



World Health
Organization

WHO's Product Development for Vaccines Advisory Committee (PDVAC): an update from the 2018 convening

Dr David Kaslow, MD (PDVAC Chair)

SAGE, October 2018

Objectives of PDVAC presentation to SAGE



- Inform on current remit of PDVAC's focus and activities
- Provide an overview of priority pipeline vaccine and monoclonal antibody candidates
- Highlight a key area where PDVAC seeks SAGE engagement in the next 12-18 months



PDVAC is 5 years old!



PDVAC formed:
To prioritize and
accelerate Vx
product
development

**Horizon scanning included
> 35 pathogens
Focus on development of preferred
product characteristics & roadmaps**

**Scope includes
monoclonal
antibodies and
delivery technologies**

**Focus includes
articulating full
public health value
(FPHV) for
vaccine/monoclonal/
technologies**

2014

2015

2016

2017

2018

- GVAP pathogens
- RSV

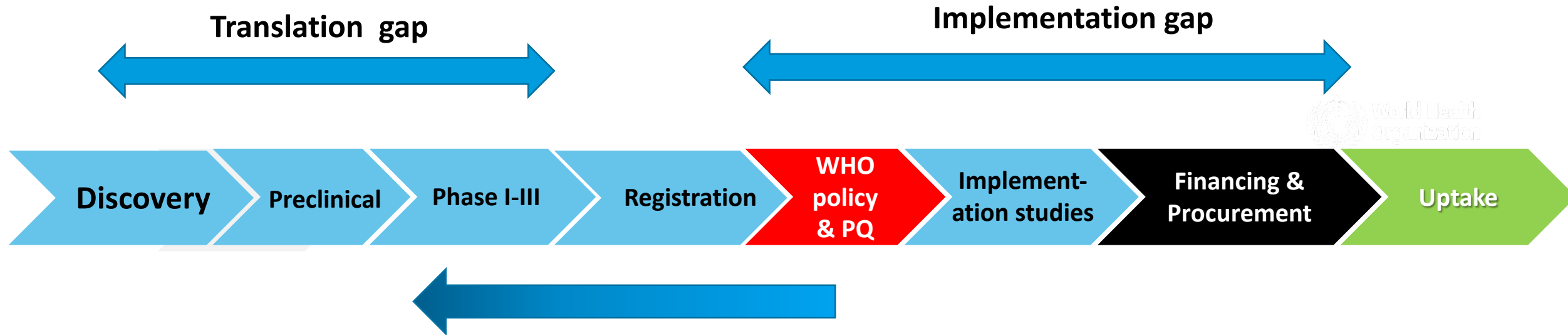
- GBS
- HSV

- Shigella
- ETEC

- GAS
- TB
- HIV

- Cross-cutting projects to help define the FPHV

What issues does PDVAC seek to address?

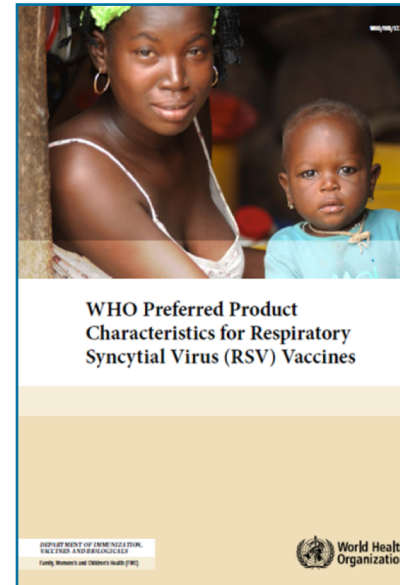
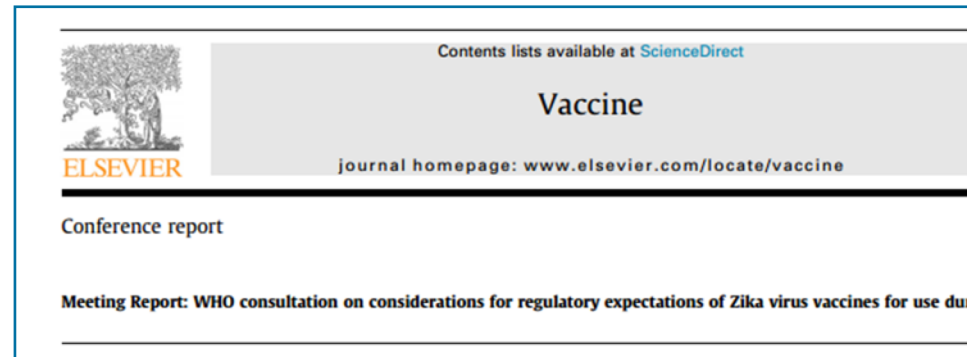
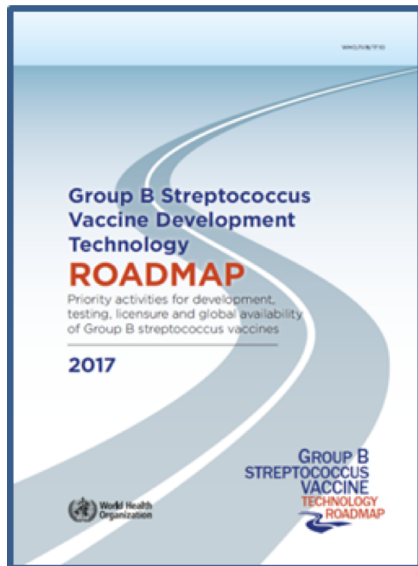
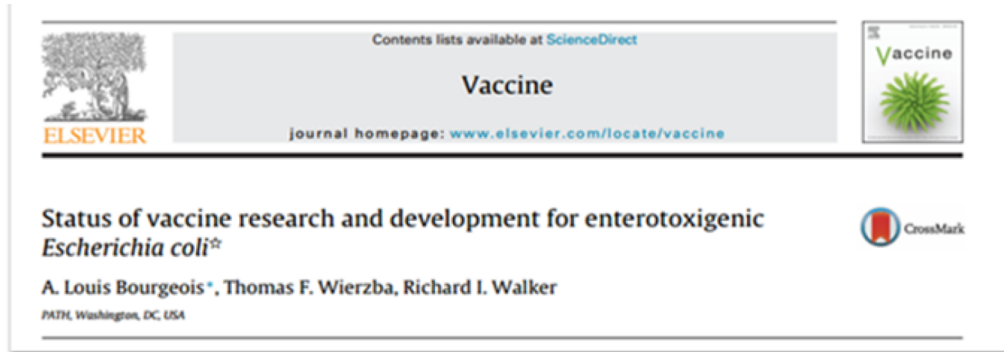


PDVAC aims to

Articulate the **FULL PUBLIC HEALTH VALUE** of vaccines and monoclonal antibodies for LMICs *early* in product development to **bridge the translation gap**

Define needs, preferences and pathways for vaccines and monoclonal antibodies to be used in LMICs to **abate policy and implementation gaps**, and **accelerate vaccine uptake and impact**.

How does PDVAC work?



Full Public Health Value Propositions (FPHVP) for Vaccines

Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization, Geneva, 17-18 April 2018



Status of activities for vaccines against PDVAC prioritized pathogens (red indicates activities since the 2017 report)

Pathogen	Landscape analysis	PPC	RM	Pathways	FPHVV initiated	Scoping consultations*
Tuberculosis	✓	✓				✓
HIV	✓					✓
Malaria	✓	✓	✓			✓
Influenza	✓	✓				✓
RSV	✓	✓	✓	✓		✓
Grp B Strep	✓	✓	✓	✓	✓	✓
HSV	✓	✓ (final draft)			✓	✓
ETEC	✓	✓ (in progress)				✓
Shigella	✓	✓ (in progress)		✓ (in progress)		✓
Grp A Strep	✓	✓ (final)			✓	✓

http://www.who.int/immunization/research/ppc-tpc/preferred_product_characteristics/en/

HIV: human immunodeficiency virus ; RSV: respiratory syncytial virus; GBS: group B Streptococcus ; HSV herpes simplex virus; GAS: group A streptococcus. PPC: Preferred product characteristics; RM: Roadmap; FPHVV: full public health value for vaccines, * meeting reports publically available

GVAP pipeline status of vaccine development for next-generation influenza, next generation malaria, tuberculosis and HIV



	Number of vaccines and mAb in clinical development					
Pathogen	Phase 1	Phase 2	Phase 3 (or beyond)	Total (vaccines)	mAb	Notes
HIV	25	5	0	30	1	Two candidate vaccines in phase 2 are in late-stage (2b/3) trials; both are heterologous prime-boost.
Influenza (next-gen vaccine)	6	4	4	14	0	Several vaccine candidates close to phase 1. Two adjuvanted inactivated candidates in phase 4 trials for induction of cross-reactive immunity.
<i>M. tuberculosis</i>	3	8	4	15	0	One vaccine in phase 2b recently reported 54% efficacy against progression from LTBI to active TB.
<i>P. falciparum</i> (malaria)	13	16	1	30	0	Phase 3+ trials are studying RTS,S/AS01 before widespread introduction; also evaluating dosing schedules for increased efficacy.

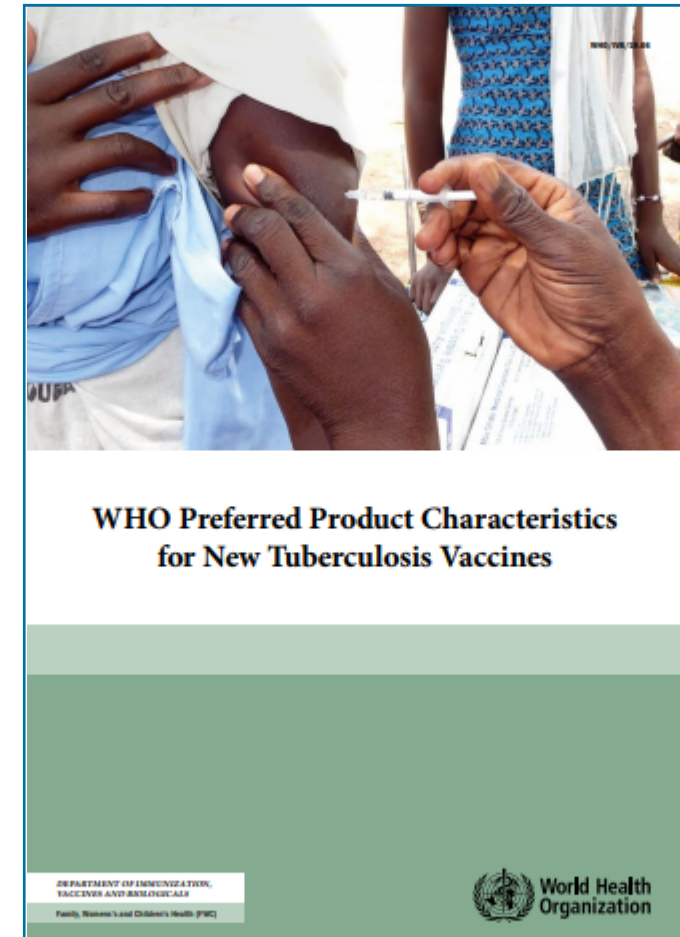
Tuberculosis strategic priorities and Preferred Product Characteristics (PPCs):

Adults and adolescents

- **OUTCOME MEASURE AND EFFICACY**
 - 50% or greater efficacy in preventing confirmed pulmonary TB
 - Supportive evidence in people with or without latent infection
 - Across geographical areas

Neonates and Infants

- **SAFETY AND EFFICACY**
 - Safety in HIV
 - Efficacy better than BCG



Opportunity to re-invigorate TB vaccine R&D



Scientific breakthroughs

- M72/AS01E: Prevention of Disease in previously exposed individuals: previously thought of as the hardest target
- Exploratory signal from BCG revaccination study : prevention of sustained infection ; other biomarkers of risk emerging

Stakeholder engagement, institutional remodelling

- High Level UN meeting on TB
- Renewed investments/opportunities (BMGF, Gates MRI, NIH, BRICS R&D initiative, others)

Planning for success: create visibility in policy pathway and financial model ensuring sustainable, accessible supply if positive results confirmed

Pipeline status of vaccine development for other PDVAC prioritized pathogens

	Number of vaccines and mAb in clinical development					
Pathogen	Phase 1	Phase 2	Phase 3 (or beyond)	Total (vaccines)	mAb	Notes
Enterotoxigenic E. coli	1	1	0	2	0	Data from PII in adults travellers in 2019.
Group A streptococcus	3	0	0	3	0	Several vaccine candidates in preclinical development.
Group B streptococcus	1	2	0	3	0	Several vaccine candidates in pre-clinical development.
Herpes simplex virus	1	1	0	2	0	Candidates in phase 2 are therapeutic. In last 12 mo, 2 in PII halted or terminated
Respiratory syncytial virus	19	4	1	24	1	Most advanced is maternal immunization
Shigella spp.	5	4	0	10	0	Most advanced are O-Ag based

Cross-cutting activities: Vaccines that impact antimicrobial resistance (AMR)



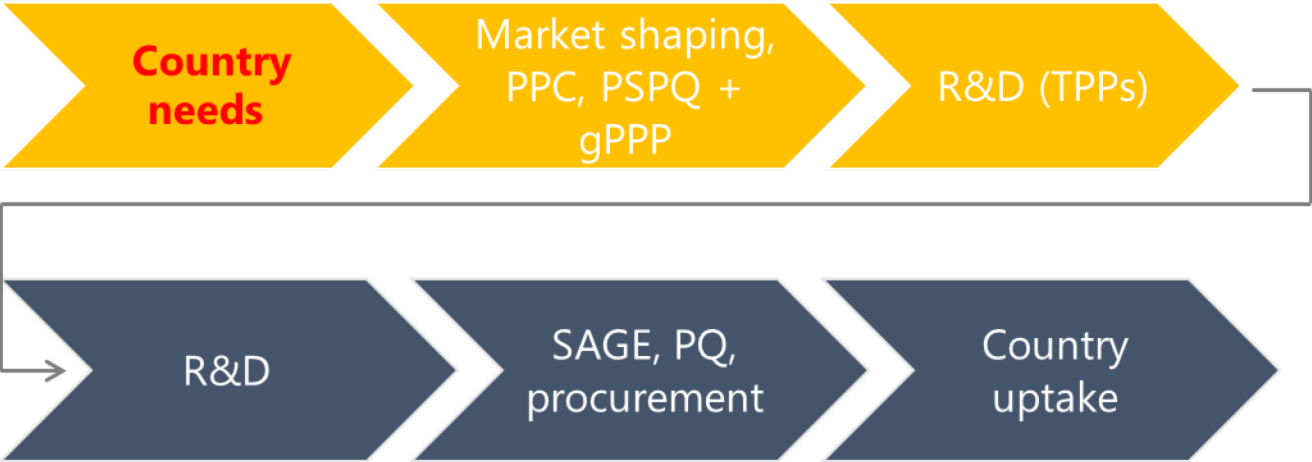
WHO IVR is embarking on an initiative to:

- Express priorities to optimize the use of vaccines to combat AMR
- Create a value attribution framework for future and available vaccines that combat AMR
 - Informed by health economic modelling
 - Considering societal impact and time trends
- Support rationalization of investments and prioritization of efforts

Evaluating and prioritizing innovative products for improved coverage & equity



Total Systems Effectiveness
Evaluating trade-offs to inform choice



BILL & MELINDA
GATES foundation



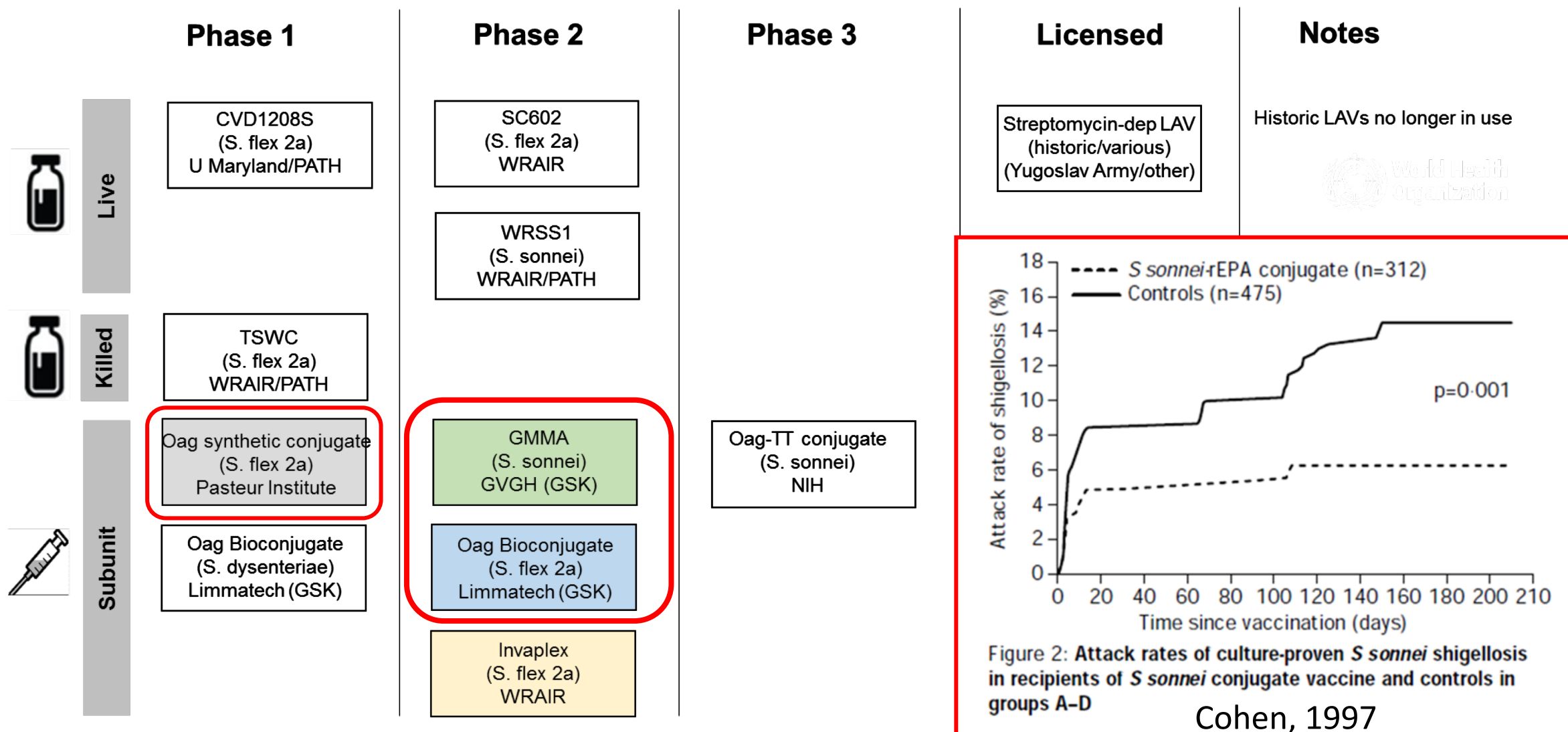
Shigella vaccine development

Shigella overview



- According to IHME, Shigella is the second most deadly diarrhoeal disease – 165,000 deaths per year.
- It also causes inflammation leading to growth faltering, is among the top 4 causes of diarrhea associated YLD's globally and is on the WHO AMR priority list
- Clinical pipeline of subunit, live and killed approaches
- Controlled Human Infection Model (CHIM) is available to demonstrate proof of concept for vaccine candidates
- Stakeholders are seeking an accelerated licensure route based on CHIM
- **PDVAC is seeking to understand how licensure based on CHIM could contribute to consideration of a WHO policy recommendation**

Shigella vaccine candidate pipeline



Heterogeneity of Shigella

S. sonnei and *S. flexneri* serotypes (% all *Shigella* case isolates)

	1a (0.3)	1b (7.5)	2a (20.2)	2b (10.9)	3a (9.4)	3b (0.1)	4a (2.9)	4b (0)	5a (0)	5b (0.3)	6 (11.0)	7a (2.0)	7b (0)	X (1.0)	Y (0.4)	Ss (23.7)
<i>S. sonnei</i>																✓
<i>S. flex</i> 2a	✓															
<i>S. flex</i> 3a																
<i>S. flex</i> 6																
Quadri- valent	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓

(How) can CHIM models accelerate
Licensure, policy recommendation and uptake

A quadrivalent mixture would protect against 88% of all *Shigella* (theoretically)

Potential role of challenge models

- Proof of concept
- Candidate prioritization
- Pathogenicity studies – correlates of protection
- Informing clinical trial designs
- Supportive data in regulatory submissions
- Pivotal data in regulatory submissions
- *Role in accelerating policy recommendations?*

- Product developers and funders are looking for guidance related to **clinical trial design and utility of CHIM to enable acceleration of Shigella vaccine development**



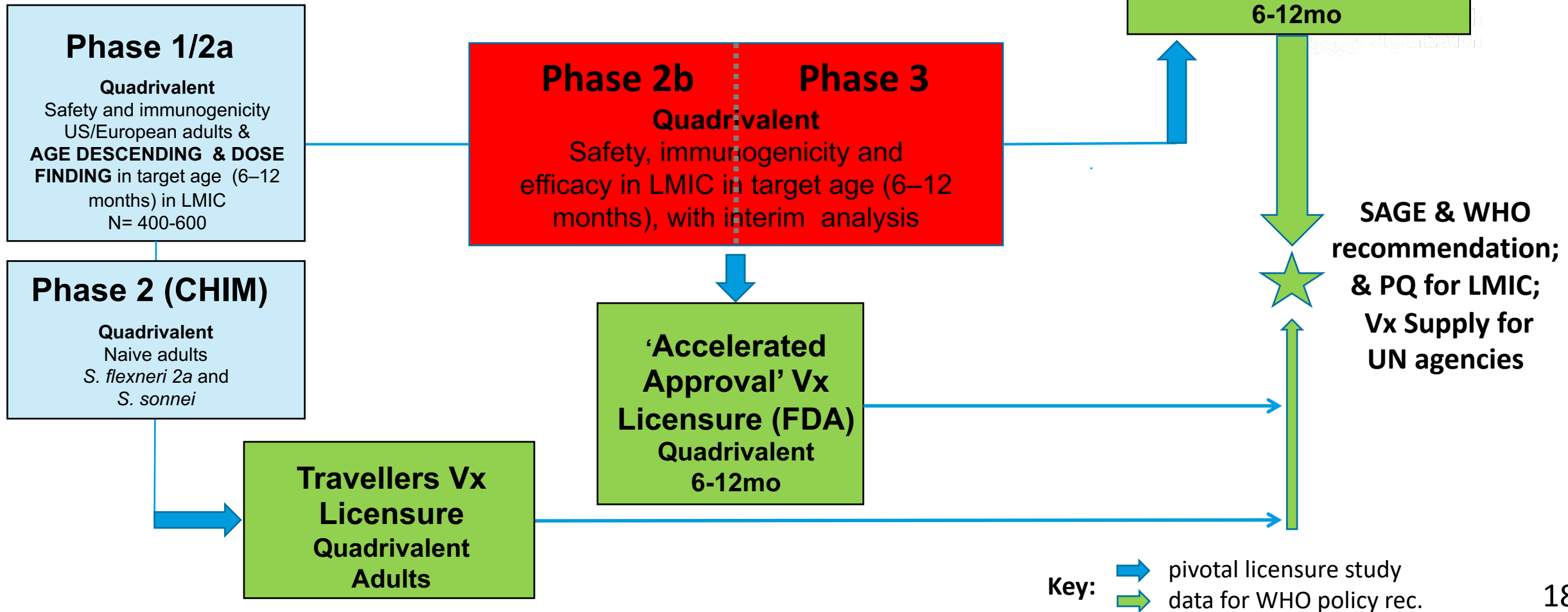
<http://apps.who.int/iris/bitstream/handle/10665/272272/WER9313.pdf?ua=1>



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

Stakeholder consultation identified three potential licensure routes

- Travellers vaccine dependant on efficacy from CHIM
- Accelerated approval supported by efficacy data from CHIM
- What role does CHIM play in licensure and a policy recommendation for LMICs?



Key questions for Shigella O-Ag candidate product development and implementation strategy



- If a Shigella vaccine is licensed for travellers/private market on the basis of CHIM, can this contribute to/accelerate WHO policy and WHO PQ consideration?
- What role would CHIM play in the licensure and introduction of Shigella vaccines by LMICs?
- What is needed to incentivise continued investment in late stage development (i.e. Phase 3 efficacy) and introduction in LMICs, once licensure for travellers is achieved?
- Will demonstration of clinical efficacy of 1 or 2 of 4 Shigella vaccine components be sufficient for LMIC licensure? Uptake?
- Is there benefit in developing a CHIM for flexneri 3a and flexneri 6, since it is unlikely to be feasible to demonstrate field efficacy?



PDVAC committee members *(new members in italics)*



- Klaus Cichutek, Paul Ehrlich Institute, Germany.
- Sinead Delany-Moretlwe Wits Reproductive Health and HIV Institute, South Africa
- Bernard Fritzell, BFL Conseils, France.
- Barney Graham, Vaccine Research Center, NIAID, USA.
- *Gagandeep Kang, Translational Health Science and Technology Institute, India.*
- Ruth Karron, Center for Immunization Research, Johns Hopkins School of Public Health, USA.
- *Jerome Kim, International Vaccine Institute, Korea*
- **David Kaslow, PATH, USA - Chair**
- Claudio Lanata, US Naval Medical Research Unit No 6, Peru.
- *Shabir Mahdi, Professor of Vaccinology, University of Witwatersrand, South Africa.*
- *Mark Papania, Centers for Disease Control and Prevention, USA*
- Yiming Shao, Department of Research on Virology and Immunology, Chinese Center for Disease Control and Prevention, China.
- Peter Smith, MRC Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, United Kingdom.
- *Marian Wentworth, Management Sciences for Health, USA.*
- ***Yakubo Beno, chair of the technical co-ordinating committee of the African Research Forum (AVAREF)***

