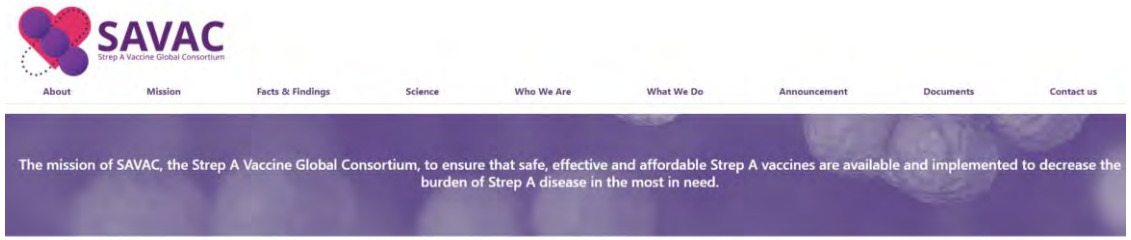






1. Review recent advances in GAS Vaccines R&D and the soon to be published FVVA (from the Strep A Vaccine Global Consortium)

2. Agree on key priorities to ensure the WHO PPC and R&D Roadmap for GAS vaccines remain current and relevant.



Strep A Vaccine Global Consortium (SAVAC)
https://savac.ivi.int/

Joint PDVAC/IVIRAC meeting – Group A Streptococcus
Outcomes

PDVAC key Conclusions and Recommendations:

- PDVAC considered the utility of a GAS Vaccine Development and Regulatory Strategy document that describes pathways of vaccine development and regulatory approvals
- Develop PPCs for priority GAS indications (e.g. pharyngitis, RHD) and articulate the needs for both HIC and LMIC contexts. The priority indications should be determined by the full value that GAS vaccines could offer against the proposed indication.
- Further rationalize and accelerate GAS vaccine development around key research priorities (e.g. surrogate markers of protection, burden estimates)

PDVAC encouraged SAVAC and the PDVAC secretariat at WHO to consider a creative partnership to undertake the revisions.

For full set of materials please see: https://www.who.int/news-room/events/detail/2022/09/30/default-calendar/pdvac---ivirac-joint-review-of-group-a-streptococcus-vaccines

Presentation outline

- Remit of PDVAC
- Types of and relationship between various technical documents
- Assessing full value of vaccines
  - Mortality and morbidity burden
- Pathogen/platform specific updates:
  - New TB vaccines
  - Dengue
  - HIV
  - mRNA hub and spokes
  - Group A streptococcus*
  - Non-typhoidal salmonella*
- Goals of this PDVAC meeting

*reviewed at PDVAC in 2022

Objectives for this PDVAC meeting

- To review the progress towards partnering with regions to identify priority pathogens for new vaccines as indicators for IA2030 strategic priority 7 (SP7);
- Review the progress of pipeline and emerging vaccine and monoclonal antibody candidates against specific pathogens, and reaffirm/identify pathogen priorities and critical activities needed to advance new products;
- To discuss the 'full-value of vaccines assessment' (FVVA) and Evidence Considerations for Vaccine Policy (ECVP) concepts and their use in prioritising vaccines for intended for low-and middle-income countries;
- To discuss how WHO/IVB can effectively drive and/or partner with immunization stakeholders to support the development of multiple vaccines and vaccine-like monoclonals for low- and middle-income countries.

SP 7 Research & Innovation Working Group

Product Development for Vaccines Advisory Committee

Intercontinental Hotel, Geneva, Switzerland

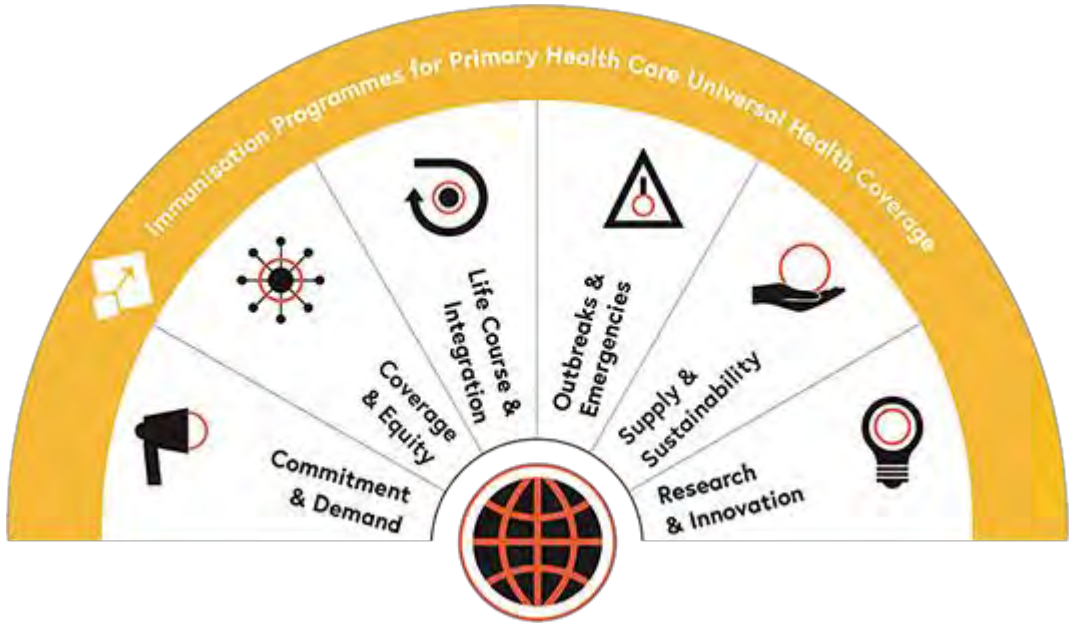
5-6 December 2022

Immunization Agenda 2030

A global strategy to **leave no one behind**

7 strategic priorities (SPs)

1. Immunization programmes for primary health care / universal health coverage
2. Commitment & demand
3. Coverage & equity
4. Life-course & integration
5. Outbreaks & emergencies
6. Supply & sustainability
7. **Research & innovation**



Goal and focus of SP7

- Fostering an enabling environment and ensuring that research and innovations that increase the reach and impact of immunization programs are rapidly and equitably made available to all countries and communities

- Supporting greater capacity for research and innovation by improving the research and innovation ecosystem and striving for both breakthrough discoveries that change the landscape (e.g., mRNA-based vaccines), while also advancing incremental innovations for continual improvements designed to leave no one behind (e.g., combination vaccines)

- Ensuring equitable access of innovative products and programs to all countries and communities

Long term Objectives

- Establish and strengthen capacity at all levels to identify priorities for innovation, and to create and manage innovation.
- Develop new vaccines and technologies; and, improve existing products and services for immunization programs.
- Evaluate promising innovations, and scale-up innovations as appropriate based on the best available evidence.

Partners and programs to leverage

- Gavi 5.0, VIPS (Vaccine Innovation Prioritisation Strategy) and VIS (Gavi Vaccine Investment Strategy renewals)
- CEPI 2.0
- WHO CAPACITI (Country-led Assessment for Prioritization in Immunization Decision-support Framework)
- COVAX and its successor, if any, post-pandemic
- GVIRF (Global Vaccine and Immunization Research Fora)
- WHO AMRVAF (Anti-Microbial Resistance Value Attribution Framework)
- WHO R&D Blueprint

Membership

Up to **18 members**, with:

- up to **12 independent** members (target 2 members / WHO region)
- up to **6 ex officio** members from core IA2030 partners
  - WHO
  - Gavi
  - CEPI
  - UNICEF
  - NIH
  - Wellcome Trust

Members	Name **Co-leads in bold**	Status
AFRO	**Kwaku Poku Asante** (AFRO)	**Confirmed**
	Helen Rees	**Confirmed**
EMRO	Ghassan Dbaibo	**Confirmed**
	Ahmed Deemas Al Suwaidi (NITAG-UAE)	**Confirmed**
EURO		*Contacted*
		Contacted
PAHO/AMRO	**David C. Kaslow** (PDVAC)*	**** Stepping down***
	Dr Cristiana Toscano (RITAG)	**Confirmed**
	John Peter Figueroa (RITAG)	**Confirmed**
SEARO	*Gagandeep Kang (SEAR ITAG)*	Contacted
	Mimi Lhamu Mynak (SEAR ITAG Bhutan)	Confirmed
WPRO	*Chris Morgan*	Contacted
		Contacted

Ex officio IA2030 core partners	Name	Contact / confirmation status
WHO PDU | EPI	Birgitte Giersing | Anna-Lea Kahn	Confirmed
UNICEF	Robert Scherpbier | Jean-Pierre Amori	Confirmed
US CDC/NIH	Jim Alexander | B. Lee Hall	Confirmed | Contacted
Wellcome Trust	Charlie Weller	Confirmed
GAVI	Marion Menozzi-Arnaud	Confirmed
CEPI	Adam Hacker	Confirmed

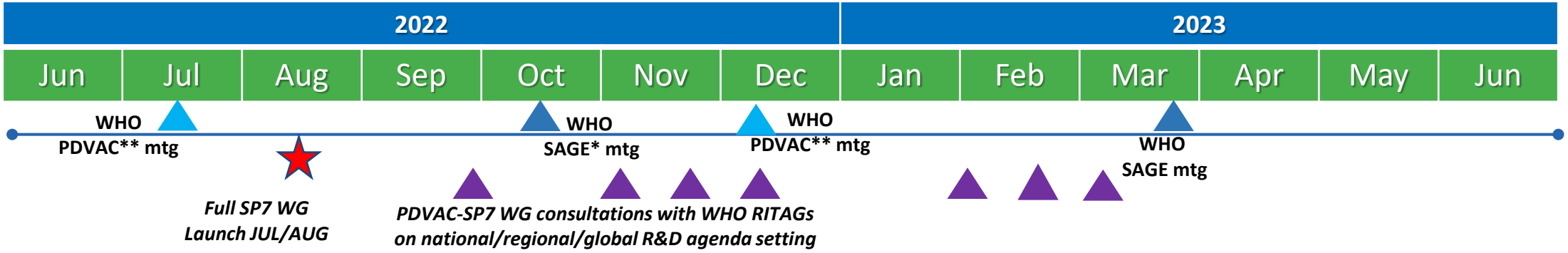
Operations

- Membership term
  - Varied to ensure continuity
  - 1- 3 year term for independent members
- Leadership
  - Global-level IA2030 partner has primary responsibility for leading the coordination and functioning of the SP7 Working Group (PATH, David C. Kaslow)
  - Co lead: A regional expert, and rotates every 3 years (Kwaku Poku Asante)
- Coordination and Alignment Sub Team (CAST)
  - Role: day to day management of SP7
- Convening
  - CAST – monthly
  - WG – quarterly

Operations

- Rhythm of business
  - To hold one or more consultative engagements
    - To review progress on objectives, status of indicators, and any updates to learning agenda and evaluation questions
    - Identify risks and issues associated with implementing the current year workplan
    - Collect proposed adjustment to workplan or indicators, based on emerging issues or changes in landscape
  - Present synthesised data to IA2030 coordinating group and WHO PDVAC
  - Review workplans and annual reports
  - Hold broad consultative engagement

SP7 2022 – 2023 workplan



Key Focus Areas and Deliverables 2022-2023

- Support LMICs in expanding, strengthening, and/or establishing local and regional capacities for immunization research and innovation
  - **Obj 7.1 indicator**: No. of countries with national agenda for research on immunization;

- Develop a mechanism to align country, regional, and global level stakeholders on priority diseases for which new vaccines are needed
  - **Obj 7.2 indicator**: (potential) process review at SAGE in Oct 2022; global "short list" of pipeline pathogen targets will be developed by WHO and first iteration endorsed by SAGE in April 2023

- Establish 2025 and 2030 IA2030 SP7 Working Group objectives to sustain progress, based on country-led R&D priorities.

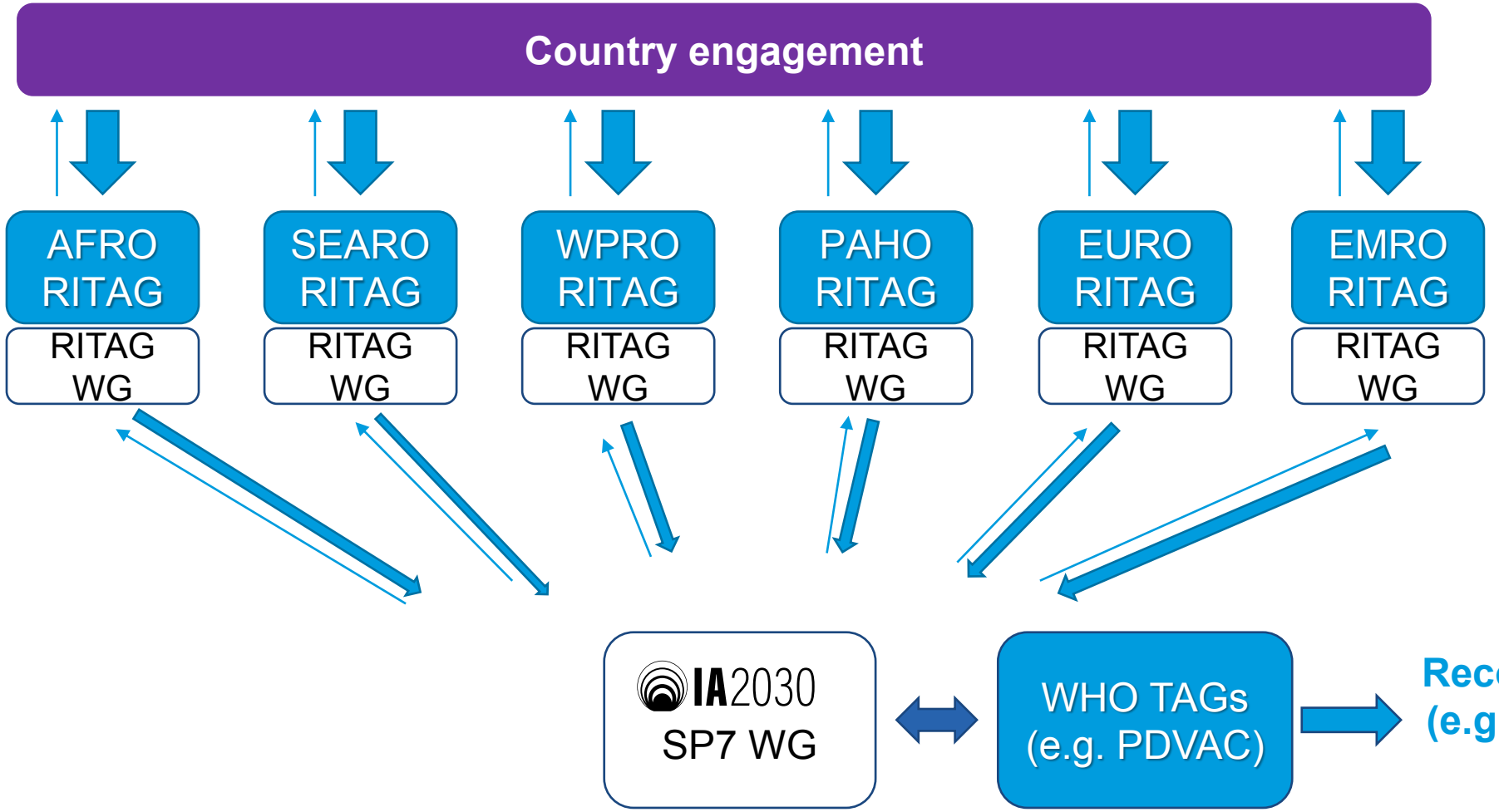
*WHO's Strategic Advisory Group of Experts on Immunization (SAGE):
** WHO's Product Development for Vaccines Advisory Committee (PDVAC): https://www.who.int/groups/product-development-for-vaccines-advisory-committee

Progress for 2022 – 2023 workplan

- Agreed on WG member recruitment process
  - Co-lead identified (Kwaku Poku Asante – Ghana)
  - Regional immunization advisor + RITAG Chair from each region were approached for 2 members with formal letters from WHO HQ
  - Ex-officio IA2030 core partner members confirmed
  - Biweekly meetings with PDVAC secretariat
  - Alignment meeting with IVB Director
  - Joint meeting with PDVAC occurred on 18 Jul 2022
  - Initial discussions on additional objective on implementation research and indicators
  - Potential engagement process developed for consideration
  - Contributed to draft 2022 IA2030 progress report for SAGE

Success of SP7 approach relies on the framework for regional engagement Potential model for consideration

Proposal: Collaborate with RITAGs and establish RITAG working groups to 'bridge' between SP7 WG and regions and countries



RITAG WGs composed of at least 2 RITAG members, plus other regional experts, including NITAG members;

2 RITAG WG members serve as regional representatives on IA2030 SP7 WG

Recommendations to SAGE (e.g., priority pathogens via PDVAC*)

* WHO's Product development for Vaccines Advisory Committee

Highlights of SP7 draft reports

- SP 7.1 Capacity for Innovation
  - Indicator
    - Proportion of countries with an immunization research agenda
  - Progress
    - Relatively few countries found to have a national agenda for research on immunization
  - Considerations to improve indicator
    - Encourage countries to develop stand-alone research agendas on immunization or integrate research priorities into broader health systems research strategies.
    - Research agendas could also be developed at the regional level and provide countries with examples as guides to defining their research priorities for immunization within their local context.

Highlights of SP7 draft reports

- SP 7.2 New Vaccine development

  - Indicator
    - Progress towards global research and development targets

  - Progress
    - Ongoing collaboration between SP7 WG and PDVAC to develop priority pathogen list
    - Development of a mechanism and methodology to identify priority pathogens for new vaccine development (PAPRIKA) reviewed by PDVAC
    - Consensus that TB, HIV, malaria and, potentially, COVID-19 should be considered global pathogen targets for new vaccine development
    - Highlighted the need to define use(s) of the priority list(s) – country vaccine production, multilateral, biotechs
    - Regional stakeholder engagements planned to identify regional and global priority list(s)

Highlights of SP7 draft reports

- SP 7.3 Evaluate promising innovations and scale up innovations

  - Indicator
    - No indicator yet, under development

  - Progress
    - Observed that no well-defined indicator for implementation /operational research exists
    - Engagement process for defining and monitoring and evaluating implementation and operational research and innovation agendas do not currently exist at national, regional, and global levels
    - SP7 WG discussing how to close the gap

Thank you!


Photo credit: Shifo Foundation
IMMUNIZATION AGENDA 2030
A global strategy to leave no one behind
IA2030

Partnering with regions and countries to identify priority pathogens for vaccines

World Health Organization

Immunization, Vaccines and Biologicals

Vaccine Prioritization & Platforms Team

PDVAC 5 December 2022

Three components to this presentation

Why do we need to identify ‘priority pathogens’?

Progress to date

Discussion

We need a ‘better’ prioritization strategy for new vaccines

World Health Organization

In line with IA2030 principles and ways of working

Immunization Agenda 2030 – grounded in regional partnership

IA2030 Vision for SP7: Research & Innovation

- Aligned priorities can focus funding and resources, and enable coordination for acceleration
- A robust priority-setting process will build awareness of disease burden, risks and threats, and potential interventions.

➢ We are seeking to **collectively** develop an approach to identify **regional and country priorities for vaccine R&D**, and a mechanism to drive progress at the country, regional and global levels

➢ The first deliverable is ***“short list”*** *of global pathogen targets for new vaccines—where vaccines do not yet exist, or where a new indication is needed*

➢ **Partnership model can be applied to other elements of the IA2030 agenda, such as implementation research**

Source: ImmunizationAgenda2030.org

Collaborative approach to identify regional priorities

World Health Organization

Multi-criteria decision analysis (MCDA)

1. Identify pathogens for prioritization

Proposed scope is 24 pathogens with vaccines in the pipeline

2. Formulate criteria to assess against

e.g. “annual deaths in the region”, “contribution to inequity”, etc.

3. Score the pathogens against the criteria

Based on the best available regional data

4. Weight criteria according to importance

Regional and country stakeholders complete a 30-minute “**Preferences Survey**”

5. Rank pathogens based on weights and scores

Survey tool multiplies Score x Weight

Regional consultations

6. Deliberate on results, make recommendations

Regional consultations* consider the ranking and make their recommendations on priority pathogens

7. Synthesize Global list based on Regional views

PDVAC aggregates regional priorities into a global “short list”

SAGE reviews and endorses short list

Priority-setting by Regions and Countries

Supporting mechanism

* Regional stakeholders will determine the timing and approach for their consultations. Only consultations conducted by February 2023 can be included the global summary presented to SAGE.

PDVAC: WHO Product Development Vaccines Advisory Committee, SAGE: WHO Strategic Advisory Group of Experts on Immunization

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Pathogen scope

World Health Organization

Starting with an open mind and making deliberate, transparent choices

Potential pathogens

- Existing roadmaps, action plans, global strategies, elimination targets
- Available regional and national R&D strategies
- ClinicalTrials.gov and ICTRP database
- Pipeline overviews and investment portfolios
- WHO Health Topics
- Web searches
- Expert advice

Animal pathogens

Eliminate to focus on human health

Human pathogens

Eliminate since R&D needs are less acute

With licensed vaccines

Without licensed vaccines [a]

Eliminate due to lower probability of success

Not in clinical development

With candidates in clinical development

Eliminate because the WHO R&D Blueprint is generating priorities

With epidemic and PHEIC potential [b]

Not emerging infectious diseases

Eliminate due to narrow interest, but give regional & country stakeholders an option to add back

Not prioritized globally

Prioritised globally (n = 24)

Pathogens with existing TPPs or VVPs in progress, or part of an existing roadmap [c]

a Pathogens where vaccines for new indications are needed were included. b. PHEIC: Public health emergency of international concern. https://www.who.int/teams/blueprint/updating-the-WHO-list-of-pathogens-with-epidemic-and-PHEIC-potential
c. Roadmaps include *Vaccines to tackle drug resistant infections*, and *Roadmap for NTDs* Abbreviations: ICTRP – International Clinical Trials Registry Platform. NTD – neglected tropical disease. TPP – target product profile. VVP – Vaccine Value proposition

Collaborative approach to identify regional priorities

World Health Organization

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Criteria for prioritization

World Health Organization

Quantitative Scoring

Annual deaths in children under 5	Deaths attributable to the pathogen in both sexes, < 5 years old
Annual deaths in people 5 and older	Deaths attributable to the pathogen in both sexes, ≥ 5 years old
Years lived with disability (all ages)	Years of healthy life lost each year due to disability or ill-health caused by the pathogen

Qualitative Scoring

Social and economic burden **per case**	Reflects individual social and economic impact such as stigma and the costs of prevention, health care, and lost productivity.
Disruption due to outbreaks	Reflects societal impact due to outbreaks and epidemics, including social disruption; impact on healthcare systems, trade or tourism; and the cost of containment measures
Contribution to inequity	Reflects disproportionate impact on socially and economically disadvantaged groups, including women
Contribution to antimicrobial resistance (AMR)	Reflects the threat of resistance, based on current levels of resistance, contribution to antibiotic use, and designation as an AMR priority
Unmet needs for prevention and treatment	Reflects the effectiveness and suitability of alternative measures

Collaborative approach to identify regional priorities

World Health Organization

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Scoring

What is scoring?

- Each criterion has 5 levels:

Very low	Low	Medium	High	Very high

- For each of the criteria, decide which pathogens belong in which level
- Should be
  - Regionally focused
  - Consistent and evidence-based
  - Practical
  - Transparent

Quantitative criteria

1. **Data from GBD 2019** for each pathogen in each region
2. **Divide the range of values into 5 equal parts**
   (max burden) ÷ 5 = step size

   Exclude HIV, TB, and malaria to enable more discrimination among lower-burden pathogens

Qualitative criteria

1. **Support team proposes scores** using a scoring rubric
2. **Regional and disease experts review**

   At least 2 experts per region and at least one expert per disease
3. **Regional consultations finalize scores**

GBD: Global Burden of Diseases Project. 2019 values used throughout.

Example Pathogen Datasheet
Respiratory Syncytial Virus

World Health Organization

Indicative scores

Criteria	African	Americas	E. Med.	European	SE Asian	W. Pacific	Global
1 Annual deaths in children under 5	72,040 High (A)	4,077 Medium (A)	10,052 Low (A)	3,404 Very high (A)	27,492 High (A)	6,588 Very high (A)	123,790 High (A)
2 Annual deaths in people 5 and older	30,023 Low (A)	39,269 Low (A)	6,401 Very low (A)	36,190 Very low (A)	63,633 Low (A)	38,477 Very low (A)	214,704 Low (A)
3 Annual years lived with disability (all ages)	8,926 Very low (A)	5,354 Very low (A)	3,034 Very low (A)	4,249 Very low (A)	23,838 Very low (A)	4,922 Very low (A)	50,426 Very low (A)
4 Social and economic burden per case	Medium (B)	Medium (A)	Medium (A)	Medium (A)	Medium (A)	Medium (A)	Medium (A)
5 Disruption due to outbreaks	High (A)	High (A)	High (A)	High (A)	High (A)	High (A)	High (A)
6 Contribution to inequity	Medium (B)	Medium (A)	Medium (B)	Medium (B)	Medium (B)	Medium (B)	Medium (A)
7 Contribution to antimicrobial resistance	Medium (B)	Medium (A)	Medium (B)	Medium (A)	High (B)	High (A)	Medium (A)
8 Unmet needs for prevention & treatment	High (A)	High (A)	High (A)	High (A)	High (A)	High (A)	High (A)

Code	Quantitative: Criteria 1 - 3	Qualitative: Criteria 4 - 8
A	Burden data from GBD	Based on data from regional sources
B	Burden calculated by other studies	Scored based on sources from other regions or pathogens
C	Data not available	--

Example Regional Datasheet
AFR Social and economic burden per case

World Health Organization

Indicative scores

Region	Criterion	Data availability	Score				
			Very low	Low	Medium	High	Very high
African Region	**4 Social and economic burden per case**	A: Based on data from regional sources		Hookworm	Chikungunya virus Intestinal pathogenic *E. coli* (InPEC) Norovirus Schistosomes	Group A streptococcus Group B streptococcus Non-typhoidal *Salmonella* *Plasmodium falciparum* (malaria) *Shigella*	Herpes simplex types 1 and 2 HIV-1 *Mycobacterium leprae* (leprosy) *Mycobacterium tuberculosis* (TB)
		B: Score inferred based on sources from other regions		Influenza *Salmonella Paratyphi*	Extra-intestinal pathogenic *E. coli* (ExPEC) *Neisseria gonorrhoeae* Respiratory syncytial virus	Cytomegalovirus *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Staphylococcus aureus*	Leishmania

Collaborative approach to identify regional priorities

World Health Organization

Multi-criteria decision analysis (MCDA)

1. Identify pathogens for prioritization

Proposed scope is 24 pathogens with vaccines in the pipeline

2. Formulate criteria to assess against

e.g. “annual deaths in the region”, “contribution to inequity”, etc.

3. Score the pathogens against the criteria

Based on the best available regional data

4. Weight criteria according to importance

Regional and country stakeholders complete a 30-minute “**Preferences Survey**”

5. Rank pathogens based on weights and scores

Survey tool multiplies Score x Weight

Regional consultations

6. Deliberate on results, make recommendations

Regional consultations* consider the ranking and make their recommendations on priority pathogens

7. Synthesize Global list based on Regional views

PDVAC aggregates regional priorities into a global “short list”

SAGE reviews and endorses short list

Priority-setting by Regions and Countries

Supporting mechanism

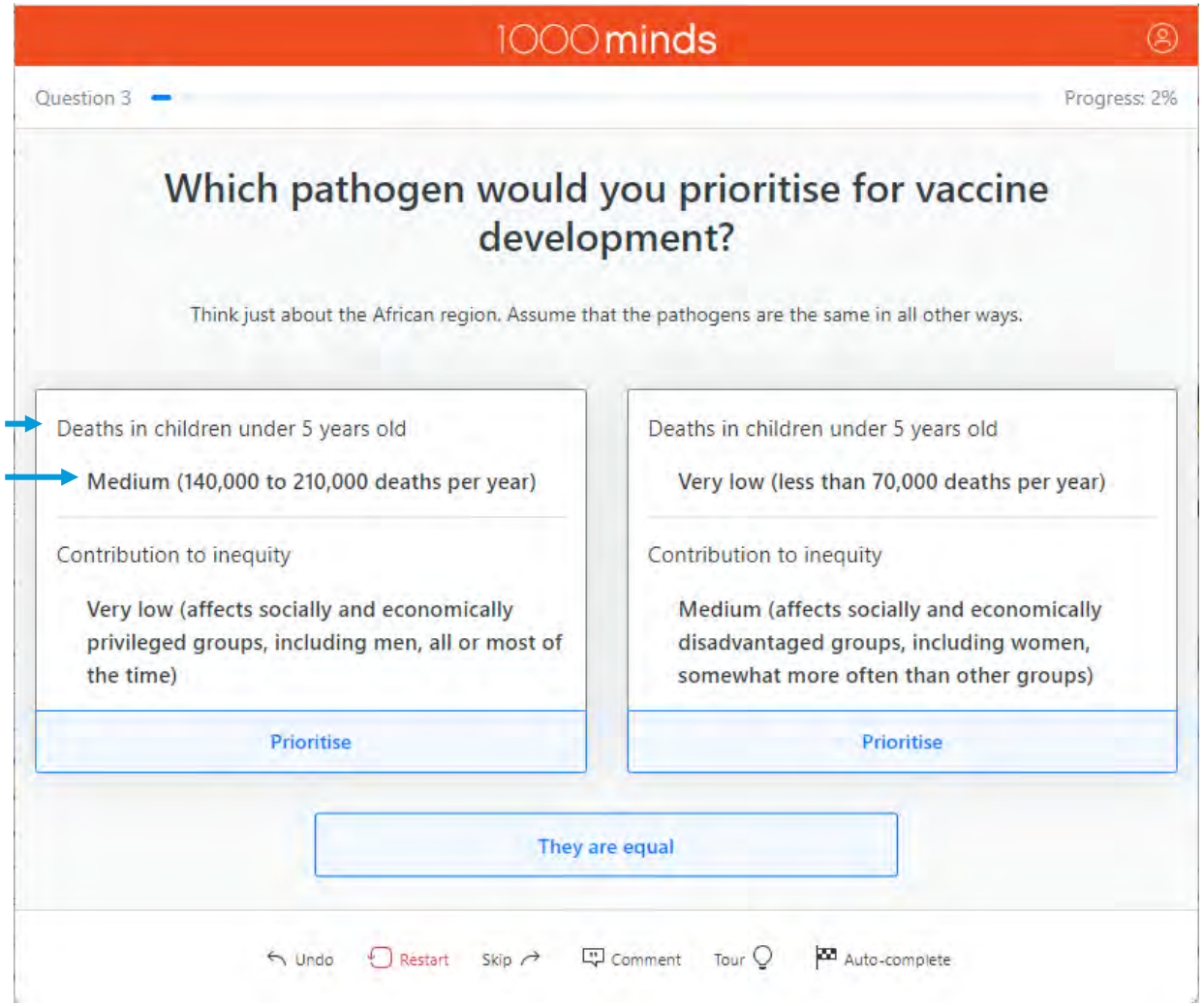
* Regional stakeholders will determine the timing and approach for their consultations. Only consultations conducted by February 2023 can be included the global summary presented to SAGE.

PDVAC: WHO Product Development Vaccines Advisory Committee, SAGE: WHO Strategic Advisory Group of Experts on Immunization

Preferences Survey

World Health Organization

Discrete choice approach

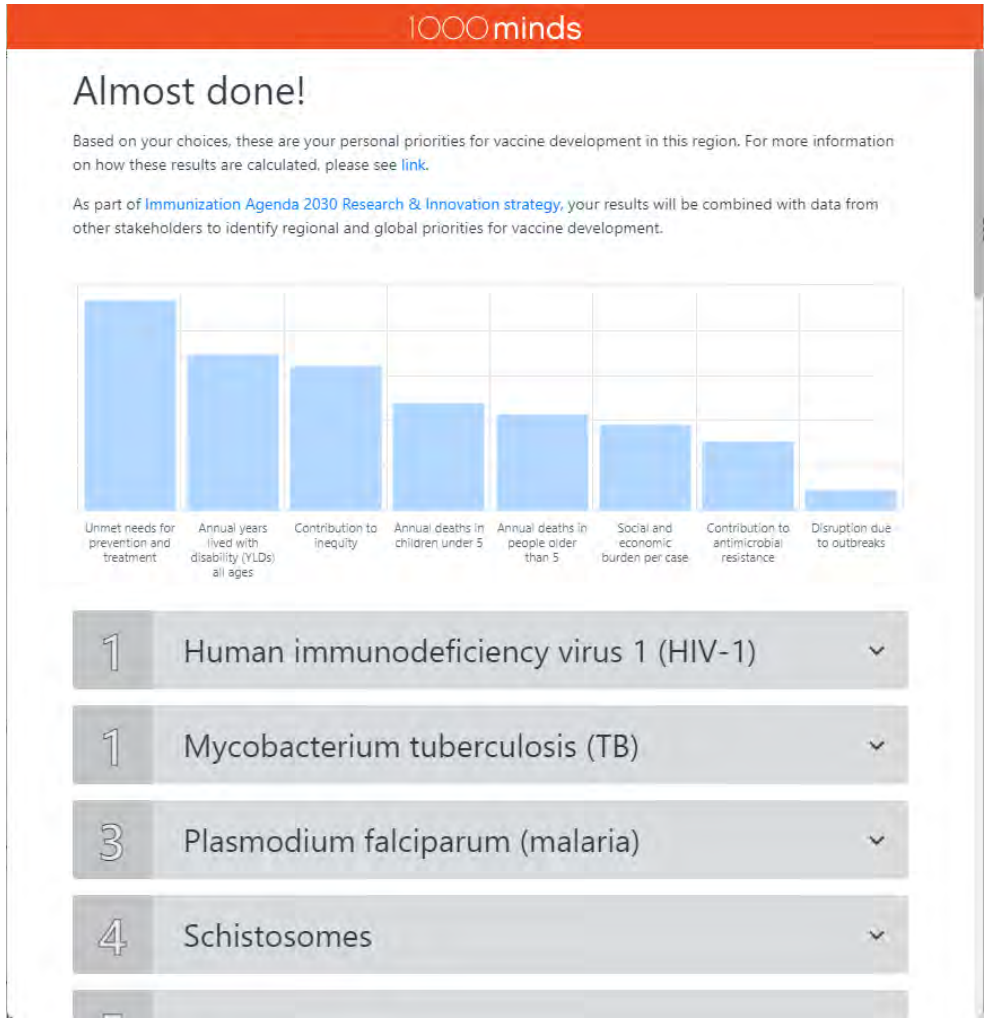


- Multi-criteria approach is designed for decisions with multiple trade-offs and diverse stakeholder perspectives
- Choice is between two hypothetical pathogens, reducing bias
- Criteria are clearly explained so non-experts can use the survey
- Translated into multiple languages to enable broader participation

Rank pathogens based on weights x scores

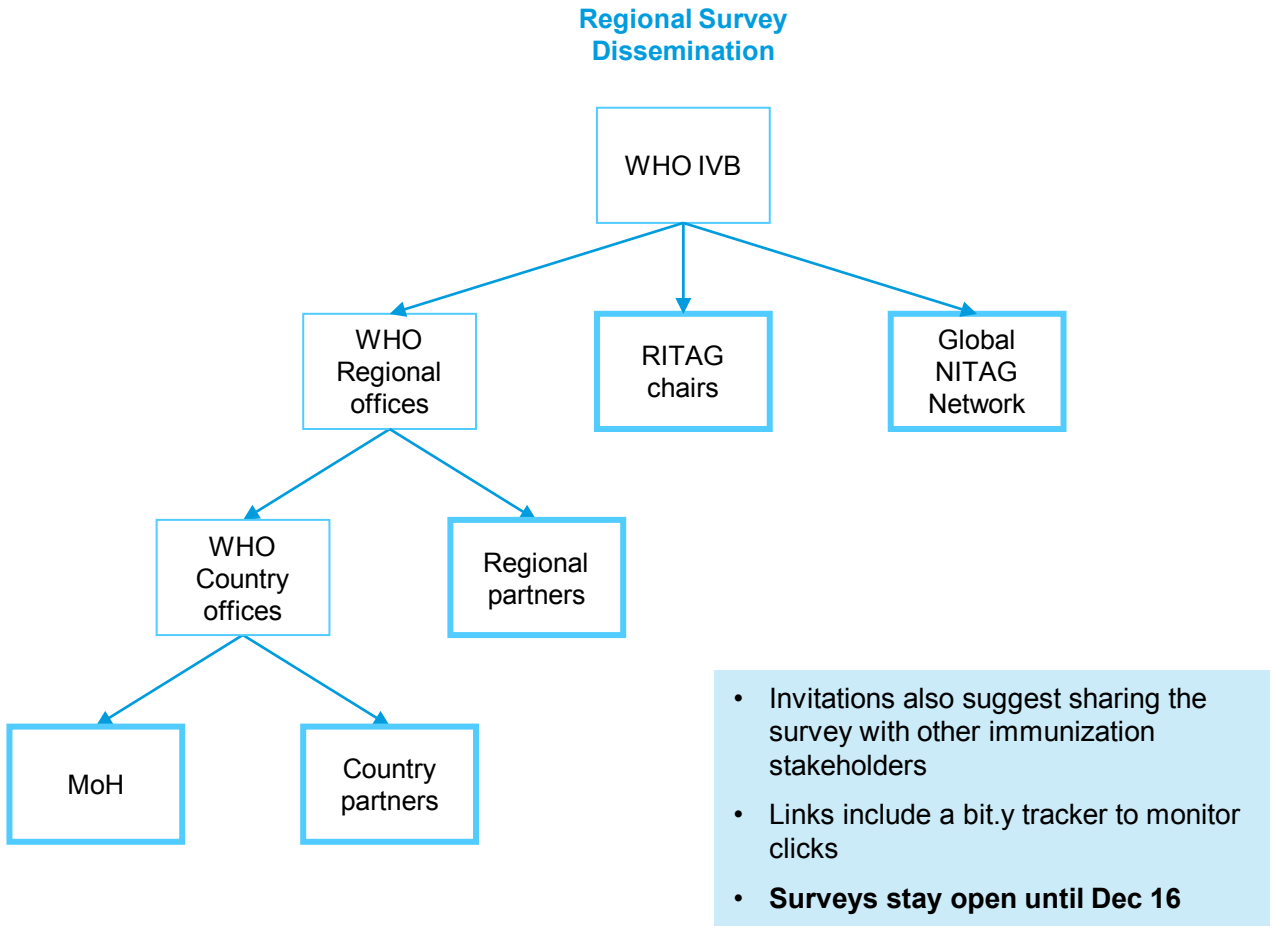
Criteria weights

Ranked priorities



- At the end of each survey, users will see:
  - What criteria they value most
  - Their personal priorities
- Data analysis will summarize priorities for each region
- Can include additional pathogens and updated scores

Survey Dissemination



- Invitations also suggest sharing the survey with other immunization stakeholders
- Links include a bit.y tracker to monitor clicks
- **Surveys stay open until Dec 16**

Starting November 22, regional surveys sent to:

1. Country experts via WHO Regional Advisors for Immunization: Benido Impouma, Daniel Salas, Quamrul Hasan, Siddhartha Datta, Yoshihiro Takashima, Sunil Bahl
2. RITAG Chairs: Helen Rees, Peter Figueroa, Ziad Memish, Adam Finn, Gagandeep Kang, Chris Morgan
3. Global NITAG Network (via Louise Henaff)
4. AFRO Science and Technology Cluster (via Moredreck Chibi)
5. PAVM and African CDC (via Nicaise Ndembi)

Global survey sent to:

1. WHO Immunization, Vaccines and Biologicals
2. IFPMA (via Paula Barbosa)
3. DCVMN (via Rajunder Suri)
4. PDVAC and SP7 WG Core representatives

Regional partners include RITAG members, UNICEF, programmatic partners. Country partners also include MoH, academics, etc.

Collaborative approach to identify regional priorities

World Health Organization

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Survey Responses

World Health Organization

as of 3 December

Region	Survey Languages	Clicks*	False Starts	Complete responses	Countries represented
African	English, French, Portuguese	133	11	14	12
Americas	English, Portuguese, Spanish	106	3	9	5
E. Med.	Arabic, English, French	201	22	23	10
Europe	English, French, Portuguese, Spanish, Russian	111	3	3	2
South-East Asian	English, Portuguese	106	18	10	5
W. Pacific	English, French (Chinese in preparation)	66	5	7	4
	Total (regions only)	**723**	**62**	**66**	**38**
Global	*English*	*144*	*17*	*21*	*11*

Observations

1. Many more clicks on survey links than complete responses
2. E. Med survey was announced at regional meeting, driving interest
3. Responses too few to make inferences

Note: No set target for number of responses, we will look at % of countries and % of population represented per region

* Clicks as of 4 December

Additional information

Can be used to understand stakeholder perspectives

Respondent Information

1. **Name and email address** for tracking only, personal identifiers will not be shared
2. **Country of work**
3. **Type of organization**
4. **Area of expertise**
5. **Years of experience**

Face Validity

1. **Perceptions**: Was the survey easy or difficult to understand?
2. **Criteria Weights**: Does the order of criteria in the bar chart seem correct to you?
3. **Ranking**: Does the order of pathogens listed seem reasonable to you?
4. **Open-ended:** In your results, what was surprising? What was as expected?

Respondents

as of 3 December

Self-descriptions

Organization	African	Americas	E. Med.	European	SE Asian	W. Pacific	Global	Total
Academic institution	6	5	7	1	3	4	2	**28**
Funding agency	0	0	0	0	0	1	1	**2**
Government	5	2	7	1	5	3	2	**25**
Healthcare provider	3	4	6	1	1	1	0	**16**
Non-governmental organisation	0	0	5	0	0	2	3	**10**
Pharmaceutical industry	0	0	1	1	0	0	10	**12**
Regulatory agency	0	0	1	0	0	0	0	**1**
UN Agency	1	1	4	0	1	1	3	**11**
OtherOrg	2	1	0	0	1	0	1	**5**
Expertise								
Disease epidemiology	8	4	12	1	3	4	6	**38**
Economics and health financing	0	1	3	0	0	0	2	**6**
Healthcare	5	6	13	0	4	3	2	**33**
Health policy	5	3	7	3	3	3	5	**29**
Regulatory affairs	0	0	1	0	1	0	2	**4**
Vaccine research and development	8	3	3	2	7	4	17	**44**
OtherExpertise	2	1	3	2	0	1	2	**11**
Experience								
Up to 10 years	0	2	1	0	3	0	2	**8**
11 - 20 years	6	2	9	0	1	0	7	**25**
21 - 30 years	3	2	6	2	2	1	6	**22**
More than 30 years	5	3	7	1	4	6	6	**32**

Notes

1. Will enable segmentation by organization type, expertise, and years of experience
2. So far, few funders, economists, or regulators, many R&D

   Note: Respondents could pick multiple organizations and areas of expertise

Next step will be regional consultation to agree on priorities

Multi-criteria decision analysis (MCDA)

Regional consultations

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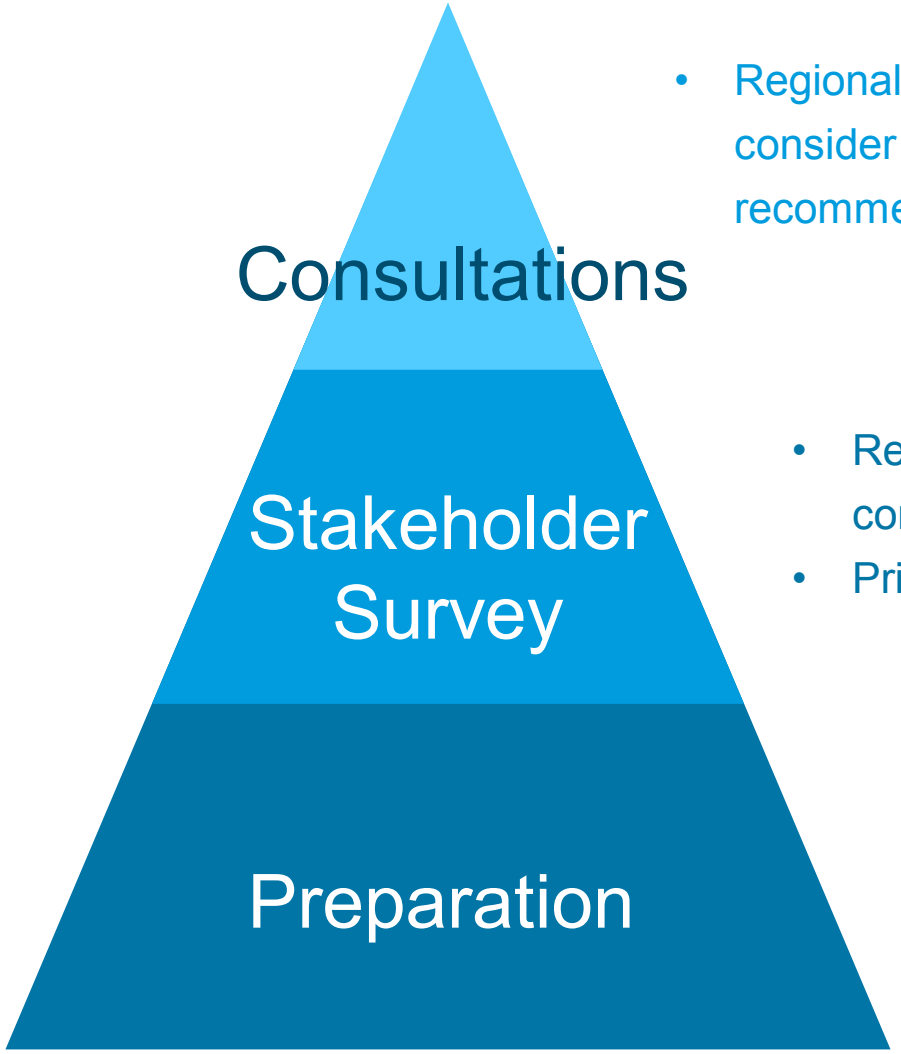
Building up to regional consultations



- Regional consultations consider survey results and recommend priorities

- Regional and country stakeholders complete a “Preferences Survey”
- Priorities analysed region-by-region

- Landscaping
- Define method
- Prepare tools (including pathogen scoring)
- Engage stakeholders

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PARTNERSHIPS FOR AFRICAN VACCINE MANUFACTURING (PAVM)

CATALYTIC FUNDING IN PLATFORMS TECHS, WHO AND OTHER mRNA Hubs

Dr Nicaise Ndembi

Head, Science Office

Africa Centres for Disease Control and Prevention

05 December 2022

The AU has set a goal to ensure 60% of the vaccines administered in Africa are locally manufactured and mandated the PAVM to oversee this task

Context

The African Union calls for a **New Public Health Order** aimed at safeguarding the health and economic security of the continent


THE LANCET
Global Health

COMMENT | VOLUME 5, ISSUE 11, E1064–E1065, NOVEMBER 01, 2017

A new public health order for Africa's health security

John Nkengasong • Benjamin Djoudalbaye • Olawale Maiyegun

Open Access • Published: November, 2017 • DOI: https://doi.org/10.1016/S2214-109X(17)30363-7

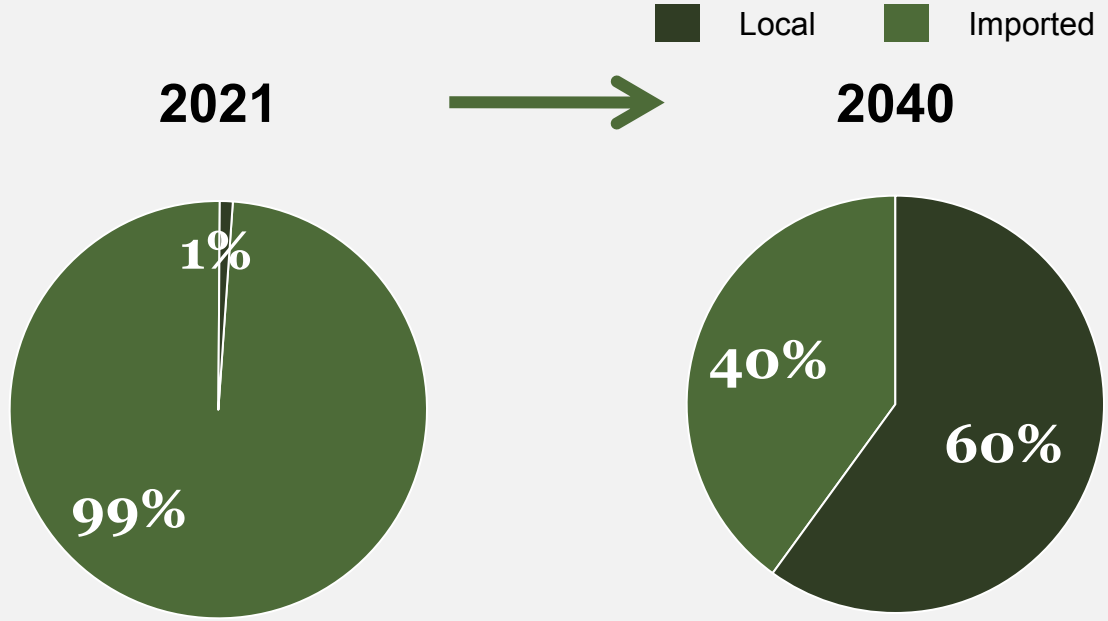
References

Article Info

On July 3, 2017, African heads of state and government issued a declaration and committed to accelerating implementation of the 2005 International Health Regulations (IHR)[1] and tasked the Africa Centres for Disease Control and Prevention (Africa CDC), the African Union Commission (AUC), and WHO with supporting the venture.[1]

The first pillar of the New Public Health Order is **expanding manufacturing of vaccines**, diagnostics and therapeutics[1]

Ambition to be enabled by the Framework for Action



The African Union has set a goal to **increase vaccine manufacturing on the African continent to meet 60% of the demand by 2040** and mandated the Partnerships for African Vaccine Manufacturing (PAVM) to **develop a Framework for Action to execute this**

1. Other pillars include: Strengthened public health institutions, Strengthened public health workforce, Respectful, action-oriented partnerships

PAVM developed a continental strategy that outlines diseases, technology platforms and manufacturing value chain steps that Africa needs to prioritise

Vaccine exists Vaccine does not yet exist

Potential disease prioritization

Prioritized 22 diseases…

Legacy

Diphtheria	Hepatitis B	Measles	Meningococcal
Whooping Cough	Yellow fever	Typhoid fever	
Tetanus	Tuberculosis	Cholera	

Expanding

HPV	Pneumococcal
HIV	COVID-19
Malaria	Rotavirus

Outbreak

Ebola	Influenza
Chikungunya	Lassa fever
Rift valley fever	Disease X

Technology focus

… requiring a breadth of technology platforms…

Traditional → Innovative

Live attenuated	**Inactivated virus**	**Subunit**	**Virus-like particle**	**Viral vector**	**RNA/DNA**

Potential value chain focus

… along the different steps of the value chain

Fill & Finish (F&F)

Fill & finish for all priority vaccines, enabling achievement of local production targets.

Drug Substance (DS)

Expand drug substance mostly in established platforms

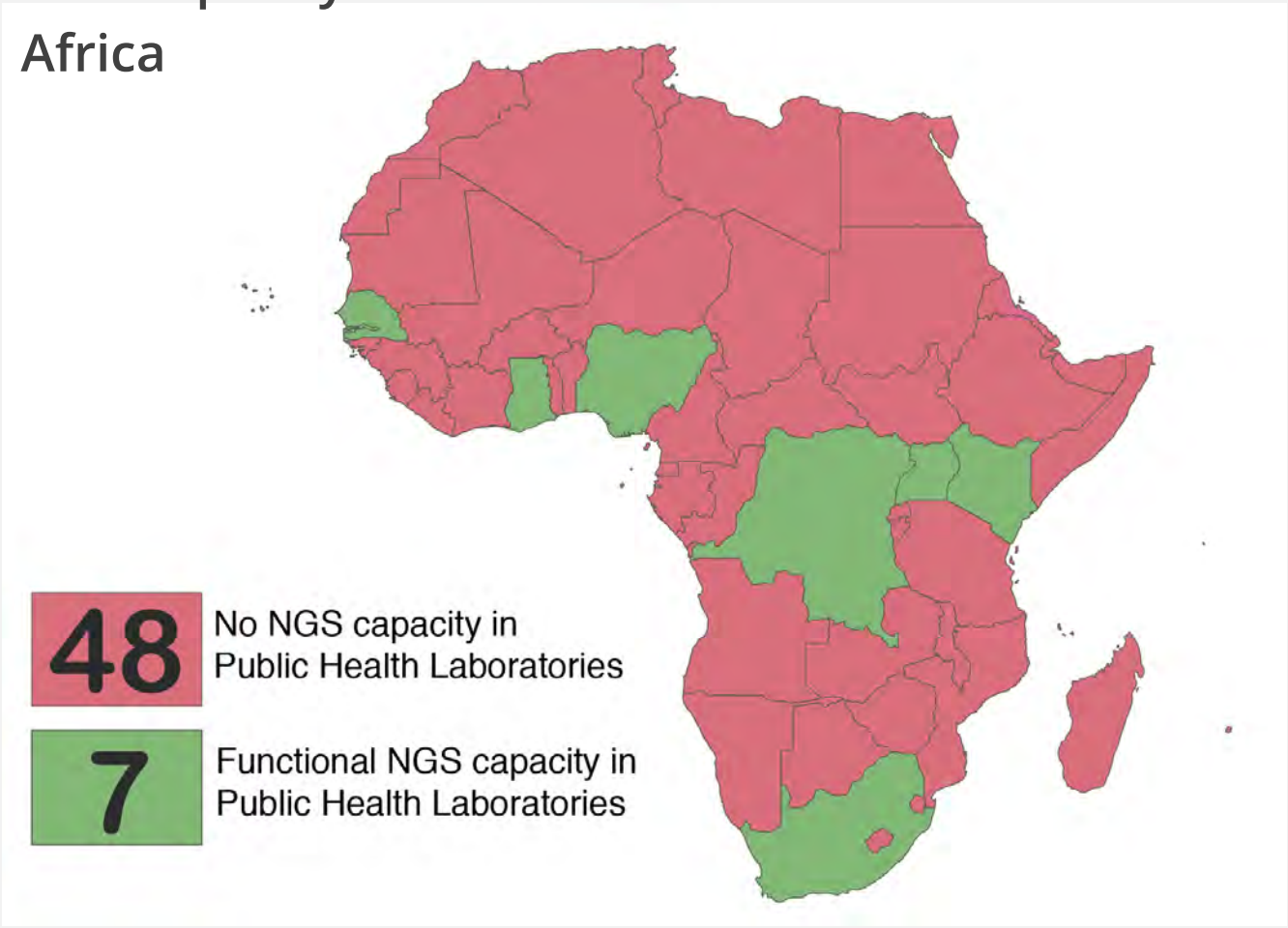
R&D

Expand R&D activities to develop new vaccines for Africa, support more efficient manufacturing and improve vaccine characteristics

PUBLIC HEALTH NGS CAPACITY IN AFRICA | THE NEED

Pre-COVID (2018/19)

NGS capacity in Public Health Institutions in Africa

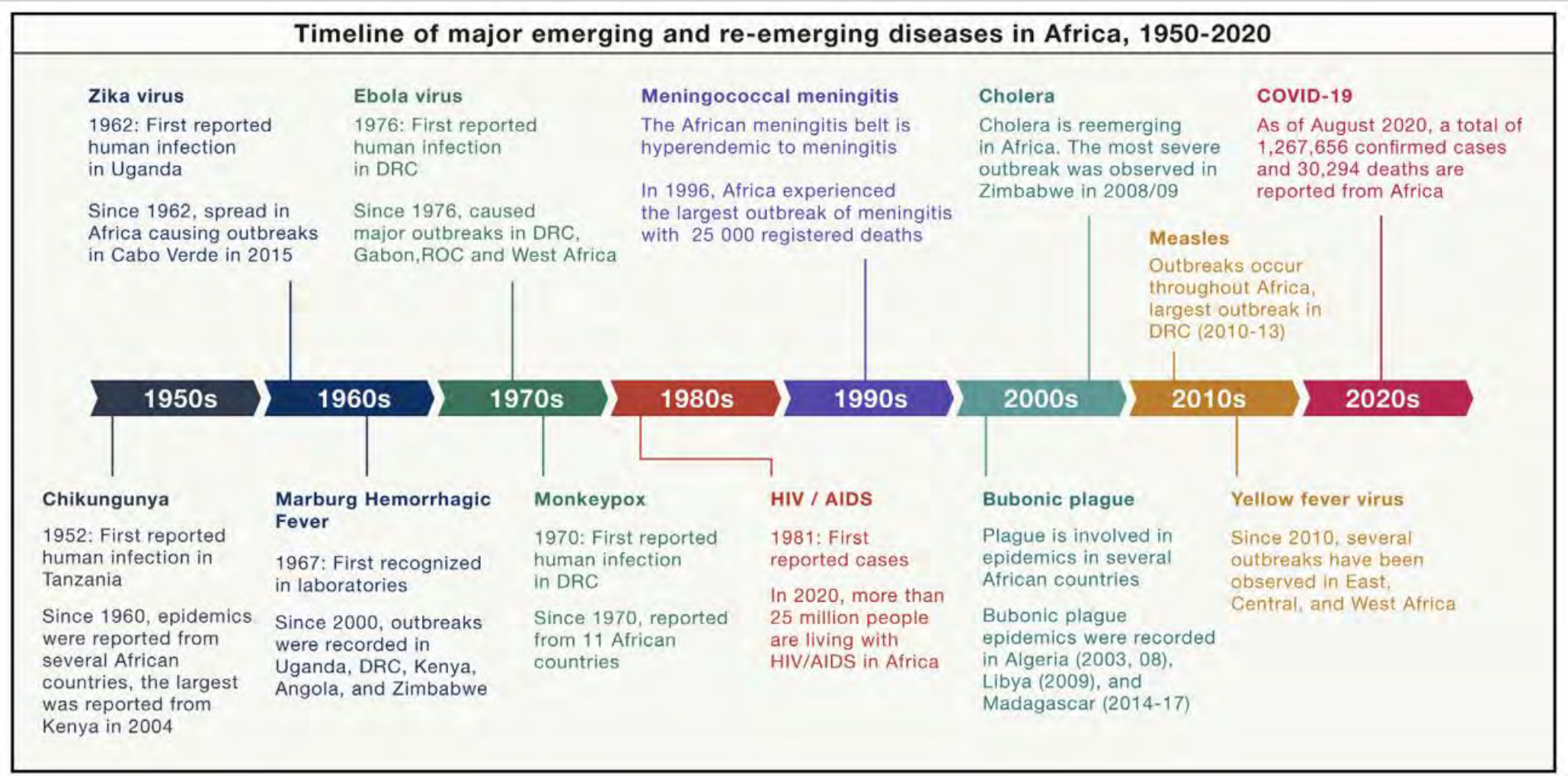


- Limited sequencing and data infrastructure
- Lack of skilled workforce in laboratory and bioinformatics
- Lack of policies and frameworks
- No coordination of sequencing activities
- Supply chain, cost & regulatory challenges

African Union

AFRICA CDC

PATHOGEN GENOMICS CAPACITY IN AFRICA | THE NEED



PUBLIC HEALTH NGS CAPACITY IN AFRICA | THE RESPONSE

In partnership with and support from :

ASLM
AFRICAN SOCIETY FOR LABORATORY MEDICINE

BILL & MELINDA GATES foundation

illumina

CDC

Oxford NANOPORE Technologies

mastercard foundation

Microsoft

1. Strengthening Africa CDC Institute of Pathogen Genomics

- Leadership, coordination, and resource mobilization
- Enabling mechanisms, policies and guidelines
- Pathogen genomics community of practice (PathoGENCoP) and technical working groups

2. African Pathogen Genomics and Bioinformatics Network

- Building a continent-wide functional and operational network
- Capacity building with NGS & data infrastructure in at aleast 20 NPHIs

3. Data architecture and systems

- Data analyses, interpretations, utilization and sharing

4. NGS Academy

- Workforce development in genomics, bioinformatics, and genomic epidemiology

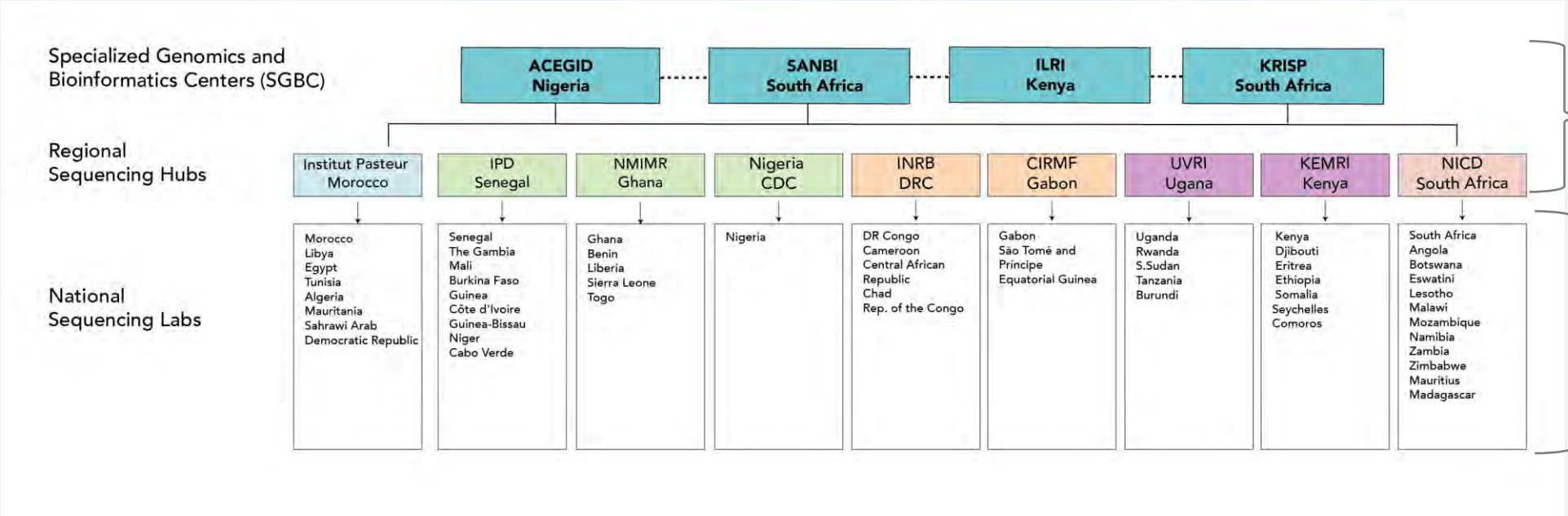
5. Implementation of high-impact genomic-use cases

- Use-cases that will have a high impact on major infectious diseases in Africa

African Union

AFRICA CDC

Africa CDC and WHO AFRO COVID-19 Sequencing Network

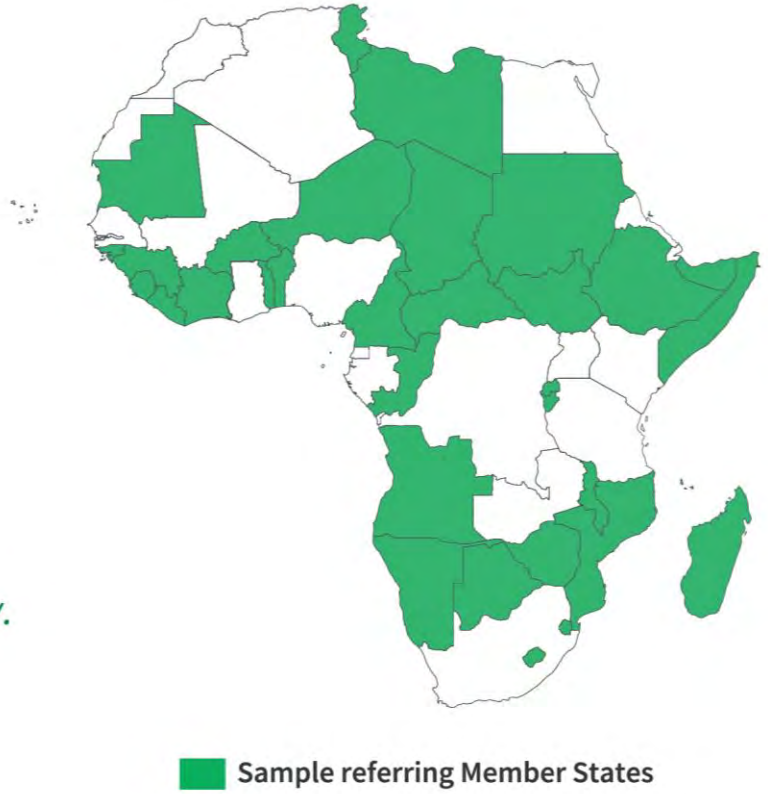


AFRICA PGI PROGRESS| SAMPLE REFERRAL FOR SEQUENCING

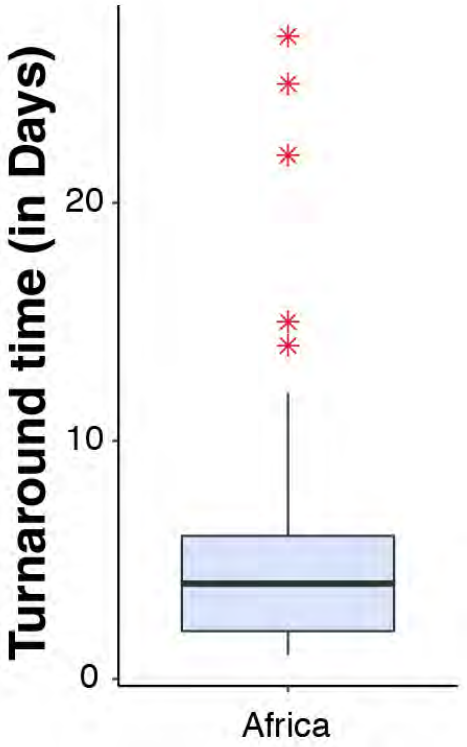
36 Member States
referred SARS-CoV-2 specimens for sequencing

33,302
SARS-CoV-2 specimens referred (124% of our target)

4 days
Average number of days from sample pick up to delivery. It ranges from 1 to 15 days.



4 days
[IQR:2-6 days]



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African Union
AFRICA CDC

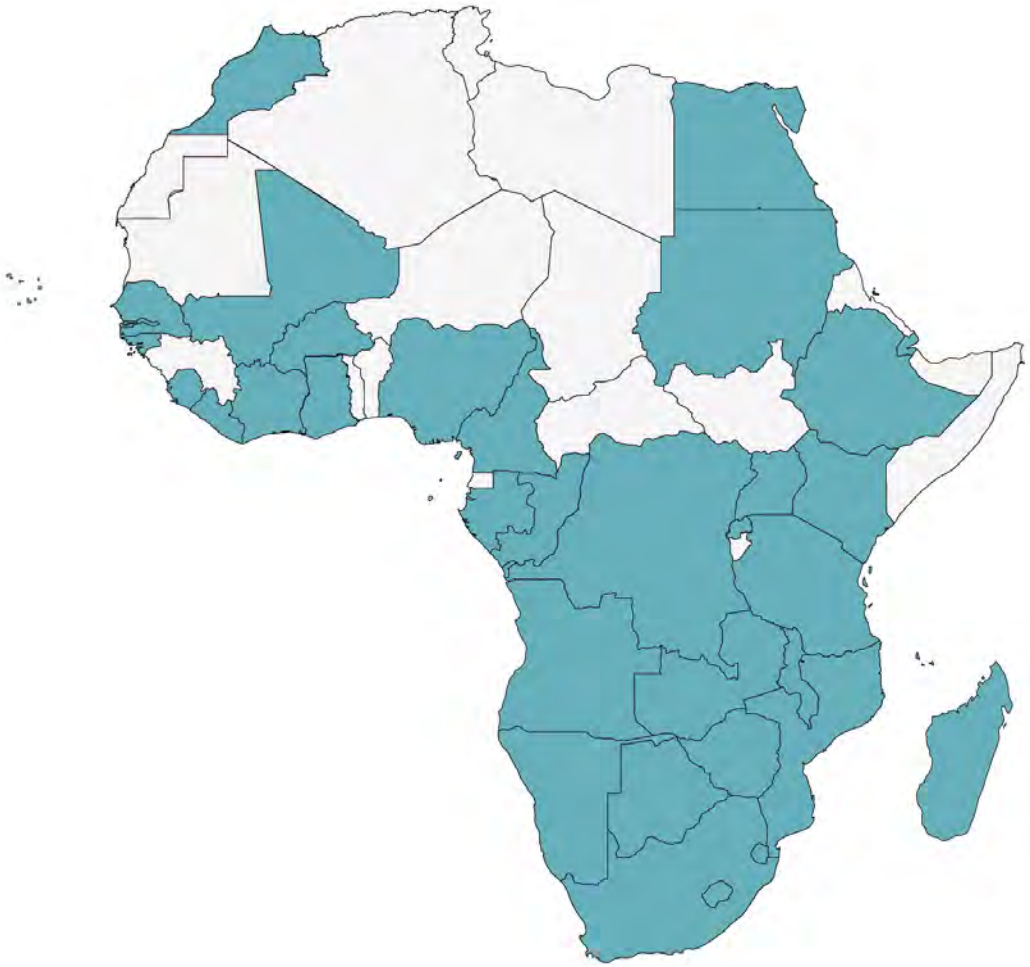
AFRICA PGI PROGRESS| SEQUENCING CAPACITY

+$8M **sub-award**
Support sample collection, personnel, supplies, ...

49 **Sequencing equipment**
8 GridION, 5 NextSeq200, 15 MiSeq/MiniSeq/iSeq, and 14 Mk1b/c

10 **NGS STAR 96 - Automation**
Regional sequencing hub automation

218K **sequencing reagents**
For >218 genomes



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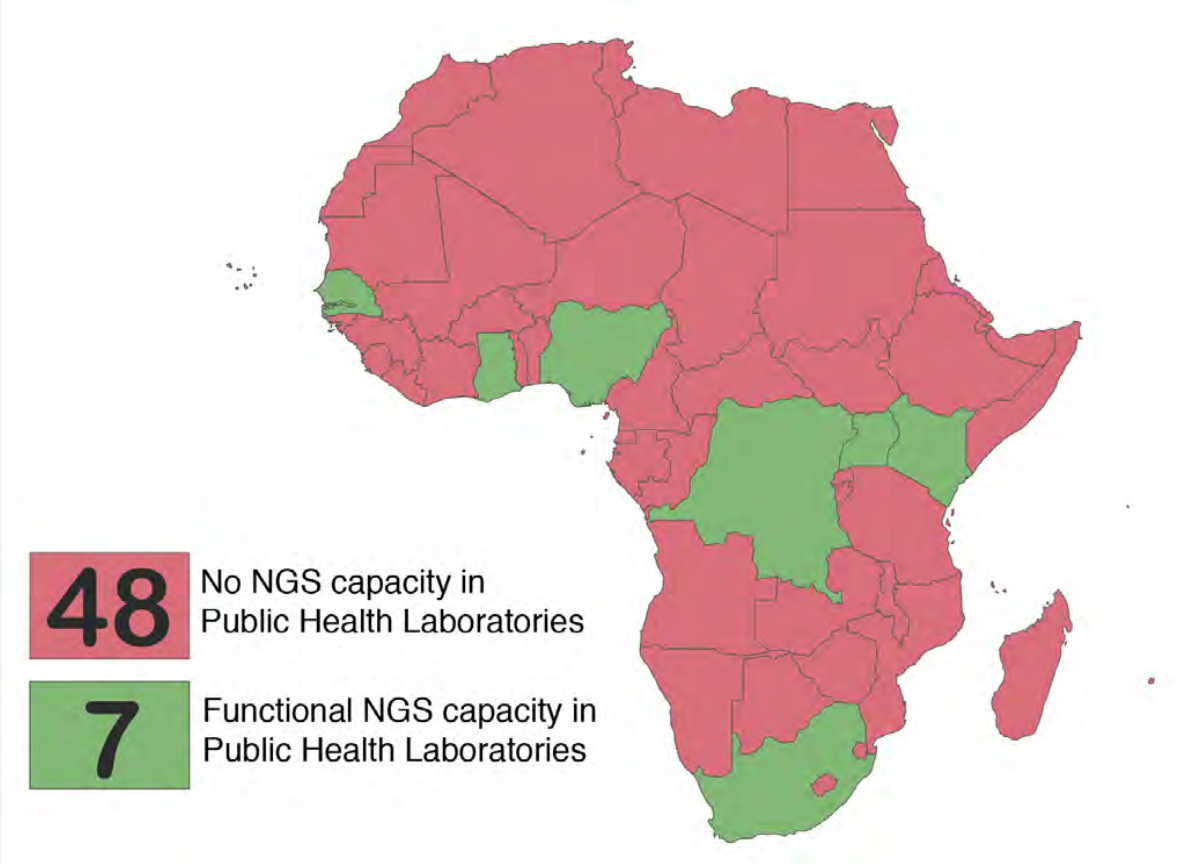
African Union

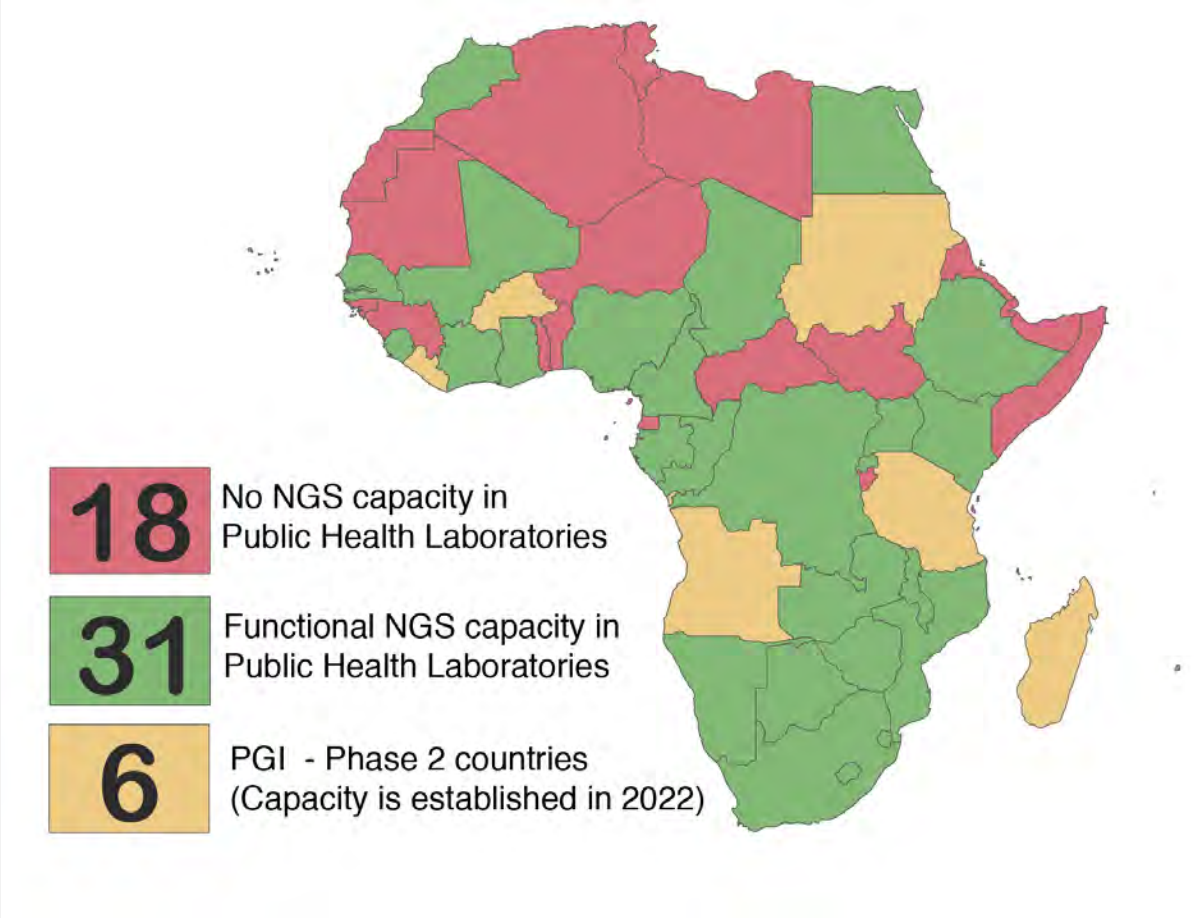
AFRICA CDC

AFRICA PGI PROGRESS| SEQUENCING CAPACITY

2018/19



2022 (as of August)



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African Union
AFRICA CDC

African Union

AFRICA CDC
Centres for Disease Control and Prevention
Safeguarding Africa's Health

THANK YOU

LEARN MORE AT

africacdc.org/covid-19

Safeguarding Africa's Health

Technology Transfer to Promote Regional Health Security

role of catalytic funding

PDVAC December 2022

World Health Organization

mRNA vaccine Technology transfer to improve long-term LMIC health security

Why mRNA ?

- Speed, adaptability, re-useability

Challenge:

- Know-how limited to a few private companies

Objective 1
Expand capabilities of existing manufacturers in LMICs

Objective 2
Establish sustainable capacity in regions with no significant capacity

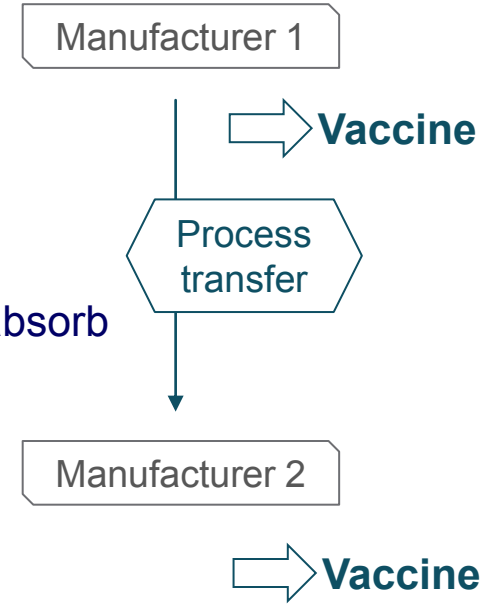
2 potential approaches for technology transfer to increasing capacity and supply

1

Bilateral technology transfer

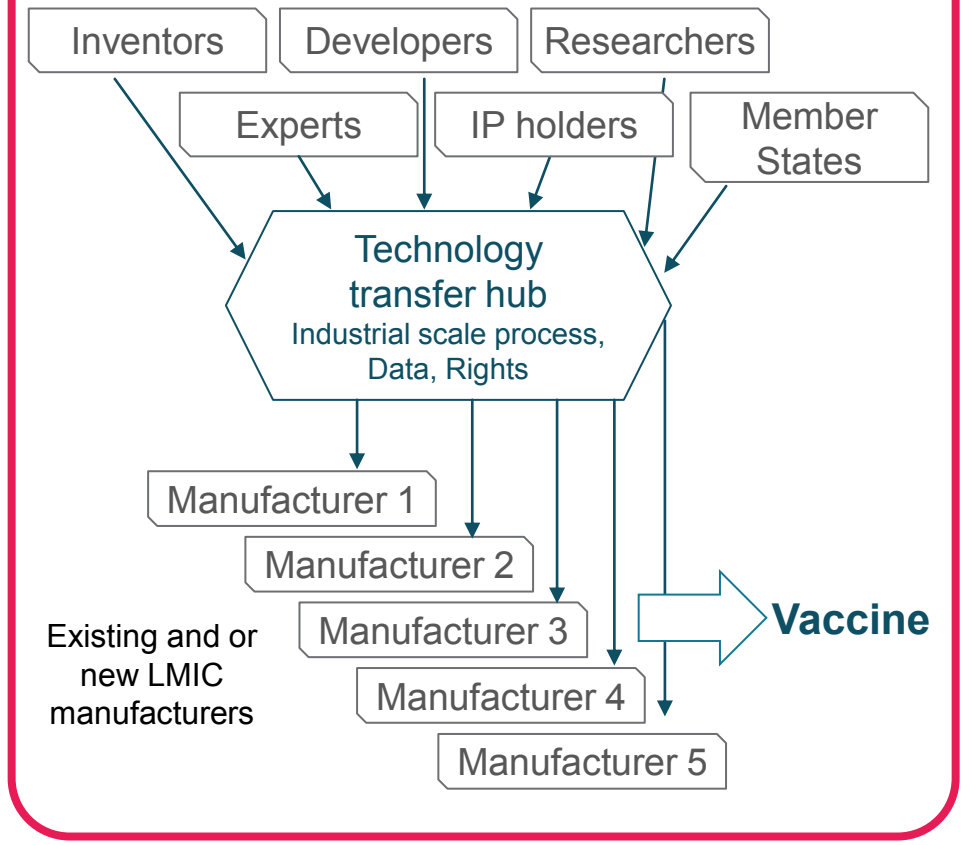
Need win-win:

- Constraints
- Capacity to absorb



2

Multilateral technology transfer technology hub model - including and beyond Covid



Chronology of the mRNA Tech Transfer Programme

Apr. 2021

Call for EOI to contribute by providing technology or hosting a hub, or both

President of France, President of South Africa, WHO DG **announce the establishment of the mRNA Technology Transfer Hub in South Africa**

June 2021

Sep. 2021

WHO/PAHO **announce selection** of Argentina & Brazil as **spokes in Latin America**

Call for EOI for **additional spokes**

Call for EOI to establish a **biomanufacturing workforce training hub**

Nov. 2021

Feb. 2022

WHO announces **15 spokes**

WHO announces the establishment of a **global biomanufacturing training hub in the Republic of Korea**

Intro training on mRNA technology initiates at the mRNA TT hub in South Africa

Mar. 2022

Spokes selected by PDVAC

- AFRO
  - Kenya
  - Nigeria
  - Senegal
  - South Africa
- EMRO
  - Egypt
  - Pakistan
  - Tunisia
- EURO
  - Serbia
  - Ukraine
- PAHO
  - Argentina
  - Brazil
- SEARO
  - Bangladesh
  - Indonesia
  - India
- WPRO
  - Vietnam

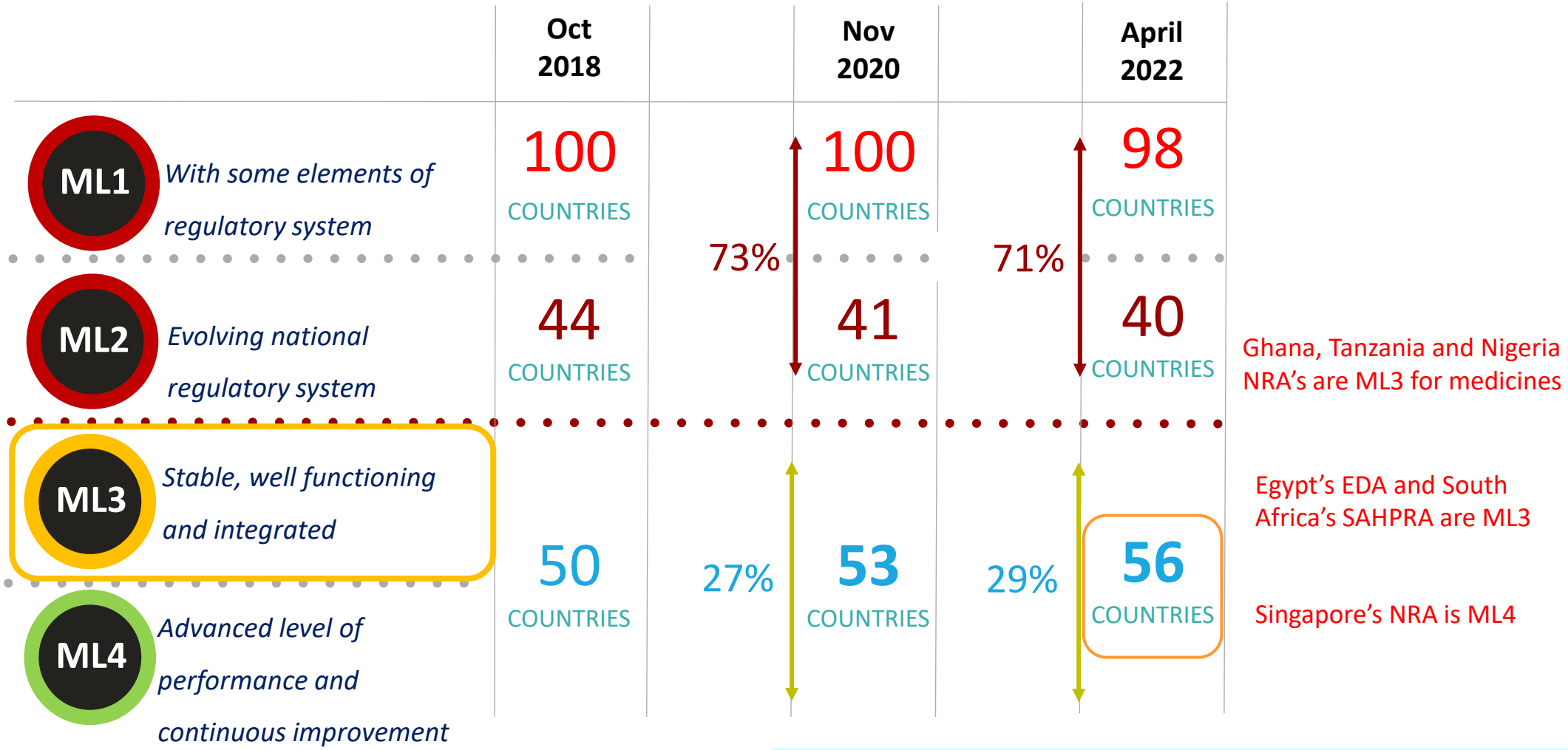
Beyond know-how transfer: The Challenges…

- Access to know-how
- Human resource capacity to absorb technology
- Regulatory agency capacity to approve product
- Business plan: CAPEX, OPEX, cost-of-goods <-> size of facility
- Sustainability between pandemics – what else to make: R&D
- Coherent regional plan: which country making what products
- Distributed Supply chain

Biomanufacturing Workforce Training Initiative

- **To address** the **shortage of skilled workforce** through training in Biomanufacturing
- **Generic training** (not product-specific, hands-on)
- The **Republic of Korea** to host the Global Training hub
  - Introductory training in July 2022-117 trainees (16 from spokes)
  - GxP training in Nov 2022 – 200 trainees (25 from spokes)
  - Korean Global Bio campus fully operational in 2026
- Link to **WHO Academy** to ensure appropriate curriculum/training

Regulatory system strengthening
Global status of national regulatory systems, April 2022



ML3 **GOAL of WHA Resolution 67.20**

ML= *(regulatory system) maturity level*

Vaccines developed in countries with weak regulatory systems, i.e., ML1/ML2, are not eligible for WHO EUL or Prequalification

Sustainability: What else can technology recipients make with mRNA Establishing LMIC R&D Network and Collaborations

mRNA vaccine developer	Country	Animal studies partners	Labs partners	Clinical sites	Disease Areas interests (Hypothetical)	R&D gaps (Hypothetical)	Resources to help address R&D gaps (Exploratory)
Spoke 1	Country 1	Univ 1, 2, ,,,	PH lab 1, 2, ,,,	Health Center 1, ,,,	**Dengue**	Access to NHP	Finding partners through the Network
Spoke 2	Country 2	Univ 1, 2, ,,,	PH lab 1, 2, ,,,	Health Center 1, ,,,	**Dengue, Zika**	FTO on Zika	MPP IP Landscape
Spoke 3	Country 3	Univ 1, 2, ,,,	PH lab 1, 2, ,,,	Health Center 1, ,,,	**HIV, Malaria, TB**	Clinical Development Plan	WHO R&D Roadmap and PPC
Spoke 4	Country 4	Univ 1, 2, ,,,	PH lab 1, 2, ,,,	Health Center 1, ,,,	**Rabies, Leishmaniasis**	Run Immuno Study	Small research grant

mRNA R&D network meeting to be held in Cape Town on 17-21 April 2023

World Health Organization

mRNA vaccine research meeting: Capetown April 19-21

- Review of mRNA research questions – what do we know about how changes to composition (lipids, nucleotides, capping, sequence etc) affect immunogenicity and reactogenicity.
- Review of potential infectious disease targets: why do we think mRNA approach will succeed
  - Probability of technical and regulatory success (PTRS)
  - Probability of policy development and procurement (PPDP)
  - Probability of population acceptance and use (PPAU)
- TB, HIV, malaria, RSV, flu, STIs, leishmania, NTDs, flavivirus, filoviruses,… etc
- RFP and catalytic funding from WHO to LMICS for research

World Health Organization

Role of Catalytic funding

- Access to know-how:
  - Funds to the hub: establish technology, SOPs, clinical batches, clinical data, tech transfer, training. ~90 million USD.
    - 15 countries receive know-how to manufacture vaccines
  - Access to equipment (novel factory-in-a-box) for LMICs
  - Support Research on novel approaches (lipids, nucleotides)

- Catalytic – if the country doesn't have 'skin in the game' these programmes tend to die….

World Health Organization

MEETING OF THE PRODUCT DEVELOPMENT FOR VACCINES ADVISORY COMMITTEE (PDVAC)

Vaccine Investment Strategy (VIS) 2024

Marta Tufet, Head of Policy
5th December 2022

gavi.org

Gavi was launched to create equal access to vaccines

High-income countries in 2014 **100%**

High-income countries in 2000 **73%**

3% Low-income countries in 2000

100% Low-income countries in 2014

% countries with national *Haemophilus influenzae* type b (Hib) vaccine programmes

Note: Only countries with universal national programmes are included. World Bank country classification has been applied to the whole time series. Source: International Vaccine Access Center (IVAC).

Today, Gavi-supported countries have higher coverage against Hib, pneumococcus and rotavirus than the rest of the world.

Gavi The Vaccine Alliance

Healthy communities, healthy economies

Gavi-supported countries, 2000–2021

keep people healthy

>981 million

children vaccinated

vaccines save lives

>16.2 million

future deaths prevented

stronger economies

>185.3 billion US$

generated in economic benefits (2000–2021)

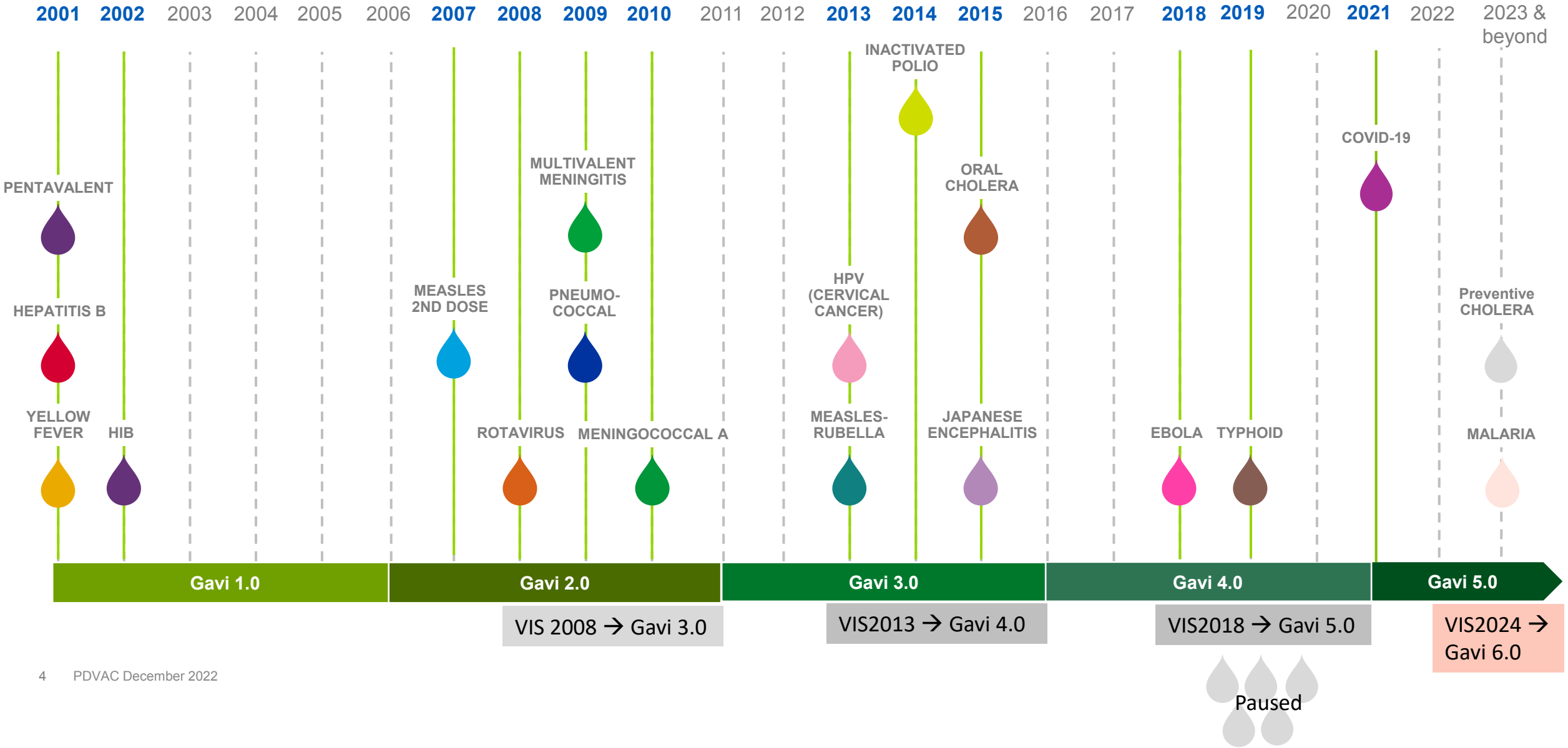
sustainable future

16 countries

transitioned out of Gavi support

Gavi The Vaccine Alliance

Accelerating access: Gavi's vaccine portfolio



What is the Vaccine Investment Strategy?

Gavi's evidence-based approach to identifying new immunisation investment priorities

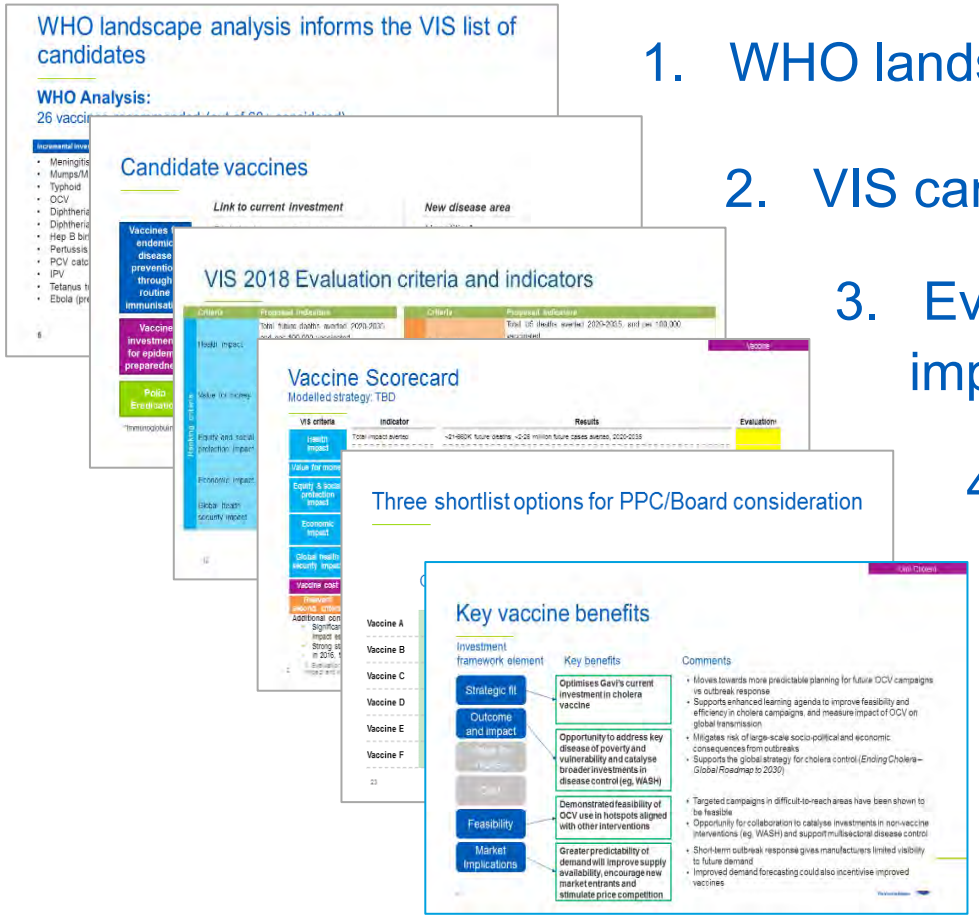
- Conducted every 5 years
- Transparent methodology
- Consultations and independent expert advice
- Analytical review of evidence and modelling

→ Strategic investment-decision making (rather than fist come first served)

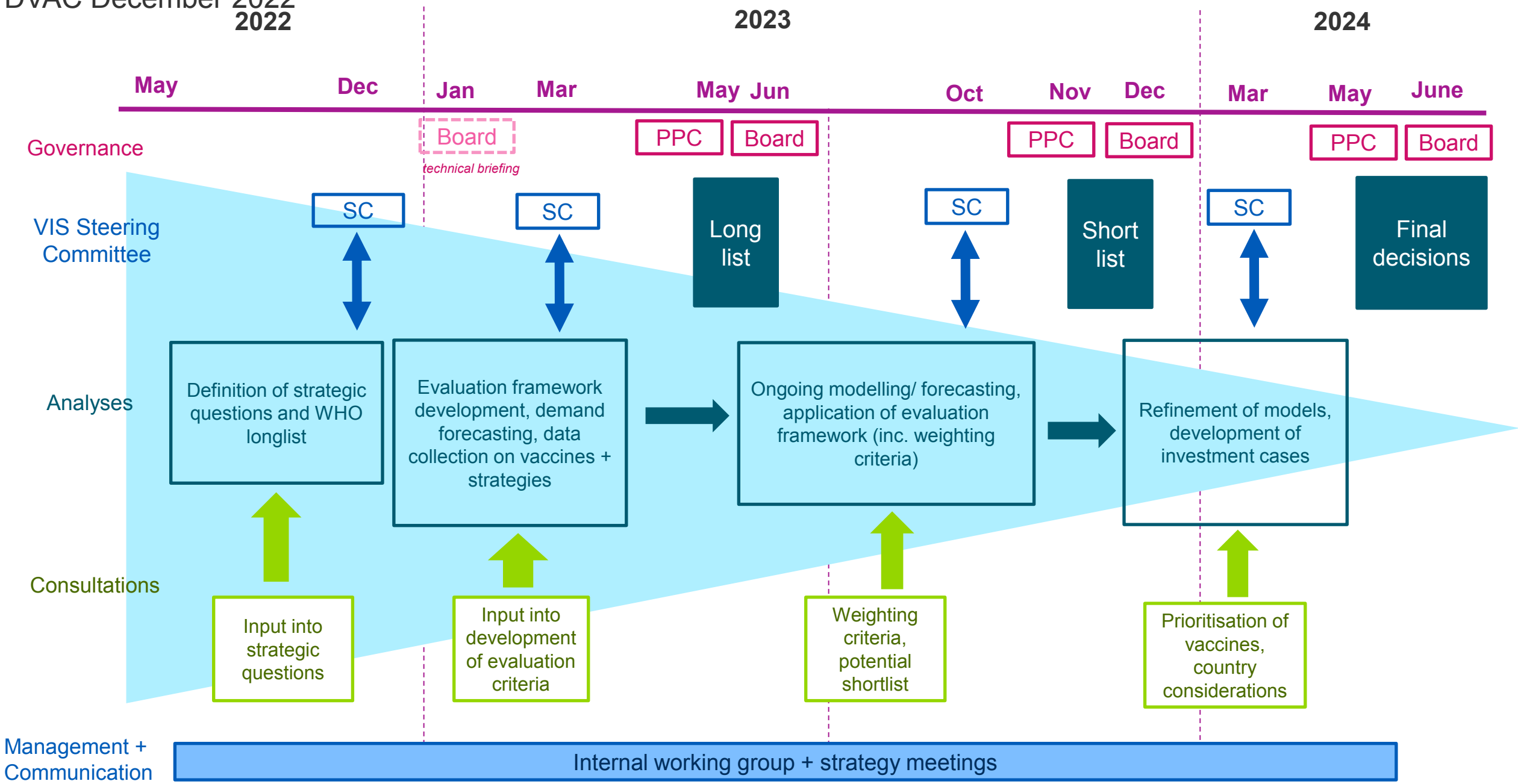
→ Predictability of Gavi programmes for long-term planning by governments, industry and donors

→ Feeds into development of Gavi strategy (and replenishment)

Main process steps for VIS



1. WHO landscape analysis
2. VIS candidate list
3. Evaluation framework (e.g., Value for money, health impact, equity impact)
4. Vaccine analyses (e.g., Financial implications, programmatic feasibility/design
5. Short list
6. Investment cases and decision


2022
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technical briefing
PPC
Board
PPC
Board
PPC
Board
VIS Steering Committee
SC
SC
Long list
SC
Short list
SC
Final decisions
Analyses
Definition of strategic questions and WHO longlist
Evaluation framework development, demand forecasting, data collection on vaccines + strategies
Ongoing modelling/ forecasting, application of evaluation framework (inc. weighting criteria)
Refinement of models, development of investment cases
Consultations
Input into strategic questions
Input into development of evaluation criteria
Weighting criteria, potential shortlist
Prioritisation of vaccines, country considerations
Management + Communication
Internal working group + strategy meetings

Evaluation framework from VIS 2018

	Criteria	Indicators
Ranking criteria:	Health impact	Total future deaths averted 2020-2035, and per 100,000 vaccinated Total future cases averted 2020-2035, and per 100,000 vaccinated
	Value for money	Vaccine procurement cost per death averted Vaccine procurement cost per case averted
	Equity and social protection impact	Disproportionate impact of disease on vulnerable groups Special benefits of vaccination for women and girls
	Economic impact	Direct medical cost averted Indirect cost averted
	Global health security impact	Epidemic potential of disease Impact of vaccination on antimicrobial resistance (AMR)

3

	Criteria	Indicators
Secondary criteria:	Other impact	Total U5 deaths averted 2020-2035, and per 100,000 vaccinated Total DALYs averted 2020-2035, and per 100,000 vaccinated Vaccine procurement cost per DALY averted
	Gavi comparative advantage	Degree of vaccine market challenges Potential for Gavi support to catalyse additional investment
	Implementation feasibility	Ease of supply chain integration Need for health care worker behaviour change Feasibility of vaccination time point Acceptability in target population Long-term financial implications
	Alternate interventions	Optimal use of current and future alternative interventions (prevention and treatment)
	Broader health system benefits	*No specific indicator – evaluated case-by-case*
Financial implications:	Vaccine cost	Total procurement cost to Gavi and countries, 2020-2035
	Operational cost	Incremental in-country operational costs per vaccinated person
	Additional implementation costs	Additional costs for introduction

Common knowledge gaps for decision-making

The components of the overall analysis require specific information:

Demand Forecasting

- Burden of disease
- Target population
- (Provisional) vaccination strategy including schedule/dosing
- Delivery strategy
- Country introduction years (based on PQ)
- Coverage estimates

Impact Modelling

Additionally:

- Efficacy
- Duration of protection
- Disease transmission
- Economic impact of disease estimates

Qualitative analyses

- Epidemic potential
- Impact on AMR
- Implementation feasibility
- Vaccination policy

Determine investment type: traditional programme, stockpile, learning agenda, according to analysis

Gavi The Vaccine Alliance

VIS 2024 Steering Committee

Strong technical and/or scientific expertise to provide guidance to the Secretariat on:

- Strategic questions, methodology and process for the VIS
- Evaluation framework, criteria, and weightings – informed by internal and other external consultations
- Assumptions and outputs of analyses and models for each disease/vaccine
- Synthesis of analytical outputs and stakeholder consultations

Composition:

- 20 individuals including Chair
- Selected independent members from open competitive call for expressions of interest
- Appointed *ex officio* members representing Alliance stakeholders and partners – Observers

First meeting 20th December 2022

Gavi The Vaccine Alliance

Thank you

Realising the potential of correlates of protection for vaccine development and licensure

PDVAC 5th Dec 2022

Debbie King, Research Lead Vaccines

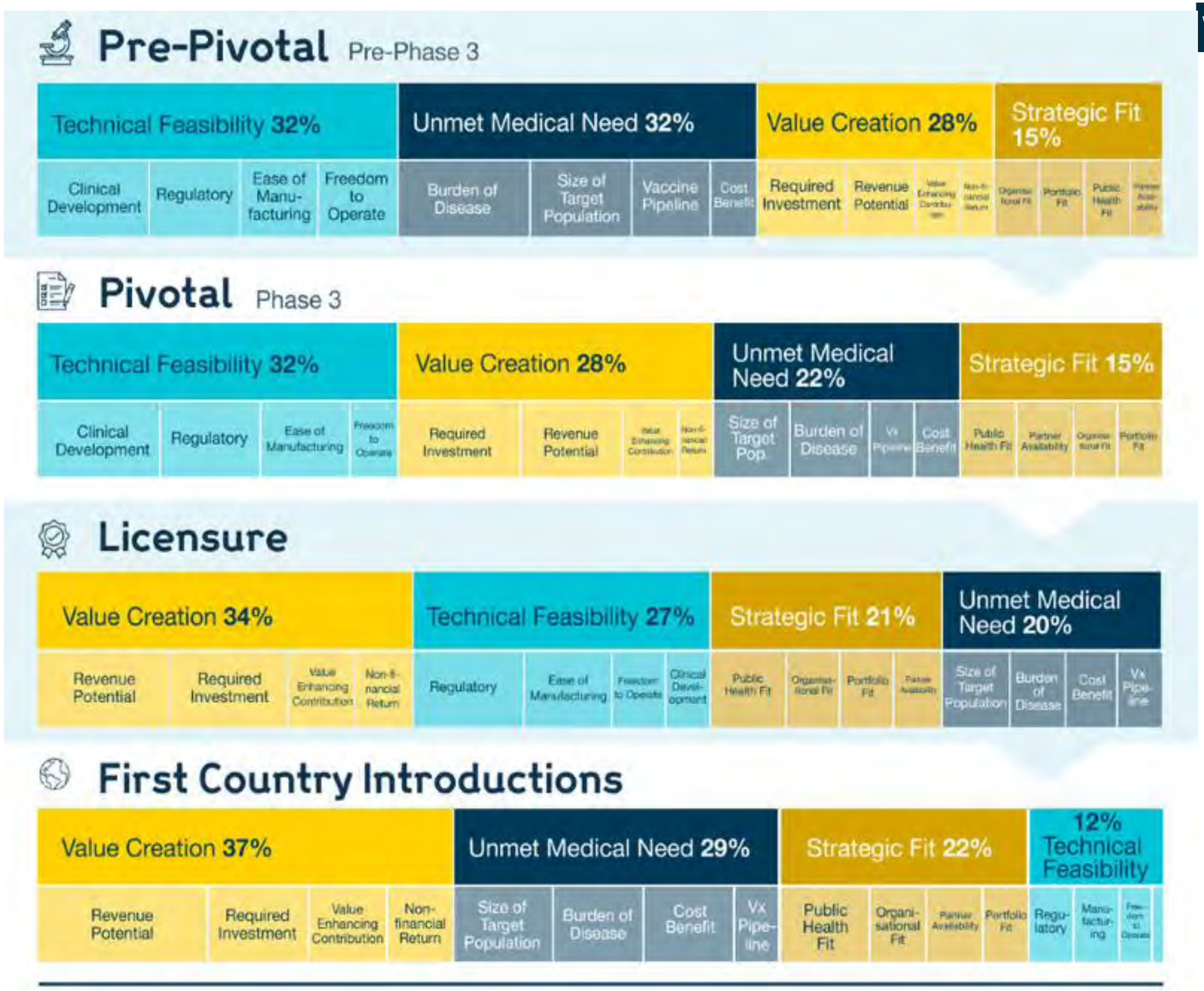
Wellcome’s Infectious Disease Strategy and background to the workshop

Infectious disease: mission, goals and outcomes

Mission: Reduce the risk and impact of infectious diseases by targeting the factors that lead to escalation

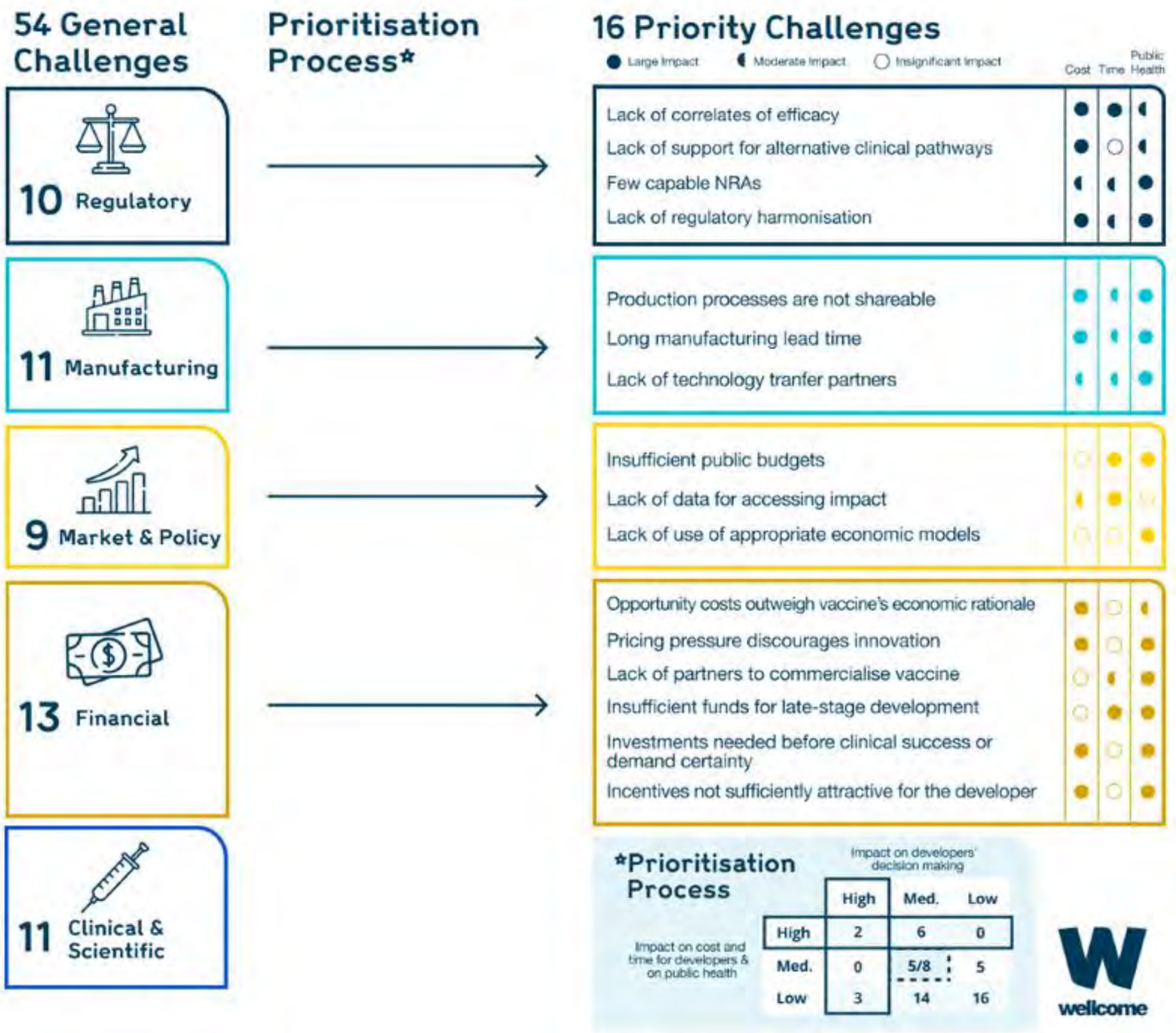
Close key knowledge gaps around sources and drivers of escalating infectious diseases	**Shift the thinking to recognise that burden is driven by escalation**	**Build an R&D ecosystem that can deliver solutions**
Sources and drivers of infections	**Early intervention leading to prevention**	**Affordable medicines and equitable access**

Understanding the Developer Decision Making Process



Prioritisation of identified challenges

Challenges identified by vaccine developers were prioritised according to impact on cost, time and public health impact.



What steps can Wellcome take to improve the vaccine ecosystem

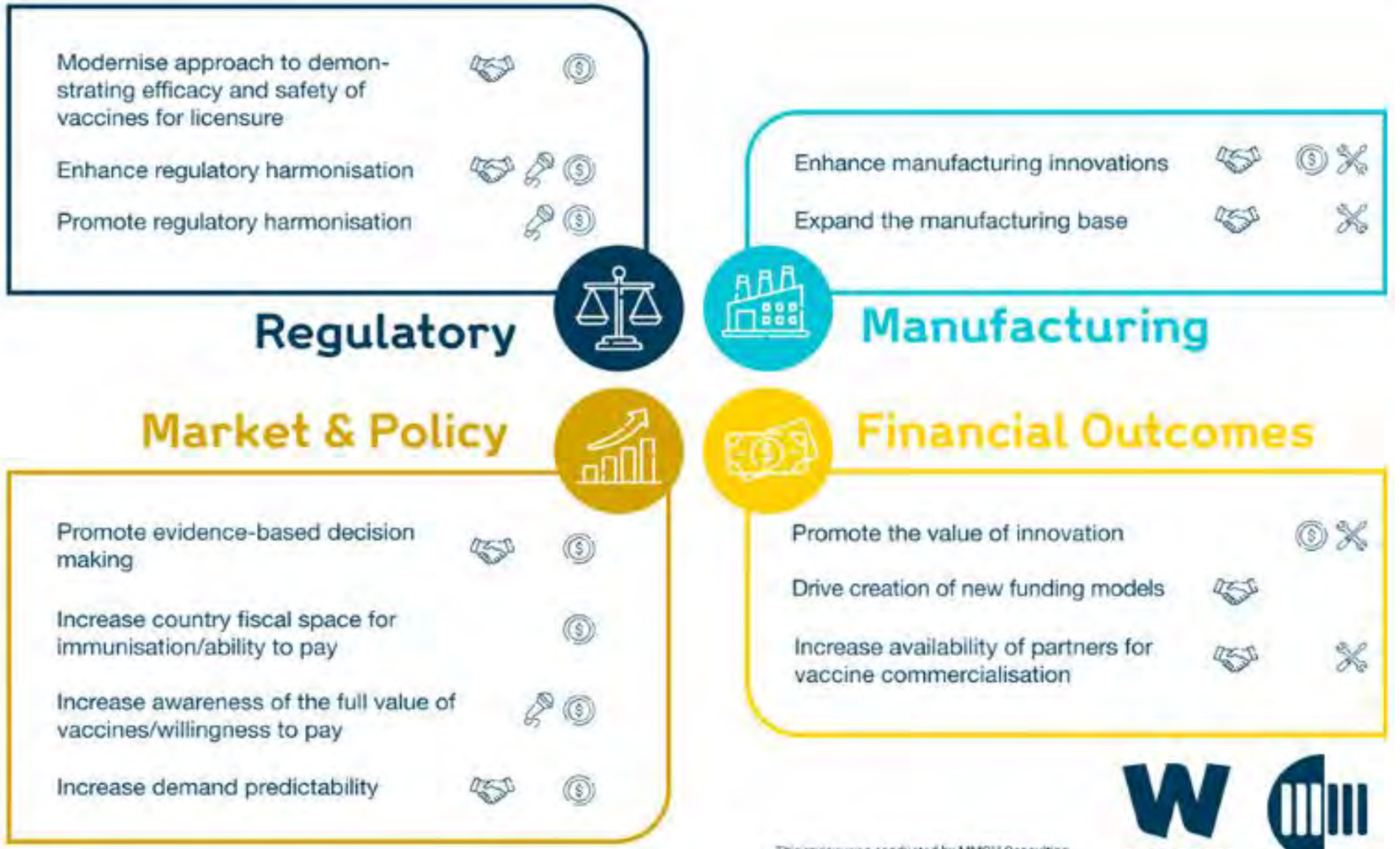
Four axes of action used to implement strategies to address current priority challenges:

Convene stakeholders to work towards a specific challenge

Advocate to stakeholders, decision makers, and the public on the intricacies of vaccine research

Finance the science of vaccine development and manufacturing, and generating evidence to support policy and advocacy

Establish incentives to initiate economic and political levers to drive system change



Workshop Introduction

Workshop overview

Goal

Our goal is to **define the overarching data requirements** needed by **each group of stakeholders** that will enable **early discovery of CoP** in the vaccine development process, and their **use throughout development, licensure and vaccine introduction** and effectiveness monitoring.

Aims of workshop:

- Identify challenges, gaps and priorities (for knowledge, tools, and coordination) for the use of CoP data by stakeholders
- Our **primary focus** for the workshop is **how CoP can be used in clinical vaccine development and authorisation/licensure**.

Deliverables:

1. Identify the overarching requirements and purpose for CoP data and form these into a matrix (**Data Purpose Matrix** for CoP data)
2. Identify a list of key pathogens where CoP would significantly advance vaccine development
3. Create a framework of recommendations / actions for research, funding and coordination for CoP
4. A published paper/report summarizing discussions at the workshop and outlining the deliverables

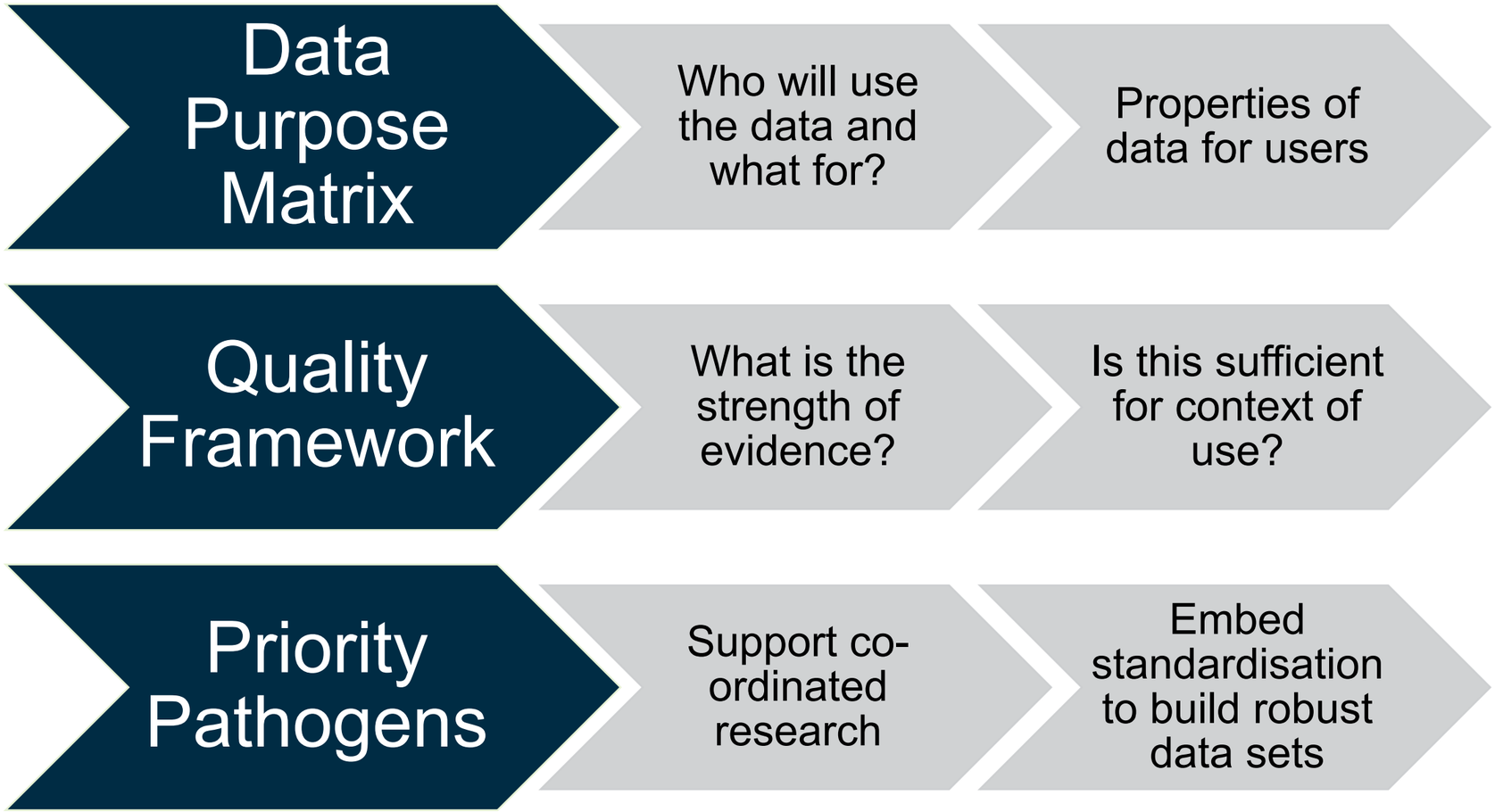
Workshop agenda

Tue 27th September	Wed 28th September	Thu 29th September
Start: 9:30/10am Session 1: Essential background Session 2: Industry perspective Session 3: Regulatory experiences Session 4: Policy-making experiences Session 5: Identifying key pathogens Session 6: Covid-19 and flu case study End: 6pm Drinks reception Dinner at Wellcome Trust: 7:30pm	Start: 9am Session 7: Statistics and modelling Session 8: GBS case study Session 9: TB case study Session 10: Alternative approach to licensure – filovirus case study Session 11: GAS and Nipah case study Session 12: Data Purpose Matrix End: 6pm Drinks reception Dinner at Wellcome Trust: 7:30pm	Start: 9am Session 13: Working groups to identify data requirements and actions Session 14: Turning gaps and priorities into actions Session 15: Planning future workshops End: 3pm

Workshop outputs

Outputs		Next steps
Tools	Data purpose matrix	Publish or further develop?
Gaps	Quality Framework for assessing evidentiary sufficiency	Establish working group to develop
	Co-ordination in early development between stakeholders	
	Standardisation on protocols, assays, sampling, international standards	
	Guidance on mucosal sampling and T-cell responses	
Survey	Stakeholder view on priority pathogens for CoP research	Align with PDVAC priority list
Publications	Commentary/viewpoint article on the need for alternative approaches when clinical efficacy is unfeasible	
	Short summary report on workshop	
	Detailed workshop report/supplement	

Workshop Outputs



Turning deliverables into actions

Deliverable	Action
Data purpose matrix	Option 1 – publish in draft form as part of short workshop report Option 2 – further develop as a tool
Key pathogen survey	Align with PDVAC prioritization for new vaccines and Wellcome ID strategy. Use to develop scope for a funding call to support correlates of protection discovery research into priority pathogens Embed requirements for standardization of measurements
Working Group Actions	Develop framework to assess evidentiary sufficiency of biomarker data Develop guidance on mucosal sampling and assessment
Publications	Commentary/viewpoint article on the need for alternative pathways for vaccine development when efficacy against clinical endpoints is not feasible Short summary report on key findings of the workshop Detailed workshop report or supplement on workshop findings

Questions to PDVAC

- Does PDVAC have any comments on the data purpose matrix, i.e. its potential use cases and when/how it could be developed for a given vaccine?

- Can the committee comment on the utility of the quality framework for assessing biomarker evidence?

d.king@welcome.org

World Health Organization | IVB

WHO Evidence Considerations for Vaccine Policy (ECVP): concept and test case.

PDVAC
5 & 6 Dec 2022

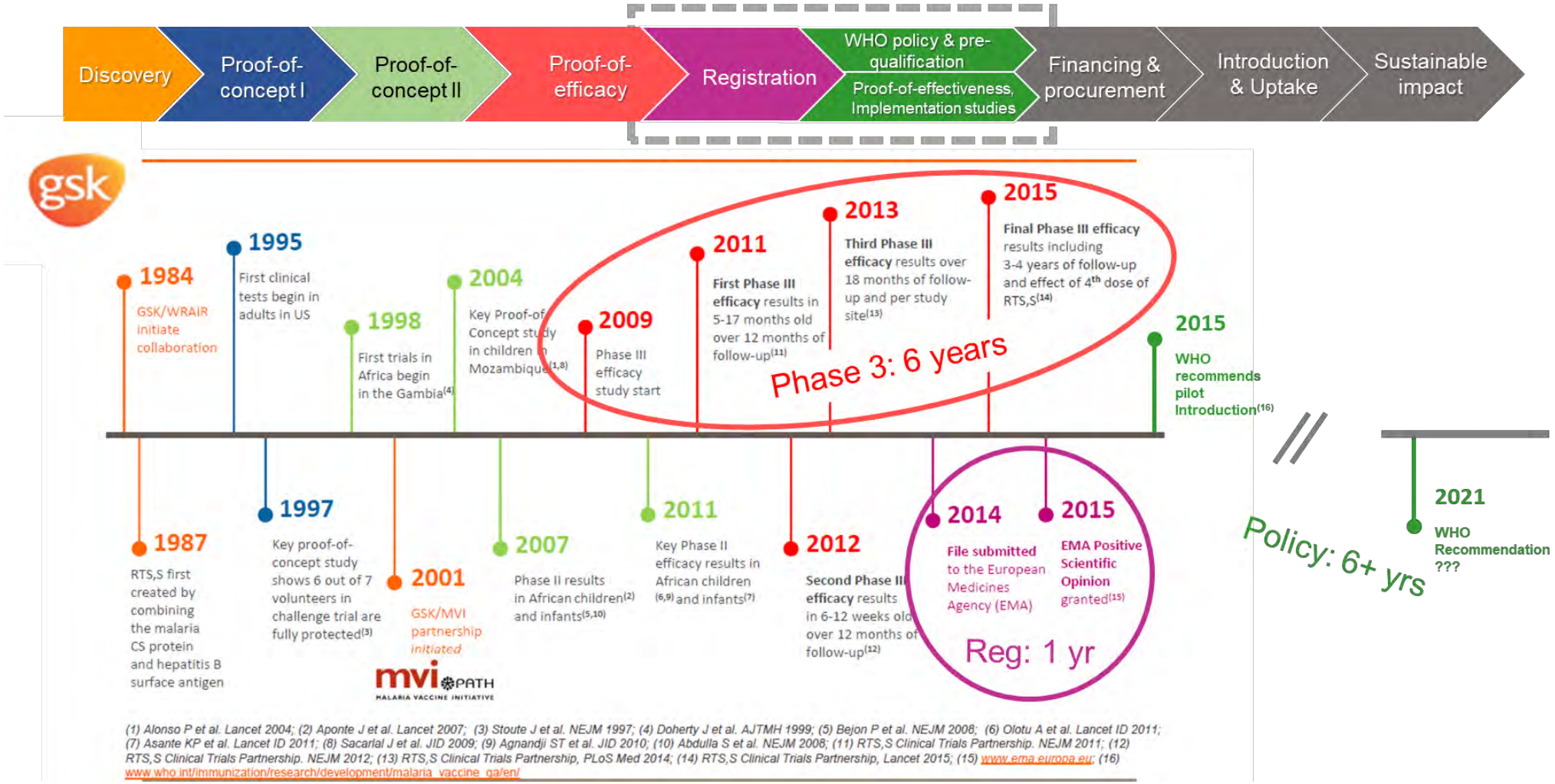
Birgitte Giersing, PhD
Team Lead, Vaccine Platforms and Prioritisation,
Dept of Immunization, Vaccines & Biologicals, WHO

Questions for PDVAC

- Is the ECVP framework useful for vaccines with an 'atypical' licensure and policy pathway to identify important policy considerations for developers and other stakeholders?

- Does PDVAC agree that, where it exists, an ECVP supersedes a PPC and there is no need to update the PPC?

Timelines for the malaria vaccine RTS,S (Mosquirix) from concept to the point of consideration for global policy recommendation



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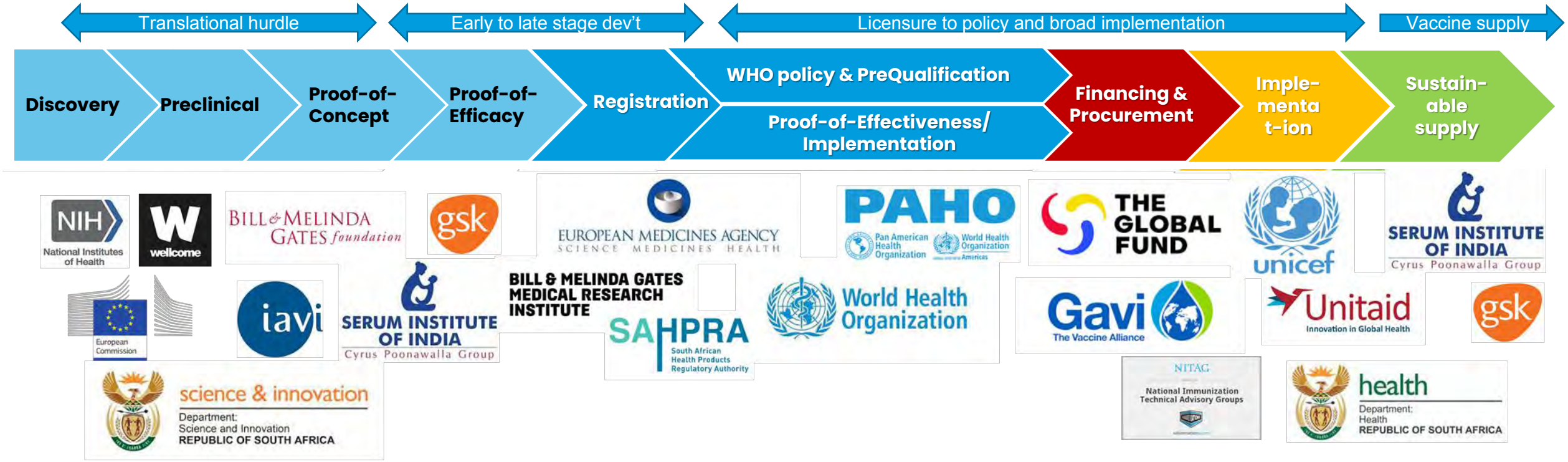
Identification of data needs for stakeholders across the continuum is crucial to accelerating access and impact



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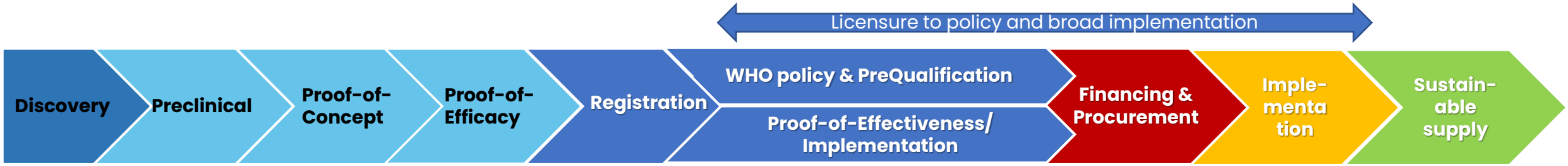
Context for the need for Evidence Considerations for Vaccine Policy (ECVP)



Preferred Product Characteristics: (PPC): defines product attributes for LMIC use

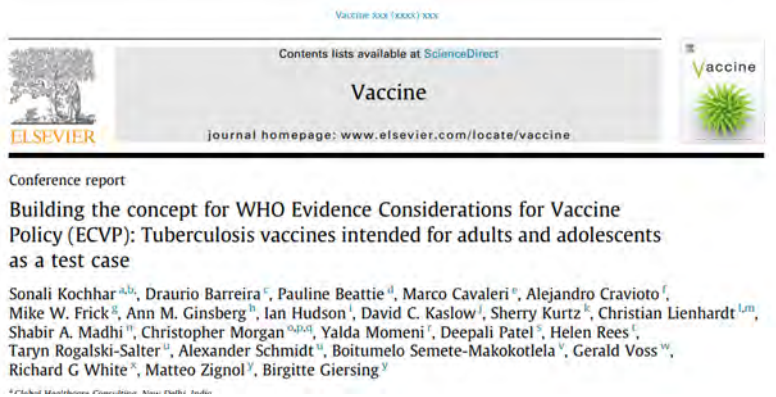
EVIDENCE CONSIDERATIONS FOR VACCINE POLICY: evidence anticipated to facilitate global policy recommendations developed ***before*** phase III clinical studies

SAGE Evidence to Recommendation framework

WHO PQ

WHO Position paper

Scientific advice meetings: Data on **safety, quality and efficacy** for licensure



Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Conference report

Building the concept for WHO Evidence Considerations for Vaccine Policy (ECVP): Tuberculosis vaccines intended for adults and adolescents as a test case

Sonali Kochhar[a,b], Draurio Barreira[c], Pauline Beattie[d], Marco Cavaleri[e], Alejandro Cravioto[f], Mike W. Frick[g], Ann M. Ginsberg[h], Ian Hudson[i], David C. Kaslow[j], Sherry Kurtz[k], Christian Lienhardt[l,m], Shabir A. Madhi[n], Christopher Morgan[o,p,q], Yalda Momeni[r], Deepali Patel[s], Helen Rees[t], Taryn Rogalski-Salter[u], Alexander Schmidt[u], Boitumelo Semete-Makokotlela[v], Gerald Voss[w], Richard G White[x], Matteo Zignol[y], Birgitte Giersing[y]

https://www.sciencedirect.com/science/article/pii/S0264410X21013955?via%3Dihub

What are these gaps in the existing guidance to navigate the end-to-end process?

PPC parameters TB vaccines (adols & adults)	WHO Policy Recommendation parameters	Gavi Vaccine Investment Strategy (VIS) parameters
Indication for use, Target population	Recommendation(s) for use (Burden / recommended targeted risk population(s) by epi setting(s); other populations (permissive /contraindicated); geographies (regional, national, subnational), etc.)	
Immunogenicity Efficacy and proposed endpoints Durability of protection Safety	Benefits (pre-clinical and clinical; direct: effectiveness / preventable disease, and duration of protection; indirect: herd effect; etc.) Harm (pre-clinical and clinical; safety/ tolerability; benefit-harm-acceptance assessment; etc.)	**Health impact** Broader health system benefits
Dose schedule Co-administration	Feasibility (implementation considerations: regimen, route, setting(s); storage, delivery, etc.) Resource Use (Costs: illness; product & implementation; Cost-effectiveness; Supply and wastage: vaccine & delivery considerations; etc.)	Implementation feasibility
'Dosage, regimen, and cost of goods should be amenable to affordable supply. Favourable cost-effectiveness should be established and price should not be a barrier to access, including in low and middle income countries.'	Values & Preferences (related to intervention & comparative health outcomes) Equity (Vaccine access; health, social, economic security, human rights/civil liberties, etc.) Acceptability (by stakeholders; affordability, etc.)	Vaccine cost **Value for money** Operational cost **Equity & social protection impact** **Economic impact** Additional implementation costs Global health security impact Gavi comparative advantage

Source: WHO Preferred Product Characteristics for New Tuberculosis Vaccines

Source: SAGE Guidelines development recommendations

Source: Gavi Vaccine Investment Strategy

Strategic intent for the Evidence Considerations for Vaccine Policy (ECVP) process and guidance: A concept in development

- For vaccine developers, **greater clarity on anticipated expectations for policy** will increase the likelihood that studies will meet requirements to generate optimal policies
- For new vaccines for priority diseases, the WHO ECVP aims to provide early information on the **clinical trial and observational data or evidence** anticipated to be needed for WHO global, regional and country-level policy making, program decisions and program implementation
- Tool to facilitate **early and ongoing communication** between vaccine developers, regulators, policymakers, funders, public health authorities, researchers and technical experts at the national, regional and global level to **mutually outline** the anticipated data and evidence
- The ECVP should be available ***before* the design of pivotal licensure trials**, to be incorporated into trial designs and strategic vaccine development work planning
- Does **not preclude or supersede the independent SAGE** recommendations required for all vaccines seeking WHO policy recommendation
- The ECVP will be **a living document** that is updated as new information becomes available; it may serve as a helpful starting point for a vaccine specific SAGE WG.

Most relevant use cases for an ECVP

- Vaccines with **'non-traditional' regulatory pathways**, for example licensure based on correlates of protection or controlled human infection models, since clinical efficacy data will not be available in the target population;

- Vaccines using **new delivery platforms or new settings** for deployment, such as for vaccines targeted to adults and adolescents;

- Vaccines likely to be introduced in settings where **other existing interventions are in use** and addition of vaccines could be effective in disease prevention, if appropriately scaled.

Structure of the ECVP guidance

The ECVP is based on SAGE's **Evidence to Recommendation** framework and includes five tables:

- Table 1: Vaccine Product Related Parameters for priority populations
- Table 2: Vaccine Delivery related Parameters for the priority populations, including delivery strategy/setting
- Table 3: Vaccination of other target populations (clinical and delivery considerations)
- Table 4: Regulc v
- Table 5: Impler n making; data used in Gavi VIS)

Gap analysis

Tables 1, 2 and 3 identify evidence needs for **initial and expanded policy** recommendations

Each section identifies:

o **High Priority** parameters in red: expected to be critical for SAGE and other policy bodies at the regional and country level;

o **Medium Priority** parameters in blue: for which data and evidence are likely to be beneficial for policy recommendation.

The TB vaccine ECVP has been posted for public consultation

World Health Organization

Health Topics | Countries | Newsroom | Emergencies | Data | A

Home / Publications / Overview / Public consultation of ECVP for TB vaccines intended for adults and adolescents

Public consultation of ECVP for TB vaccines intended for adults and adolescents

25 September 2022 | Technical document

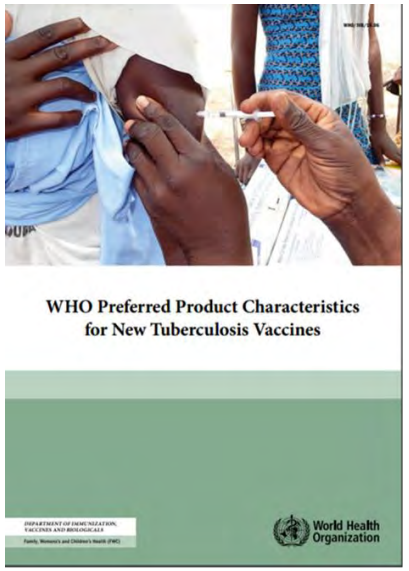
Download (1.2 MB)

Overview

WHO's IVB department has developed a novel kind of guidance for vaccine development stakeholders, referred to as Evidence Considerations for Vaccine Policy, or ECVP. The ECVP document aims to provide early information on the data and evidence that is likely to be required to support WHO policy recommendations. The first ECVP exemplar has been drafted for new Tuberculosis (TB) vaccines intended for adults and adolescents, in collaboration with a global expert technical advisory group.

The primary audience for this TB vaccine ECVP includes all stakeholders intending to support the product development, regulatory approval, introduction and widespread use of new TB vaccines intended for adults and adolescents, in low- and middle-income countries, with the aim of reducing delays between vaccine regulatory approval and vaccine introduction.

We invite all those interested in the ECVP for new Tuberculosis (TB) vaccines intended for adults and adolescents to review this draft document and provide comments on both the general utility of the document, and the specific guidance developed for new TB vaccine. Please use the comment form to capture your comments and return to: vaccines@who.int. **Please use the term "TB vaccine ECVP" in the subject line, otherwise your comments will not be received.** The document will be posted until the **28th October 2022** for comment.



ECVP specific for new TB vaccines: Public consultation CLOSED 28th October

Aim to finalise and publish by early 2023

[Public consultation of ECVP for TB vaccines intended for adults and adolescents (who.int)]

Acknowledgements – PDVAC and the WHO TB vaccine ECVP working group

- **WHO secretariat:** Birgitte Giersing & Dereck Tait (consultant)
- **ECVP working group chairs:** Sonali Kochhar & Helen Rees

- **ECVP working group members** (alphabetical order):
- Marco Cavaleri - EMA
- Huang Fei – China CDC
- Mike Frick - Treatment Action Group
- Gagandeep Kang – CMC Vellore/SEARO RITAG
- Noni McDonald - Dalhousie University
- Yalda Momeni - UNICEF
- Andrew Pollard – University of Oxford
- Richard White - LSHTM
- Yauba Saidu – CHAI/ Cameroon NITAG

- **ECVP working groups observers** (alphabetical order):
- Ann Ginsberg – BMGF (TB)
- Ian Hudson – BMGF (DAC)
- Shelley Malhotra – IAVI
- Alexander Schmidt - GMRI
- Marta Tufet/Cate Bennett - Gavi
- Susan Wang – US CDC
- Charlie Weller – Wellcome Trust

Questions for PDVAC

- Is the ECVP framework useful for vaccines with an 'atypical' licensure and policy pathway to identify important policy considerations for developers and other stakeholders?

- Does PDVAC agree that, where it exists, an ECVP supersedes a PPC and there is no need to update the PPC?

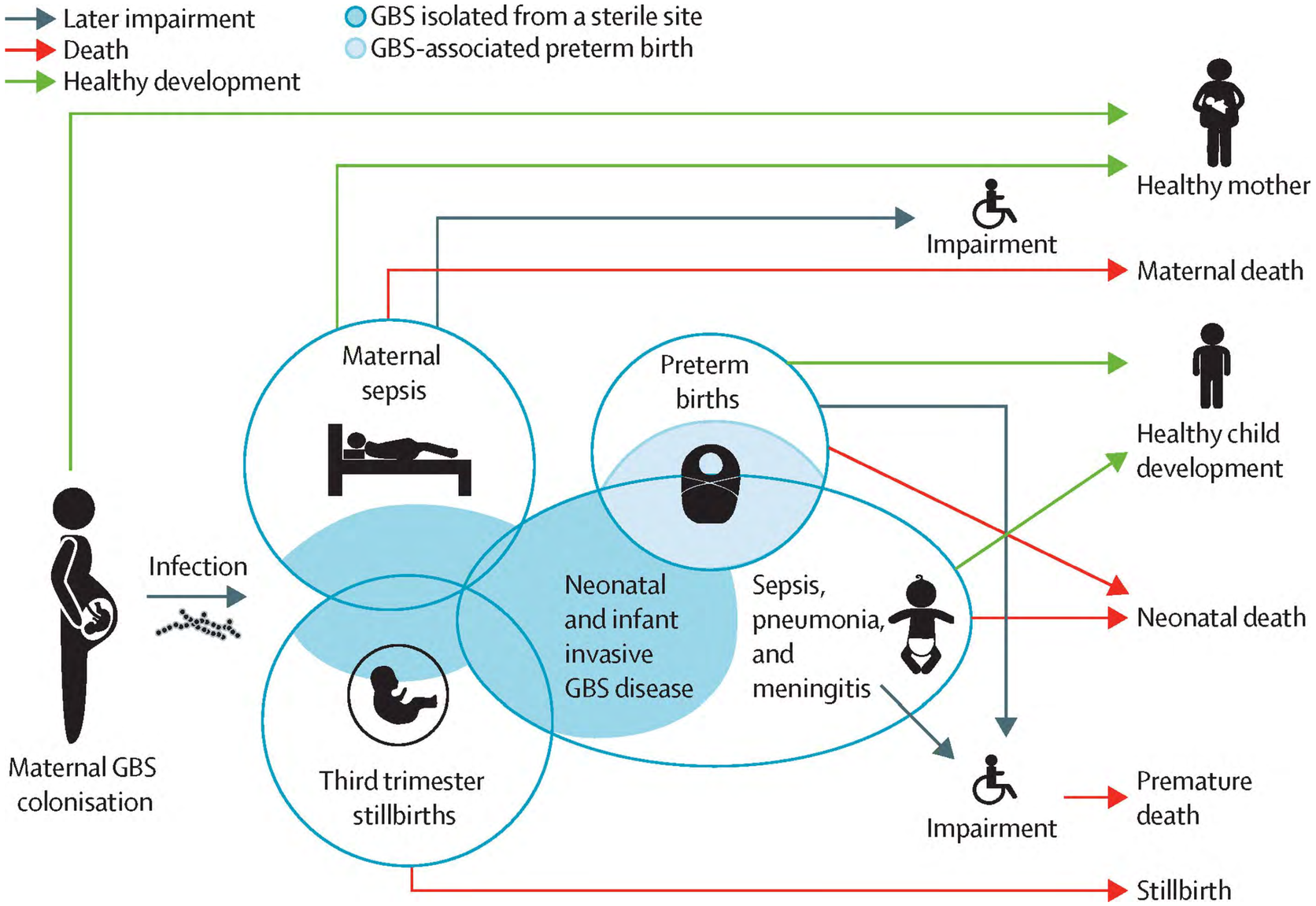
Technical Advisory Group *GBS vaccines*

Chairs: David Goldblatt, and Sonali Kochhar

WHO: Annelies Wilder-Smith, Richard Isbrucker

IVB

Disease burden



- 390000 infants experience invasive GBS cases per year
  - 91000 (44000–187000) child deaths.
  - 46000 (20000–111000) GBS stillbirths annually
- Sub-Saharan Africa accounts for approximately 15% of the world's population but about half of the burden of GBS cases and deaths
- GBS-associated preterm births at 518000 (wide uncertainty 36000–1142000)
- 40000 (14000–112000) survivors predicted to develop moderate and/or severe NDIs each year.

- Next step: Calculate DALYs permitting quantitative comparison with other diseases

Gonçalves BP, et al; GBS Danish and Dutch collaborative group for long term outcomes; GBS Low and Middle Income Countries collaborative group for long term outcomes; GBS Scientific Advisory Group, epidemiological sub-group; CHAMPS team. Group B streptococcus infection during pregnancy and infancy: estimates of regional and global burden. Lancet Glob Health. 2022 Jun;10(6):e807-e819. doi: 10.1016/S2214-109X(22)00093-6. Epub 2022 Apr 28. Erratum in: Lancet Glob Health. 2022 May 12

Several hurdles across vaccine life cycle threaten to obstruct vaccine development and equitable introduction

GBS Evidence gaps

Epidemiological
- Long-term outcomes after iGBS
- Preterm birth risk associated w/ GBS
- Risk factors for iGBS
- Stillbirths due to GBS

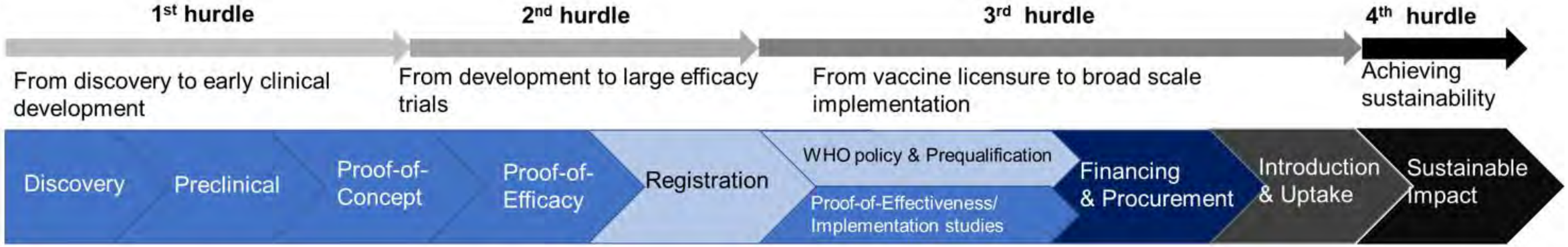
Economic
- Acute cost data
- Long term economic burden for iGBS survivors and their families
- Global economic modelling

Vaccine Market Size
- Market size estimates to enable planning

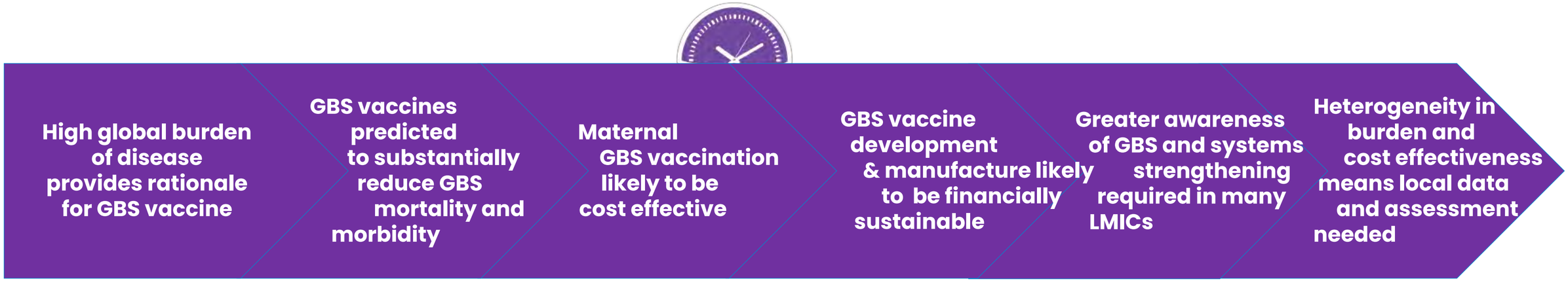
Programmatic
Health system preparedness for vaccine implementation and M&E

http://www.nature.com/news/2008/080611/full/453840a.html; www.lancet.com Vol 387 May 7, 2016 ; https://www.nature.com/articles/d41586-018-07758-3, ttps://stm.sciencemag.org/content/11/497/eaaw2888.full

Several hurdles across vaccine life cycle threaten to obstruct vaccine development and equitable introduction



GBS Full Value of Vaccine Assessment Findings

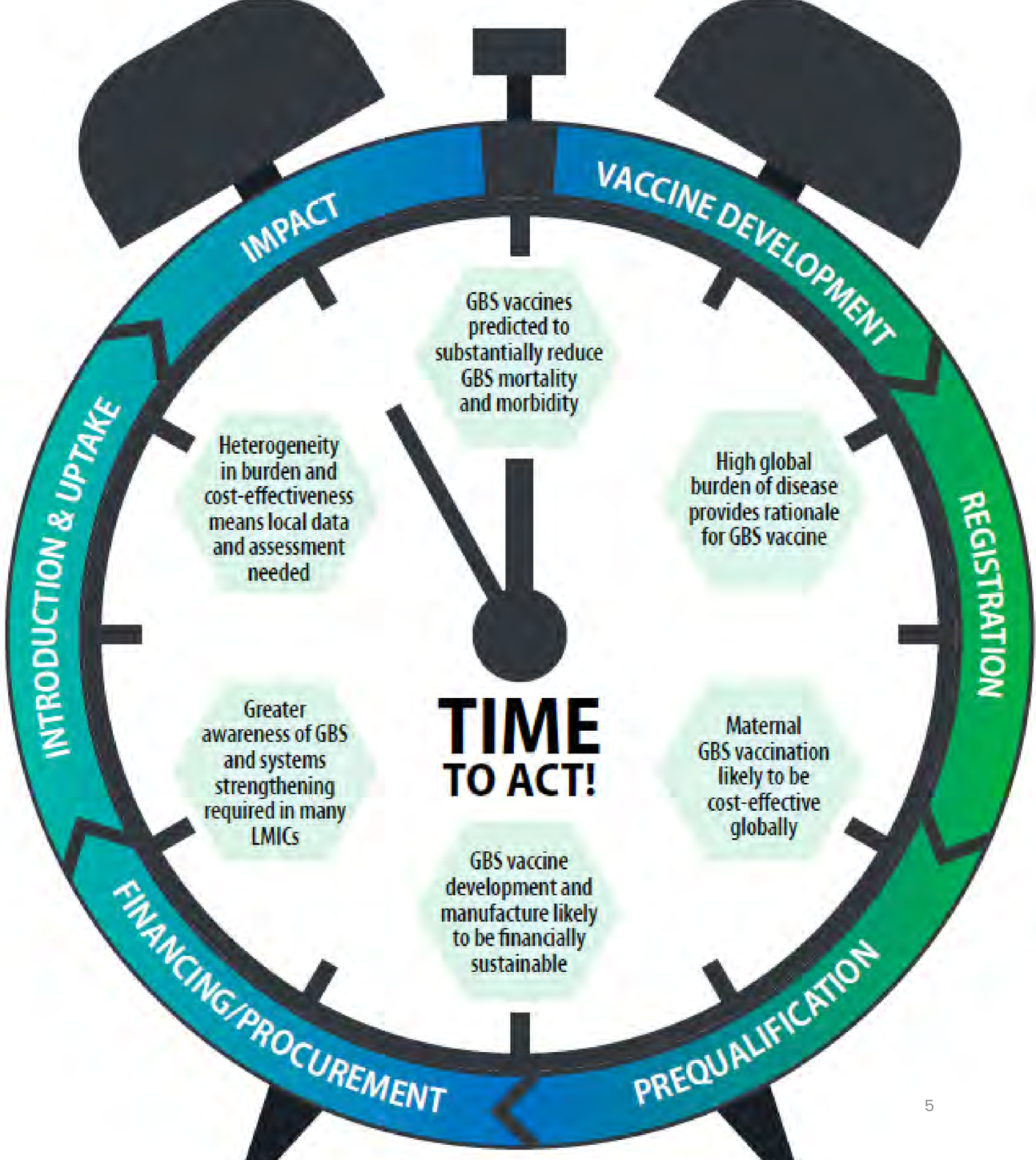


390000 infants experience invasive GBS cases per year, resulting in 91000 (44000–187000) child deaths. In addition, there are 46000 (20000–111000) GBS stillbirths annually.

Next steps for the TAG GBS

Translating Evidence into action

- Further discussion at global level to assess additional evidence and translate it into policies
- Completion of regional/national research gaps
- Pathway to licensure for a GBS vaccine needs to be agreed by regulators
- Strengthening of Health system preparedness for vaccine implementation and monitoring & evaluation



Imperial College London

Status of the Pipeline and Correlates of Protection

David Goldblatt, Professor of Vaccinology and Immunology
Co-Chair WHO GBS-TAG

Status of Pipeline

Safety and immunogenicity of a novel hexavalent group B streptococcus conjugate vaccine in healthy, non-pregnant adults: a phase 1/2, randomised, placebo-controlled, observer-blinded, dose-escalation trial

Judith Absalon, Nathan Segall, Stan L Block, Kimberly J Center, Ingrid L Scully, Peter C Giardina, James Peterson, Wendy J Watson, William C Gruber, Kathrin U Jansen, Yahong Peng, Samantha Munson, Danka Pavliakova, Daniel A Scott, Annaliesa S Anderson

Lancet ID 2021

Ia, Ib, II, III, IV, and V
CRM_{197} Conjugate

PRIME Dry Spell Over As EMA Says Yes To Pfizer & BioCryst

05 May 2022 | NEWS

FDA Grants Breakthrough Therapy Designation to Pfizer's Group B Streptococcus Vaccine Candidate to Help Prevent Infection in Infants Via Immunization of Pregnant Women

September 07, 2022

Phase 1/2 study (NCT03765073), randomised, placebo controlled, observer blinded. Safety and immunogenicity of GBS6 in healthy pregnant women aged 18 to 40 years, who were vaccinated during the second or early third trimester of pregnancy, 639 recruited (Results expected March 2024) (SA/UK/USA)

Bill & Melinda Gates Foundation Announces New Commitments for Vaccine Candidates With the Potential to Reduce Newborn and Infant Deaths in Lower-Income Countries

September 28, 2022

A $100 million grant will support:

1. Manufacturing for Phase 3 clinical trials and, if successful, World Health Organization prequalification.
2. Fund development of an affordable multidose vial for delivery of the vaccine in lower-income countries via public-sector purchasers, including Gavi, the Vaccine Alliance.

(This grant builds on a previous foundation investment for $17 million to help support Pfizer's Phase 1/2 clinical trials)

Safety and immunogenicity of a prototype recombinant alpha-like protein subunit vaccine (GBS-NN) against Group B Streptococcus in a randomised placebo-controlled double-blind phase 1 trial in healthy adult women

Per Fischer [a], Andrzej Pawlowski [b], Duojia Cao [b], David Bell [c], Geoff Kitson [a], Michael Darsley [a], Bengt Johansson-Lindbom [b,*]

Vaccine 2021

A group B *Streptococcus* alpha-like protein subunit vaccine induces functionally active antibodies in humans targeting homotypic and heterotypic strains

Andrzej Pawlowski,[1] Jonas Lannergård,[1] Majela Gonzalez-Miro,[1] Duojia Cao,[1] Sara Larsson,[1] Jenny J. Persson,[1] Geoff Kitson,[2] Michael Darsley,[2] Ane Lilleøre Rom,[3,4] Morten Hedegaard,[3] Per B. Fischer,[2] and Bengt Johansson-Lindbom[1,2,5,*]

Cell Reports Medicine 2022

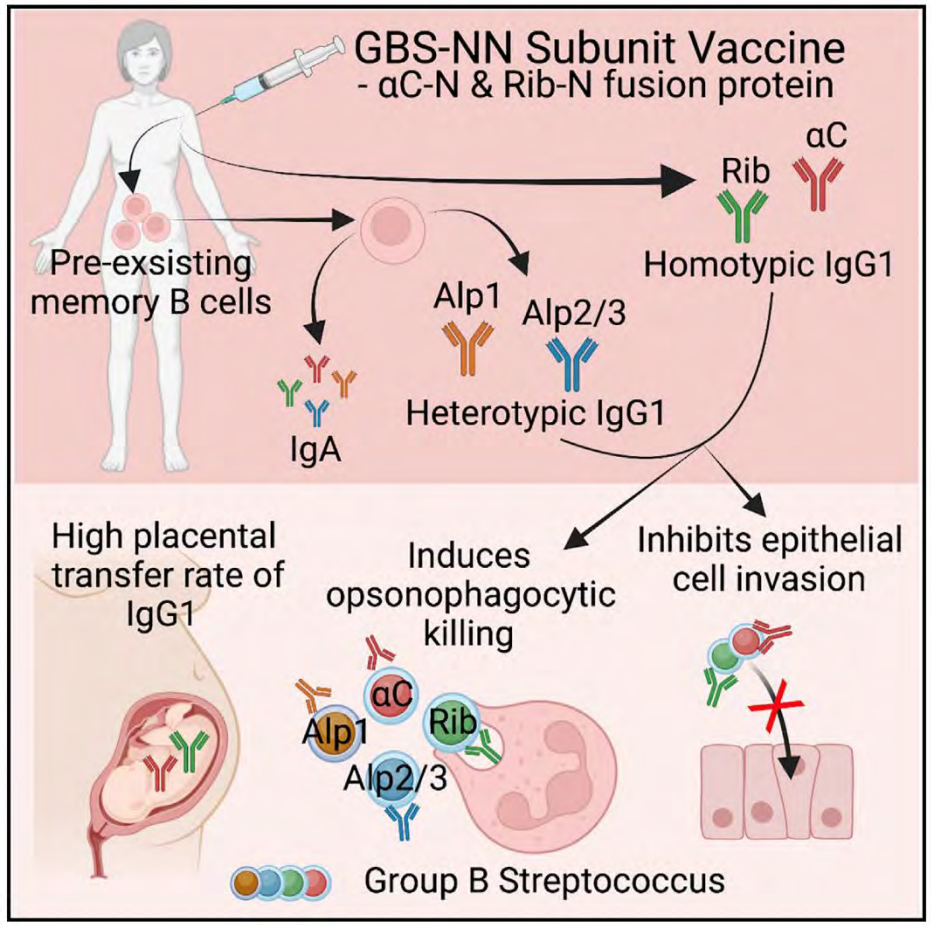
ClinicalTrials.gov

Find Studies

Home > Search Results > Study Record Detail

Group B Streptococcus Vaccine in Healthy Females (MVX0002)

GBS-NN2



FIERCE Biotech

Research Biotech Medtech CRO Special Reports Trending Topics Podcasts

BIOTECH

MinervaX raises $57M for Group B streptococcus vaccine race with Pfizer

By Phil Taylor • Dec 15, 2020 08:05am

Early-onset disease incidence requires large vaccine efficacy trial

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

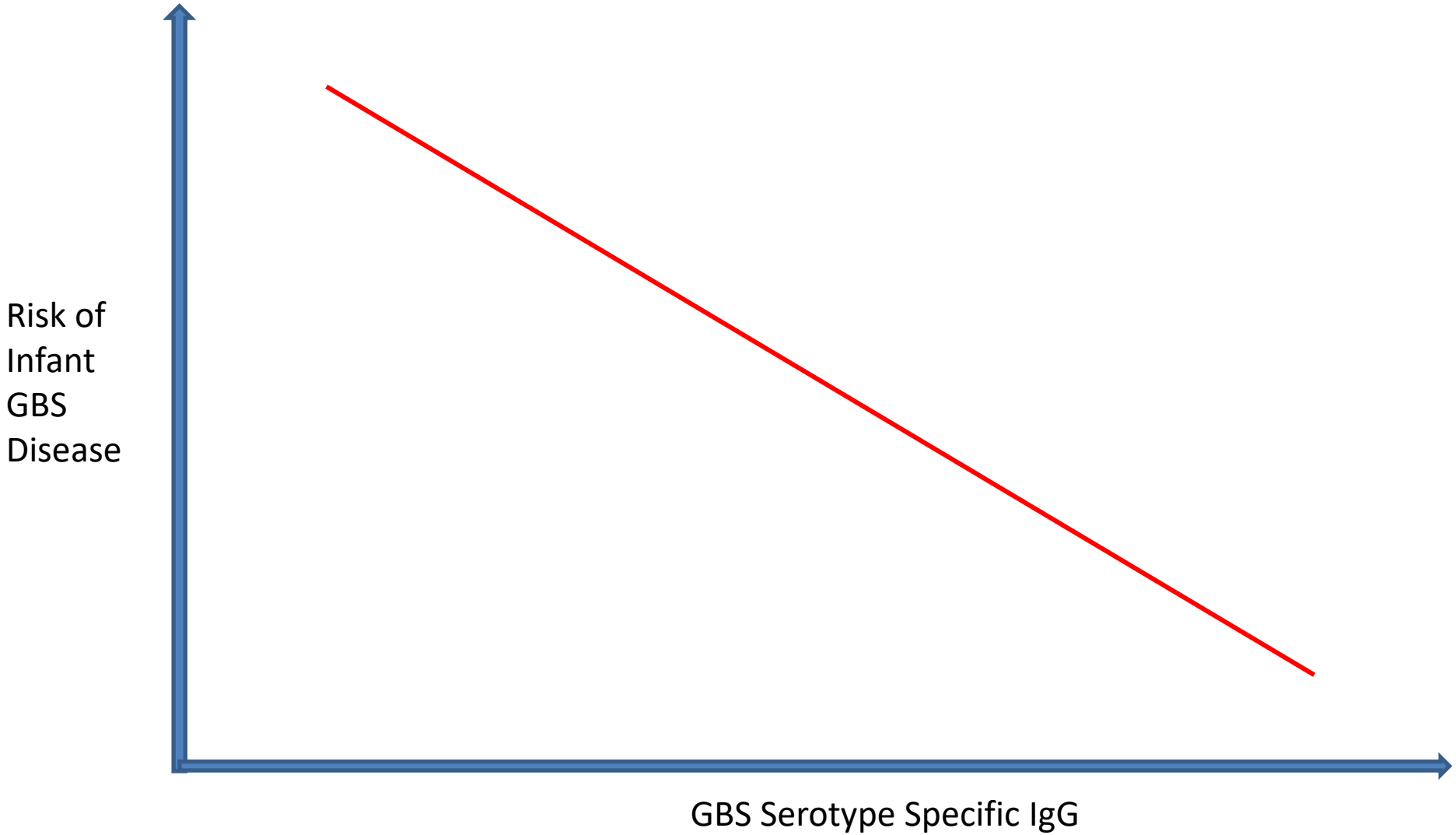
Considerations for a phase-III trial to evaluate a group B *Streptococcus* polysaccharide-protein conjugate vaccine in pregnant women for the prevention of early- and late-onset invasive disease in young-infants

Shabir A. Madhi[a,b,c,*], Ziyaad Dangor[b,c], Paul T. Heath[d], Stephanie Schrag[e], Alaine Izu[b,c], Ajoke Sobanjo-ter Meulen[f], Peter M. Dull[f]

Assumptions for a 1:1 randomized controlled GBS clinical vaccine efficacy trial in a high disease incidence area

Population disease incidence Per 1000 live births	Cases due to Vaccine serotypes	Cases eligible per protocol	Case incidence Per 1000 live births	Vaccine efficacy	Lower 95%CI bound	Sample size
2.0	75-85%	70-80%	1.05-1.35	75%	>20%	40,000 – 60,000

Madhi, Vaccine 2016


Risk of Infant GBS Disease
GBS Serotype Specific IgG

Under the U.S. Food and Drug Administration's (FDA's) "traditional approval" pathway demonstration of GBS vaccine effectiveness could be based either on a clinical disease endpoint or alternatively, a scientifically well-established biomarker demonstrated to be predictive of vaccine effectiveness. Confidence that a proposed marker(s), as induced by the vaccine, can predict protection against disease is the critical question in determining whether a marker can be used for traditional approval.

FDA, 2018 VRBPAC

Serocorrelates of protection against infant group B streptococcus disease

Kirsty Le Doare, Beate Kampmann, Johan Vekemans, Paul T Heath, David Goldblatt, Moon H Nahm, Carol Baker, Morven S Edwards, Gaurav Kwatra, Nick Andrews, Shabir A Madhi, Ajoke Sobanjo ter Meulen, Annaliesa S Anderson, Bart Corsaro, Per Fischer, Andrew Gorringe

2019

WORKSHOP REPORT

Group B *Streptococcus* Correlate of Protection Methodology

10 and 11 February 2021

2021

Clinical Infectious Diseases
MAJOR ARTICLE

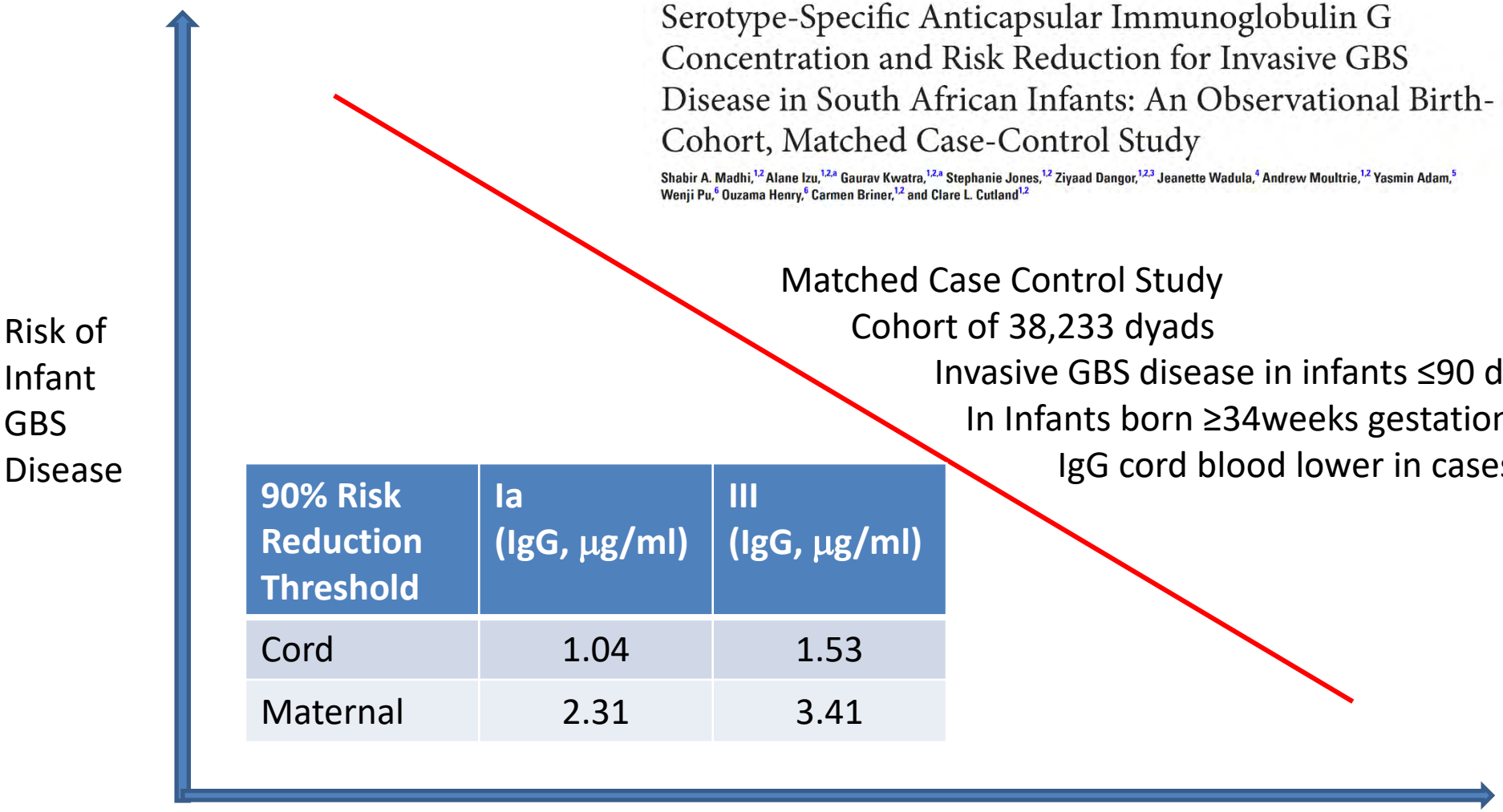
Association of Group B *Streptococcus* (GBS) Serum Serotype-Specific Anticapsular Immunoglobulin G Concentration and Risk Reduction for Invasive GBS Disease in South African Infants: An Observational Birth-Cohort, Matched Case-Control Study

Shabir A. Madhi,[1,2] Alane Izu,[1,2,a] Gaurav Kwatra,[1,2,a] Stephanie Jones,[1,2] Ziyaad Dangor,[1,2,3] Jeanette Wadula,[4] Andrew Moultrie,[1,2] Yasmin Adam,[5] Wenji Pu,[6] Ouzama Henry,[6] Carmen Briner,[1,2] and Clare L. Cutland[1,2]

2021

Matched Case Control Study
Cohort of 38,233 dyads
Invasive GBS disease in infants ≤90 days
In Infants born ≥34weeks gestational age:
IgG cord blood lower in cases vs controls (Ia and III)

90% Risk Reduction Threshold	Ia (IgG, μg/ml)	III (IgG, μg/ml)
Cord	1.04	1.53
Maternal	2.31	3.41

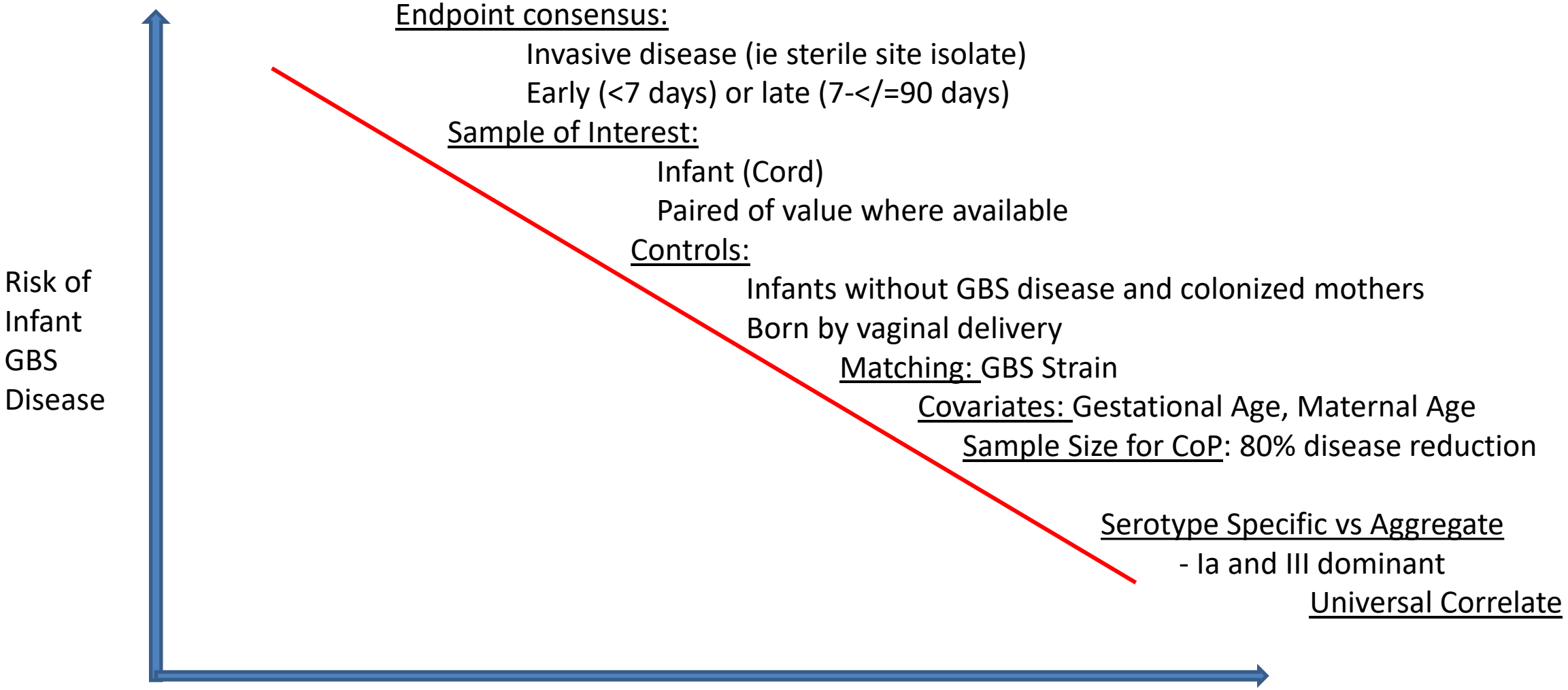


FDA Guidance:

Binding vs Functional (sample volume)

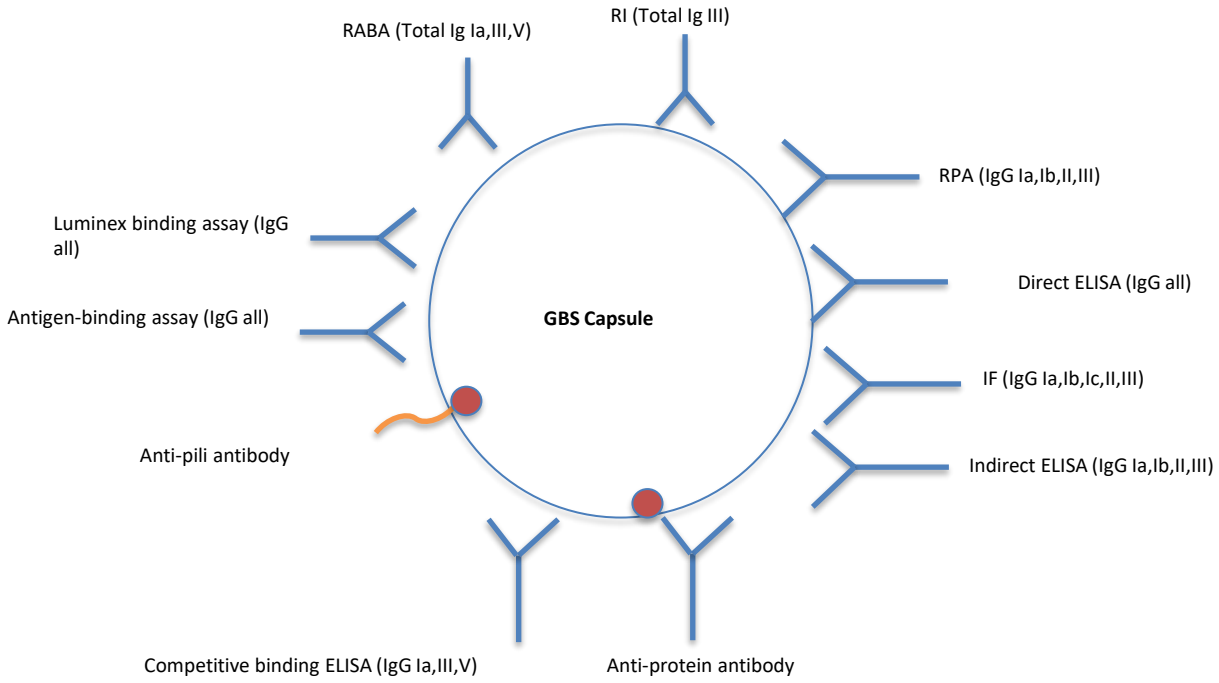
Risk ratios across range of antibody Concentrations

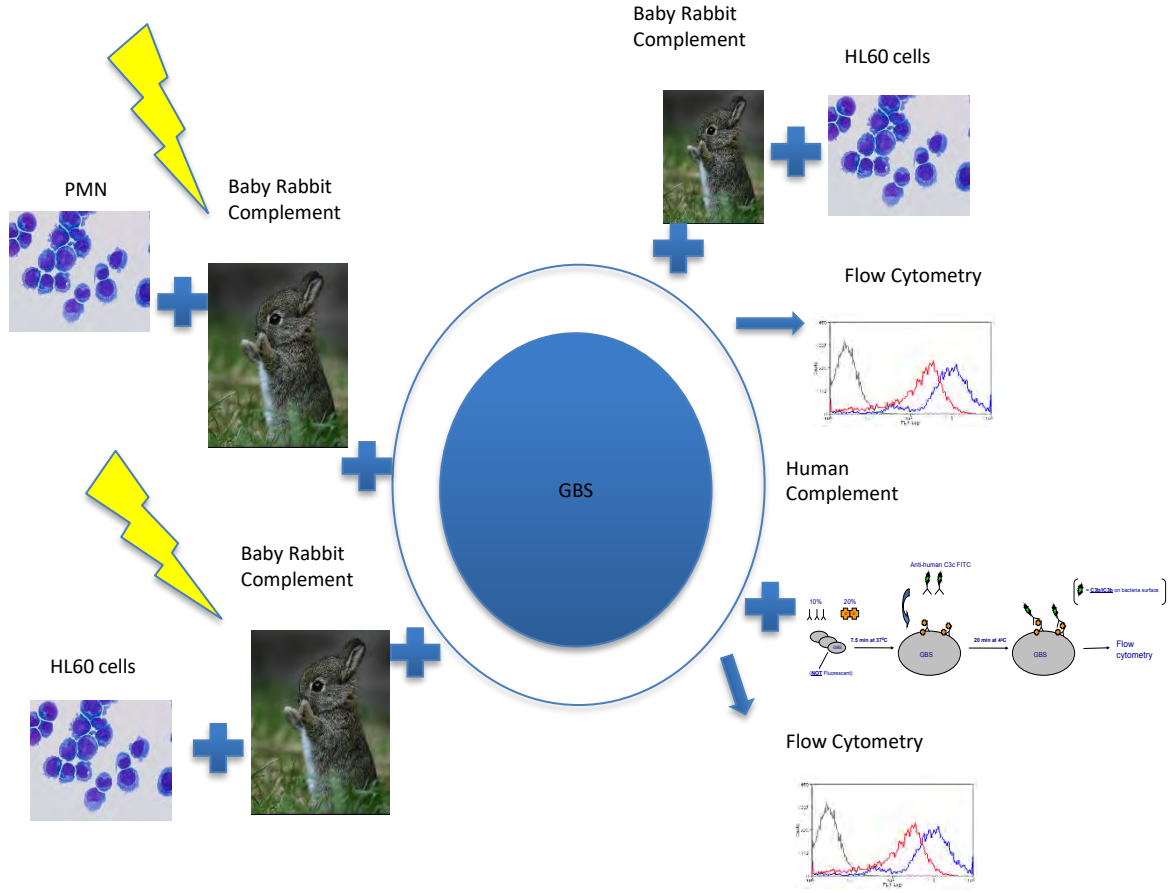
Infant concentrations rather than maternal



	RMPRU	CDC	UK	Uganda
Cases	112	375	150 (of which 100 STIII)	120
Controls	GBS swab positive controls 4 per case infants without GBS disease, cord blood.	GBS swab positive controls from ABC sites with infants without GBS disease, aiming 2250 controls	GBS swab positive controls from cord blood in term infants without GBS disease (serum from prospective cohort). Aiming for 3:1 controls to cases minimum	GBS swab positive controls from cord blood in term infants without GBS disease (serum from prospective cohort). Aiming for 3:1 controls to cases minimum
Matching	Serotype, gestation, HIV, maternal age	Disease to colonising serotype	Disease to colonising serotype	Disease to colonising serotype
Study start and end dates	2014-2016, re-enrollment started 2018	2019-2023	2019-2022	Pilot starts 2019
Final analysis available	End 2019	End 2023	End 2020 (pilot), main study end aim 2022 (dependent on results of pilot)	End 2020 (pilot), main study end aim Q1 2024 (dependent on results of pilot)
Samples	Serum	DBS	Serum and DBS	Serum and DBS
Covariates	HIV status, maternal age, gestation, mode of delivery	Gestation, race, gender, birth weight, duration of birth hospitalisation, ethnicity, maternal age, gravida, number of antenatal visits, RF for GBS disease, any positive GBS result, IAP, age of blood spot, age of infant on testing DBS, transfusion status (DBS)	Gestation, gender, birth weight, ethnicity, maternal age, gravida, RF for GBS disease, IAP, mode of delivery. For blood spots, age at which blood spot taken.	Gestation, tribe, gender, birth weight, maternal age, gravida, RF for GBS disease, HIV status, malaria, IAP, mode of delivery. For blood spots, age at which blood spot taken.
Primary endpoint	All cause STIa and STIII disease (MIA in all and OPkA in subset)	TBC	All cause STIII and STIa disease (MIA and OPkA)	All cause STIII and STIa disease (MIA and OPkA)
Risk reduction	80%	70 and 80%	80% but considering a range	80% but considering a range

34 different Anti-Capsular and anti-surface-protein assays and 9 functional assays





Slide courtesy of Kirsty Le Doare

GBS assay standardization consortium (GASTON)

Objective 1: development of standard reagents and identification and review of assays for standardization

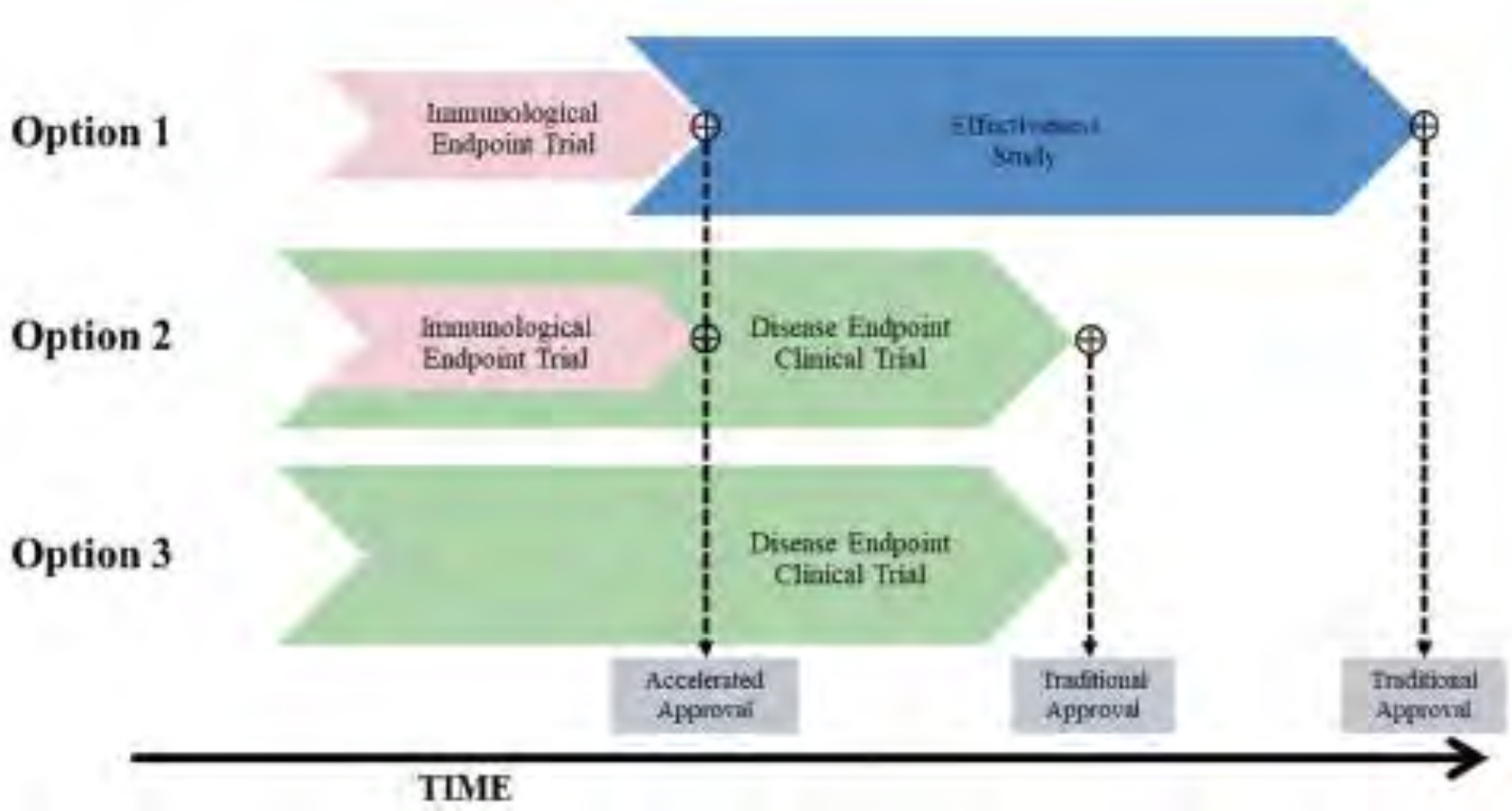
Objective 2: To standardized protocols for existing ELISA and functional GBS assays using standard reagents

Objective 3: To validate standard protocols and standard reagents across laboratories to establish a prediction of disease protection

Industry expertise

Slide courtesy of Kirsty Le Doare

Three potential ways forward



Absolon, Human Vaccinology 2022

Questions for PDVAC

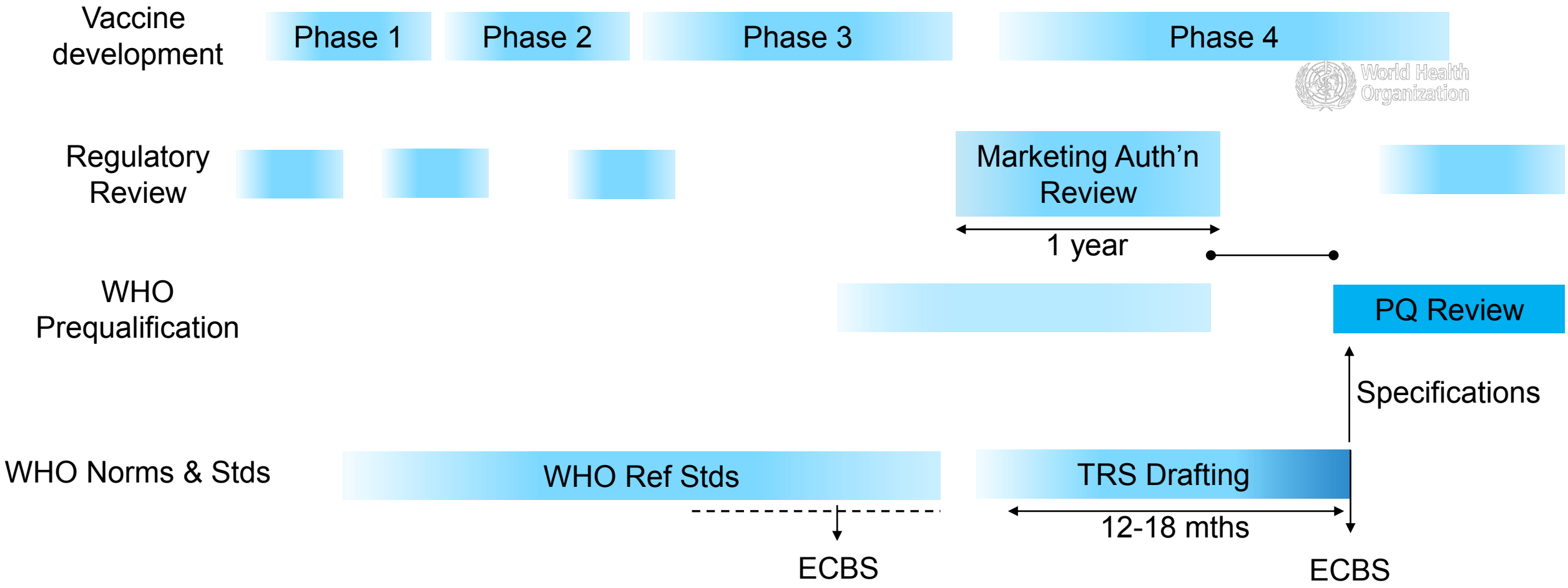
- Would development of an ECVP be helpful for GBS vaccines?

World Health Organization

Thoughts on Regulatory Timeline and Workshop for GBS Vaccines

Richard Isbrucker,
WHO, Norms & Standards for Biologics Unit (NSB)

Regulatory and NSB timeline



Regulatory and TAG Workshop

Planned for Q2 2023

Engage regulators in countries where GBS vaccines are entering clinical trials and eventually marketed

- Epidemiological studies
- Understanding the vaccines
- Correlates of protection – role in marketing authorization

Start the discussions and planning of TRS earlier

Engage NITAGs (?)

Can (should?) this workshop overlap with similar workshops for other vaccines (e.g. mRNA, Shigella, RSV)

World Health Organization

WHO

20, Avenue Appia
1211 Geneva

Switzerland

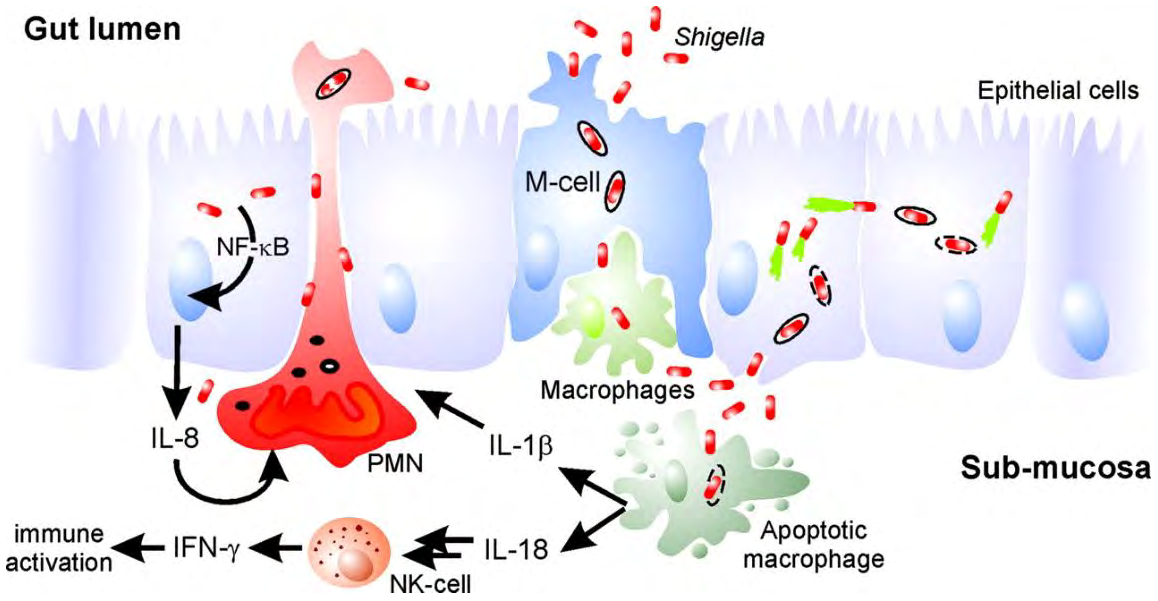
www.who.int

THE SHIGELLA VACCINE PIPELINE

Cal MacLennan
Bill & Melinda Gates Foundation
WHO PDVAC
Geneva. December 5, 2022.

SHIGELLOSIS

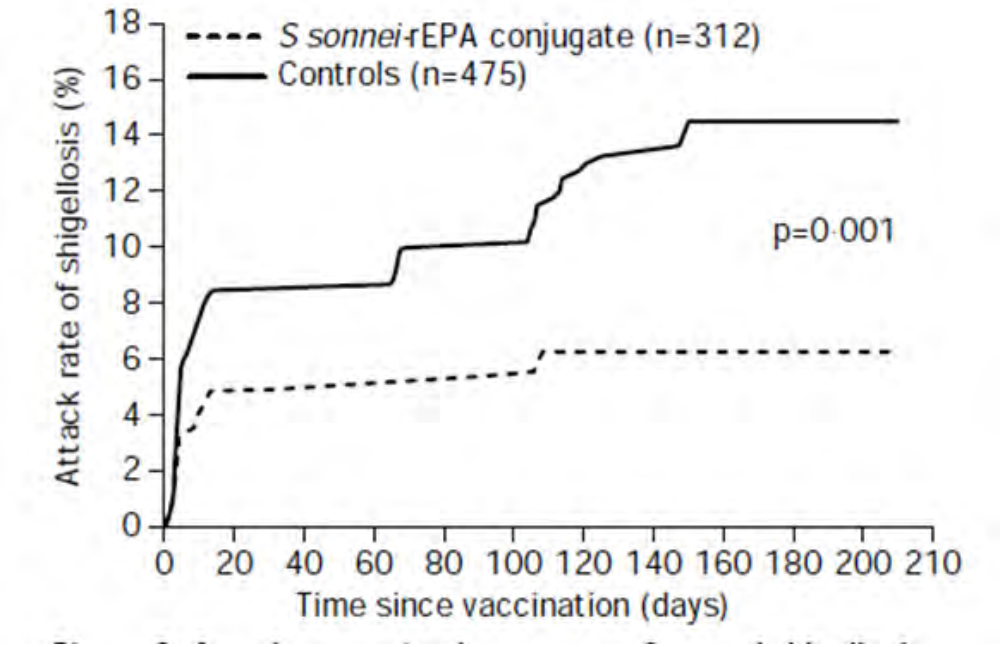
- Main bacterial cause of diarrheal deaths globally
- Presentation as dysentery or watery diarrhea
- Children under-5 years in LMICs, peak in 2nd year
- Growing antimicrobial resistance
- Longitudinal growth faltering
- Traveller/military indication



- *Shigella* genus – Gram-negative bacteria
- 4 species: *Shigella flexneri, sonnei, dysenteriae, boydii*
- Multiple serotypes distinguished by O-antigen of LPS
- Protection following infection is serotype-specific
- Most prevalent: *S. flexneri* 2a, 3a, 6 & *S. sonnei*

PHASE 3 EFFICACY WITH SHIGELLA SONNEI CONJUGATE VACCINE IN YOUNG ADULTS & MODALITIES OF PROTECTION

- **25 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…
- …but many years later, the same 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…



(Cohen D et al, Lancet 1997)
(Passwell JH et al Vaccine 2010)

- More recent evidence from animal and human studies for additional protection through antibodies to Ipa proteins of *Shigella* type 3 secretion system

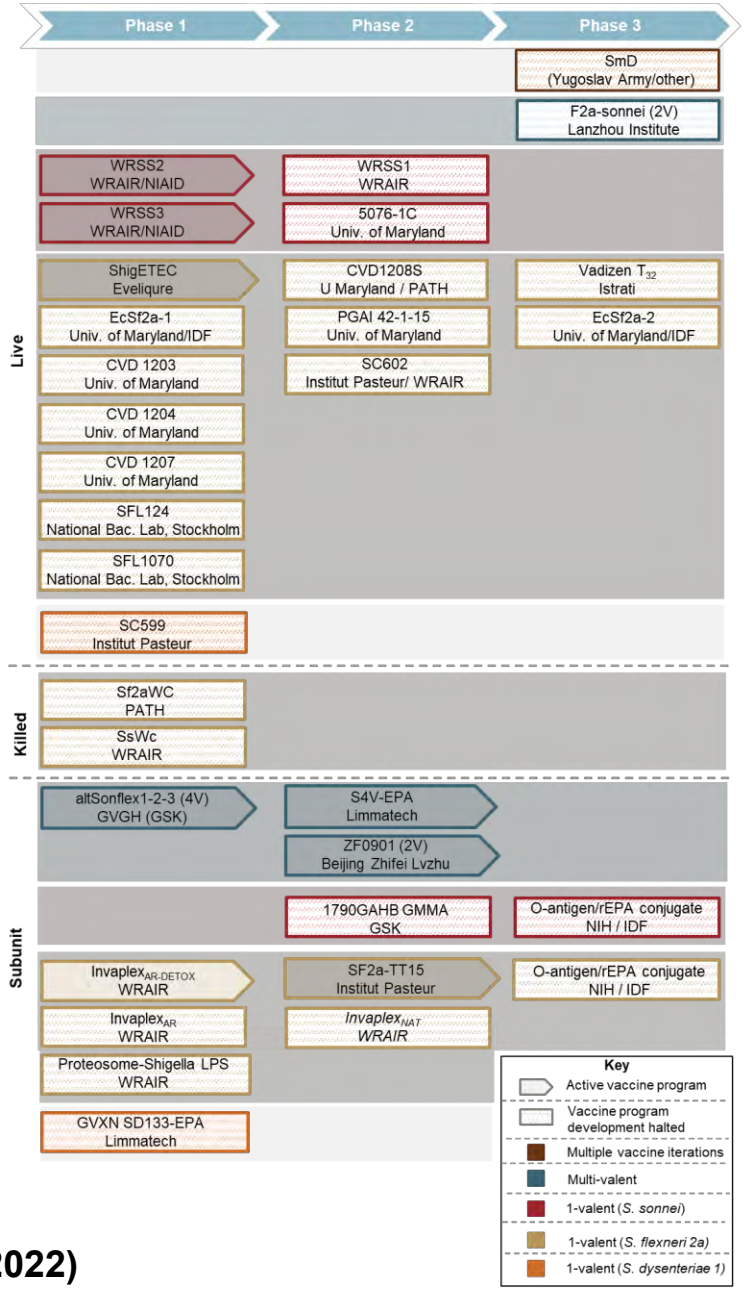
SINCE PDVAC 2019

- 3 vaccines (2 x 4V, 1 x MV) in descending-age dose-finding studies in Kenya
- 3 vaccines (3 x MV) in CHIM studies
- 2 x 4V vaccines with IpaB as carrier protein in Advanced Preclinical stage

- Dani Cohen published on serum O-antigen IgG as COP with proposed threshold levels of protection based on re-analysis of two historic efficacy studies with NIH S. sonnei O-antigen/rEPA conjugate
- Kristen Clarkson published immunological findings from LimmaTech S. flexneri 2a O-antigen/EPA bioconjugate CHIM study
- Robert Frenck published findings from GVGH S. sonnei NOMV (GMMA) vaccine CHIM study

SHIGELLA CANDIDATE PIPELINE

- Multiple candidate vaccines over time
- Broadly divided between live attenuated and subunit approaches
- Historically, efficacy shown with both approaches



(MacLennan CA, et al. Vaccines 2022)

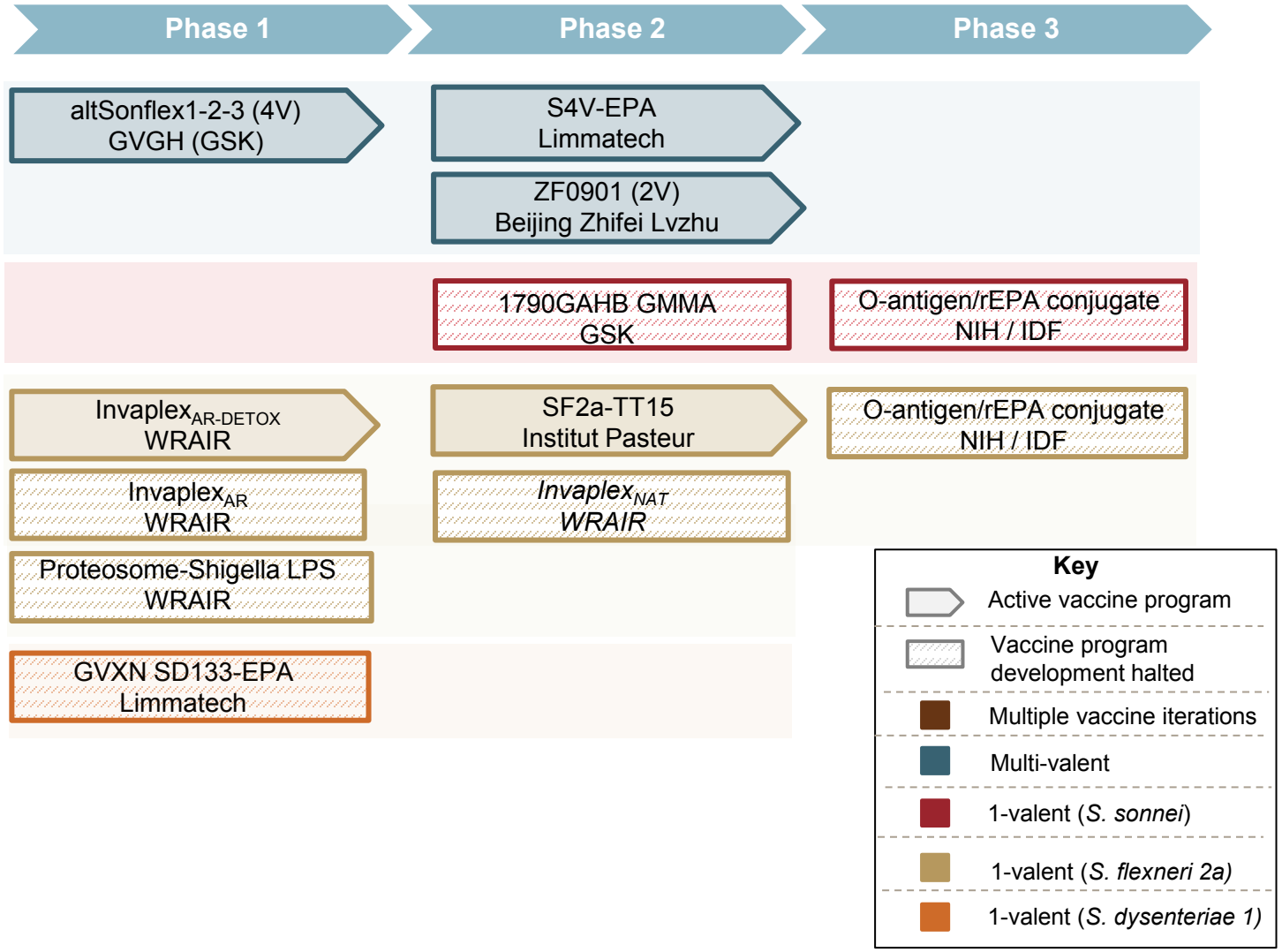
PREFERRED PRODUCT CHARACTERISTICS (PPC)

- **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)

SHIGELLA 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

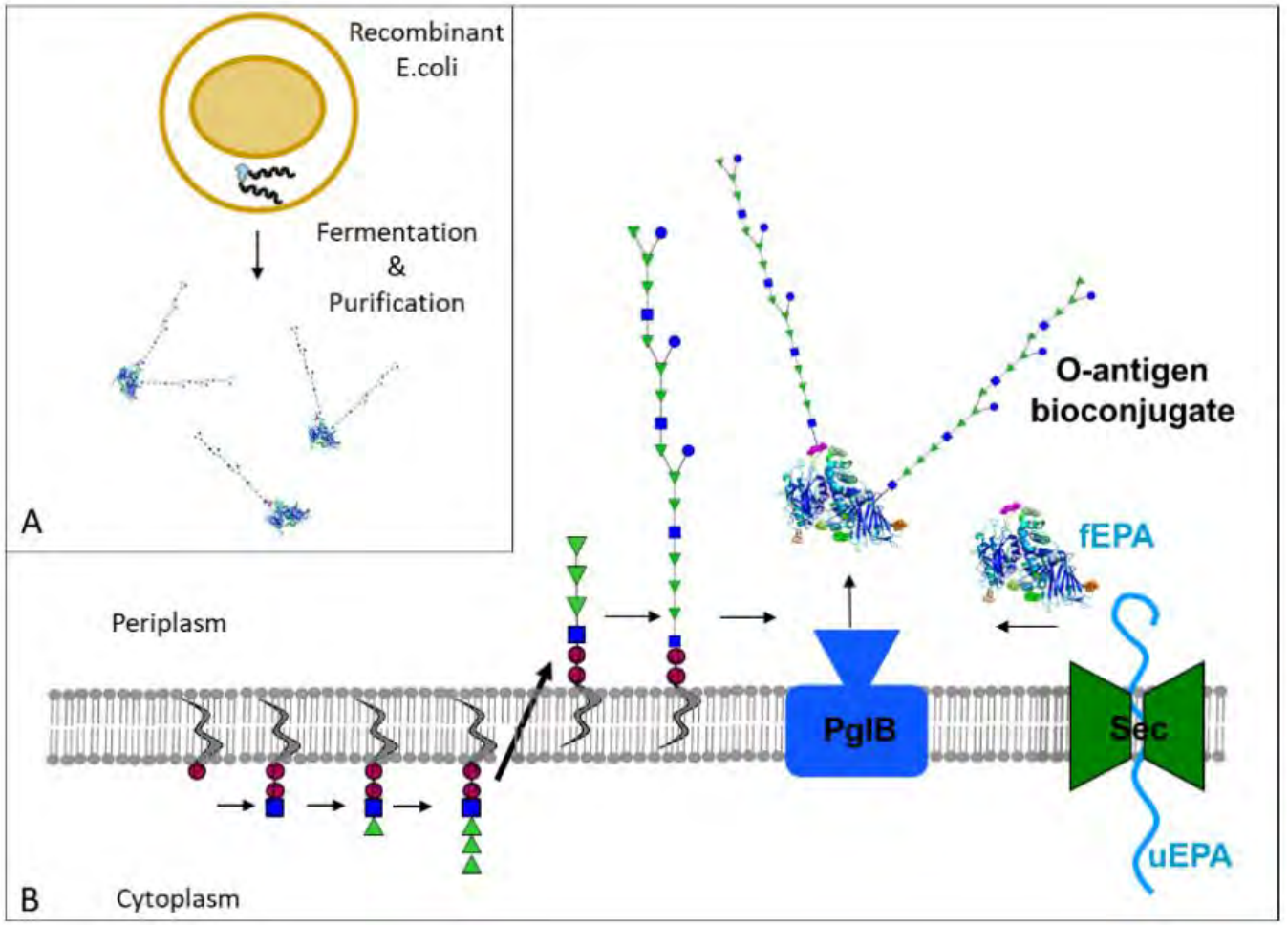


BIOCONJUGATE – LIMMATECH/GSK, ZURICH

- Recombinant *E. coli* as vaccine factories
- Conjugation within *E. coli*
- O-antigen repeats assembled in cytoplasm & polymerised in periplasm
- EPA carrier protein transferred to periplasm
- Oligosaccharyltransferase PglB covalently bonds O-antigen to EPA
- Glycoconjugate assembled in periplasm

4V *Shigella* vaccine

- Completing descending-age, dose-finding study in Kenya



(Martin P, Alaimo C, Vaccines 2022)

BIOCONJUGATE – LIMMATECH/GSK, ZURICH

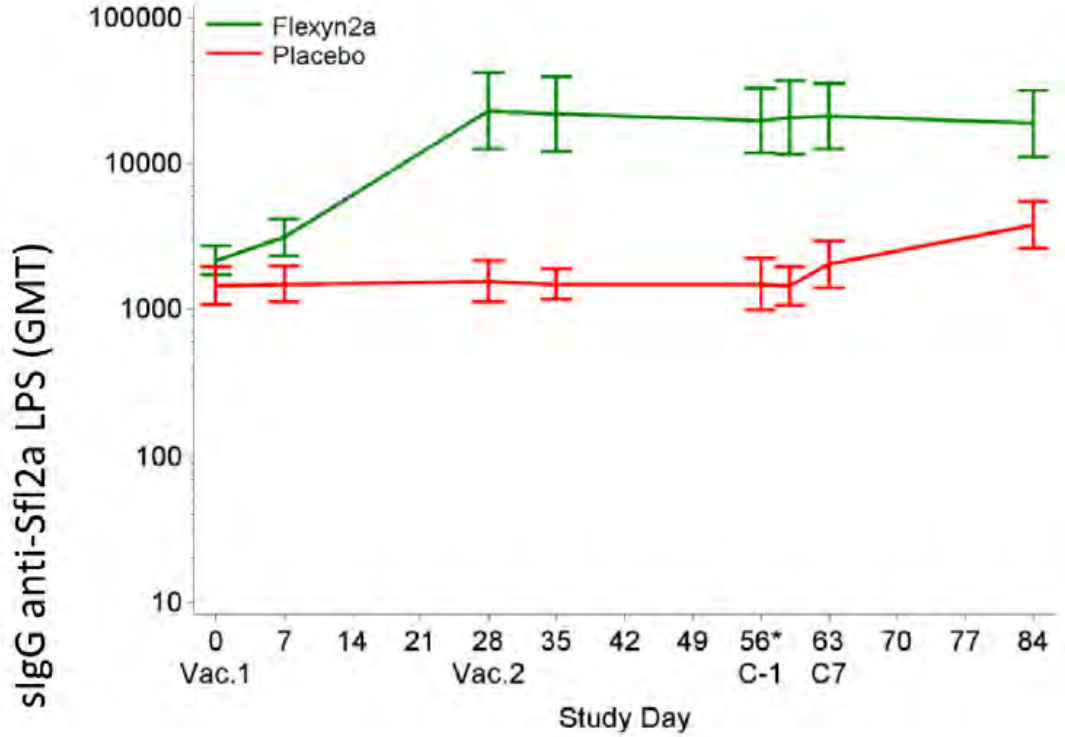
Monovalent *S. flexneri* 2a vaccine

- Controlled human infection model (CHIM) study, Johns Hopkins University
- 52% efficacy with secondary endpoint
- Correlation between serum O-antigen IgG levels and efficacy

4V *Shigella* vaccine

- Completing descending-age, dose-finding study in Kenya

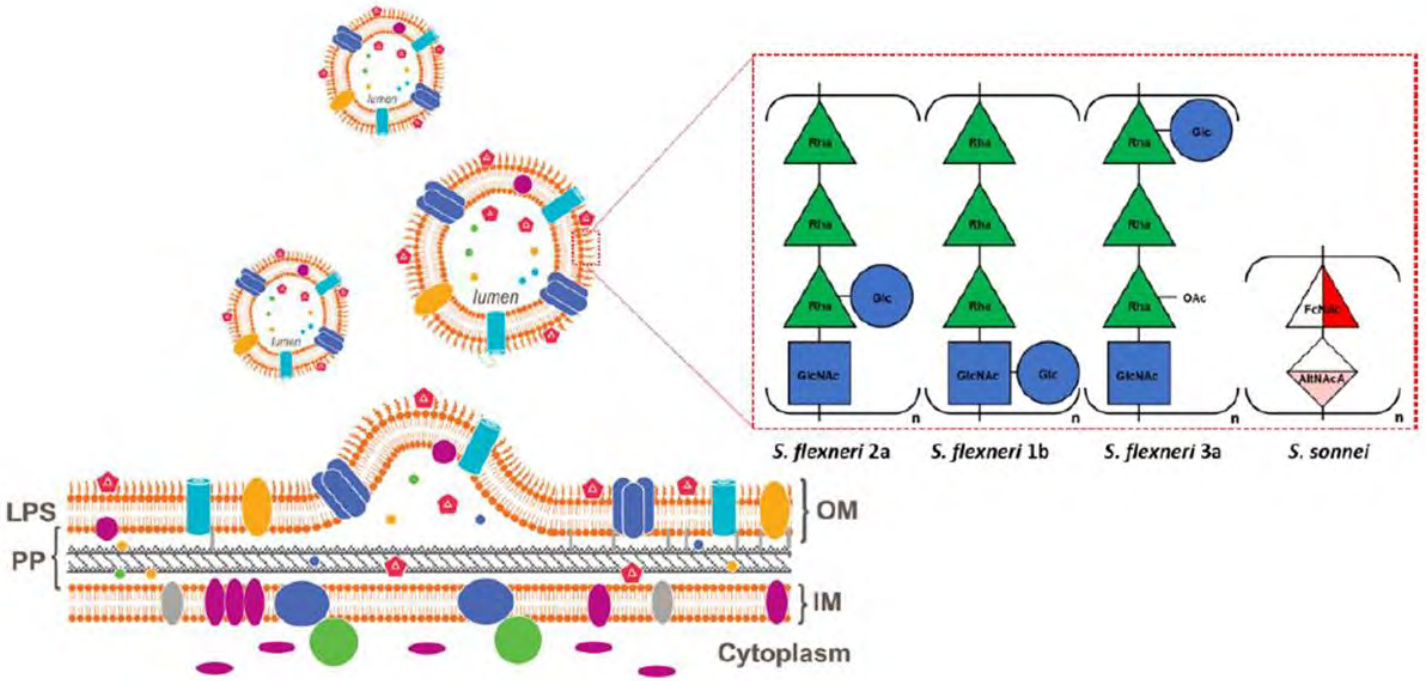
(Talaat K et al, EBioMedicine 2021)



	Attack Rate N(%)		Vaccine Efficacy	
	Flexyn2a *N* = 30	Placebo *N* = 29	(%)(95%CI)[§]	p-value*
Shigellosis (primary definition)	13 (43.3)	18 (62.1)	30.2 (−15 to 62.6)	0.11
More Severe Shigellosis (post-hoc definition)	8 (27.6)	16 (53.3)	51.7 (5.3 to 77.9)	0.015
Shigellosis (post-hoc Consensus paper [23] definition)	11 (36.7)	17 (58.6)	37.5 (−9.6 to 64.3)	0.07
Secondary Endpoints				
More Severe diarrhea	2 (6.7)	7 (24.1)	72.4	0.065
Received Early Administration of Antibiotics	9 (30.0)	18 (62.1)	51.7 (9 to 76.8)	0.0093
Received IV Fluids	7 (23.3)	13 (44.8)	47.9 (−11.8 to 78.3)	0.053
Number of subjects with moderate-severe diarrhea	15 (50.0)	17 (58.6)	14.7	0.34
Number of subjects with diarrhea of any severity	17 (56.7)	21 (72.4)	21.7	0.16

OUTER MEMBRANE VESICLES (OMV) – GVGH/GSK, SIENA

- Upregulated release of OMV from following deletion of *tolR*
- Reduced reactogenicity through deletion of *msbB* encoding acyl transferase
- Fermentation & purification by tangential flow filtration
- Formulation on aluminium hydroxide
- Simplicity of manufacture and low potential cost of goods



(Micoli F, et al, Vaccines 2022)

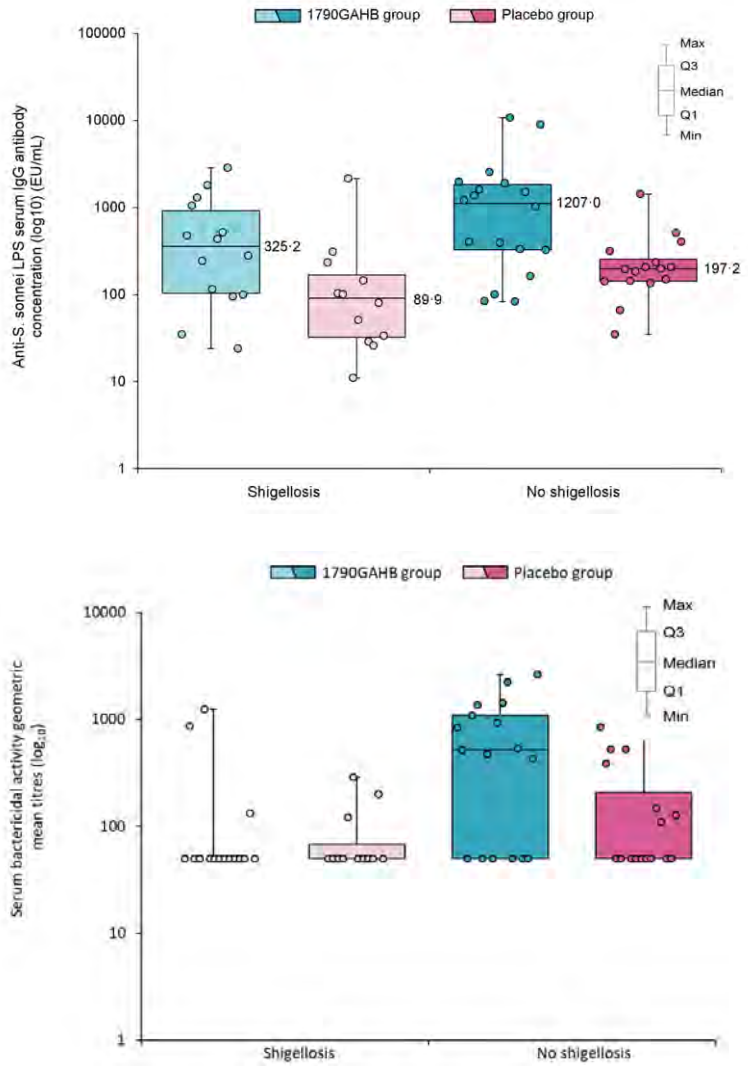
OMV – GVGH/GSK

Monovalent *S. sonnei* vaccine

- CHIM study Cincinnati
- Lack of efficacy
- Low quantities of O-antigen (1.5 ug) in vaccine
- Pre-challenge O-antigen IgG & SBA titers higher in ‘no shigellosis’ vs ‘shigellosis’ groups

4V *Shigella* vaccine

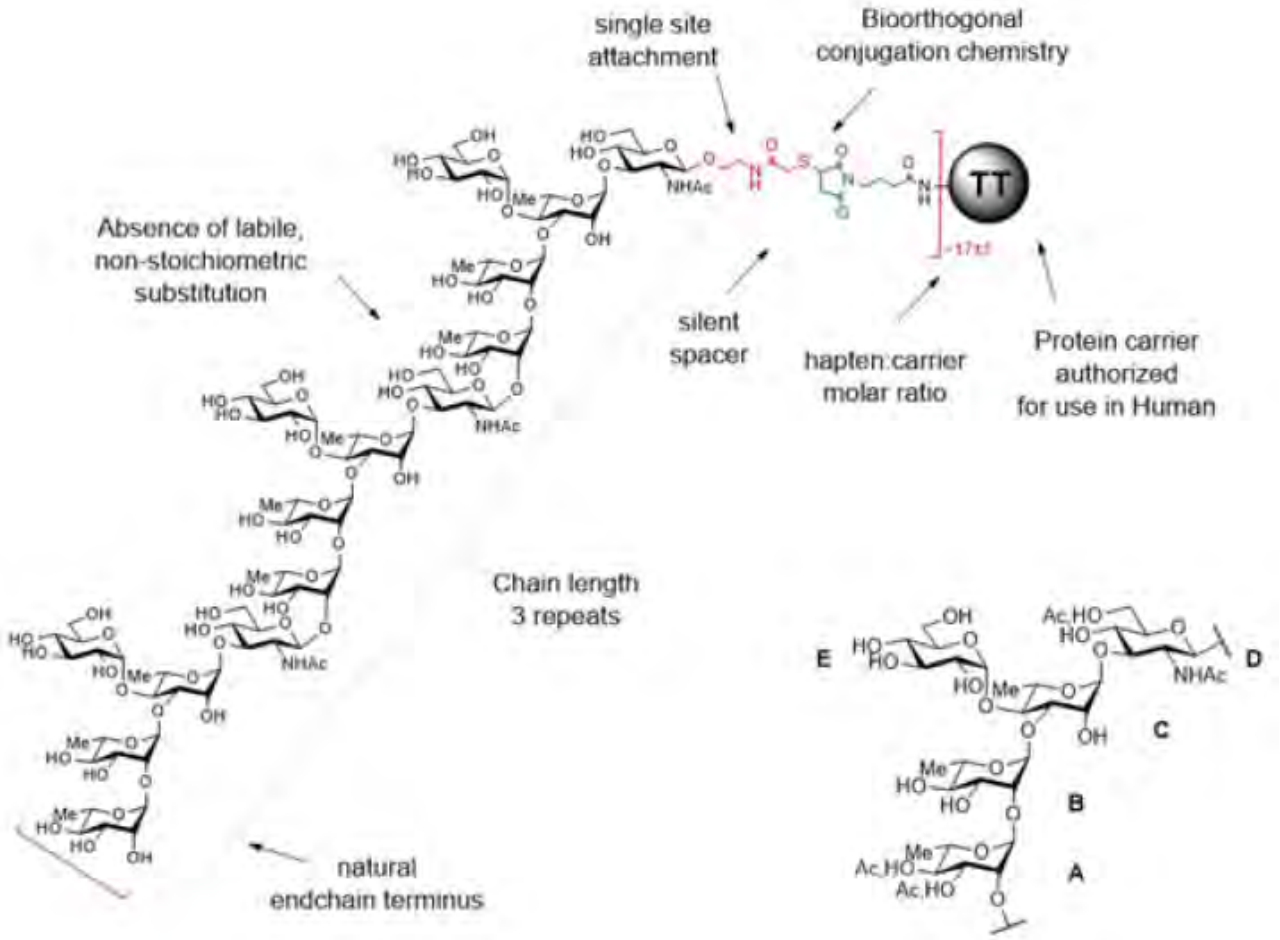
- New *S. sonnei* component with increased O-antigen
- Completing Phase 1 study in Belgian adults & starting age-descending dose-finding study in Kenya



(Frenck RW, EClinicalMedicine 2021)

SYNTHETIC O-ANTIGEN CONJUGATE – INSTITUT PASTEUR

- Chemical synthesis of defined short-chain O-antigens
- Conjugated to tetanus toxoid carrier protein

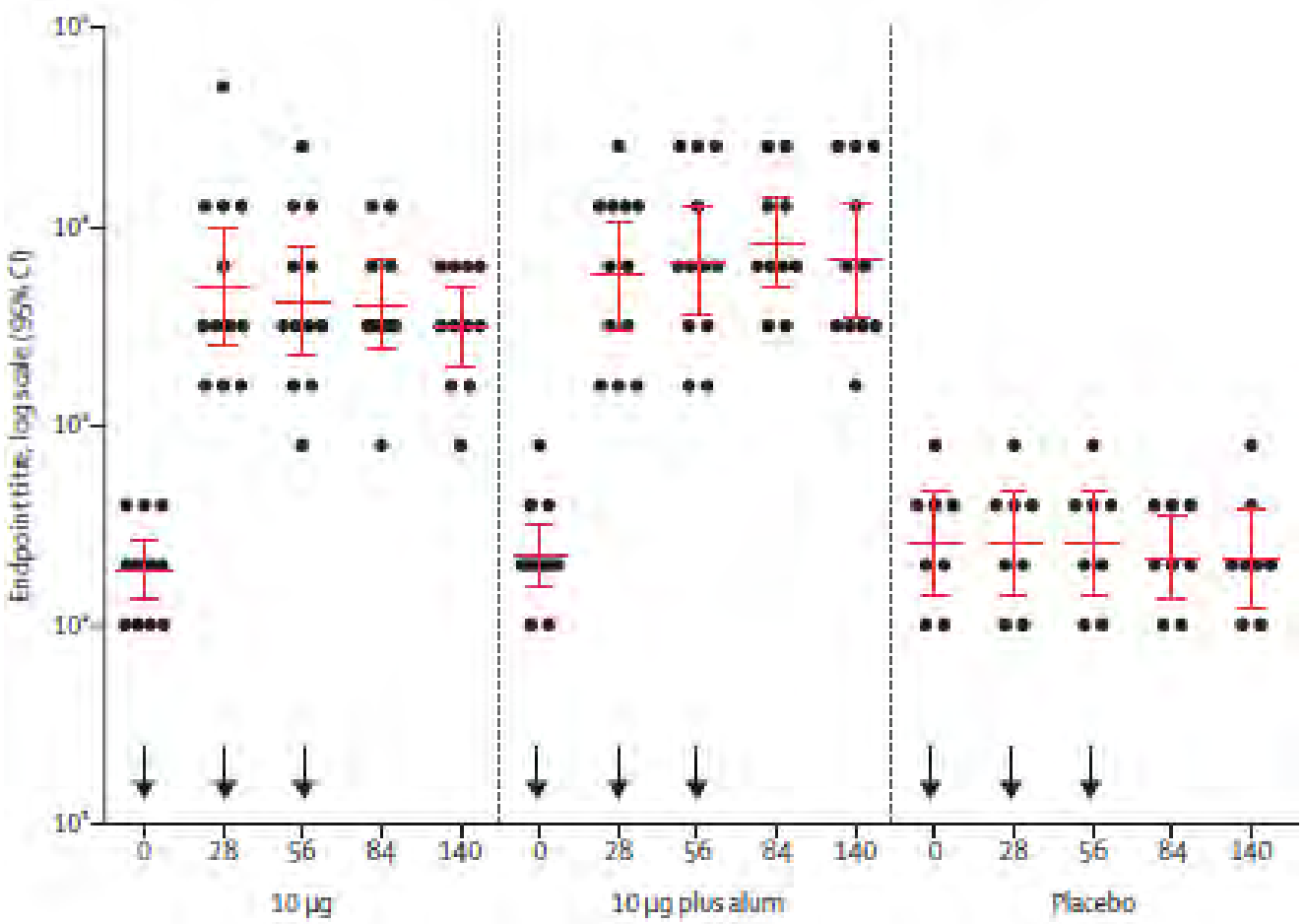


(Phalipon A, Mulard L, Vaccines 2022)

SYNTHETIC O-ANTIGEN CONJUGATE

Monovalent *S. flexneri* 2a vaccine

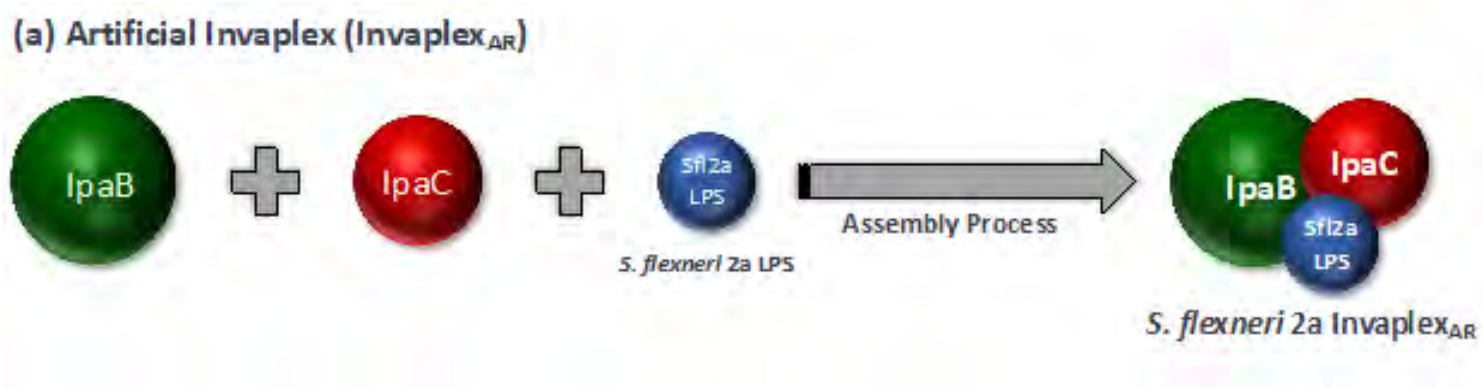
- Phase 1 study in Israeli adults
- 27-fold rise in serum O-antigen IgG
- Currently in
  - Descending-age, dose-finding study in Kenya
  - CHIM study at University of Maryland



(Cohen D, Lancet Infect Dis 2020)

INVAPLEX – WALTER REED ARMY INSTITUTE OF RESEARCH

- *Shigella* Invasin complex
- *Shigella* lipopolysaccharide complexed with conserved Ipa B and C *Shigella* proteins from type 3 secretion system
- 1st generation: Native Invaplex - complexes isolated from wild-type *Shigella*
- 2nd generation: Artificial Invaplex - combination of purified LPS and recombinant IpaB/IpaC
- 3rd generation; Detoxified Artificial Invaplex for parenteral administration



	Invaplex$_{NAT}$ (cGMP Lot 1307)	Invaplex$_{AR}$ (cGMP Lot 1835)	Invaplex$_{AR\text{-}Detox}$ (cGMP Lot 1972)
Stage of Clinical Development	Phase 1: Safe and immunogenic P2b: Less immunogenic and not protective	Phase 1: Safe and immunogenic	Phase 1: Safe and highly immunogenic

(Turbyfille KR, Vaccines 2022)

ZF0901 SHIGELLA BIVALENT CONJUGATE VACCINE BEIJING ZHIFEI LVZHU BIOPHARMACEUTICAL CO

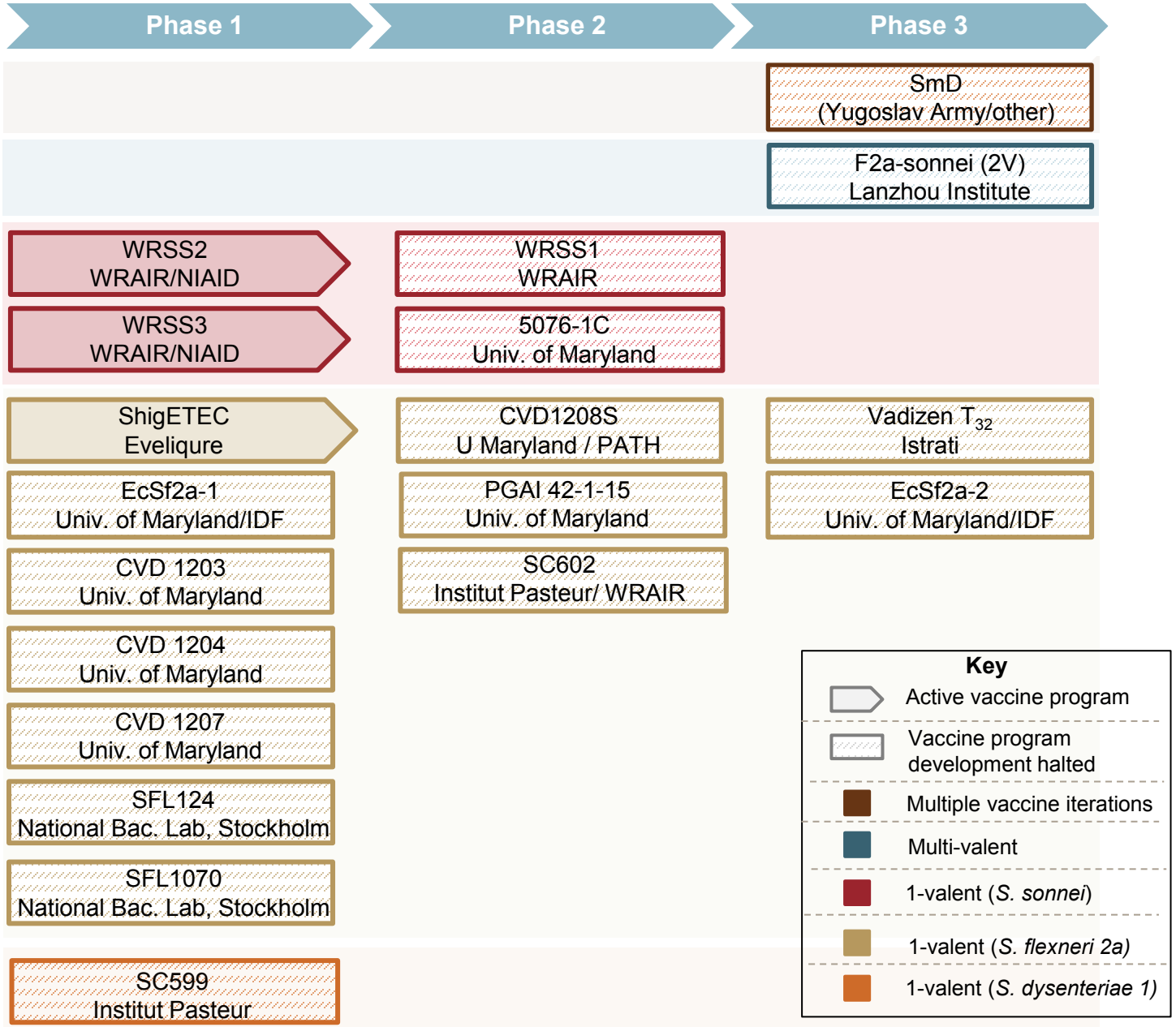
- *S. sonnei* & *S. flexneri* 2a O-antigens conjugated to tetanus toxoid
- Phase 2 descending-age study in China – currently in Phase 3 study
- 5 ug or 10 ug each O-antigen +/- aluminium phosphate
- Safe & immunogenic

(Mo Y, Vaccines 2022)

6–12 Months Old		Half Dose (n = 83)	Full Dose (n = 84)	Full Dose without Adjuvant (n = 75)
S. flexneri 2a				
	Conversion rate (%)	66.27 (55.05, 76.28)	64.29 (53.08, 74.45)	64.00 (52.09, 74.77)
Con (EU/mL)	Pre-	0.36 (0.27, 0.48)	0.30 (0.24, 0.39)	0.30 (0.23, 0.40)
	Post-	4.26 (3.07, 5.91)	3.08 (2.22, 4.28)	2.59 (1.69, 3.97)
	Fold rise	11.83 (7.99, 17.52)	10.15 (6.97, 14.77)	8.52 (5.61, 12.94)
S. Sonnei				
	Conversion rate (%)	89.16 (80.41, 94.92)	84.52 (74.99, 91.49)	85.33 (75.27, 92.44)
Con (EU/mL)	Pre-	0.19 (0.14, 0.24)	0.23 (0.17, 0.30)	0.22 (0.17, 0.30)
	Post-	6.85 (5.28, 8.89)	5.63 (4.22, 7.50)	6.01 (4.57, 7.90)
	Fold rise	36.47 (24.13, 55.11)	24.64 (15.96, 38.04)	27.02 (17.63, 41.42)

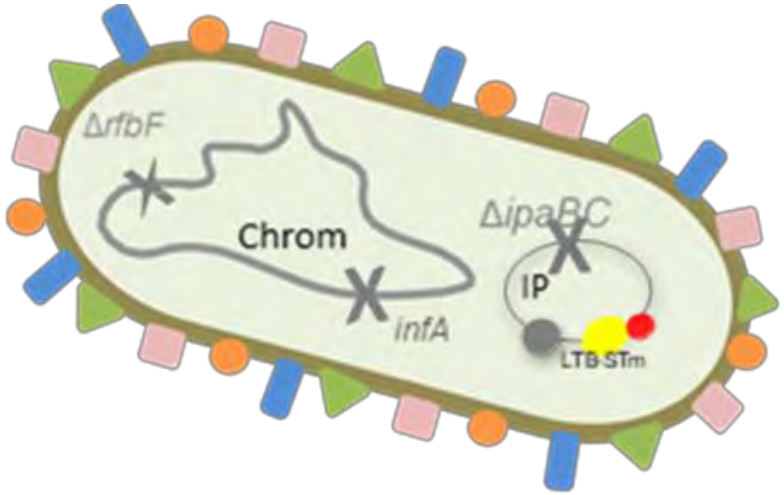
LIVE ATTENUATED VACCINES

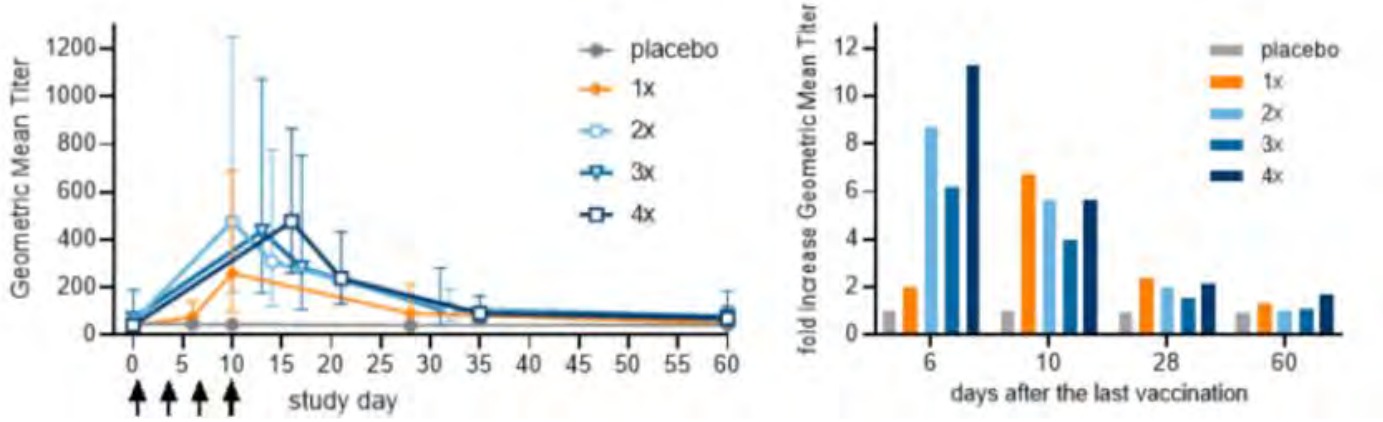
- Builds on efficacy from historic but discontinued Yugoslav ‘SmD’ and Istrati ‘Vadizen T_{32}’ vaccines
- Perennial challenge of balancing acceptable reactogenicity with sufficient immunogenicity
- Additional challenge of poor response among children in low- and middle-income settings
- Development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



SHIGETEC – EVELIQURE, VIENNA

- Combination *Shigella*/ETEC vaccine
- *S. flexneri* 2a chassis
  - Lacking O-antigen & invasion genes
  - Expressing ETEC toxoids
- Safe and immunogenic in Phase 1 dose-escalating study





Serum IgA anti-ShigETEC lysate responses

(Girardi P et al, Vaccines 2022)

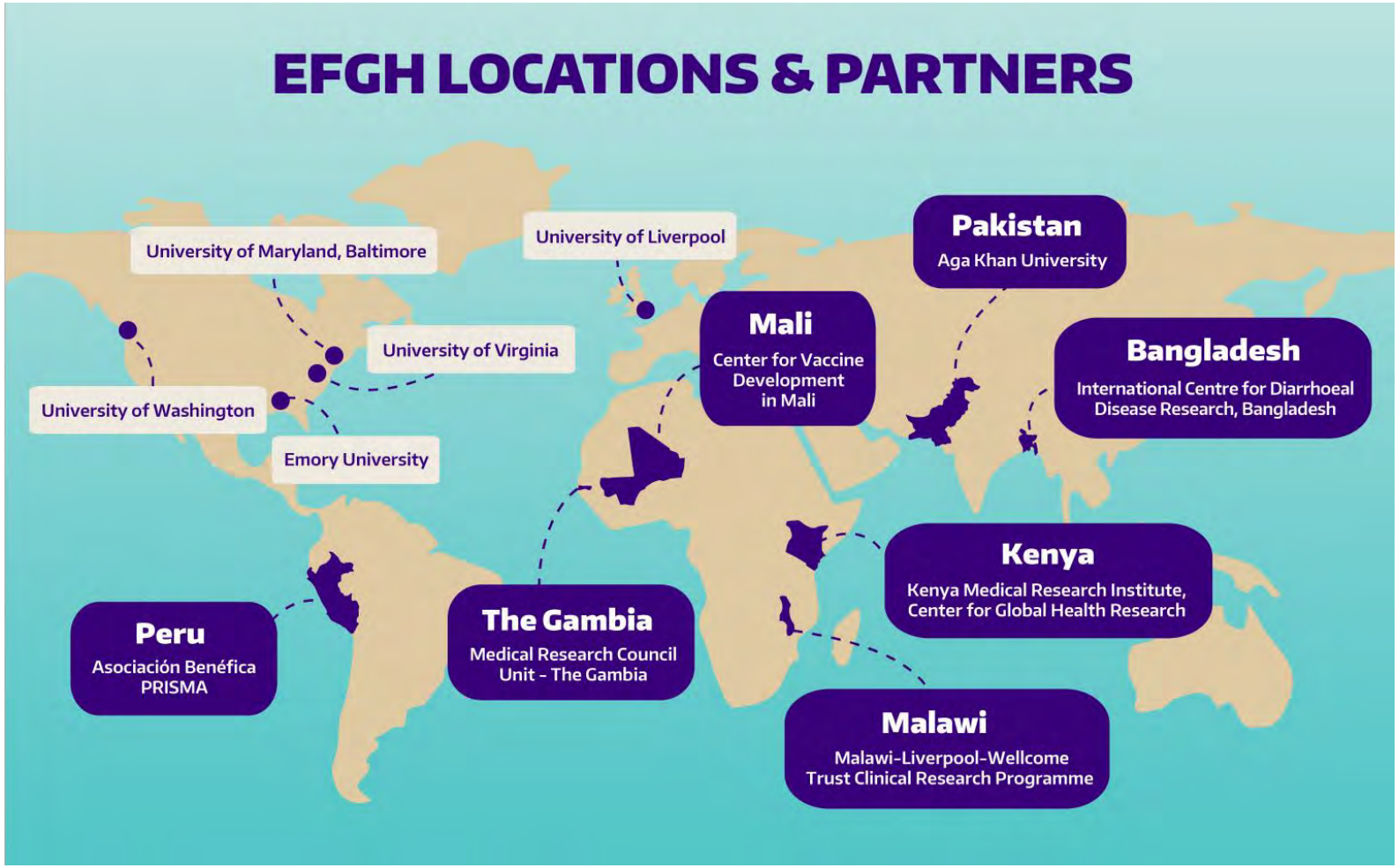
EFGH Goals

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/

(***slide courtesy of P Pavlinac***)

EFGH Consortium



ENTERICS FOR GLOBAL HEALTH
EFGH

Funded by
BILL & MELINDA GATES foundation

(*slide courtesy of P Pavlinac*)

EFGH Specific Aims

Primary Aims

- Determine the incidence of *Shigella*-attributed diarrhea in children 6 to 35 months of age in each of the EFGH country sites.

Secondary Aims

- Determine the incidence of *Shigella* diarrhea by serotype, severity definition, laboratory method (culture vs. qPCR), age, and by season.
- Describe the prevalence of resistance to commonly used antibiotics in *Shigella* isolates in each EFGH country site.
- Determine the risk of death, hospitalization, persistent diarrhea, diarrhea recurrence, and linear growth faltering in the 3 months following an episode of *Shigella* MAD.
- Compare various severity definitions in their ability to distinguish *Shigella* from non-*Shigella* attributable diarrhea and ability to predict risk of death or hospitalization in the subsequent 3 months.
- Quantify the cost incurred by families and health care systems due to *Shigella* morbidity and mortality.
- Identify optimal laboratory methods for *Shigella* culture by:
  - comparing the isolation rate of *Shigella* between two transport media for rectal swabs (Cary-Blair and modified Buffered Glycerol Saline [BGS])
  - comparing the isolation rate of *Shigella* between two fecal sample types (rectal swabs and whole stool) among the subset of children who produced whole stool in The Gambia and Bangladesh country sites.

(***slide courtesy of P Pavlinac***)

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 required for sufficient serotype coverage

- Key question: Are candidates sufficiently immunogenic to confer protection in LMIC children?
- Each candidate in need of a manufacturing partner for late-stage clinical development

PATH | 2022 VASE CONFERENCE

Vaccines Against *Shigella* and ETEC

Selected Highlights from Two Aspects of PATH's *Shigella* Vaccine Value Proposition Analysis

Bill Hausdorff, PhD
Lead, Public Health Value Propositions
Center for Vaccine Introduction and Access,
PATH
Washington DC

Two Key Questions

Question 1

What is the perceived value of a Shigella vaccine to LMIC policy makers and health care workers?

What are the drivers of that value?

Country-level study

J. Fleming et al (manuscript in preparation)

Question 2

To what extent could a Shigella vaccine effective against stunting avert large economic consequences (e.g., loss of income)?

Loss of income economic model

C. Puett et al (manuscript submitted)

*Supported by Grants from Bill and Melinda Gates Foundation and Wellcome Trust

PATH

Stakeholder preferences

A study to identify preferences and priorities for prospective *Shigella* vaccines in target populations

Study overview

In 2021-2022, PATH conducted a mixed-methods study to assess the feasibility and acceptability of *Shigella* vaccines.

Objective—to identify the **vaccine delivery attributes** that affect the willingness of participants to introduce a *Shigella*-containing vaccine.

Study interviews gathered qualitative and quantitative information across countries and audiences

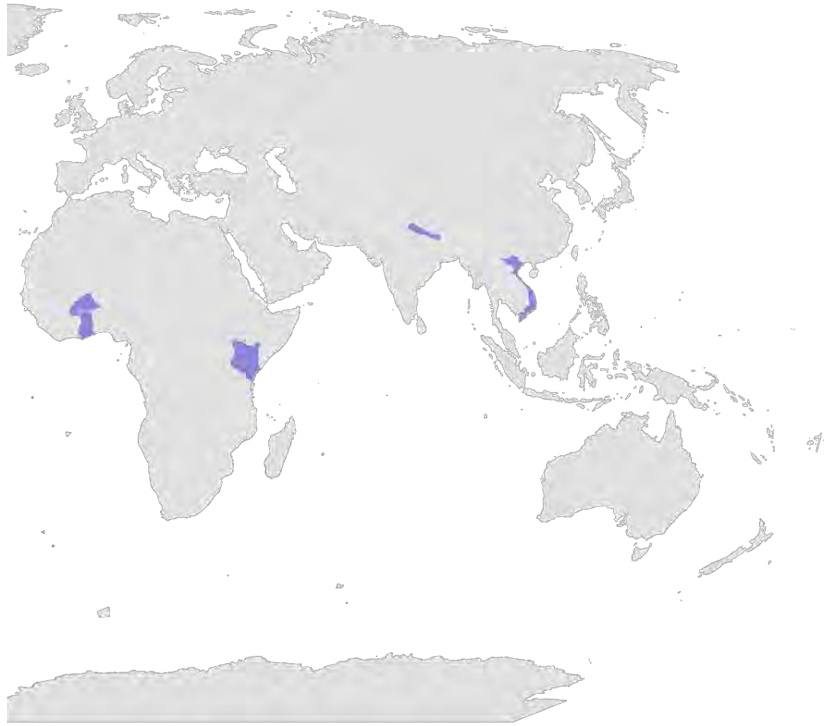
Study overview

Conducted semi-structured interviews to quantitate levels of prioritization and describe decision-making rationale.

Participants:

- **National stakeholders**–individuals with authority/influence over vaccine introduction decisions (MOH/NITAG) or public health diarrhea control, nutrition, or immunization.
- **Healthcare providers** –heads of health facilities or worked in immunization in 4 or 5 facilities within a day's drive of the capital.

Study sites: Burkina Faso, **Ghana**, **Kenya**, **Nepal**, **Vietnam**



J. Fleming et al (manuscript in preparation)

Study sample size

Study overview

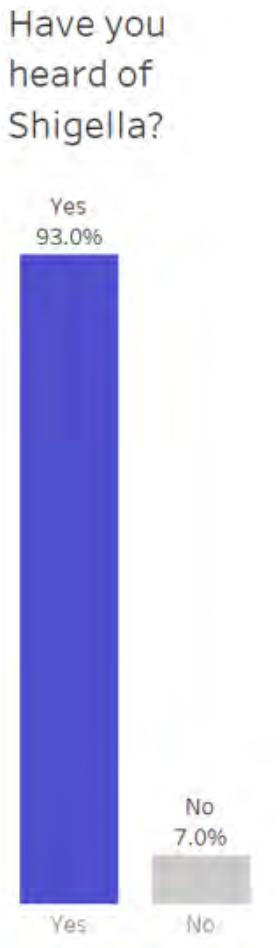
	Burkina Faso	Ghana	Kenya	Nepal	Vietnam	Total
National stakeholders	7	6	5	5	9	32
Healthcare providers	13	11	10	10	10	54
Total	20	17	15	15	19	86

J. Fleming et al (manuscript in preparation)

Stakeholder preferences

Selected Results:
1. Awareness of Shigella was high

Prioritization of health concerns

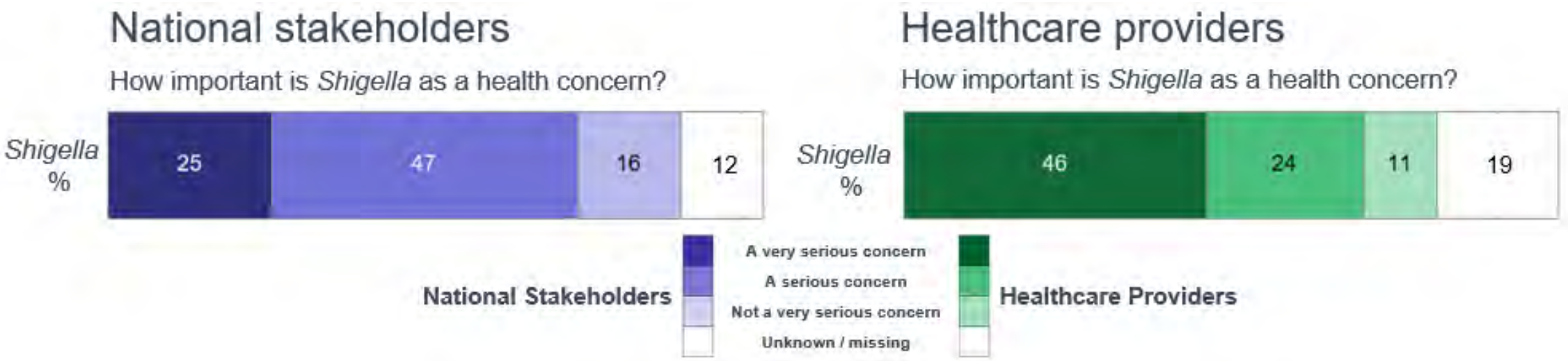


- 93% of respondents were aware of *Shigella*
- We did not ask about other enteric pathogens

J. Fleming et al (manuscript in preparation)

2. Importance of *Shigella* as a health concern for children under 5 varied across groups

Prioritization of health concerns



- **National stakeholders** prioritized *Shigella* lower and cited multiple causes of diarrhea; relatively low *Shigella* burden compared to other VPDs; other control interventions in place
- **Healthcare providers** prioritized *Shigella* higher and spoke of *Shigella's* impact on children's health and existing challenges with diagnosis and treatment

J. Fleming et al (manuscript in preparation)

Stakeholder preferences

Participants were asked to prioritize a *Shigella* vaccine and given progressively more background information

Study overview

	Information provided
Level 1	• None
Level 2	• Global *Shigella* burden estimates and vaccine characteristics (see table). • National *Shigella* burden estimates and hypothetical 60% vaccine effectiveness.
Level 3	• The ability of *Shigella* vaccine to slow the pace or prevent antibiotic resistance.
Level 4	• The role of *Shigella* in growth stunting, impaired physical and cognitive development, lower education attainment, and earning power as adults. • National estimates of *Shigella*-attributable stunting and potential impact of a 60% effective vaccine.

Global *Shigella* burden estimates	Hypothetical vaccine characteristics
Annual morbidity under five years: 75 million diarrhea cases Annual mortality under five years: 64,000 deaths	**Effectiveness: 60%** Availability: 2025-2030 Presentation: Injectable Schedule: 1 or 2 doses given mid-to late in first year of life (9 months) Cost and funding support: Around US$1/dose Initial support by Gavi

Sources: Khalil, *The Lancet Infectious Diseases*, 2018; WHO PPC, 2021; Anderson, *The Lancet*, 2019; Victora, *The Lancet*, 2008; Black, *The Lancet* 2013; Grantham-McGregor, *The Lancet*, 2007.

PATH

J. Fleming et al (manuscript in preparation)

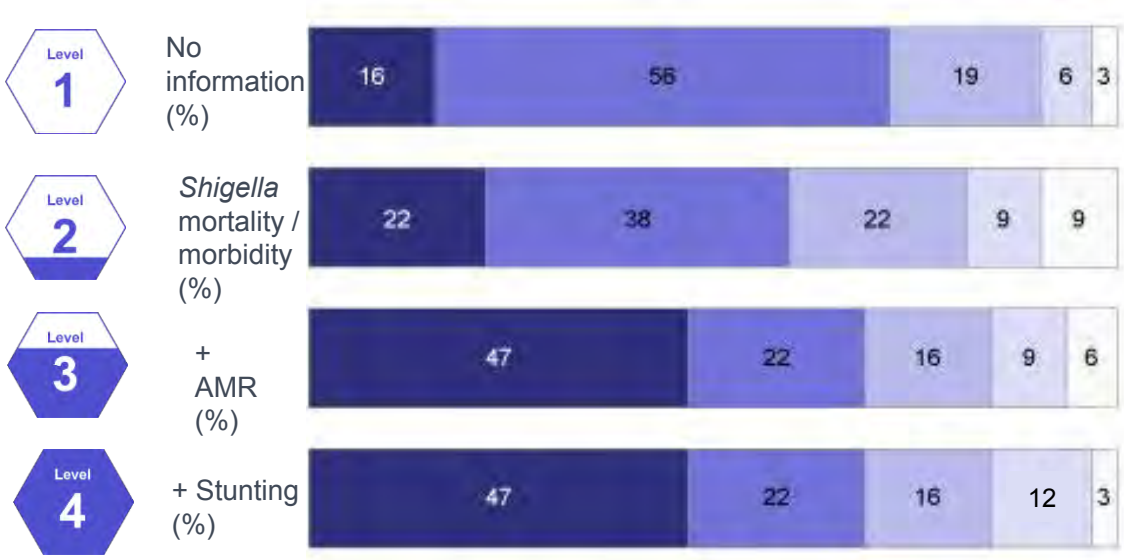
Stakeholder preferences

3. Prioritization of *Shigella* vaccine rose with information on additional impacts, notably AMR and stunting

Shigella vaccine prioritization

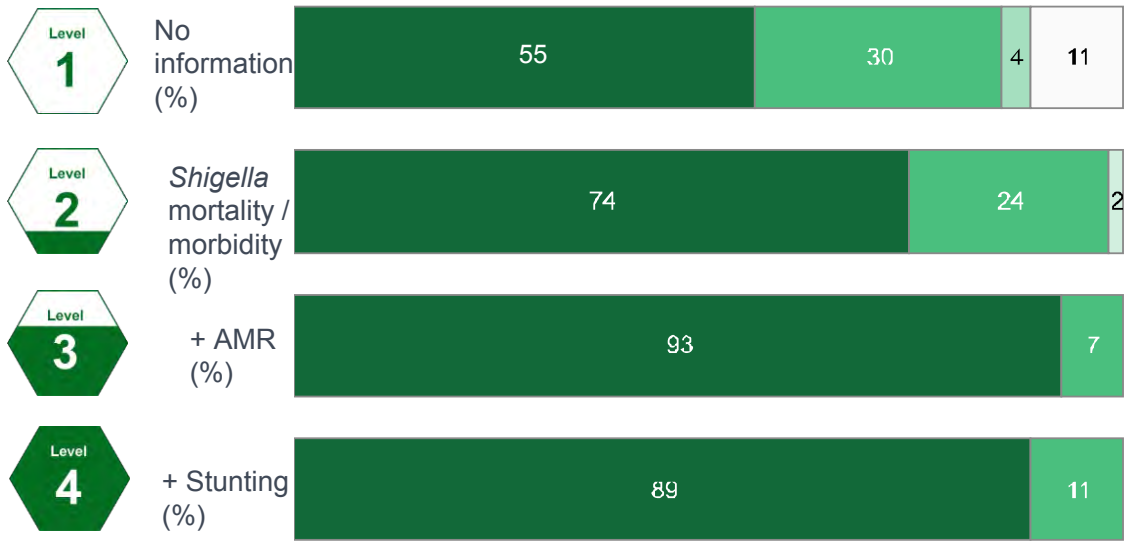
National stakeholders:

What is the priority of a *Shigella* vaccine?



Healthcare providers:

What is the priority of a *Shigella* vaccine?



National stakeholders

High priority
Medium priority
Low priority
Not a priority
Missing

Healthcare providers

J. Fleming et al (manuscript in preparation)

Stakeholder preferences

Conclusions (1)

Based on in-person mixed methods study:

1. LMIC Stakeholders and Health Care Workers have heard of *Shigella*,

2. But most don't view a *Shigella* vaccine as being of high priority

3. Perceived priority increases when provided information about Shigella's link with growth stunting and antimicrobial resistance

4. But considerable uncertainty about true burden, and true impact a vaccine could have

J. Fleming et al (manuscript in preparation)

Stunting and economic impact model: Starts with… the independent association of height with wages

Evidence that taller people earn higher wages, but why?

- Physical capacity.
- Self-esteem, social power, authority, prestige.
- Non-cognitive “social” skills.
- Cognitive skills (start forming in early childhood).
- Taller, more educated workers enter more skill-intensive occupations.
- Parents “invest” more (schooling, nutrition) in taller children.

Literature review showed:

- Independent association of stature with wages
- Gave estimates for “height premium” to use in model.
  - Height premium = linkage between increased height and improved income

C. Puett et al (manuscript submitted)

Shigella, stunting, and economics

By preventing stunting, what could be the effect of an infant *Shigella* vaccine on wages in adults?

Stunting and economic impact model: development and results

Evidence before this study

- Studies in the nutrition field have quantified future economic productivity benefits of improving child linear growth compared with cost of delivery.

Added value of this study

- This is the first analysis of the productivity benefits of **vaccine**-reduced growth faltering.

Implications of all available evidence

- If it prevents stunting, the economic value of *Shigella* vaccination may be much greater than previous estimates that focus on acute impact

Standard metric: Benefit-Cost Ratio. BCR >1 means >$1 of benefit per $1 of cost

PATH

C. Puett et al (manuscript submitted)

An overly simplistic summary of the model

- Assume that *Shigella* vaccination prevents X cm of *Shigella*-induced stunting/child (z score shift)*
  - *depends on % of stunting actually due to *Shigella* & true vaccine efficacy against *Shigella* stunting
- That translates into Y cm more height/adult
- Every cm increase is associated with greater wage income/adult = ("height premium")
- Assuming high % of child population is vaccinated, over working lifetime that translates into a substantial increase in overall wage income in the population
- Increase in wage income means increases in overall GNI.
  - Note: To make increases in later years worth less than increases now—apply a "discount" percentage

Assuming vaccine cost is $2/dose, plus imm. program costs, can calculate Benefit-Cost Ratio (BCR)

Benefit-cost ratios are generally above parity in all regions, showing dramatic economic benefit of vaccination

Stunting and economic impact model: development and results

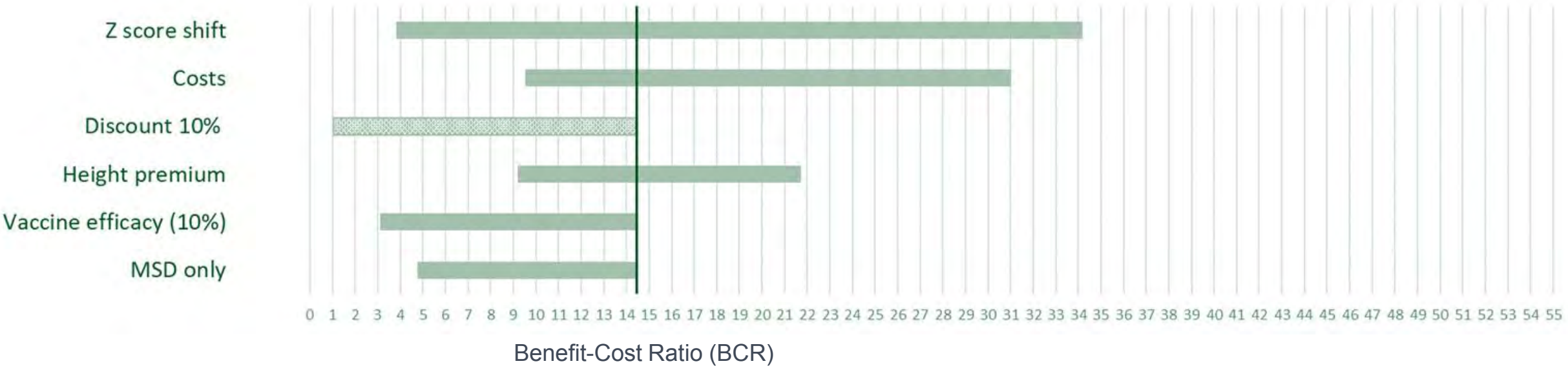
Discounting	3%	6%
LICs and LMICs only		
AFRO	**8.52**	2.63
AMRO	3.32	1.18
EMRO	2.90	0.97
EURO	4.06	1.36
SEARO	**21.67**	5.95
WPRO	6.56	1.92
Gavi	14.45	4.11
Global	11.60	3.34

- Benefit-cost ratios are strongest in the SEARO Region, followed by the AFRO Region.
- EMRO is the only Region below parity,
  - and this was only at a conservative 6% discounting measure.

C. Puett et al (manuscript submitted)

Sensitivity analysis of Gavi-eligible countries

Stunting and economic impact model: development and results



- Height premium was a range (0.55%–1.3%) because it depends on many country-specific factors.
- HAZ shift and costs vary considerably by country and year due to assumptions behind disease burden and vaccine coverage.

C. Puett et al (manuscript submitted)

Conclusions (2)

Based on economic model relating stunting to loss of wage income:

1. Essentially any impact of a *Shigella* vaccine on childhood stunting could translate into extremely positive benefit-cost ratios

2. Regional variability in BCRs reflect regional differences in economic indicators, medical costs, magnitude of stunting

3. These positive impacts hold true for most regions, including GAVI, even if vaccine efficacy is assumed to be only 10%.

C. Puett et al (manuscript submitted)

Clinical and regulatory development strategies for *Shigella* vaccines

PDVAC December 2022

Birgitte Giersing, PhD

World Health Organization | IVB

Potential mechanisms for accelerated regulatory approval

Accelerated approval based on a surrogate marker of efficacy, with a requirement that post-approval effectiveness studies are completed to confirm the surrogate marker as a correlate of protection (CoP), or that it provides clinical benefit in 'real-world' conditions

Conditional marketing authorisation (CMA) where vaccines may be approved on less comprehensive clinical data than typically required if the benefit of immediate availability outweighs the risk.

Approval based on CHIM may be a viable route, even in absence of a correlate of protection, since they provide an efficacy readout

O-antigen IgG levels provide a putative threshold of protection

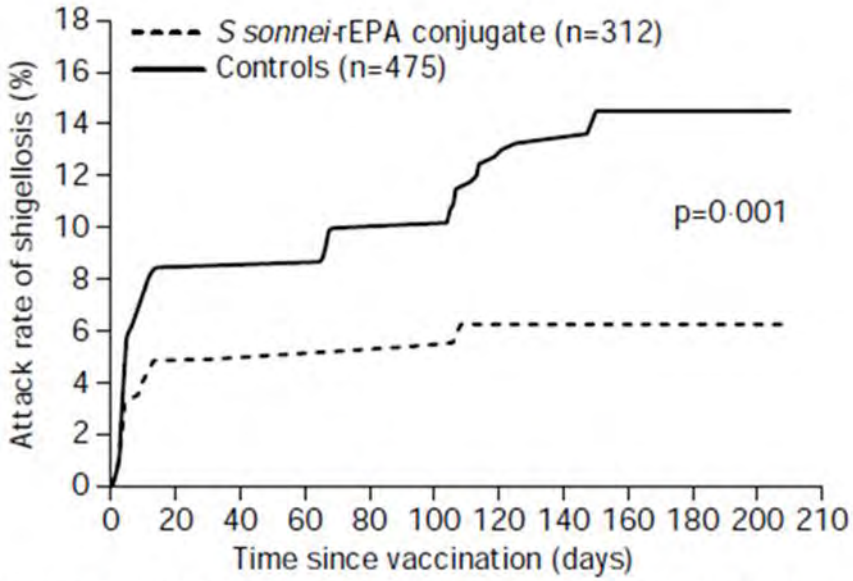


Figure 2: **Attack rates of culture-proven *S sonnei* shigellosis in recipients of *S sonnei* conjugate vaccine and controls in groups A–D**

Table 2
Serum IgG anti–*S. sonnei* lipopolysaccharide at the cut-off 7.4 (ln 1600) on day 17 after vaccination and cases of *S. sonnei* shigellosis

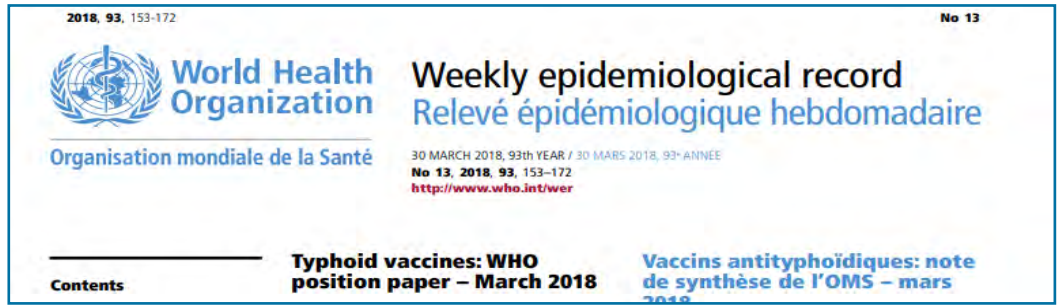
IgG anti–*S.sonnei* LPS	No. without *S. sonnei* shigellosis	%	Cases of *S. sonnei* shigellosis	%
Complete-cases analysis: individuals with available sera on day 17 post-vaccination				
IgG < ln 1600	237	67	15	94
IgG ≥ ln 1600	118	33	1	6
Total	355	100	16	100
Imputed dataset: multiple imputation for missing values of sera on day 17 postvaccination[a]				
IgG < ln 1600	288	66.5	25	92.6
IgG ≥ ln 1600	145	33.5	2	7.4
Total	433	100	27	100

[a] After multiple imputation (predictive mean matching method).

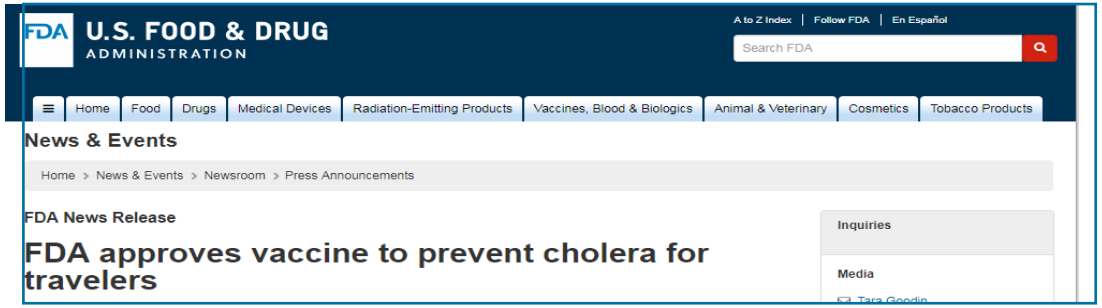
Source: Cohen et al, 1997; Cohen et al, 2022.

World Health Organization | IVB

Precedence for regulatory approval on the basis of CHIM



http://apps.who.int/iris/bitstream/handle/10665/272272/WER9313.pdf?ua=1



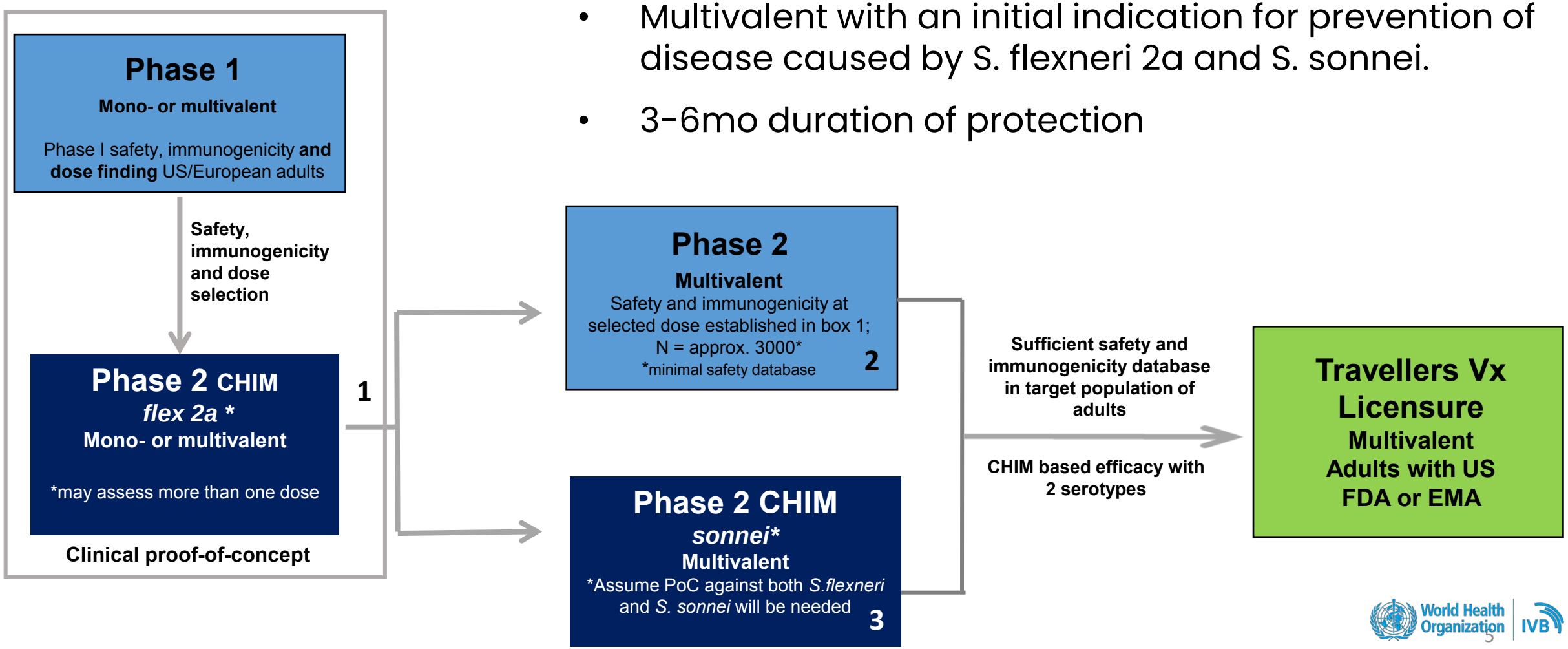
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm506305.htm

- CHIM established for two Shigella serotypes *(S. sonnei and S.flexneri 2a)*
- Role of CHIM in cholera and typhoid conjugate vaccine licensure / recommendation
- BUT: CHIM studies are conducted in adults; in high income settings
- ➢ It is not known how responses in CHIM studies will translate into young children in low resource settings.

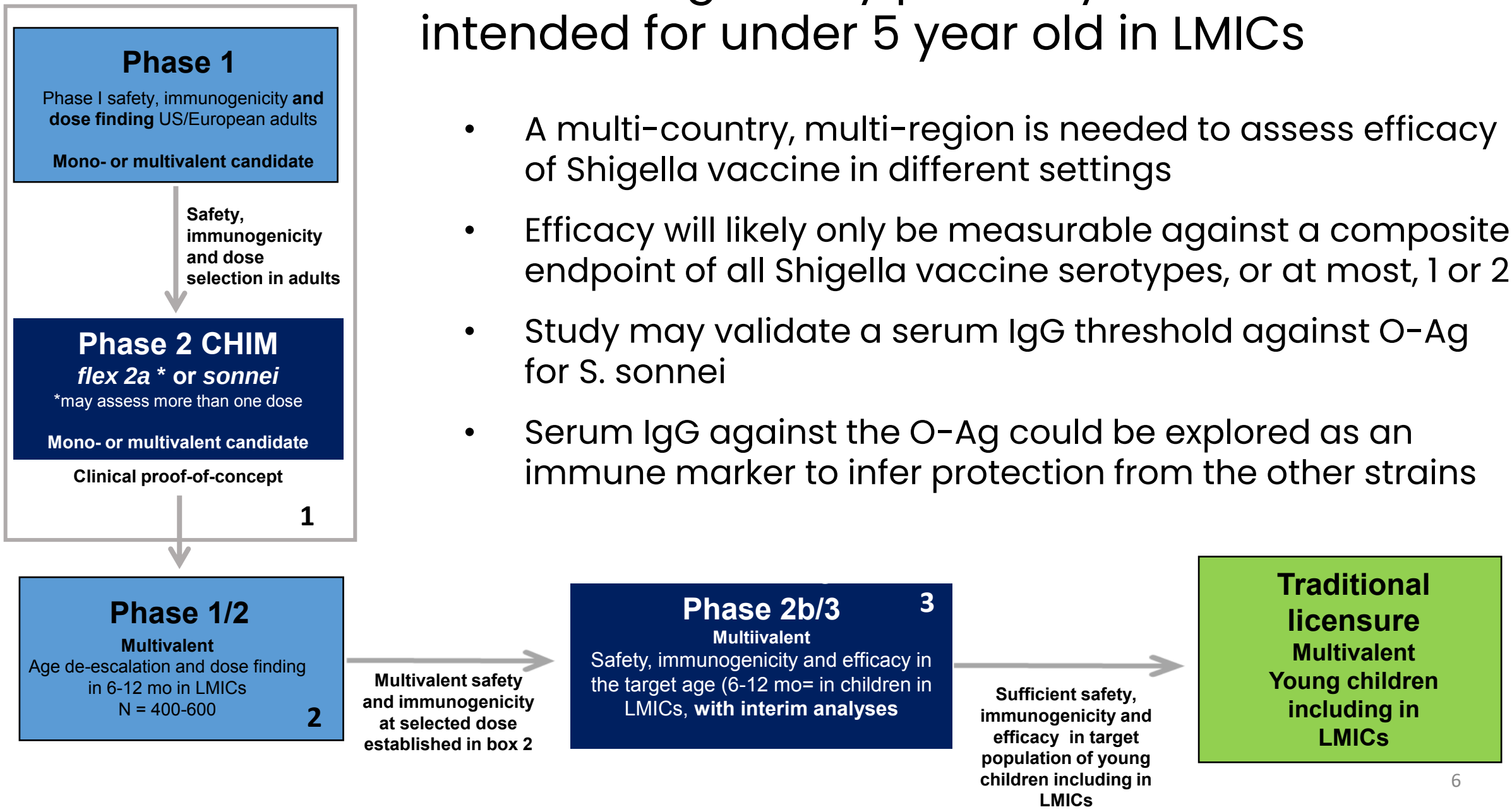
World Health Organization | IVB

Potential regulatory pathway for *Shigella* vaccines intended for high-risk adults

- Designed from the outset as a bivalent, or
- Multivalent with an initial indication for prevention of disease caused by S. flexneri 2a and S. sonnei.
- 3-6mo duration of protection

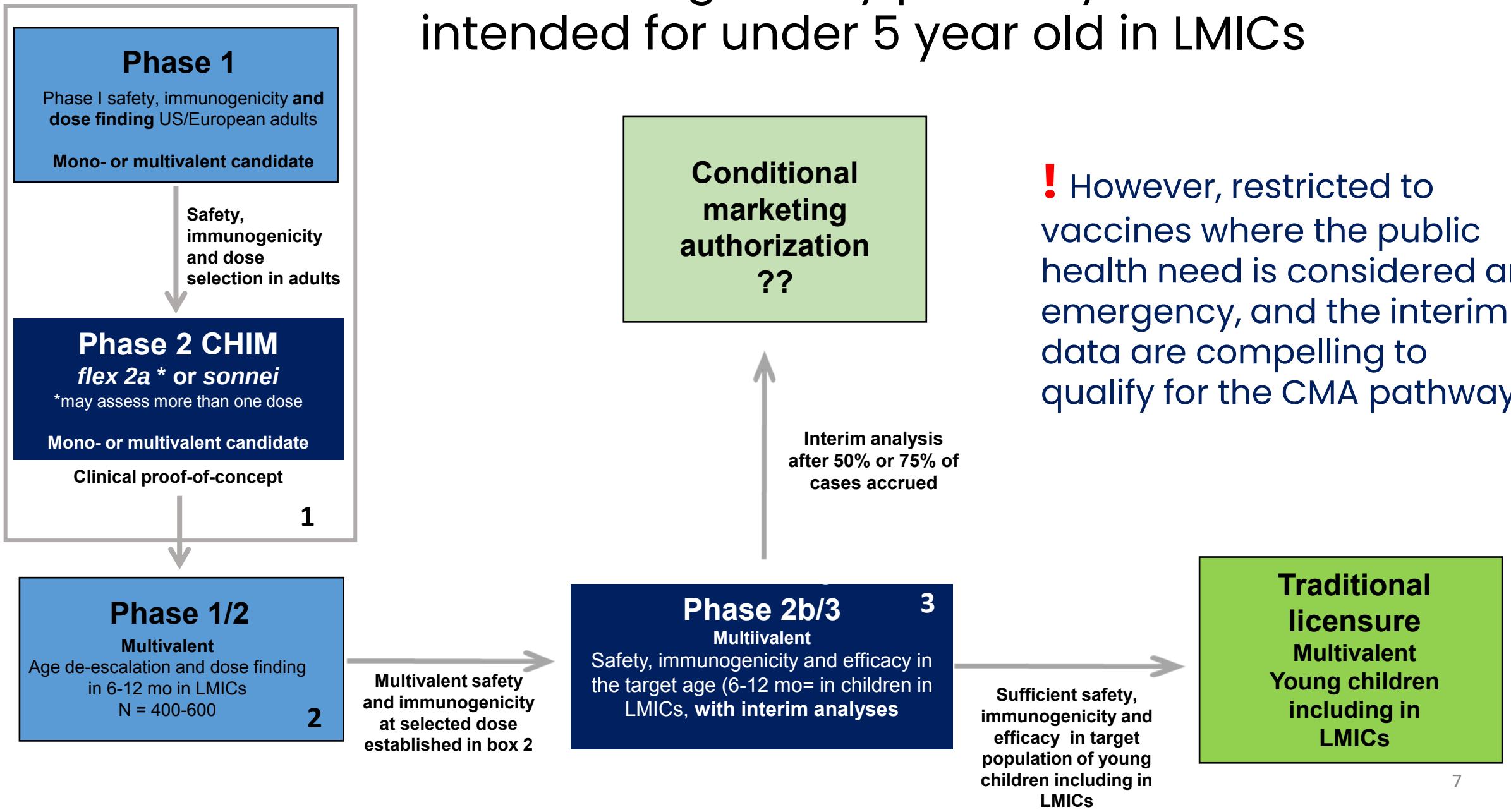


Potential regulatory pathway for vaccines intended for under 5 year old in LMICs



- A multi-country, multi-region is needed to assess efficacy of Shigella vaccine in different settings
- Efficacy will likely only be measurable against a composite endpoint of all Shigella vaccine serotypes, or at most, 1 or 2
- Study may validate a serum IgG threshold against O-Ag for S. sonnei
- Serum IgG against the O-Ag could be explored as an immune marker to infer protection from the other strains

Potential regulatory pathway for vaccines intended for under 5 year old in LMICs



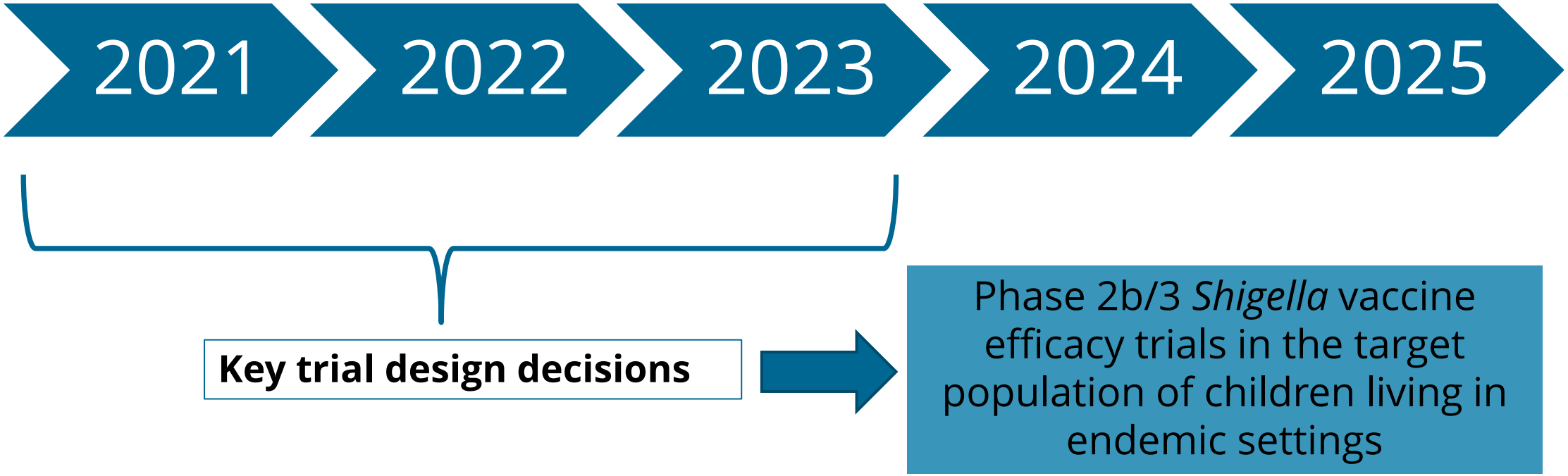
! However, restricted to vaccines where the public health need is considered an emergency, and the interim data are compelling to qualify for the CMA pathway.

Conclusions of the regulatory and policy pathway analysis

- For broad implementation of a Shigella vaccine, including in children in low resource settings, **a multi-site field efficacy study is needed to support a global policy decision**
- The CHIM may support licensure of a travellers' indication and enable earlier regulatory approval and use in high-risk adults.
- The conditional marketing authorization pathway is considered very unlikely for Shigella vaccines as it is reserved for public health emergencies
- The adult travellers and endemic paediatric Shigella vaccines could be developed in parallel, but the **vaccine attributes will need to meet the WHO PPC to be considered for WHO policy.**
- A strategy 'dual-market strategy' may de-risk investment in the endemic pediatric indication, and accelerate manufacturing capacity and regulatory approvals.

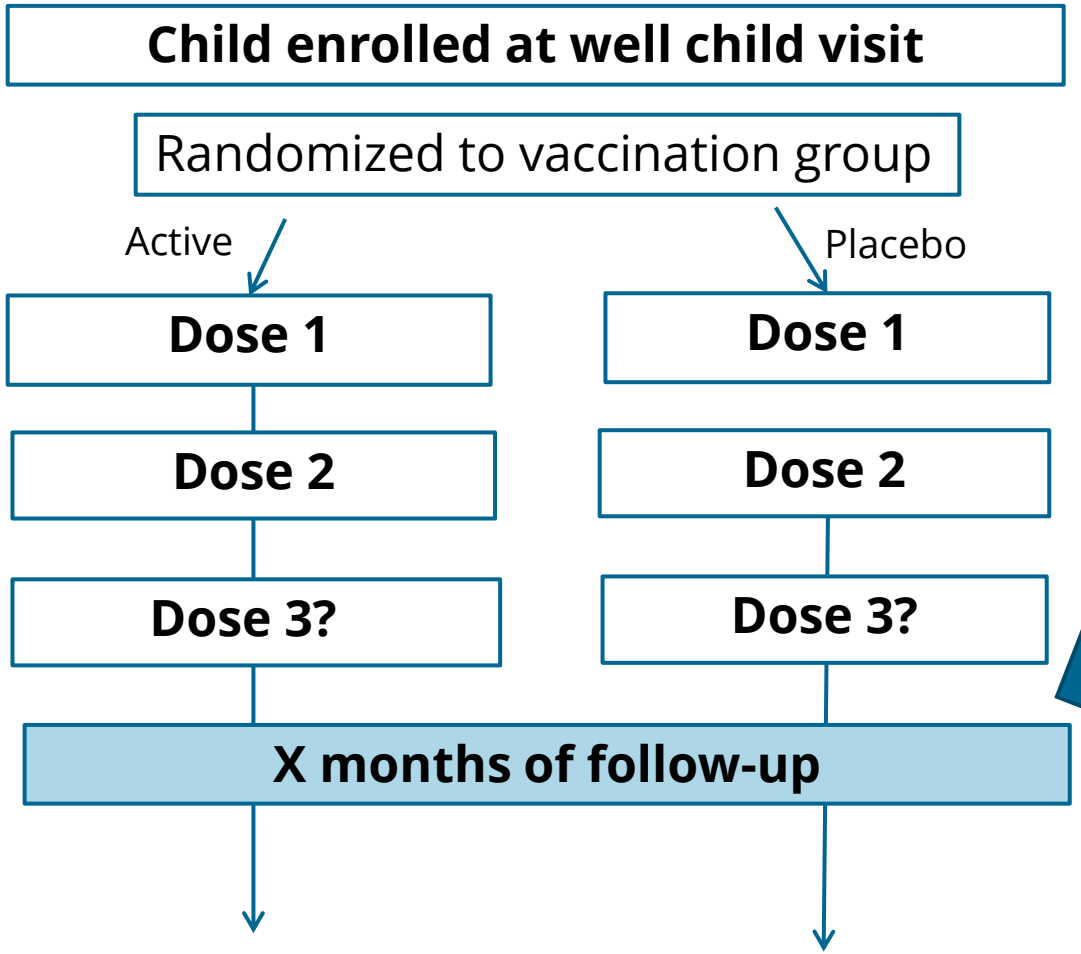
Rational: Vaccine timeline

Several promising Shigella vaccines are in development (eg. Shigella 4V)



Slide courtesy of Patty Pavlinac

Possible Efficacy Trial



Key trial design decisions

Age and schedule

Length and follow up

Primary clinical outcome

- Moderate or severe diarrhea
- Medically attended diarrhea
- All diarrhea

Primary microbiologic outcome

- culture-confirmed
- qPCR-confirmed

Slide courtesy of Patty Pavlinac

Recent recommendations around pediatric field efficacy trial design

Vaccine 37 (2019) 4814–4822

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Clinical endpoints for efficacy studies

Chad K. Porter [a,*], Ramiro L. Gutierrez [a], Karen L. Kotloff [b]

[a] Enteric Disease Department, Naval Medical Research Center, Silver Spring, MD, USA
[b] Division of Infectious Disease and Tropical Pediatrics, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, USA

2019

vaccines

MDPI

Article

Pivotal *Shigella* Vaccine Efficacy Trials—Study Design Considerations from a *Shigella* Vaccine Trial Design Working Group

Patricia B. Pavlinac [1,*], Elizabeth T. Rogawski McQuade [2], James A. Platts-Mills [3], Karen L. Kotloff [4], Carolyn Deal [5], Birgitte K. Giersing [6], Richard A. Isbrucker [6], Gagandeep Kang [7], Lyou-Fu Ma [8], Calman A. MacLennan [8], Peter Patriarca [9], Duncan Steele [8] and Kirsten S. Vannice [8]

2022

Slide courtesy of Patty Pavlinac

Consensus building around clinical end-points for regulatory approval and policy in LMICs.

- WHO is planning consultation with regulators, including those in which the phase III study will be conducted
- Inclusion of National, regional and global immunization technical advisory groups that make recommendations to governments for vaccine introduction
- We will have the results of the criteria survey in Q1 2023.
- Regulatory convening, likely in the Africa region: approx. May 2023

LimmaTech® Biologics
better technology for better health

LMTB Shigella Program

WHO PDVAC

December 5, 2022

Shigella

Clinical Development of a Multivalent Shigella Bioconjugate Vaccine

S. flexneri 2a-EPA Phase I

Safety and immunogenicity in adults, First in Man

- Good safety profile
- Robust humoral response (IgG, IgA) with > 90% responders and functional antibodies (SBA)

S. flexneri 2a-EPA Phase IIb challenge study

Clinical Proof of Concept for efficacy in Adults

- 52% VE against severe shigellosis (p= 0.015)
- >70% VE against more severe diarrhea (>10 episodes/day) (p=0.02)
- Reduction in Disease Severity Score (p=0.02)

Development multivalent bioconjugate **Shigella4V**

Final product composition

- Tetravalent bioconjugate vaccine consisting of the O-antigen polysaccharides of S. flexneri 2a, 3a, 6 and the S. sonnei

Phase I/II with multivalent Shigella bioconjugate in infants

Immunogenicity in target population

- Very good safety profile Immunogenicity results beg of 2023

Two-pronged development: Global Health and Travelers

Riddle MS, Clinical and Vaccine Immunology 2016; Talaat KR, EBioMedicine 2021; Clarkson KA, EBioMedicine 2021; Martin P, Vaccines 2022

Shigella

Phase I/II with Multivalent Shigella Bioconjugate in Infants

- Phase 1/2, age descending, dose finding, controlled and randomized
- Two clinical sites in Kenya
- Four dosages with/wo Alum
- Two intramuscular injections, three months apart and a booster 6 months after second immunization
- Infants (9 months ± 1 mo): 472 enrolled, 440 received 2nd vaccination; 410 received booster vaccination
- 6 months follow up after booster injection
- Co-administration of Measles-Rubella
- LSLV performed in Nov 2022

Shigella

CMC Strategy

Pediatric/LMIC Market

- >= 2 dosings
- Amont/dose TBD
- Target ~1.5 US$/dose
- Multi-dose vials
- Targeting GAVI, UNICEF first

Travelers Market

- Single dosing
- Amount/dose TBD
- Higher price
- Prefilled syringe
- Marketing HIC first

➢ Discussions ongoing with LMIC manufacturers

Shigella

Regulatory Path

Pediatric/LMIC Market

- Benefit of information obtained from travelers' strategy
- Phase III efficacy study in the field
- First country Registration in a functional NRA
  - Global health pathways for innovative products: EMA article 58, Swissmedic MAGHP
- WHO prequalification
- Countries registration

Travelers Market

- Pre-IND meeting to validate clinical plans (strategy already discussed in the past with FDA)
- Efficacy data based on CHIM studies
- Benefit from information obtained from infants
- Phase III safety package and consistency lots
- Licensure from stringent regulatory agencies, eg. FDA, EMA

Towards Phase III, preparation and considerations

- LimmaTech Shigella Bioconjugate Vaccine approaching phase III in mid 2025
- Phase III study design and data should meet the needs of both regulators and policymakers

Key considerations for the design of pivotal Shigella vaccine efficacy trials

- The indication covering the strains included in the vaccine
- Clinical case definition: medically attended diarrhea accompanied by one or more signs of dehydration, dysentery, hospitalization; or scoring based as mVesikari ≥9
- Microbiologic case definition: culture or quantitative polymerase chain reaction (qPCR).
- Primary endpoint: efficacy of the vaccine against the first episode of moderate to severe diarrhea
- Policy relevant secondary endpoints: MSD of all serotypes, LSD, hospitalization, z-score, antibiotic use
- Optimal timing of vaccination with the objective is to protect children by 1 year of age
- Phase III sample size (depending if qPCR or culture and definition of endpoint)

LimmaTech® Biologics

better technology for better health

Thank you

December 5, 2022

Status of the ETEC Vaccine Landscape and Plans for Pediatric Indication

2022 WHO Product Development for Vaccines Advisory Committee (PDVAC) Consultation

Dr. A. Louis Bourgeois, PhD, MPH
Science Officer, Enteric and Diarrheal Diseases
PATH's Center for Vaccine Innovation and Access

PATH

ETEC vaccine landscape: Factors impacting the development and status of lead candidates - Overview of the 2022 scene

- Uncertainty and transition have remained the earmarks of ETEC vaccine development over the last 2 years since PDVAC 2020.
- Uncertainty regarding FVVA* for ETEC vaccines stems from persisting questions regarding:
    - Morbidity burden: Does ETEC play a sufficient role in acute illness and the pathogenic pathway leading to EED, stunting, and malnutrition; is it an AMR threat?
    - Technical feasibility: Will candidates (oral or parenteral) be sufficiently immunogenic and protective in the target age-group (6–9 months)
    - Do we have the right antigens to provide broad protection against important ETEC pathotypes?
    - Are development timelines adequate to ensure vaccines will be available while they are still needed?
- FVVA uncertainty has led to continuing funding constraints, with one major donor de-prioritizing ETEC; others (FCDO and Wellcome) are emerging from strategy reviews with the impact uncertain; and encouraging sign is that EDCTP and U.S. DoD recently increased ETEC investments for advanced candidates.
- Despite these issues, the vaccine portfolio remains robust with an impressive level of activity and progress since the last reviewed at PDVAC in 2020.

* FVVA = Full Value of Vaccine Assessment

ETEC vaccine landscape: Factors impacting the development and status of lead candidates—Overview of the 2022 scene (cont.)

- Since 2020, WHO has helped guide ETEC vaccine development by finalizing preferred product characteristics (PPC); facilitating the drafting/publication of the ETEC vaccine development roadmap manuscript in the journal "Vaccine" and facilitating the development of the ETEC vaccine value profile that is now under review by "Vaccine".

- The ETEC vaccine community remains optimistic that global burden estimates will become more robust and supportive of continued vaccine prioritization and development as a clearer role for ETEC in both **acute** and more **long-term morbidity** continues to emerge (Strategic goals of vaccine development)

    - At the recently VASE 2022 conference – the **inflammatory nature of ETEC** (LTST and LT only strains) infection was confirmed in CHIMs; Field studies identified a **role for ETEC in neonatal diarrhea** (0-3 mths of age in Peru), as well as a significant role for ETEC along with *V. cholerae* in annual surges of acute watery diarrhea seen at the icddrB hospital over the 2008-2022 time period. **In Mar-Apr 2022, ETEC was implicated in ~14% of the 62,000 cases of cholera-like illness seen at the hospital (1100-1300 patient seeking care/day)**, with 30-50% of the strains being resistant to multiple antibiotics.
    - Recent paper in Nature communications (https://www.biorxiv.org/content/10.1101/2022.08.24.504189v2) indicate a potentially greater role for LT enterotoxin as a driver of enteropathic change in the small intestinal epithelia that could contribute to stunting, EED and malnutrition.
    - Antigen discovery efforts continue to point to EtpA, EatA, YghJ as additional antigens that could improve vaccine coverage

- Recent positive trial results and formulation advancements, as well as improved diagnostics (RLDT) and intriguing immune profiling results in both travelers and LMIC infants should also help strengthen the case for ETEC as a priority WHO vaccine target.

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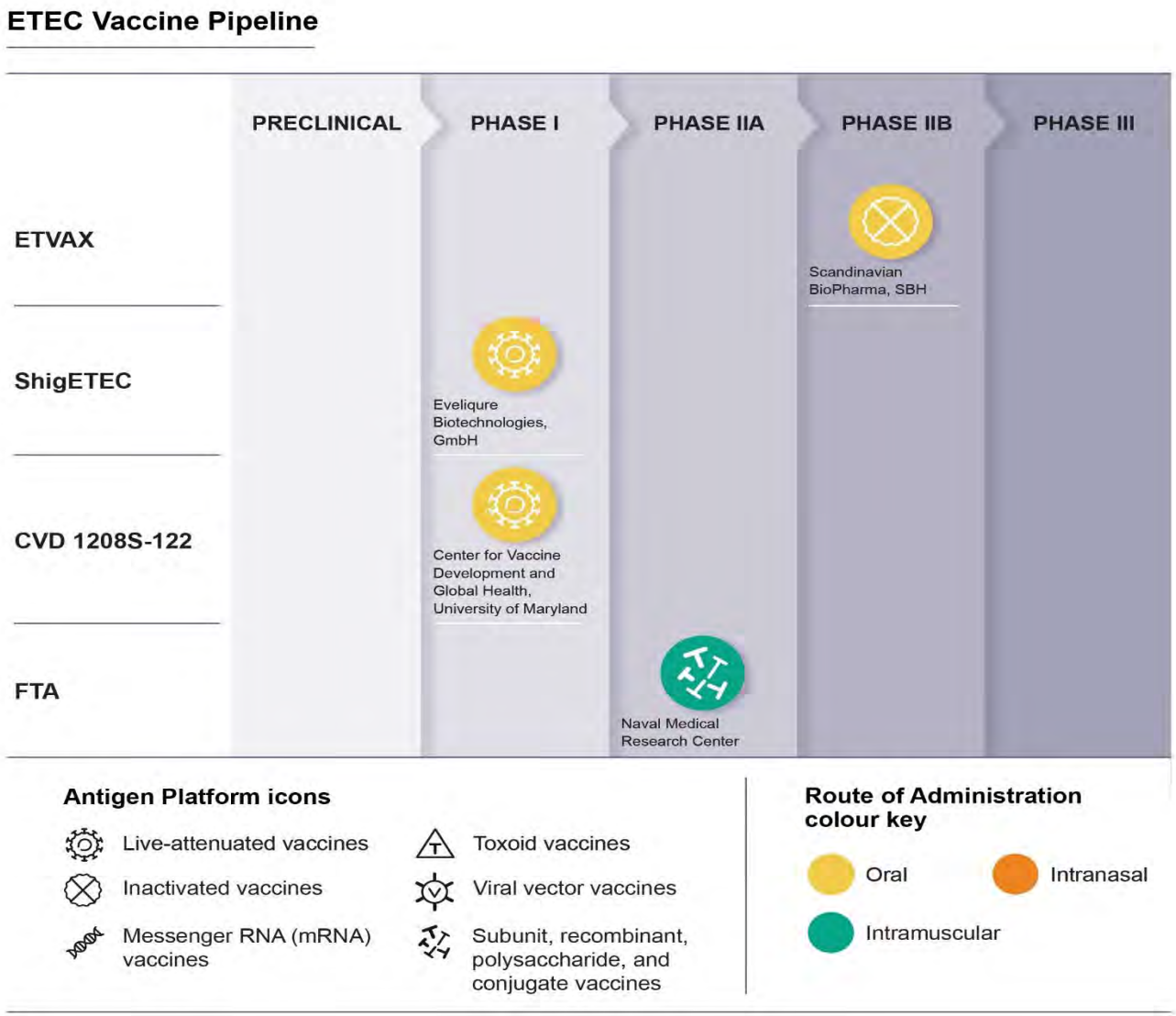
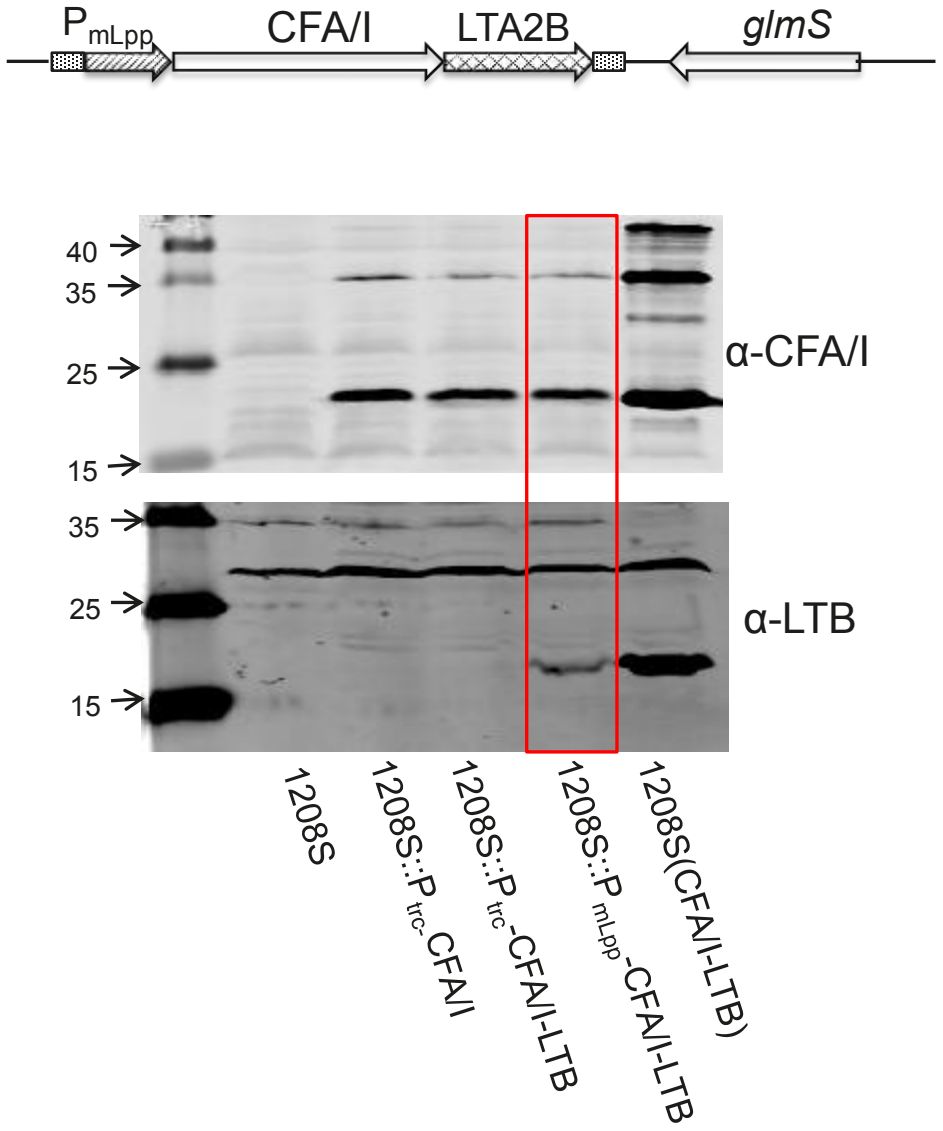
ETEC vaccine candidate in clinical trials from WHO ETEC value profile

(under review by Vaccine)



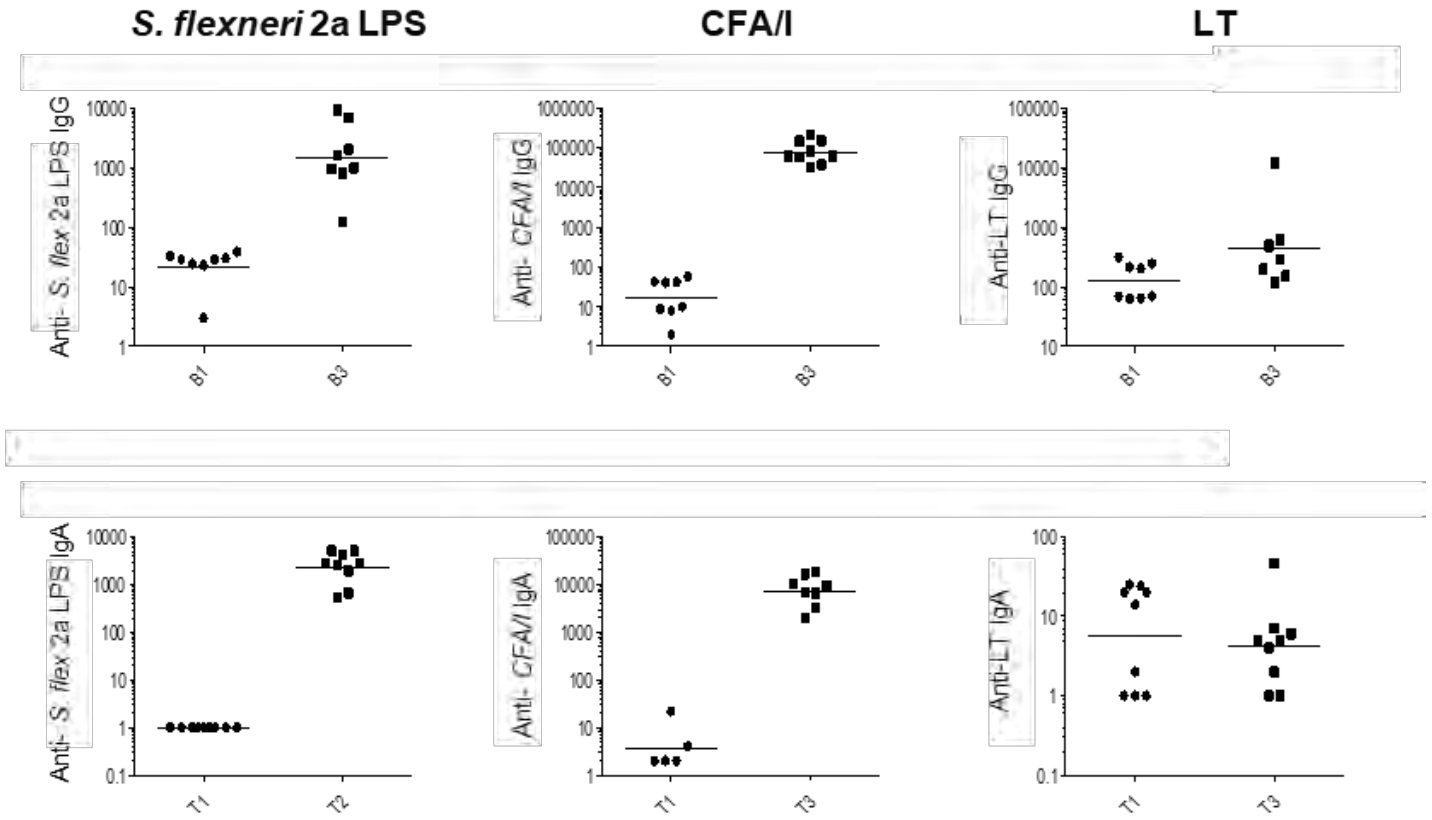
S. flexneri 2a CVD 1208S::CFA/I-LThA2B (CVD 1208S-122)

- *S. flexneri* 2a strain CVD 1208S
  - *ΔuaBA*, Δ*sen,* Δ*set*
  - Safe and immunogenic in volunteers (Kotloff, 2007)
- Engineered to express CFA/I and LTA2B subunit from genes inserted at a chromosomal site
- Manufactured as cGMP product
- Phase 1: **November 2022**
- Funding: NIH NIAID AI132257 and U01 AI14393

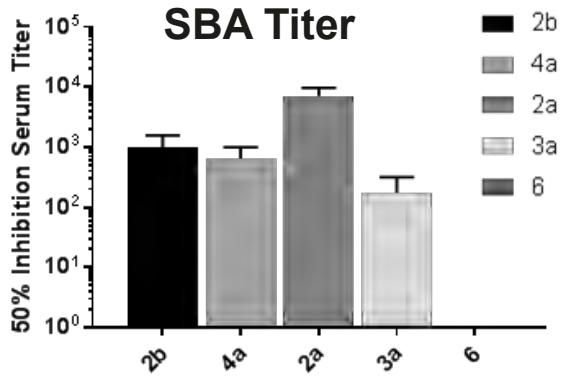


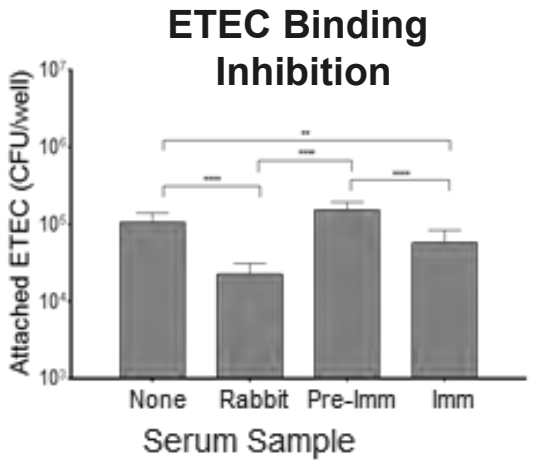
Advancement of CVD 1208S-122

Antibody Responses in Guinea Pigs Immunized with 2 Doses of CVD 1208S-122
(combined data from 2 studies)



- **Pre-clinical Studies**
  - Guinea pig safety: Sereny test
  - Guinea pig immunogenicity
  - Protection against *Shigella* challenge
  - Functional anti-CFA/I antibodies

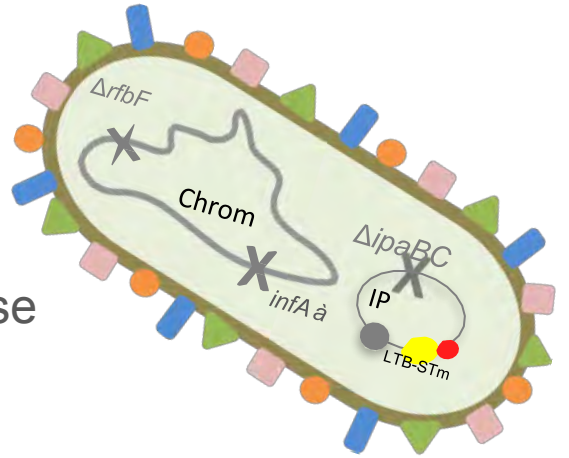




CENTER FOR VACCINE DEVELOPMENT AND GLOBAL HEALTH

CVD·GLOBAL HEALTH

Universal Shigella-ETEC Combination Oral Vaccine (ShigETEC)



- **Shigella vaccine platform:** Removal of LPS O-antigen induces broad antibody response against conserved structures to protect against all types of Shigella
- **ETEC coverage:** LT-B/STm(N12) fusion protein expressed from the invasion plasmid to induce protective antibody response (toxin neutralizing antibodies)

Phase 1: concluded in Europe in 2021

- **Safe, well tolerated**
  - Induction of systemic and mucosal immune response against ShigETEC vaccine strain and LTB and ST

Phase 2: challenge studies in the US

- Three separate controlled human challenge studies, starting mid 2023
- Two different Shigella species (*S. flexneri* 2a, *S. sonnei*)
- One LT+/ST+ ETEC strain

- ETEC challenge study planned in 2024 H2

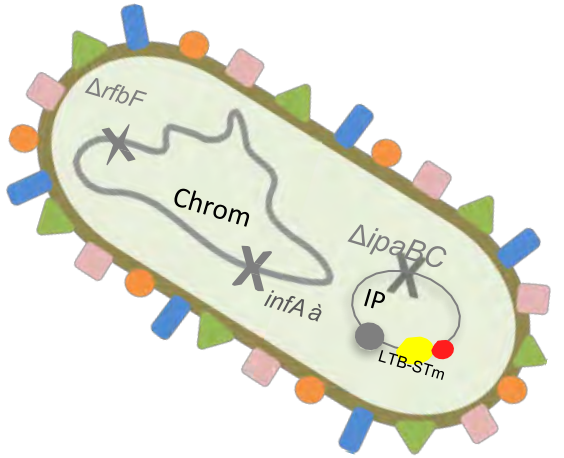
Phase 2 supported by NIAID Contract, partners:

Johns Hopkins University

Cincinnati Children's Hospital Medical Center

WRAIR, NMRC, Antigen Discovery

Universal Shigella-ETEC Combination Oral Vaccine (ShigETEC)



ShigETEC Phase 1b study in Bangladesh, Q3 2023

- **Two Stage Clinical Trial:**
  - Safety and immunogenicity of oral ShigETEC vaccine in Bangladeshi adults and paediatric participants of different age groups
  - Age-descending, dose escalating, placebo-controlled, double-blind study
    - Stage 1: in healthy adult participants
    - Stage 2: pediatric study
      - healthy children (2-5 years)
      - toddlers (12-23 months) and
      - infants (6-11 months)
  - Seroepidemiology study
  - Formulation development

Supported by the EU Horizon 2020 Consortium (SHIGETECVAX) partners of Eveliqure:

EVI / European Vaccine Initiative (Heidelberg, Germany)
University of Göteborg (Sweden)
ICDDR'B (Dhaka, Bangladesh)
PATH (Seattle, US)

ETEC adhesin vaccine (FTA) components: Candidate status and parenteral delivery proof-of-concept – **revisit in some detail because of combo interest**

ETEC FTA program overview

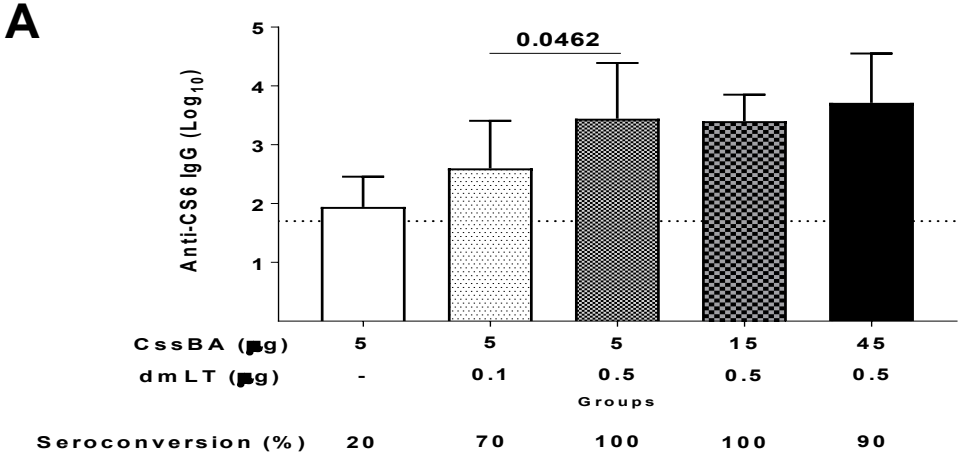
CF class	Molecule	Biochemical	Immunogenicity	NHP efficacy	Clinical trials
5a	CfaEB	Structure	+	++	Ph 1, 2b
5b	CsbDA-CooA	Structure	+	+	
5c	CotDA	Structure	+	+	
CS6	CssBA	Modeled	+	+	Ph 1

CssBA+dmLT Phase 1 trial (intramuscular)

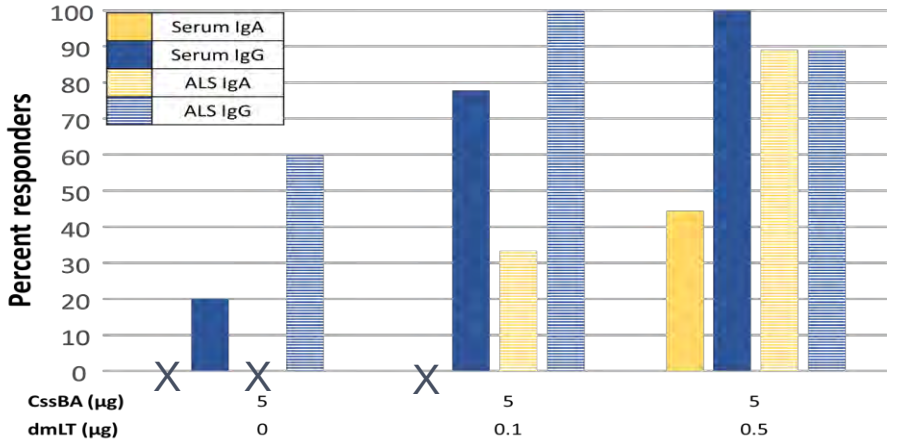
- Addition of dmLT had significant impact on serum (IgG and IgA) and mucosal anti-CssBA IgA responses **(see panels A and B)**
- Increasing doses of CssBA up to 45 µg + 0.5 µg of dmLT lead to 100% of subjects being positive for anti-CssBA IgA α4β7 positive PBMCs and fecal IgA
- **The fold rise in anti-CssBA fecal IgA correlated with the peak number α4β7 positive PBMCs in peripheral blood (r=0.81 by Spearmen's; p = 0.0013)**
- Anti-CssBA antibody responses persisted for over 1 year in the highest dosing group and had increased avidity
- Preliminary efficacy evaluation using a CHIMs with ETEC strain B7A is being planned with IDCRC Program, NIH
- Subunit vaccine based on CfaEB, CssBA and EtpA or EatA cover for 80-90% ETEC (NIH RO1 pending)

CssBA Phase 1 results: Safe at all dose levels

A



B



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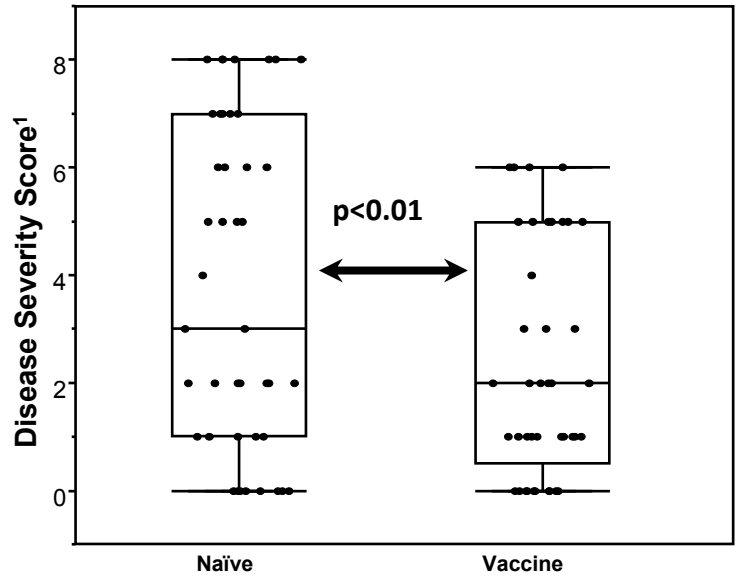
Fimbrial Tip Adhesin (FTA) Vaccine Monovalent Vaccine Development

2012	2013	2014	2015	2016	2017	2018	2019	2020	2021-22
Phase 1 CfaE +/- mLT (ID & TCI)		Phase 2b CfaE + mLT (ID), H10407 challenge				Phase 1 CssBA +/- dmLT (IM)		Phase 2B CssBA +/- dmLT (IM)	

Pending funding- IDCRC, NIH

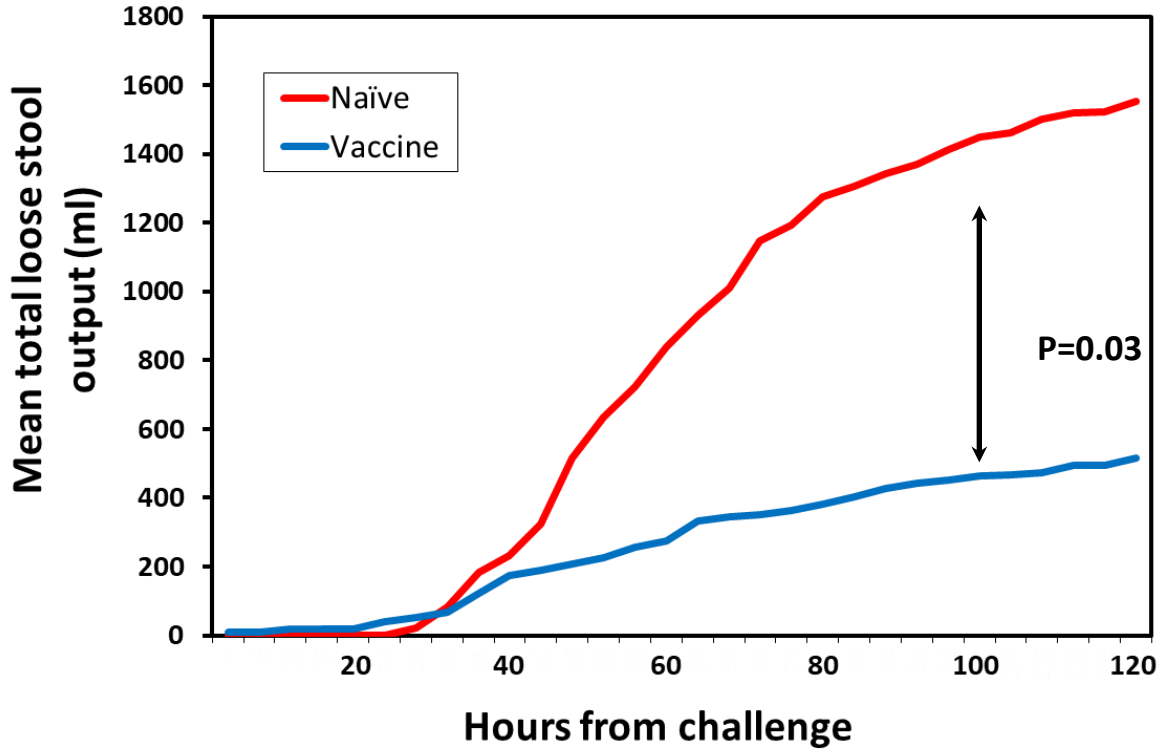
Protective Efficacy Estimate=

- **per protocol = 30%, P=0.13**
- **per disease score >5 = 72%, P=0.004**
- **ETEC proteomic array analysis indicated broader class 5** fimbrial response pattern may be a marker for protection.



CfaE Vaccination Reduces Disease Severity

[1]Disease severity score is a composite score of objective and subjective disease parameters. Range 0 (no disease) – 8 (severe disease). Porter et al. Plos One, Mar 2016



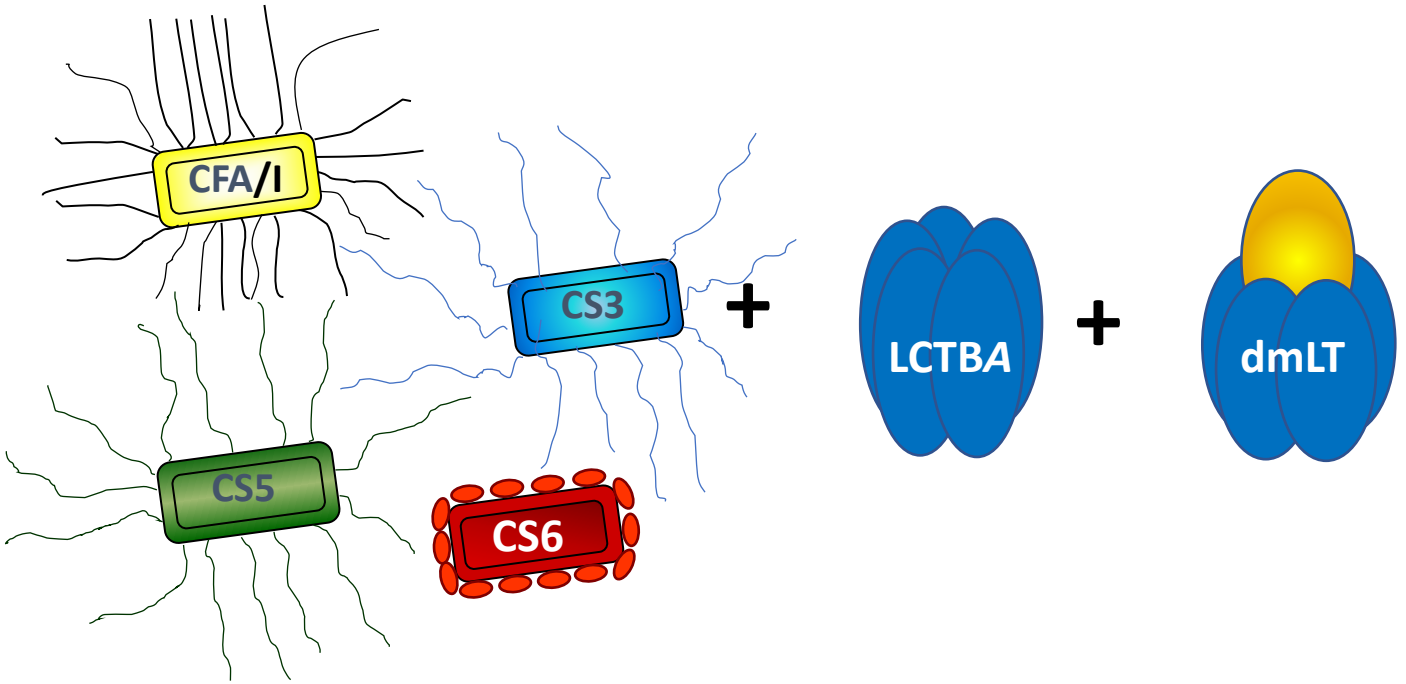
Data slide courtesy of SC. Porter, NMRC

ETVAX Vaccine Composition

A multivalent vaccine containing four of the most common colonization factors plus an LT toxoid and a dmLT adjuvant

Giving the vaccine together with an adjuvant enhanced the magnitude, breadth and kinetics of the intestinal immune responses in infants.

ETVAX® being an inactivated vaccine potentially lends itself for co-administration with other vaccines. Potential targets already identified.



Ca 2 x 10^{10} cells/strain

1 mg/dose

10µg/dose

ETVAX® - Great vaccine coverage

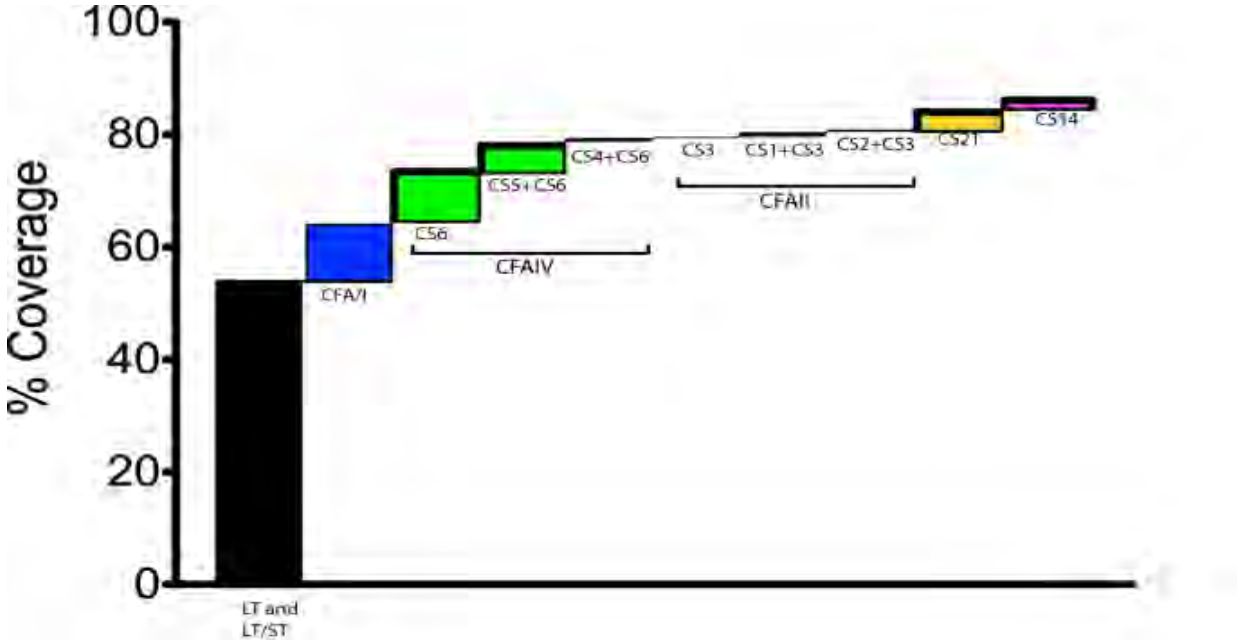
ETVAX® is estimated to have the potential to protect against at least 80% of all clinical ETEC strains

90 % vaccine coverage shown in clinical field trial in Benin (data on file)

Potential cross-protection against other CF's as suggested from serological cross-reactivity in adults (S Leach et al 2017) and in Bangladeshi children (Qadri & Svennerholm unpublished)

Recent proteomic array data from CIDRZ in Zambia observed a similar **broader class 5 fimbriae response** after ETVAX immunization in infants, as well as responses to proteins shared by ETEC and other diarrheagenic *E. coli (***EspB and YghJ/Ssle**) (C. Mubanga and K. Mwape – VASE 2022)

Pilot ETEC array analysis of travelers given ETVAX (OEV-123) suggests broader class 5 fimbriae response may be marker for protection (J Campo et al –VASE 2022) – further validation needed in travelers and in infants



Cross-reactive mucosal immune responses against CFs in OEV-122

Mucosal	CS5	CS7
ALS Adults	10	9 (90%)
ALS Children 1-5 years	23	21 (91%)
Feces Children 6-11 months	20	17 (85%)

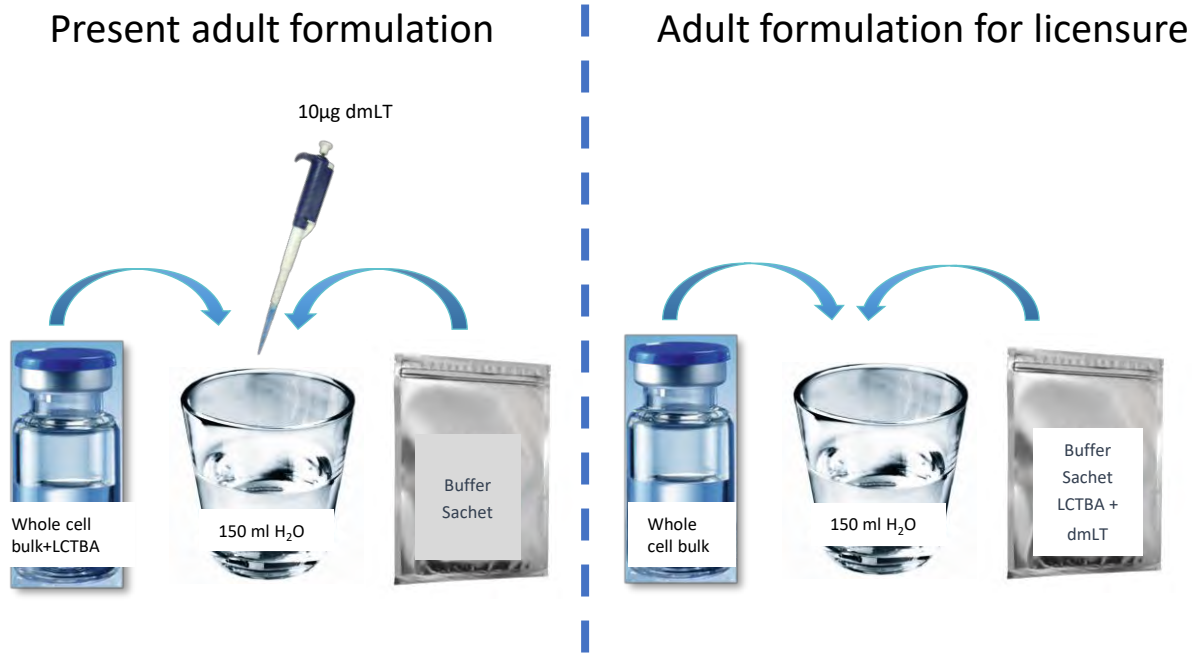
Mucosal	CFA/I	CS1	CS14	CS17
ALS Adults	12	3 (25%)	3 (25%)	NT
ALS Children 1-5 years	26	9 (35%)	15 (58%)	9 (35%)
Feces Children 6-11 months	20	12 (60%)	13 (65%)	12 (60%)

Data courtesy of A-M Svennerholm and F. Qadri

Isidean et al 2011, Vaccine 29: 6167-6178

ETVAX® travelers formulation
An oral 2 dose vaccine

A full immunization requires 2 doses orally taken at least 1 week apart, with the last dose taken at least 1 week before travel.



A non-inferiority trial comparing the present formulation to the formulation intended for licensure is currently ongoing (OEV 125) in Gothenburg, Sweden. Recent top line results demonstrates **Non-inferiority**

ETVAX® pediatric indication
An oral 3 dose vaccine

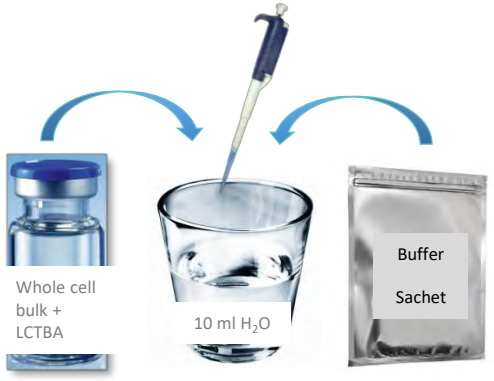
Three vs two doses of the **ETVAX®** vaccine in phase OEV124 Zambia trial

Phase IIB in the Gambia

Present endemic pediatric formulation

~11 ml

2,5 µg dmLT

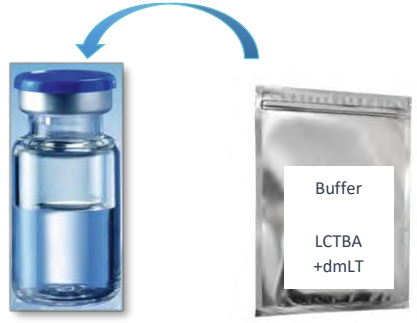


¼ dose

Commercial presentation

Endemic pediatric formulation **self-contained**

~10 ml

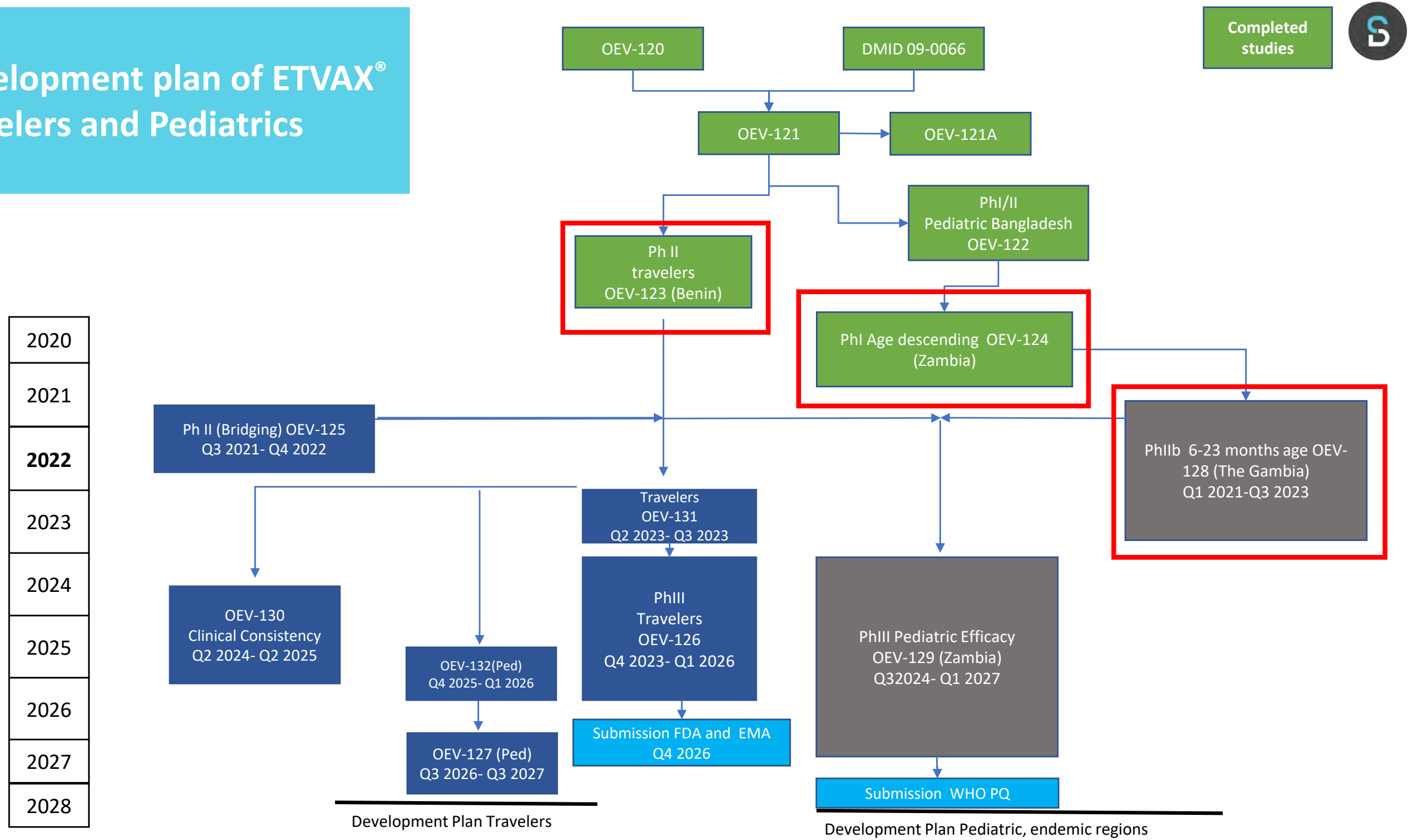


Whole cell bulk + PBS ∑ 10 ml

Dry dmLT/LCTBA, effervescent powder

The contents of the mixed powder, monovalent bulks and PBS constitutes a complete dose, no further additions are required

Development plan of ETVAX®
Travelers and Pediatrics



Ph II
travelers
OEV-123 (Benin)

- Safety, immunogenicity and protective efficacy in Finnish traveller's
- 743 (18-65 years) Finnish traveller's spending 14 days in Benin, West Africa
- ETEC was found in 75% of all severe TD
- Broad significant protective efficacy against more severe TD allowing for co-pathogens

PhI Age descending OEV-124
(Zambia)

- Age descending, dose finding, safety and immunogenicity
- Comparison of 1/8 and ¼ dose; ¼ dose found to be superior
- 3 doses (0, 14 and 90 days) superior to 2 doses (0 and 14)
- Significant increase against CFA/I, CS3, CS5 and LTB.
- Same response rate also to CS6, significance not reached due to high response rate in placebo recipients

PhIIb 6-23 months age
OEV-128 (The Gambia)
Q1 2021-Q3 2023

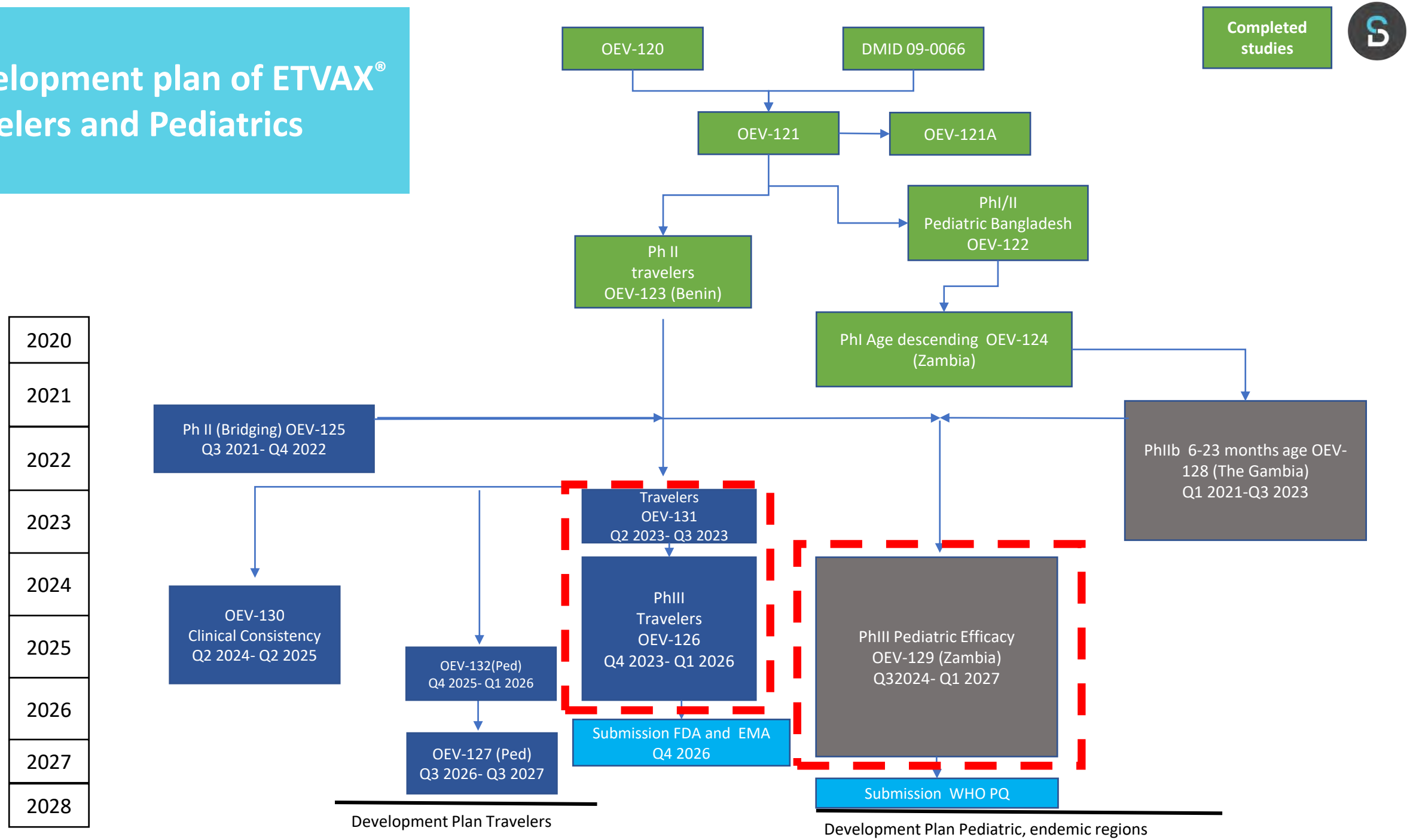
- Safety, immunogenicity and **protective efficacy**
- 4537 children aged 6-18 months fully vaccinated with 3 doses vaccine/placebo
- Children followed for 12-18 months after the 3rd dose. High incidence of ETEC.
- **Last patient out 31 October 2023**
- Top line results expected March 2024
- Based on clinic-based surveillance though Nov 2022, 913 diarrhea cases seen, **402 (44%) were MSD and 110 MSD cases (28%) were ETEC associated**. ETEC VPO's TBD.

Promising findings Benin (OEV-123)
Secondary objective - efficacy

- Antibiotic or antisecretory drug treatment was given to significantly fewer vaccine responders than to placebo recipients (p=0.03), indicating that ETVAX® reduced the severity of enteric illness.

	Moderate-to-severe disease (4 or more stools plus a symptom) among vaccine responders against any ETEC, and allowing for concomitant presence of EAEC, EPEC, EIEC/Shigella, Salmonella sp., Campylobacter sp., and parasites	Diarrhea of any cause (including viral pathogens) affecting daily activities among vaccine responders with ≥16 loose stools in 24 hours
Responders (≥4-fold seroconversion to LTB)	PE=52% (p=0.006; 95% CI=18-72%),	PE=56% (p=0.025, CI= 9-83%),
All	PE=41%, p=0.02; 95% CI=7-63%).	PE=43% (p=0.05)
	Representing 25% of all TD	Representing 22% of all TD

Development plan of ETVAX® Travelers and Pediatrics



Planned Phase III trials in Western adults and children in LMIC

Travelers
OEV-131
Q2 2023- Q3 2023

PhIII
Travelers
OEV-126
Q4 2023- Q1 2026

Traveler´s phase III trial: A challenge study using a CS1+CS3 $ST^{+}LT^{+}$ strain E24337,
including a pre-study to verify the challenge dose;
under discussion with FDA

PhIII Pediatric Efficacy
OEV-129 (Zambia)
Q32024- Q1 2027

Phase III trial in children 6-18 months old planned to Lusaka, Zambia, including 7500 children, financed by EDCTP

ETVAX Key Recent Accomplishments

Successful clinical trial program

- High incidence of ETEC in children and travellers - highlighting ETECs importance as the major cause of severe TD.
- Safety has been demonstrated in travelers and infants in LMIC.
- There is a broad significant protective efficacy demonstrated against more severe TD independently of cause in travellers
- Consistent with this, antibiotic or antisecretory drug treatment was given to significantly fewer vaccine responders than to placebo recipients indicating that ETVAX® reduced the severity of enteric illness in the few breakthrough cases that occurred.

Commercial manufacturing in place for DS

- Successfully performed tech. transfer and upscaled to 1000 L for all antigens in collaboration with euBiologics in Korea.
- SBH has started GMP manufacturing of GMP clinical trial material and developed a strategy and timeline for the commercial product.
- Successful development of the commercial presentation demonstrated in OEV125.

Regulatory progress

- Meetings performed with EMA and FDA. IND updated with information of new formulation. Draft protocol in place for LMIC (OEV-129) and travelers (OEV-126)

Funding

- Funding secured for the phase III study in Zambia

HORIZON 2020
USAMMDA
eubiologics

ETEC vaccine and funding landscapes: Summary of current status and developments impacting on the pediatric indication

- Despite uncertainty of ETEC burden and concerns about complexity and timelines for vaccine development, the pipeline has remained robust with promising oral and parenteral candidates in clinical development.
- European funders have helped to maintain and stabilize funding for ETEC vaccine development.
- Four ETEC candidates are in Phase 1/2B studies or poised to begin Phase 1; all led candidates rebounding from impact of COVID-19 pandemic.
- Encouraging results for lead oral (ETVAX) and parenteral (FTA) candidates indicate both are effective at inducing mucosal immune responses to key antigens and dmLT can improve these responses. A broader class 5 fimbriae response may be a marker for protection, but more analysis needed in travelers and infants.
- With continued success, ETVAX licensure and WHO prequalification may be possible in 5-6 years.
- All lead candidates are compatible with combination vaccine strategies that may improve FVVA.
- Maintaining ETEC funding is critical to ensure continued progress of the most promising candidates.

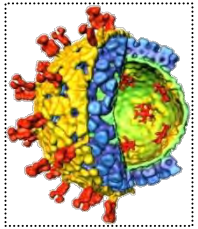
UPDATE ON NEXT GENERATION ROTAVIRUS VACCINES

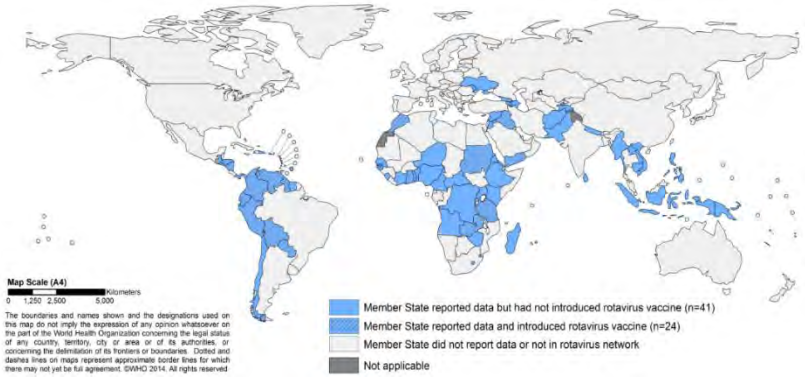
December 5, 2022

Duncan Steele
Deputy Director and Strategic Lead
Enteric and Diarrheal Diseases
Bill & Melinda Gates Foundation

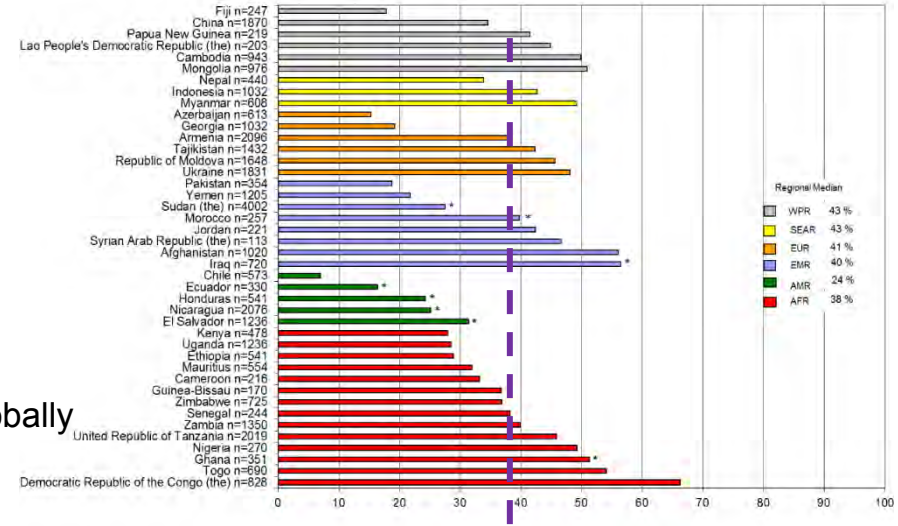
Acknowledgements:
Stan Cryz and colleagues
PATH

WHO COORDINATED GLOBAL ROTAVIRUS SURVEILLANCE NETWORK DEMONSTRATES ~40% OF ALL DIARRHOEAL HOSPITALIZATIONS





~40% of all acute gastroenteritis hospitalizations globally



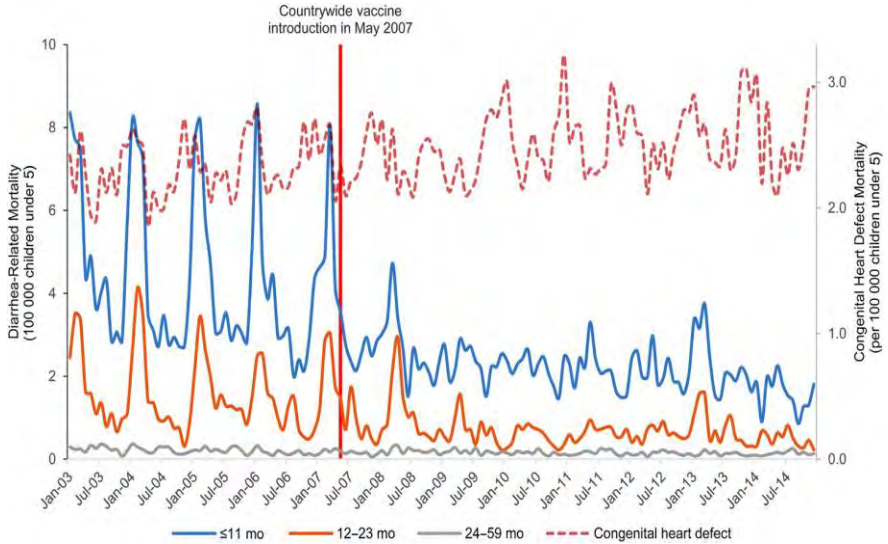
- Rotavirus afflicts all children irrespective of geographic location or socio-economic status
- Infects younger children in LMICs
- Current global estimates ~200,000 childhood deaths globally
- Ten countries account for almost 4/5 of global deaths
- Four countries (India, Nigeria, Pakistan, DRC) account for ~50% of all rotavirus deaths

EFFICACY AGAINST SEVERE ROTAVIRUS GASTRO-ENTERITIS IN THE FIRST YEAR OF LIFE (≥11 ON THE VESIKARI SCALE) IN AFRICA AND ASIA

Region	Vaccine	Countries	Vaccine Efficacy	95% CI
Africa	Rotarix	Malawi, South Africa	61.7	44.0, 73.2
Africa	RotaTeq	Ghana, Kenya, Mali	64.2	40.2, 79.4
Africa	RotaSIIL	Niger	66.7	49.9, 77.9
Asia	Rotavac	India	56.4	36.6, 70.1
Asia	RotaSIIL	India	36.9	11.7, 53,6
Asia	RotaTeq	Bangladesh, Vietnam	51.0	12.8, 73.3

Madhi SA, Cunliffe NA, Steele AD et al. NEJM 2010; 362: 346-357; Zaman K, Anh DD, Victor CV et al. Lancet 2010; 376: 615-23; Armah GE, Sow S, Breiman RF et al. Lancet 2010; 376: 606-614; Bhandari N, Rongsen-Chandola T, Bavdekar A et al. Lancet. 2014; 383: 2136-43; Isanaka S, Ousmane G, Langendorf C, et al. NEJM 2017; 376:1121-30; Kulkarni PS, Desai S, Tewari T, et al. Vaccine 2017; 35: 6228-6237

ROTAVIRUS VACCINES: IMPACT ON DIARRHOEAL DEATHS

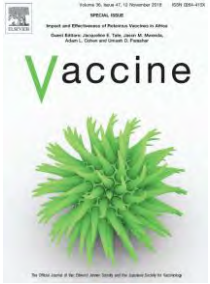


No. of diarrhoea related deaths pre and post vaccine introduction

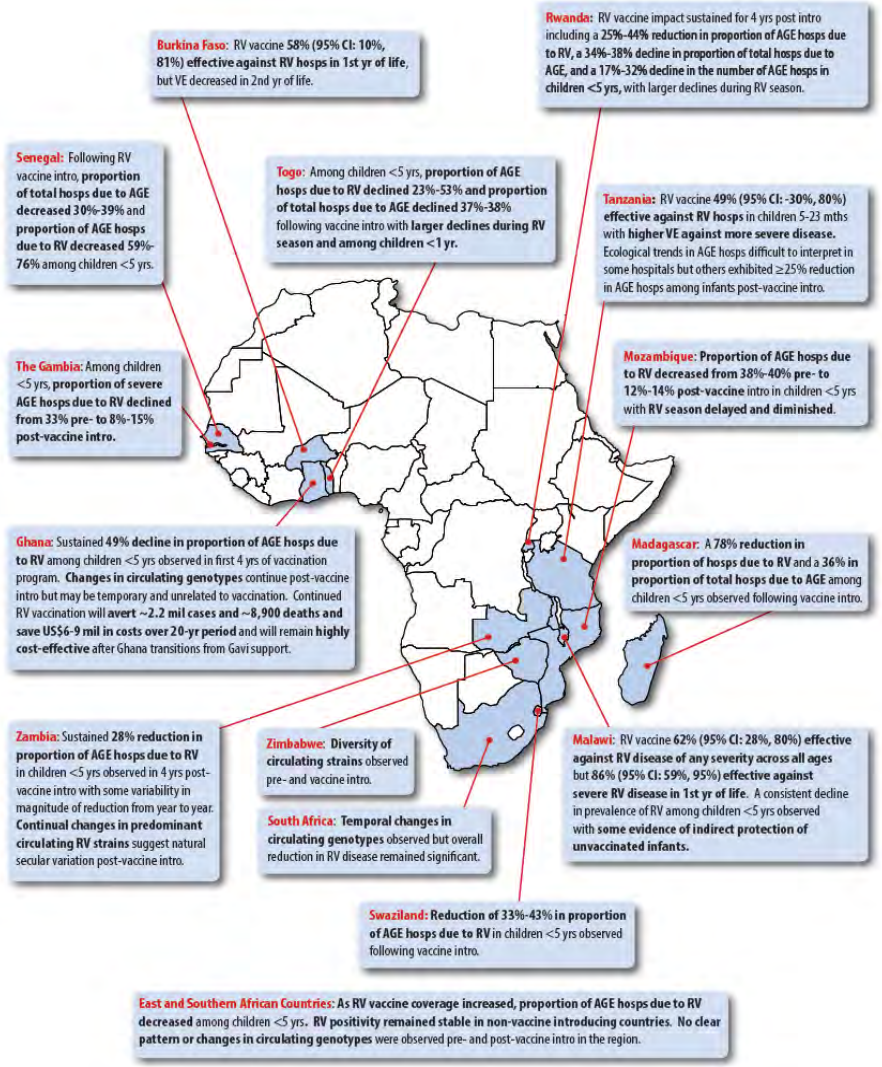
	Rotavirus vaccine introduction	Reduction in all-cause diarrheal deaths in children <5yrs following introduction
Bolivia	2008	36-43%
Brazil	2006	22%
El Salvador	2006	0-36%
Honduras	2009	16-20%
Mexico	2007	43-55%*
Panama	2006	50%**
Venezuela	2006	57-64%

Richardson V, Parashar U, Patel M. *NEJM* 2010; 365: 772-3
Sanchez-Uribe, Esparza-Aguilar, Parashar, Richardson CID, 2016, 62 S133-39

AFRICAN DATA – *VACCINE* SUPPLEMENT



- Published in November 2018
- 20 articles from 14 African countries
- Data on
  - Vaccine Effectiveness
  - Impact
    - Rotavirus hospitalizations
    - All-cause diarrhoea hospitalizations
    - All-cause diarrhoea deaths
  - Cost-effectiveness



REDUCTION IN ROTAVIRUS ASSOCIATED GASTRO-ENTERITIS HOSPITALIZATIONS FOLLOWING ROTAVIRUS VACCINE INTRODUCTION –

WHO GPDS – is sentinel site surveillance system to identify causes of hospitalized diarrhoea in low- middle income countries (Built on Global Rotavirus surveillance network)

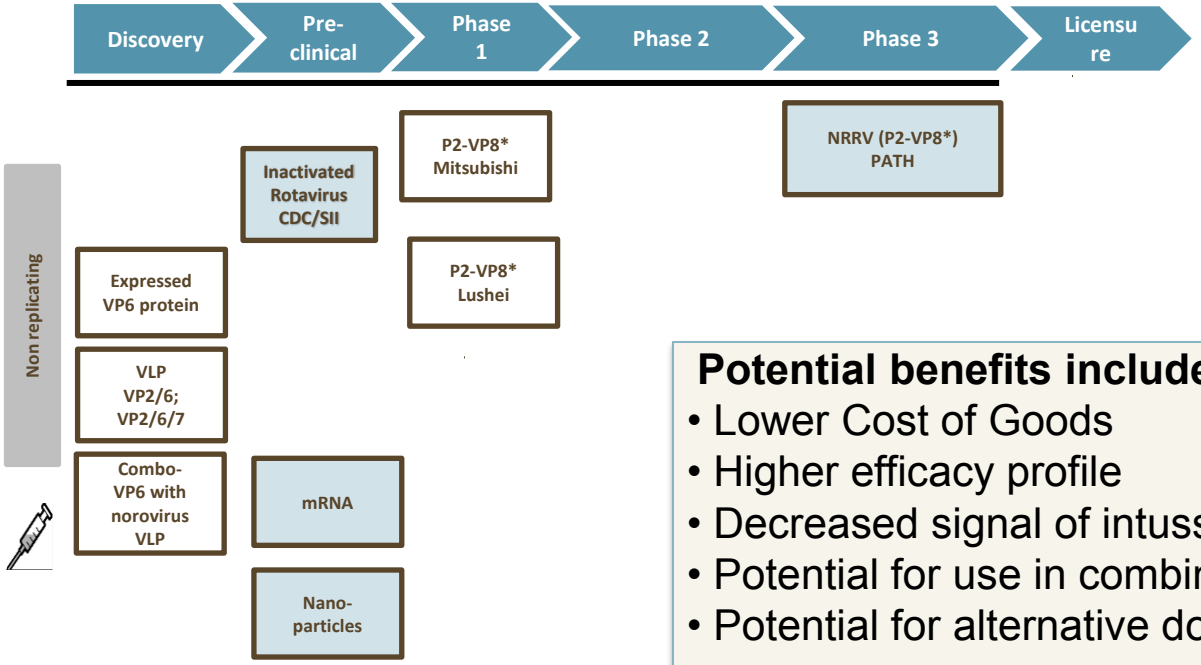
- 33 sites from 28 countries across all WHO regions
- standardized protocol & qPCR testing for detection
- Evaluate most important enteric pathogens

Consistent reduction of rotavirus disease when vaccine introduced, but still a significant cause of disease

	Percentage of RV based on vaccine	
	Not introduced	Introduced
Overall	42·1 (33·2, 53·4)	20·8 (18·0, 24·1)
African Region	48·3 (34·4, 65·5)	21·3 (18·1, 25·0)
Americas	NA	16·0 (12·9, 19·5)
European	39·2 (25·3, 58·3)	15·7 (11·9, 20·6)
South-East Asian	35·7 (28·3, 44·9)	19·2 (13·1, 27·6)
Western Pacific	25·3 (18·0, 35·8)	12·4 (8·1, 18·8)

Cohen A, Platts-Mills J, et al. Lancet Glob Health 2022; 7: e009548

NEXT GENERATION NON-REPLICATING, PARENTERAL ROTAVIRUS VACCINES

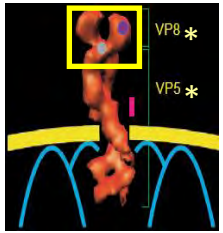


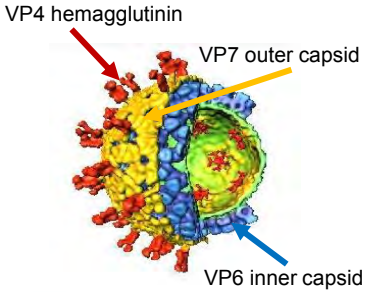
Potential benefits include:

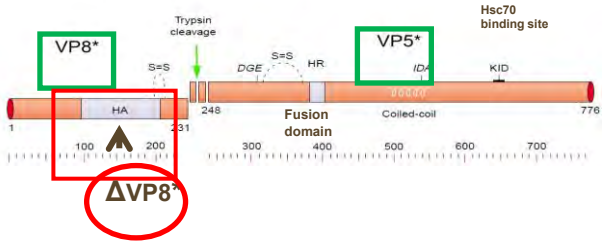
- Lower Cost of Goods
- Higher efficacy profile
- Decreased signal of intussusception
- Potential for use in combination vaccines
- Potential for alternative dosing schedules

NON-REPLICATING ROTAVIRUS VACCINE (NRRV – P2-VP8* TRI-VALENT VACCINE)

- Developed by PATH, using NIH constructs.
  - SK Biosciences, Korea - commercial partner
- Trivalent vaccine candidate based on:
  - truncated VP8 subunits of P[4], P[6] and P[8] genotypes (major circulating human rotavirus genotypes)
  - fused to tetanus toxin P2 CD4 epitope
  - expressed in E.coli (T7 promoter)
  - adsorbed to aluminum hydroxide
  - parenteral IM administration route







Wen X et al. Vaccine 2014; Wen X et al. HVI 2015

CLINICAL DEVELOPMENT OF P2-VP8* MONOVALENT CANDIDATE

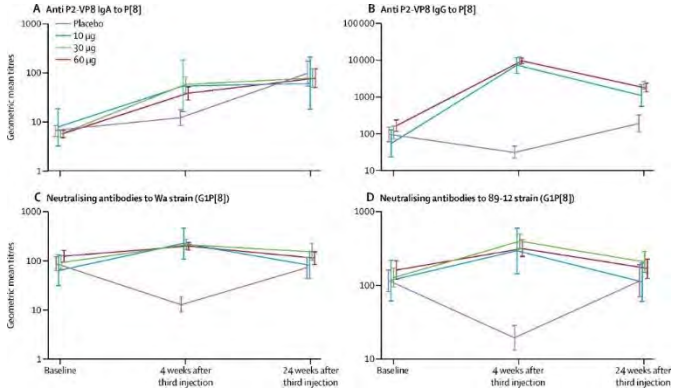
Phase 1 safety study in US adults

Monovalent P2-VP8* P[8] was well tolerated and immunogenic

- 4-fold rises of both IgA and IgG responses observed
- Increasing GMTs with dose and titres
- Homologous N-Abs observed in ~50% of subjects
- Responses to P[4] and P[6] had lower GMTs

Phase 2 age-descending, dose-escalating study of the monovalent vaccine candidate (P2-VP8* P[8]) in toddlers and infants in South Africa

Serum antibody geometric mean titres (unadjusted)

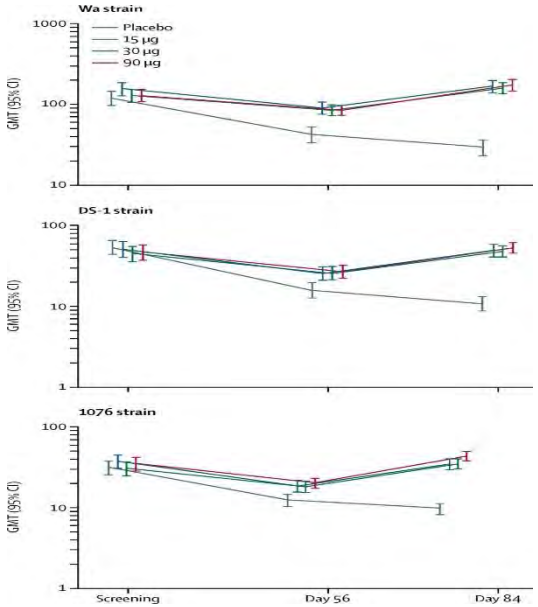


Fix A, Harro C, McNeal M et al. Vaccine 2015; 33:3766-72; Groome MJ, Koen A, Fix A et al, Lancet Infect Dis 2017; 17:843-53

AGE-DESCENDING, DOSE-ESCALATING STUDY OF THE TRIVALENT P2-VP8* VACCINE IN SOUTH AFRICAN INFANTS

- Phase 1/2 study in South Africa Healthy adults, toddlers and infants
- Dose-escalation: 15 => 30 => 90 µg of total antigen
- Infants received 3 IM doses, one month apart, co-administered with EPI vaccines
- Enrolled in two stages, DSMB review before progression to Phase 2
- All dose-levels in infants well tolerated and no safety signals observed
- Immunogenicity results showed robust immune responses (n=139/arm)

- *A priori* "go" criteria were met and a decision to progress to Phase 2b/3 efficacy study, with early futility read.
- Initiated in 3 African countries in January 2020 -> put on hold with COVID-19
- Re-started in June/July 2021



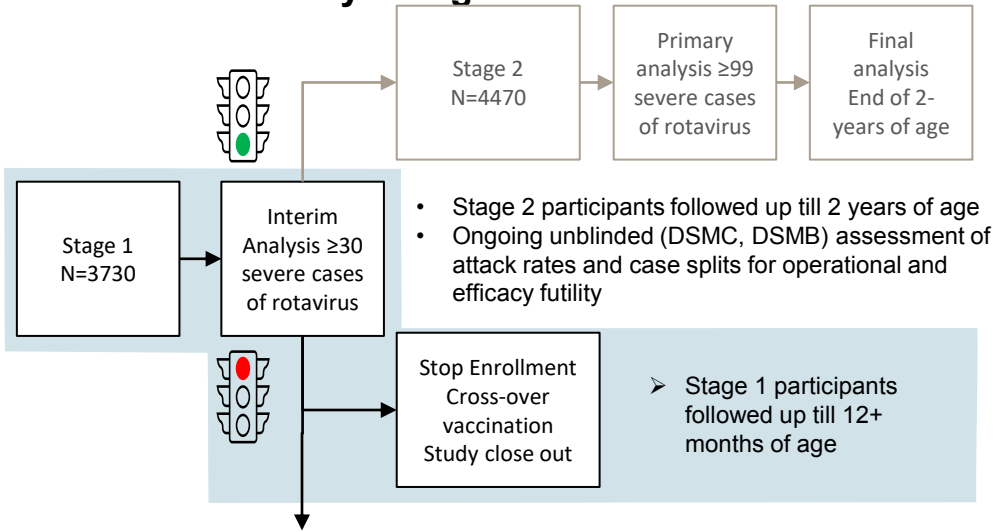
Groome MJ, et al, Lancet Infect Dis 2020; 20: 851-63

RATIONALE FOR ACCELERATED DEVELOPMENT

- Current oral rotavirus vaccines provide sub-optimal protection for children in low-income settings
- The NRRV program was **accelerated at-risk** based on Phase 2 data where ≥70% seroconversion in neutralizing antibodies for all 3 antigens (P[4], P[6] and P[8]) were seen and infants who were given NRRV had decreased viral shedding after Rotarix 'challenge'
- Phase 3 study design included an interim futility analysis to provide confidence to proceed or to quickly kill an inferior vaccine
  - Key assumption was that an injectable rotavirus vaccine needed to be superior to live, oral vaccines for country adoption
  - Provided the potential for a combination vaccine
- Formulation work undertaken to assess potential combination strategies
- Prime-boost strategy in clinical development in South Africa (data available by mid-2023)

NRRV IS NOT SUPERIOR TO ORAL ROTAVIRUS VACCINE

Phase 2b/3 Study Design



- Stage 2 participants followed up till 2 years of age
- Ongoing unblinded (DSMC, DSMB) assessment of attack rates and case splits for operational and efficacy futility

➢ Stage 1 participants followed up till 12+ months of age

Interim Analysis Results

Following an interim analysis, the DSMB determined that the Phase 3 NRRV trial should not continue as planned because it did not meet agreed upon prespecified futility criteria

Possible explanations for trial outcome

Immune responses to VP8 subunit alone are not enough to elicit protection against severe disease from wildtype infection

Novel circulating rotavirus strains present in the community are not protected by the immune responses generated by the vaccine

Correlation between reduction in shedding of Rotarix challenge seen in Ph2 study and protection against wild-type disease is not a suitable correlate for efficacy


THE WORK IS
COMPLICATED.
WHY WE DO IT IS NOT.