A year in review

2018-2019

WHO PDVAC meeting

26-28 June 2019

Birgitte Giersing

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World Health Organization

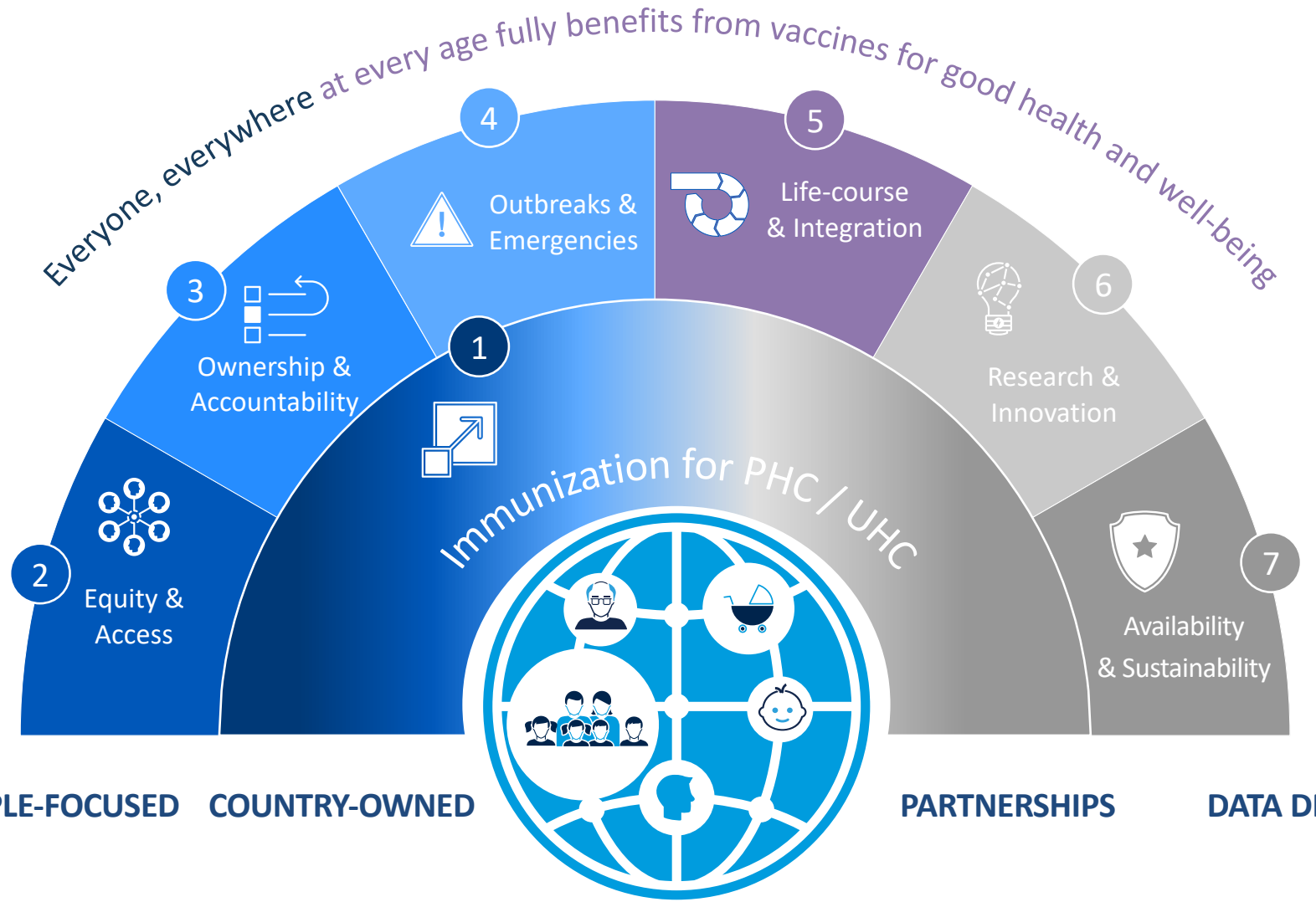
Overview and objectives of this of this ‘Year in Review’ presentation

- To provide a high level overview of the current status and issues regarding pathogens previously prioritized by PDVAC – that will not have a dedicated plenary session
- To review the kind of activities that PDVAC engages in (where should PDVAC be focusing its efforts?)
- To solicit information from participants with respect to the work that PDVAC is doing; are there gaps?

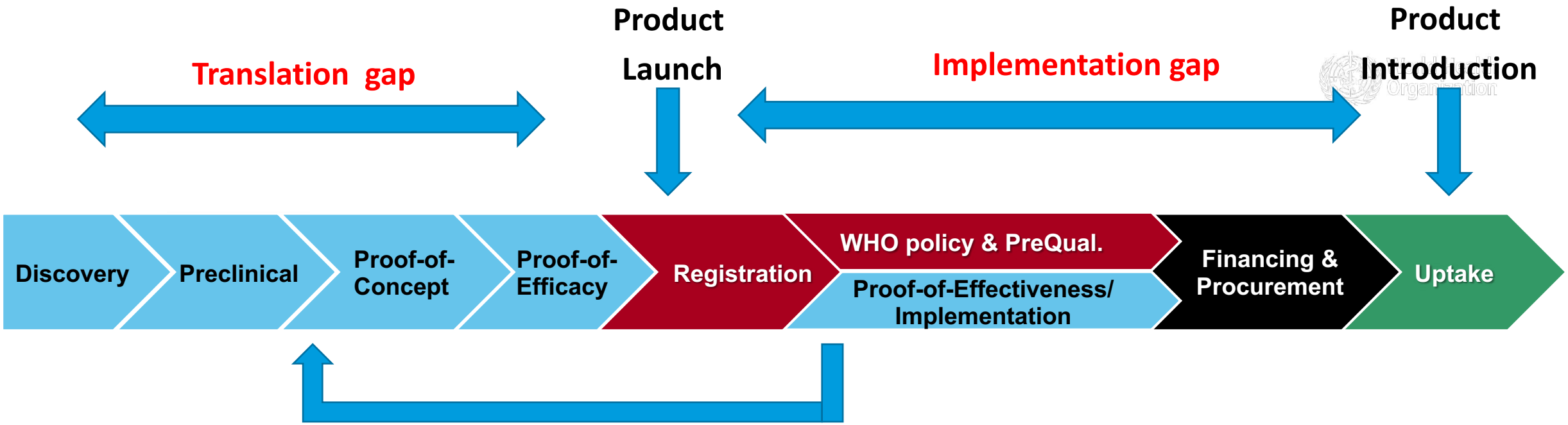
- Following this presentation by WHO, Barney Graham (PDVAC member and xx NIAID, NIH) will provide an update on the Universal Influenza Roadmap and associated activities

Broader context: Latest visual for strategic framework

Fig. 6 – The seven strategic priorities for 2021-2030.



What is the scope and objective of PDVAC?



Articulating the public health value, PPCs, roadmaps *early in product development* help to define the vaccine value, encourage investment and mitigate against the implementation gap

- ✓ Vaccines
- ✓ Monoclonal antibodies
- ✓ Delivery technologies

What are the typical activities and products that PDVAC engages in?

Pathogen-specific documents developed by WHO's PDVAC	Purpose/description
Preferred product characteristics (PPC)	Describe **preferred characteristics** for vaccines **with emphasis on the LMIC use context**
Vaccine R&D roadmap	Provides a **high-level vision, near and long term goals,** and **strategic framework** of **priority activities**
Considerations for product development pathways	Considers the manufacturing, clinical development, regulatory, policy and commercialization **pathways and barriers**
Full value of vaccines	Describes the **full health, economic and societal value** of a vaccine to **a broad range of global stakeholders, including from a LMIC perspective, and aims to articulate the full direct (individual) and indirect (population) effects** of a vaccine

Additional guidance to inform product development of pipeline vaccines for LMIC contexts

World Health Organization

WHO generic guidance that informs vaccine development	
Generic Preferred Product Profile for Vaccines (gPPP) (2015)	Recommendations on **presentation and packaging** of new vaccines for use in LMICs
Assessing the programmatic suitability of vaccine candidates for WHO prequalification (2014)	**Process and criteria** for prospective **vaccine PQ** in terms of their programmatic suitability for LMICs

Status of WHO guidance document development for vaccines against PDVAC prioritized pathogens

World Health Organization

Pathogen	Landscape analysis*	PPC	RM	Pathways	VP underway
Tuberculosis	✓	✓ (P&T)		✓	
HIV	✓				
Malaria	✓	✓	✓		
Influenza	✓	✓ (improved Vx)			
RSV	✓	✓	✓	✓	
GBS	✓	✓	✓	✓	✓
HSV	✓	✓ (P&T)	✓ (STI RM)		✓
GC	✓	(✓)			
ETEC	✓	(✓)			
Shigella	✓	(✓)		(✓)	
GAS	✓	✓		✓	✓

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

HIV: human immunodeficiency virus ; RSV: respiratory syncytial virus; GBS: group B Streptococcus ; HSV herpes simplex virus; GAS: group A streptococcus.
P: prophylactic, T: therapeutic; PPC: Preferred product characteristics; RM: Roadmap; VP: value proposition; * meeting reports publically available

Overview of cross-cutting initiatives

World Health Organization

Value Attribution Framework For Vaccines Against Antimicrobial Resistance

Total Systems Effectiveness

Enteric burden of disease (mortality) models

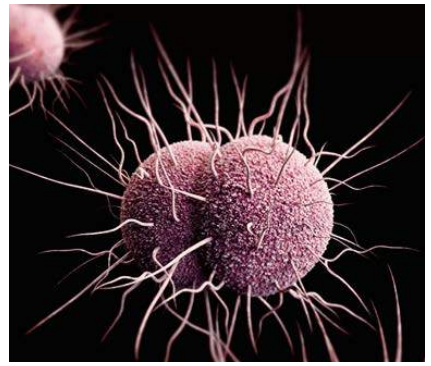
Vaccine Innovation Prioritization Strategy

World Health Organization

Full value of vaccines

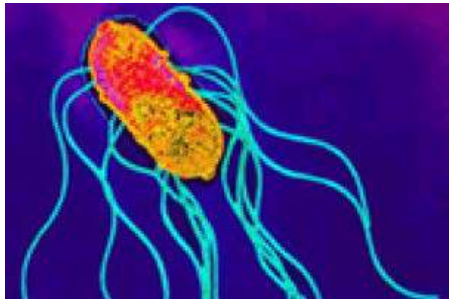
New areas of engagement for IVR and PDVAC

Gonorrhoea vaccines: Estimated 87 million cases each year globally; increasingly important due to AMR



Consultation on public health need and preferred product characteristics (in partnership with RHR funded by Bactivac)

Paratyphoid A vaccines: Estimated 3.4M cases, 19,200 deaths each year globally, AMR is a major threat including the potential for XDR and azithromycin resistance.



Consultation on public health need and potential use cases (combination) funded by BMGF and Wellcome Trust

Horizon scanning: what other vaccines should PDVAC and IVR be tracking going forward?

Historical criteria for engagement:

- Unmet burden of disease in LMICs
- Candidates in the pipeline (early stage)
- A clear role for WHO to facilitate or accelerate product development

How should we set the PDVAC scope and IVB research priorities going forward?

Areas of horizon scanning going forward:

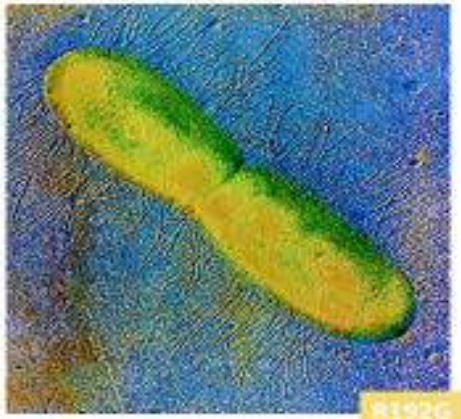
Chlamydia, Norovirus, Dengue, Otitis media, Staph aureus, AMR pathogen list, ….

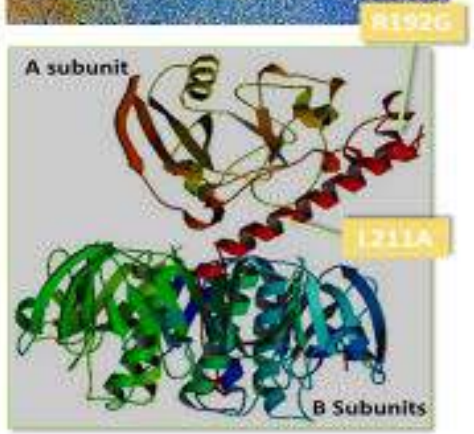
Vaccine development updates for specific priority pathogens

Enteric vaccines development: ETEC

Current ETEC vaccine landscape—Standalones and combinations

	Oral administration	Parenteral injection
Clinical candidates	ETVAX inactivated (SBH, UG, PATH) ACE527 live attenuated (PATH; NVSI; UGA)	FTA (PATH, NMRC, IDRI)
Preclinical candidates	CVD GuaBA mutants expressing ETEC Ags. (UMB, PaxVax) ShigETEC (EveliQure) Ty21a expressing *Shigella* LPS and MEFA (Protein Potential) STM expressing ETEC, Campy Ags. (IVI, UGA, NMRC, WASHU, WRAIR, Tulane, PATH) (New candidate)	MEFA (ILLU, JHU, PATH) LT/ST conjugate toxoids (Univ. of Bergen) Flagellin, EtpA, EatA, EaeH, YghJ (WASHU)





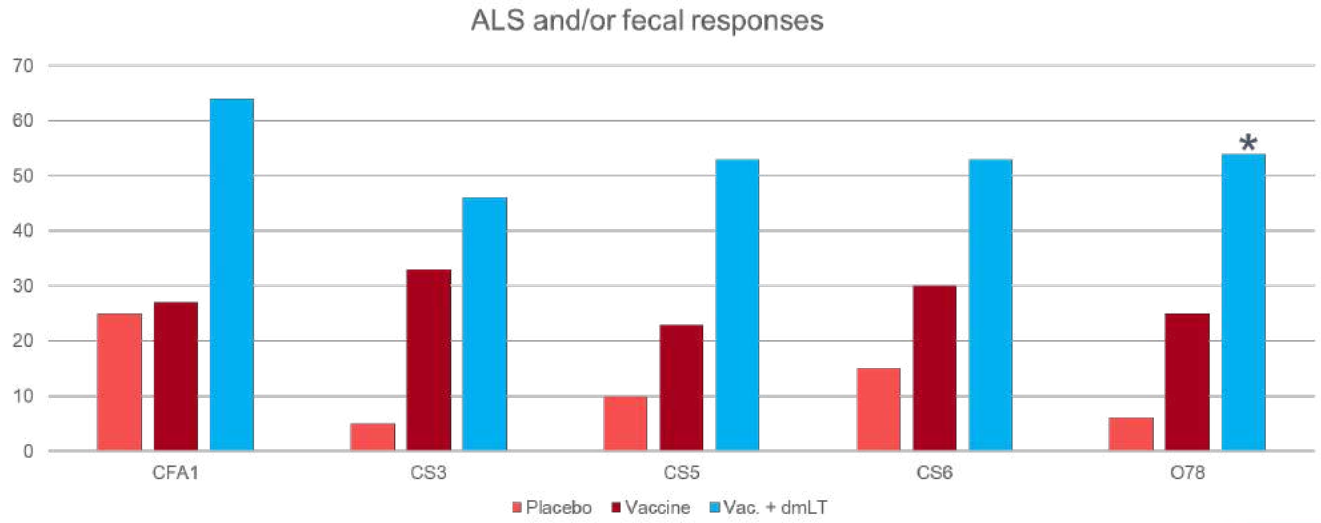
Note: Most candidates induce immunity against LT toxin and primary and secondary bacterial adhesins or proteins aiding toxin delivery; LT-ST toxoid is not seen as standalone vaccine but as a potential supplement to both whole cell or subunit approaches

= Vaccines in or poised to begin clinical trials; STM = inactivated mutant Shigella with truncated LPS giving conserved protein Ags greater exposure

(Kim et al 2018. Frontiers. Microbiol)

Slide courtesy of Lou Bourgeois, PATHc

6-11-month-old infants given the **ETVAX** inactivated whole-cell ETEC vaccine



OEV-123 Phase 2B efficacy trial in Finnish Travelers – Well executed

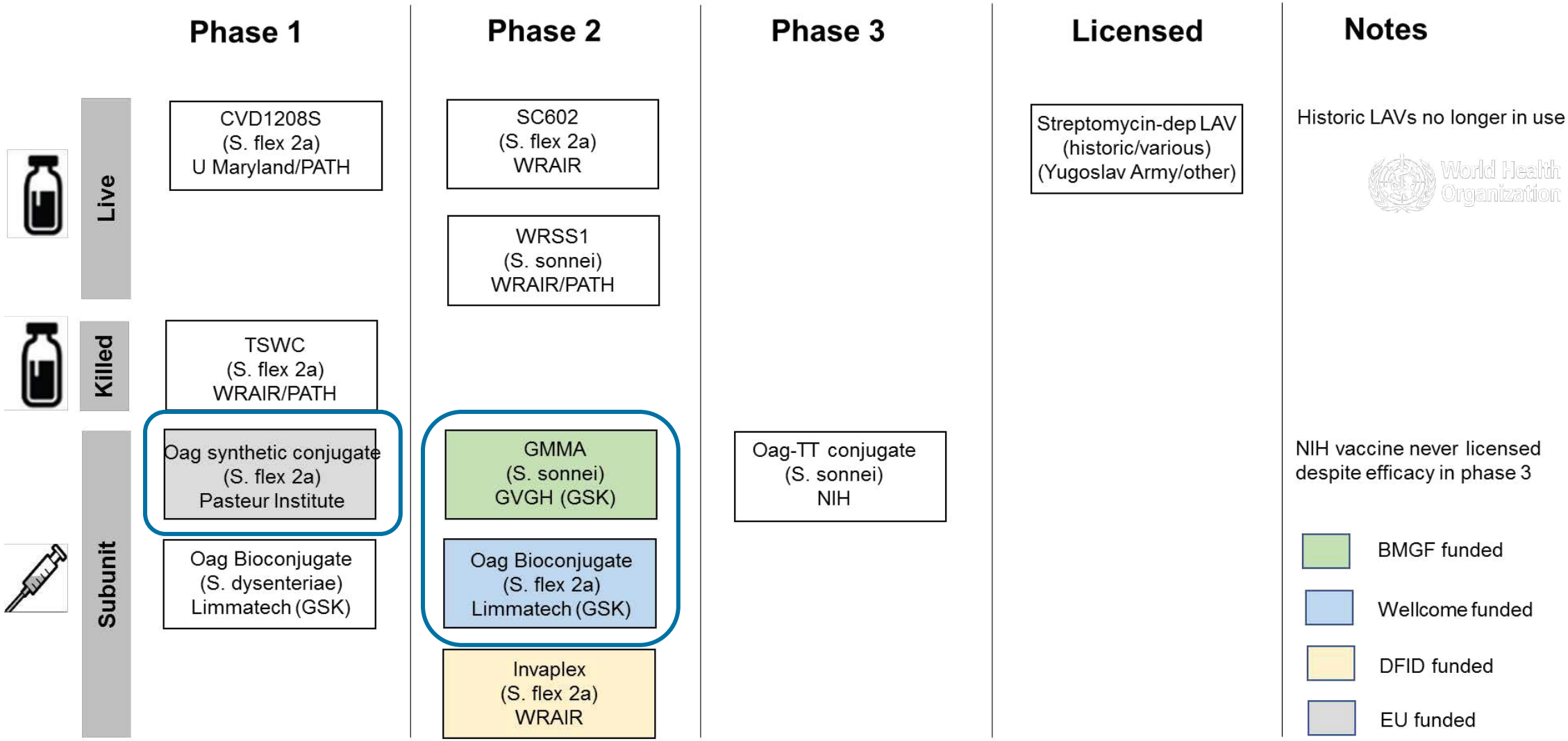
- The ETVAX vaccine has been **safe** and **well tolerated**
- **All 743 volunteers** have travelled to Benin
- The incidence of TD is very high >60% experience TD.
- The vaccine coverage fits the clinical findings
- **ETEC** is found in approx **35% of all TD cases**

Ongoing late phase development program in Africa funded by EDCTP

- Phase I age-descending trial in Zambia
  - Establish the exact safe and immunogenic dose in young children (6-23 months of age)
  - Explore the potential benefits of a booster dose
  - FPI summer 2019
- Phase IIb study in The Gambia
  - Approximately 5,000 children 6-18 months of age
  - Estimate the protective efficacy of the vaccine during a 1-2-year period
  - Study will follow after the Zambian trial

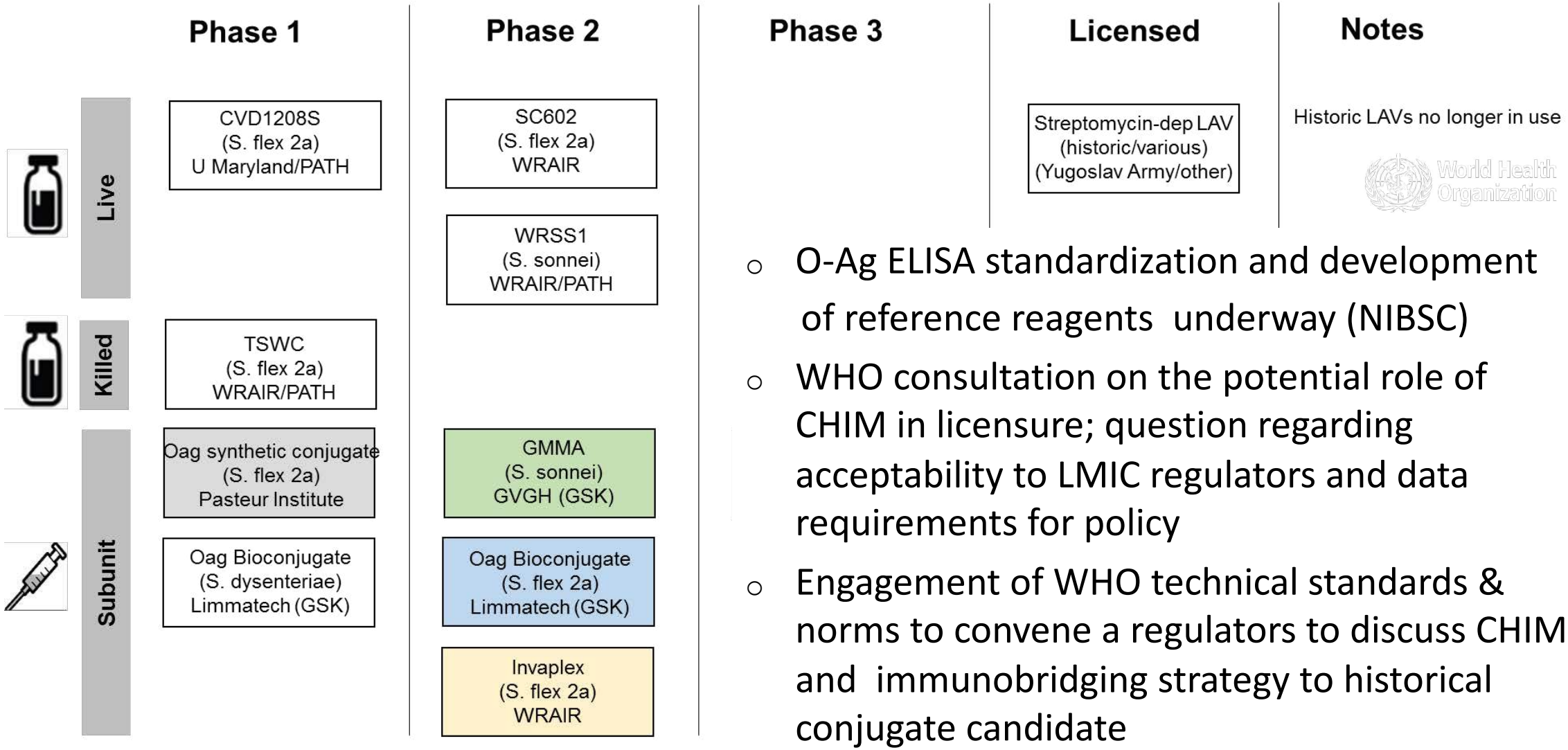
Slide courtesy of Lou Bourgeois, PATH

Shigella vaccine candidate pipeline



Courtesy of Calman MacLennan, BMGF

Shigella vaccine candidate pipeline



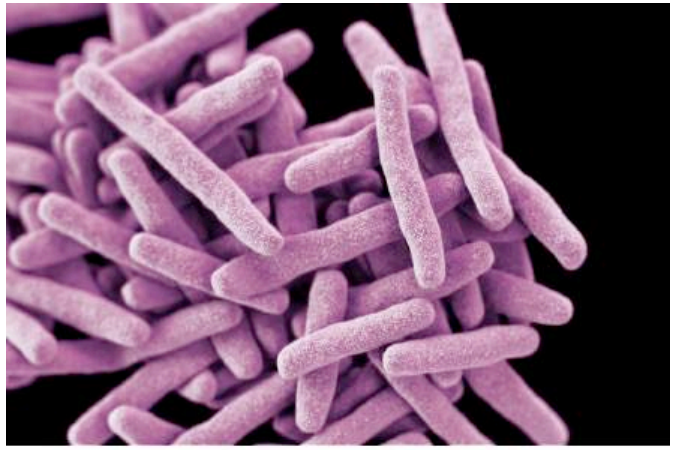
- O-Ag ELISA standardization and development of reference reagents underway (NIBSC)
- WHO consultation on the potential role of CHIM in licensure; question regarding acceptability to LMIC regulators and data requirements for policy
- Engagement of WHO technical standards & norms to convene a regulators to discuss CHIM and immunobridging strategy to historical conjugate candidate

Tuberculosis vaccine development

World Health Organization

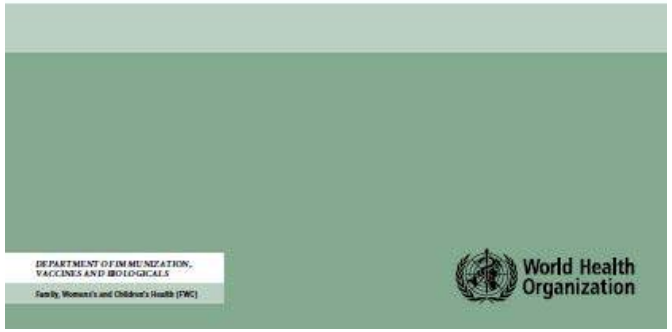
Next steps:

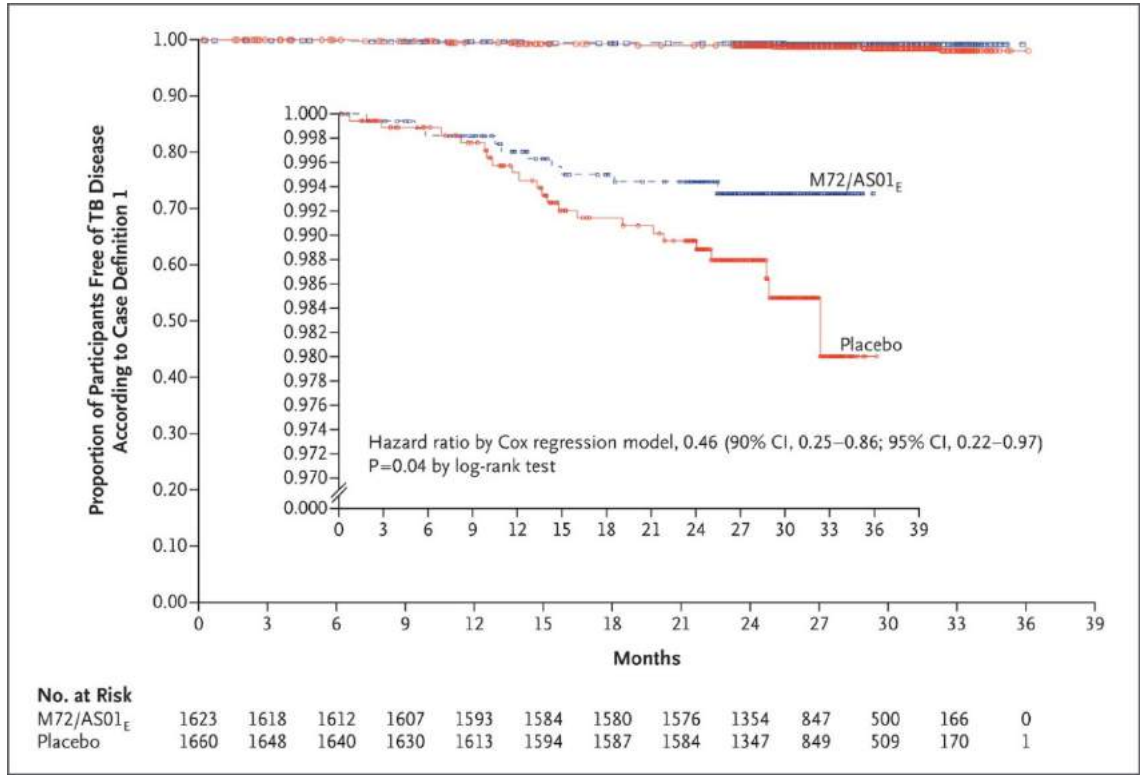
Move M72/AS01 forward



WHO Preferred Product Characteristics for New Tuberculosis Vaccines

WHO Preferred Product Characteristics for Therapeutic Vaccines to Improve Tuberculosis Treatment Outcomes





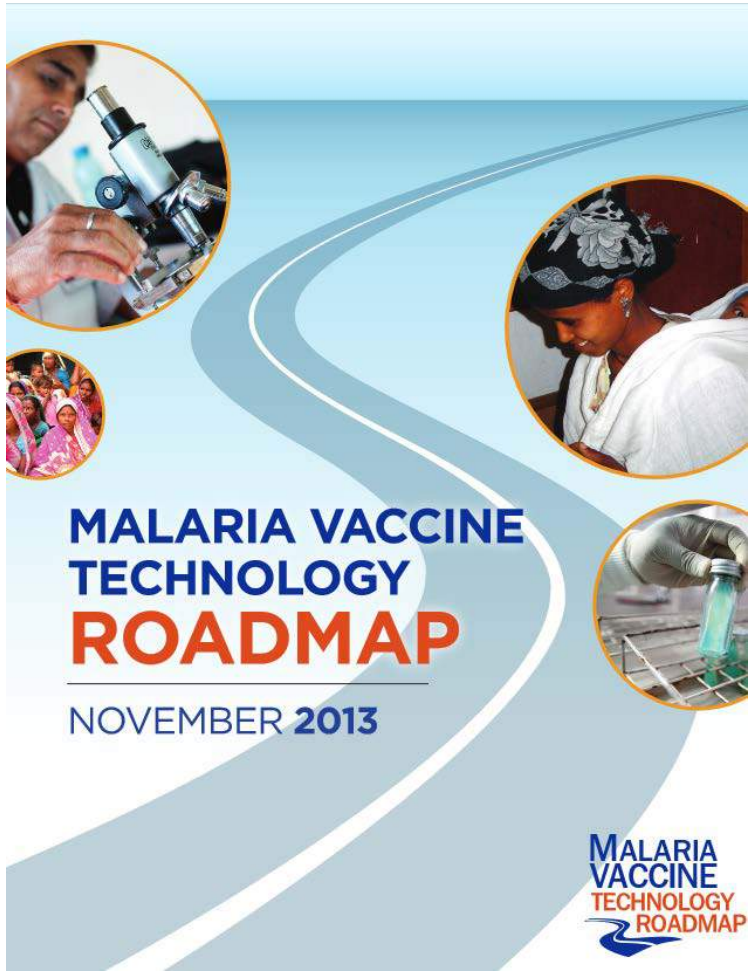
R&D Technical Roadmap

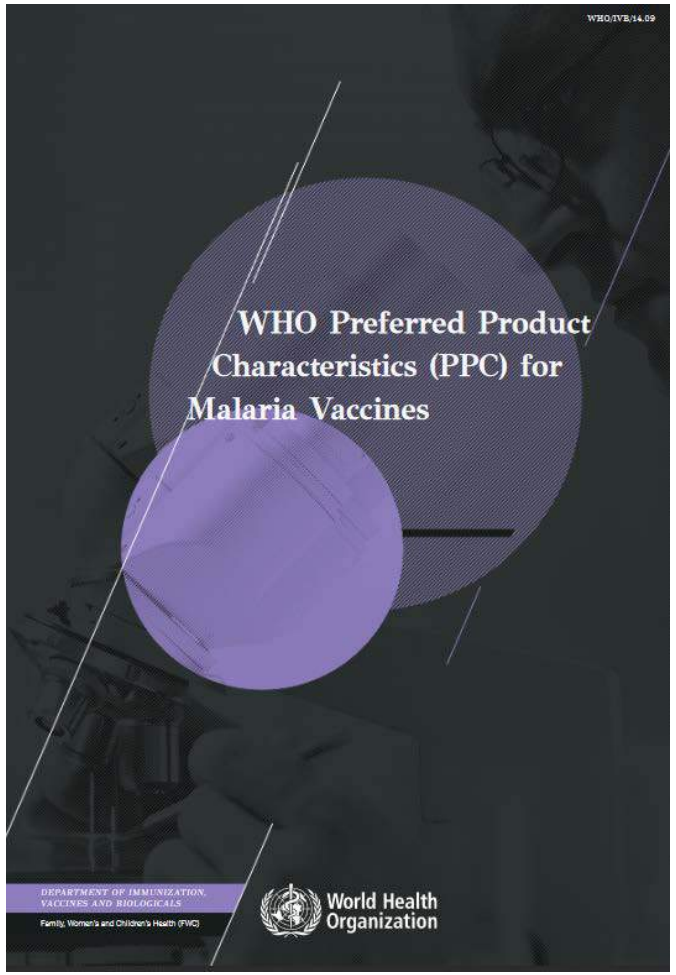
Public Health Value Proposition

Malaria vaccine development

Consultation on malaria vaccines and biologicals R&D

MALVAC meeting
July 15-17th, Geneva, Switzerland





Recent updates:

- RTS,S MVIP
- RTS,S fractional dose regimen to be evaluated in conditions of natural exposure
- RTS,S pre-seasonal administration
- R21, a RTS,S biosimilar developed in Jenner, Oxford, manufactured in Serum Institute India
- Sanaria moving to Phase 3 ?
- Progress in blood stage and man-to-mosquito challenge models

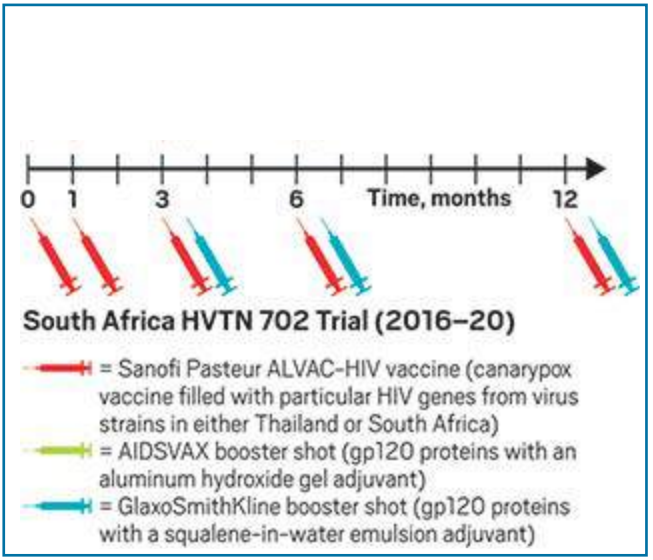
HIV vaccines and BNAbs for prevention

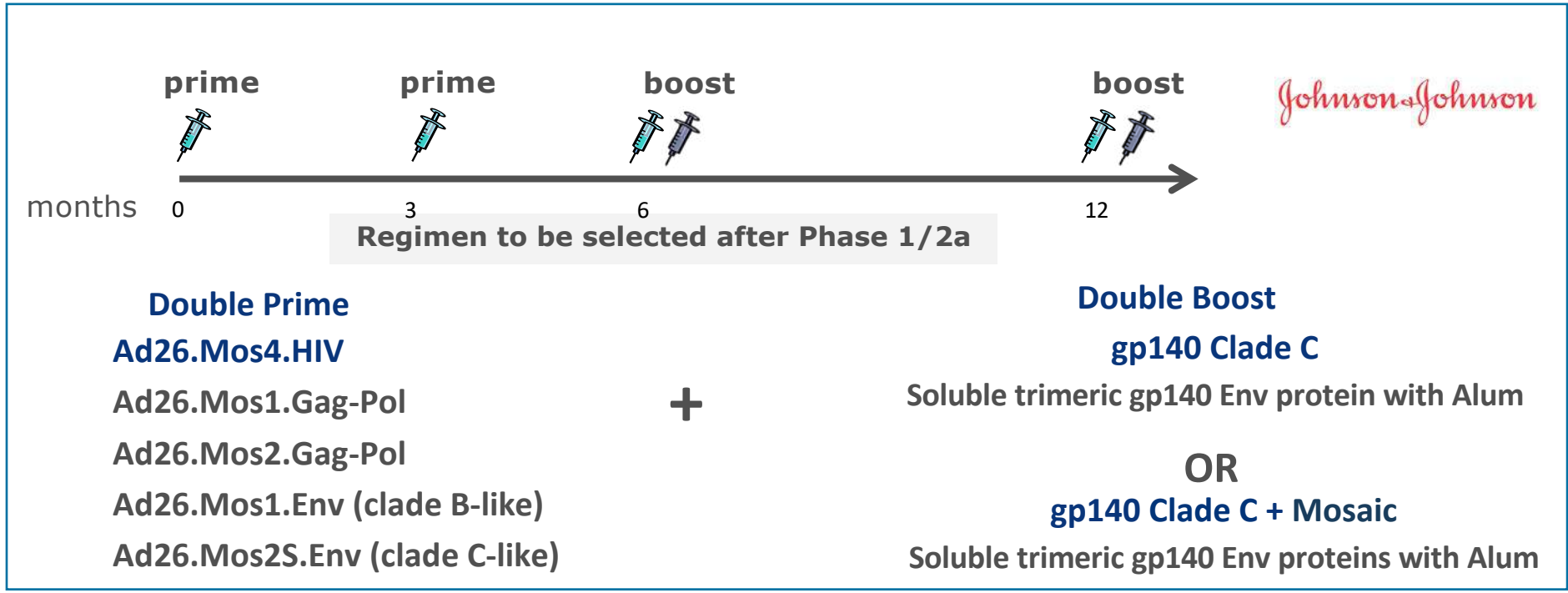
Summary profiles of large-scale efficacy trials

HVTN 703 & 704: Antibody Mediated Prevention (AMP) VRC01 studies – Fully enrolled, with 4,625 participants in US, Brazil, Peru, Switzerland, Tanzania, Zimbabwe, Botswana, RSA, Kenya, Malawi and Mozambique.

HVTN 702: Fully enrolled, with 5,407 healthy, HIV-negative men and women between 18 and 35 years old. HVTN 702, underway in South Africa.

HVTN 705: Fully enrolled, with 2,637 healthy, HIV-negative women in South Africa, Malawi, Mozambique, Zambia, and Zimbabwe between the ages of 18 and 35 years.





WHO focus on downstream pathways
IVB – UNAIDS – WHO HIV collaboration

2018 HIV vaccine R&D WHO consultation outcome :

- Expression of key considerations about the down-stream pathway.
- Report submitted to Lancet HIV

Next steps:

- Preparation of consultation about ethical considerations for evaluation of new tools for prevention of HIV, in era of PreP
- Collaborations considered with IAS, IVI, IAVI to work on PPCs and PHVP, Roadmap for vaccines and BNAbies
- Continued discussions with developers about decision pathways

Actions for access planning

Product development:

- Aim for simplification of administration schedules; test product combination options to reduce number of injections

End-to-end planning:

- *Develop an action roadmap* that considers the full pathway to access and use, taking into consideration public stakeholders and presenting a vision for programmatic suitability and financing
- *Evaluate full public value* of immunoprophylaxis strategies
- *Determine preferred product profil*e, defining use case precisely, target population, considering programmatic suitability in relation to efficacy, taking into account value proposition and user acceptability

Licensure and policy pathway:

- Engage WHO regulatory; define WHO norms and standards both for monoclonal antibodies and for heterologous prime boost regimens
- Engage LMIC constituted regulatory networks with capacity support
- Consider and plan for EMA Article 58 pathway, in close collaboration with WHO, for appropriate product

Industry and manufacturing:

- Define requirements in terms of production capacity, market access plans, cost of goods, business model, technology transfers. Business-legal agreements should define packaging and dispatching strategies and responsibilities of different manufacturers involved in the production of combined complex immunization regimen

Health systems preparation, country ownership

- Engage international, country, community leadership to make sure all perspectives are considered.
- Clarify the role of integrated health care delivery vs dedicated HIV programs
- Identify and enable financing mechanisms in advance

GBS vaccine development:
Leading IVB activities

World Health Organization

- Role of immune correlates of protection on pathway to licensure and policy decision
- Immuno-assays: towards WHO standards
- Endpoints: standard case definitions and ascertainment
- Epidemiologic characterization: surveillance standards
- Defeating Meningitis 2030
- Full Public Value Proposition

World Health Organization

WHO Preferred Product Characteristics for Group B Streptococcus Vaccines

WHO RSV work: Topics of focus in last year

- Defining the causal role of RSV infection on long-term respiratory sequelae – recurrent wheeze and asthma

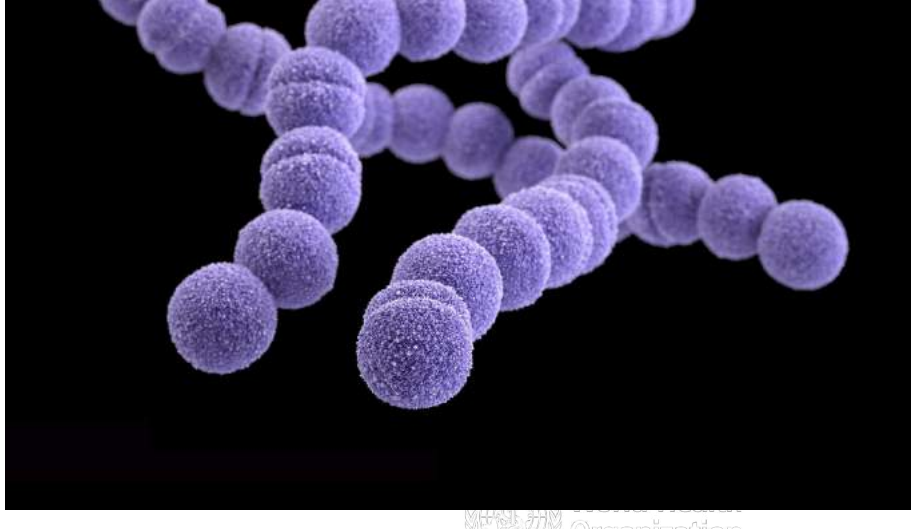
- Defining RSV epidemiology and its relevance for RSV preventive products

- Supporting development of Guidelines for Quality, Efficacy and Safety of RSV Vaccines (with Technology Standards and Norms)

- Policy related discussions about specific RSV vaccines and mAbs (With RSV Technical Advisory Group)

Group A Streptococcus

Towards a Global Strategy for the Prevention and Control of ARF/RHD



SEVENTY-FIRST WORLD HEALTH ASSEMBLY
Provisional agenda item 12.8

A71/25
12 April 2018

Rheumatic fever and rheumatic heart disease

Report by the Director-General

1. In May 2017, the Executive Board, at its 141st session, noted an earlier version of this report[1] and adopted resolution EB141.R1 on rheumatic fever and rheumatic heart disease. Paragraphs 15 and 18 in this report contain new text in response to comments from Member States.

Group A streptococcal diseases

World Health Organization

Superficial infection

- Pharyngitis
- Pyoderma

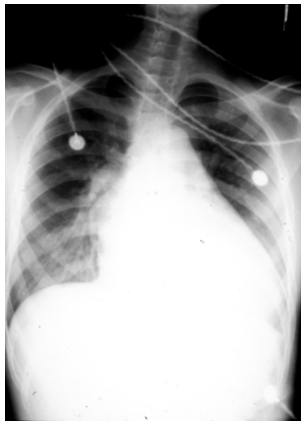
World Health Organization

Invasive diseases

- Septicaemia
- Pneumonia, osteomyelitis…
- Necrotising fasciitis

Toxin mediated diseases

- Scarlet fever
- Streptococcal toxic shock syndrome



Post-streptococcal autoimmune sequelae

- Acute rheumatic fever / rheumatic heart disease
- Post-streptococcal glomerulonephritis

Updated estimates of global Strep A burden

World Health Organization

TABLE 40.1 Summary of Estimated Global Burden of GAS Diseases

Disease	Year of Publication	Number of Existing Cases	Number of New Cases Each Year	Number of Deaths Each Year
Rheumatic heart disease (RHD)	2017 2005	33.4 million[9]	282,000[2]	319,000[9]
History of acute rheumatic fever without carditis, requiring secondary prophylaxis[2]	2005	1.88 million	188,000*	
RHD-related infective endocarditis[29]	2016			14,000
RHD-related stroke	2016 2005	640,000[2]		134,000[29]
Acute post-streptococcal glomerulonephritis[2]	2005	§	472,000	9,000
Invasive group A streptococcal diseases[2]	2005		663,000	163,000
Pyoderma[6]	2015	162 million		
Pharyngitis[2]	2005		616 million	

500,000 – 600,000 deaths each year

All estimates rounded down.

*New RHD cases were calculated based on the proportion of incident acute rheumatic fever cases expected to develop RHD. The remainder of incident acute rheumatic fever cases are included in the "History of acute rheumatic fever without carditis" row. Therefore the total number of new acute rheumatic fever cases each year is 188,000 + 282,000 = 470,000

§No satisfactory data available to identify glomerulonephritis-induced chronic renal impairment or end-stage renal failure on the global scale.

Ω Inferred from relevant reference.

Hand et al, Hunters Tropical Medicine and Emerging Infectious Disease, 10th edition. In press.

http://www.who.int/immunization/research/development/en/

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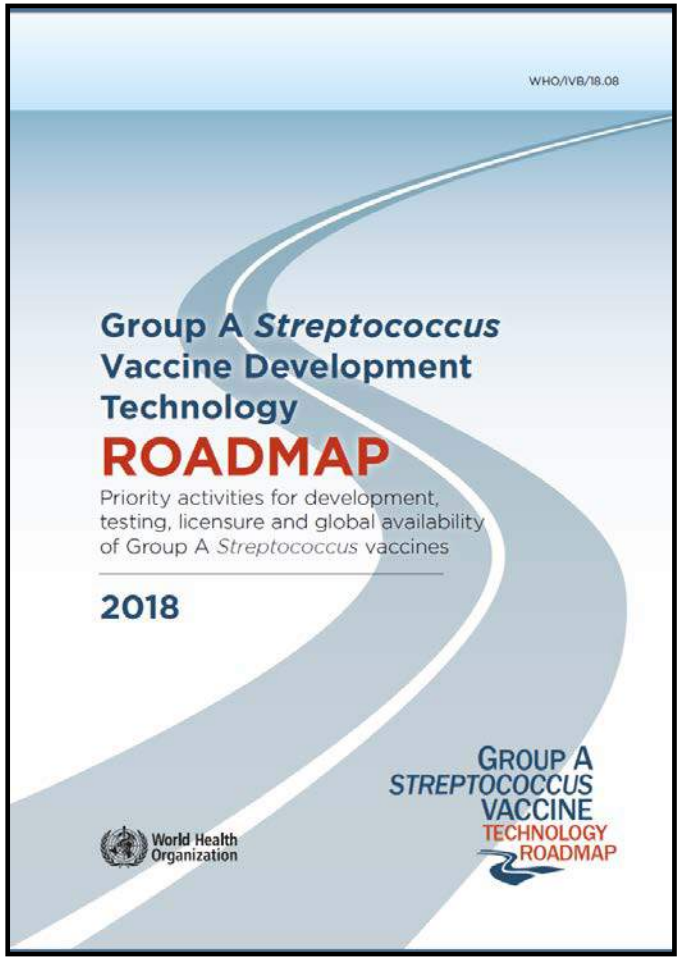

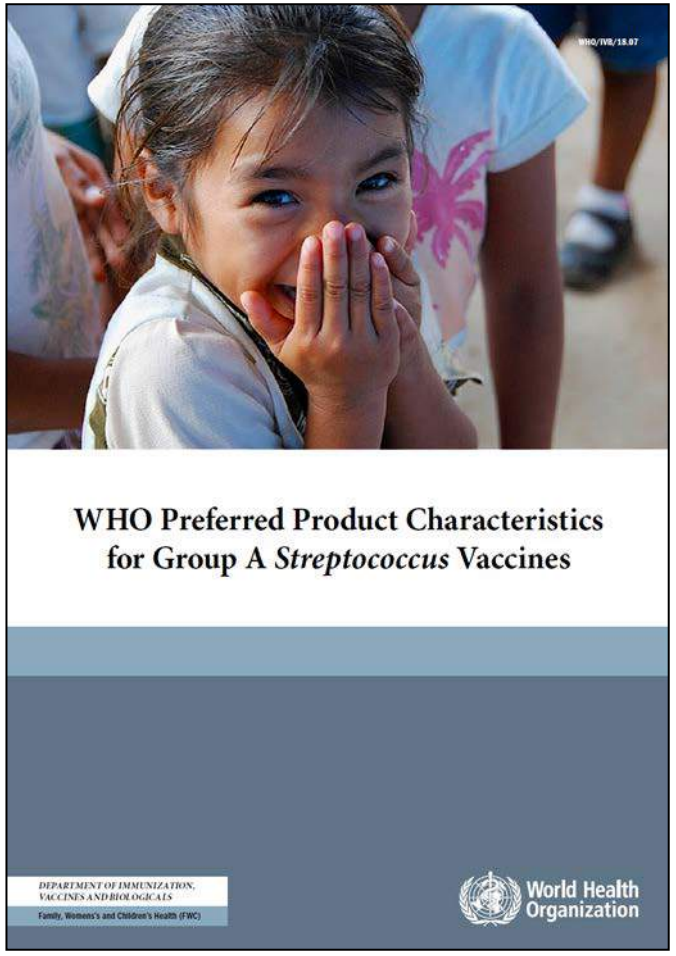

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GAS vaccine R&D technical roadmap
Strategic goals

Near-term: To demonstrate favorable safety and proof of efficacy of a candidate vaccine against GAS pharyngitis and skin infections in children.

Long-term: to develop safe, globally effective and affordable GAS vaccines for prevention of acute infections (pharyngitis, skin infections, cellulitis, invasive disease) and associated antibiotic use, and secondary immune-mediated sequelae (kidney disease, rheumatic fever and rheumatic heart disease) and associated mortality.

While the medical need is highest in high endemicity LMIC, the potential value of a vaccine, primarily for prevention of GAS pharyngitis, skin infections, cellulitis and invasive disease and associated antibiotic use in HIC, is also acknowledged.

February 24th 2019

AU $35m Strep A vaccine funding announced

The Hon Greg Hunt MP
Minister for Health
Member for Flinders

The Hon Ken Wyatt AM, MP
Minister Senior Australians and Aged Care
Minister for Indigenous Health
Member for Hasluck

MEDIA RELEASE

24 February 2019

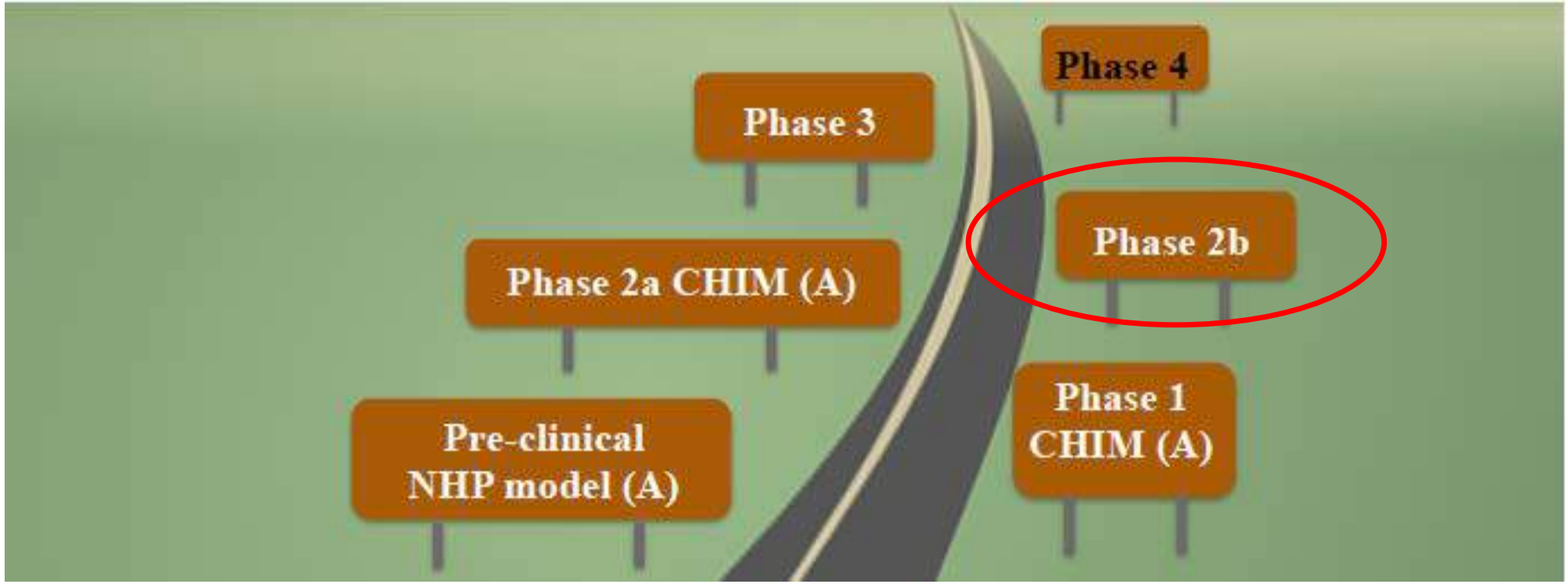
$35 Million for Vaccine to End Rheumatic Heart Disease

The eradication of rheumatic heart disease, a deadly and devastating illness largely affecting Indigenous communities, is taking a major step forward, with the Morrison Government investing $35 million in the development of a vaccine to combat the disease.

The funding announced today by Indigenous Health Minister Ken Wyatt AM is being provided from the Medical Research Future Fund (MRFF).

It will allow manufacture and testing of a number of vaccines currently being developed and fast-tracking and funding of clinical trials in Australia. The aim is to accelerate availability of a vaccine for use in Australia and internationally.

"Today is a game-changing step," said Minister Wyatt. "Ending RHD is a critical, tangible target to close the gap in Indigenous life expectancy.



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Global Strep A vaccine consortium

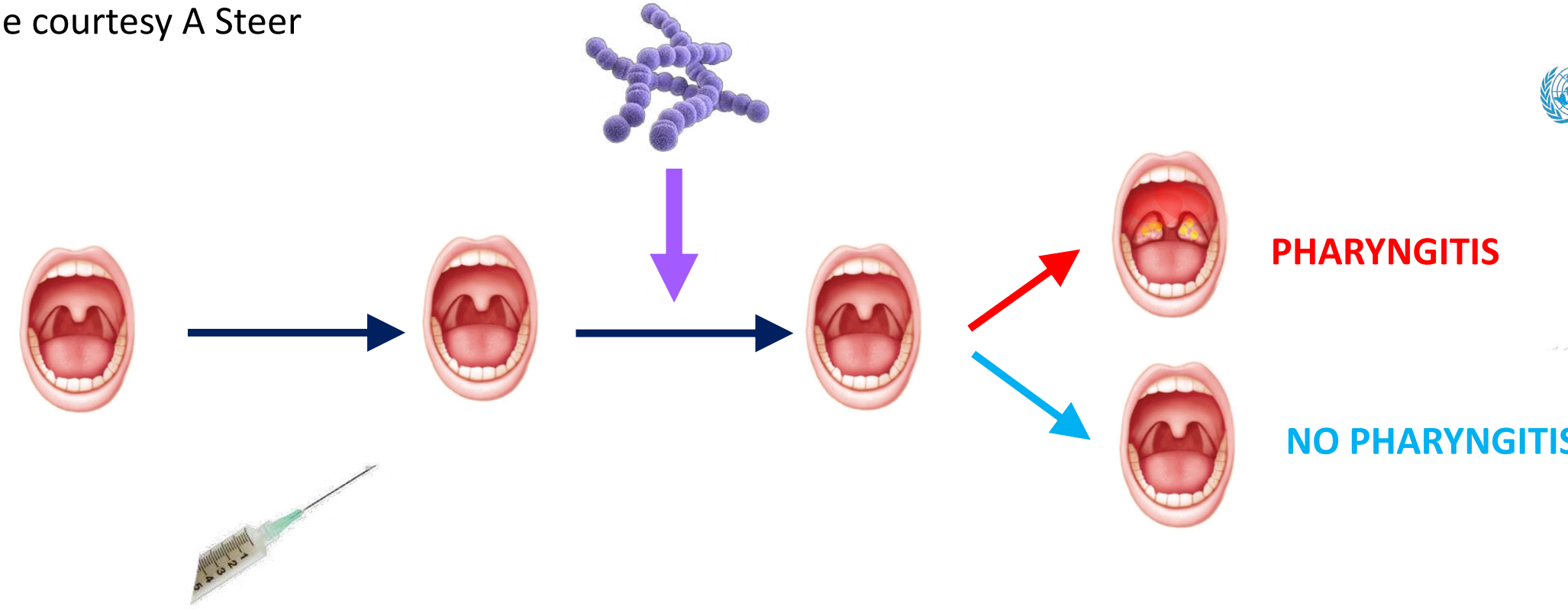
- Advocacy, coordination, industry liaison, vaccine pipeline
- Contribute to implementation of the WHO Tech R&D Roadmap
- Investment case (Public Health Value Proposition)

Critical aim – a Phase 2b efficacy trial for pharyngitis!

Slide courtesy A Steer

Slide courtesy A Steer

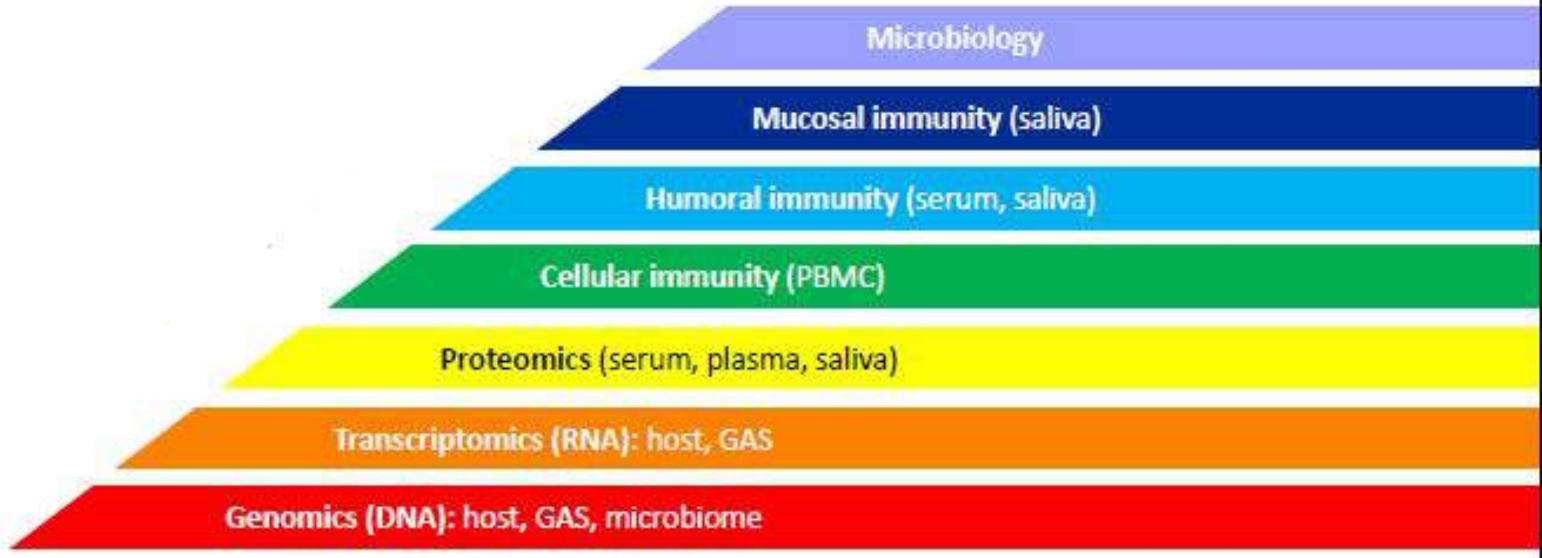
World Health Organization



Vaccine

OR

Placebo



Vaccines for sexually transmitted infections (STIs)

World Health Organization

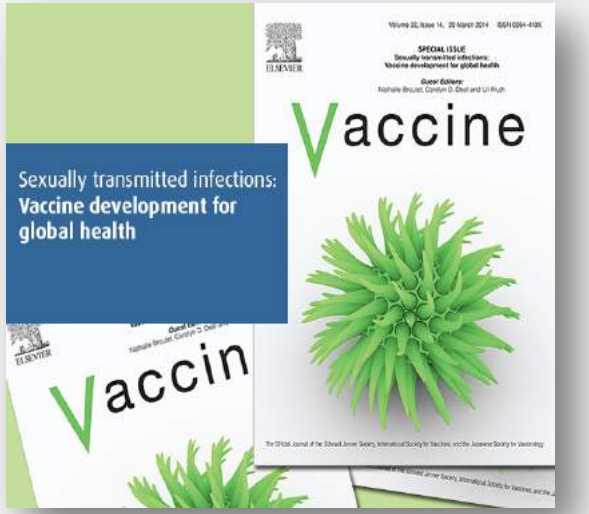
Outline

- STI vaccine roadmap
- HSV vaccines: progress and plans
- Gonorrhoea vaccines: new activities
- Chlamydia vaccines: update
- Opportunities for WHO engagement

STI Vaccine Roadmap

World Health Organization

- Global roadmap to advance STI vaccine development
- Critical next steps from pre-vaccine development through vaccine introduction



Vaccine 34 (2016) 2939–2947

Contents lists available at ScienceDirect

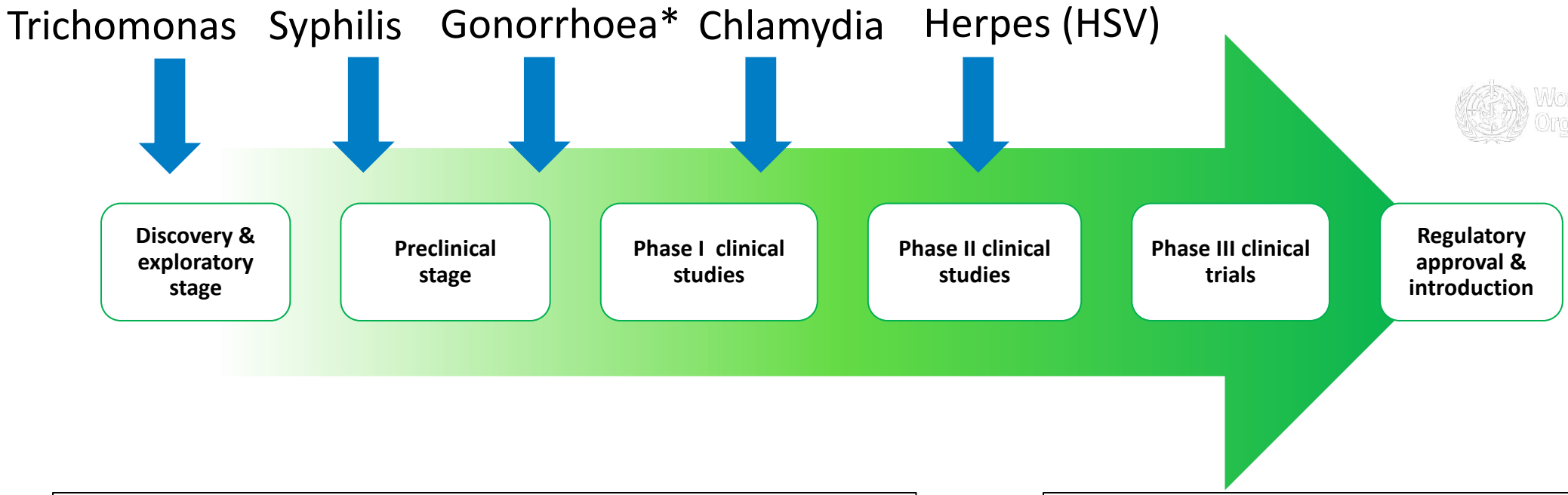
Vaccine

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

The global roadmap for advancing development of vaccines against sexually transmitted infections: Update and next steps

Sami L. Gottlieb[a,*], Carolyn D. Deal[b], Birgitte Giersing[a], Helen Rees[c], Gail Bolan[d], Christine Johnston[e], Peter Timms[f], Scott D. Gray-Owen[g], Ann E. Jerse[h], Caroline E. Cameron[i], Vasee S. Moorthy[a], James Kiarie[a], Nathalie Broutet[a]

Current status of the development pathway of STI vaccines



*Licensed *N meningitidis* B vaccine may also have some activity against *N gonorrhoeae*

HSV = herpes simplex virus
Chlamydia = *Chlamydia trachomatis*
Gonorrhoea = *Neisseria gonorrhoeae*
Syphilis = *Treponema pallidum*
Trichomonas = *Trichomonas vaginalis*

HSV vaccines: progress and plans

World Health Organization

Toward reducing the impact of genital HSV infection:

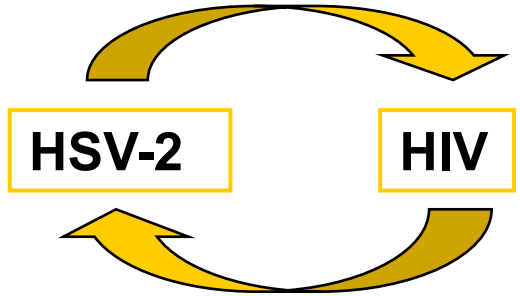
World Health Organization

Genital ulcer disease

Impact on sexual & reproductive health

Neonatal herpes

HIV acquisition and transmission risk



Progress: HSV vaccine PPCs published

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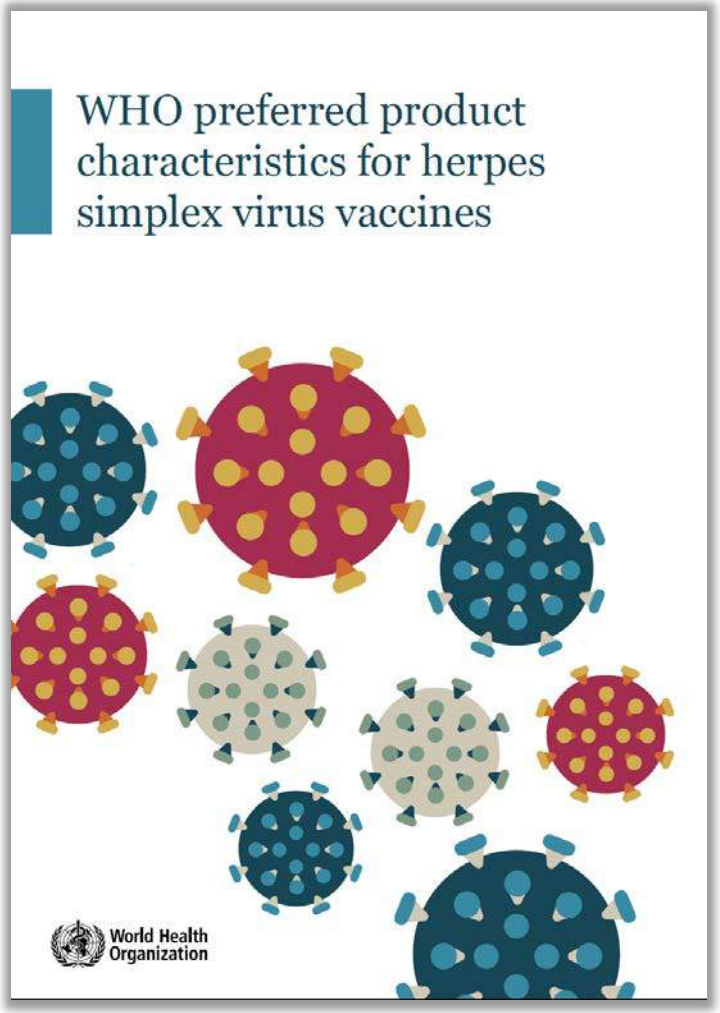

Available at: https://www.who.int/reproductivehealth/publications/HSV-Vaccine-PPCs/en/

Progress and next steps: HSV vaccine full public health value proposition

World Health Organization

- Current activities to outline public health and financial rationale for HSV vaccines:

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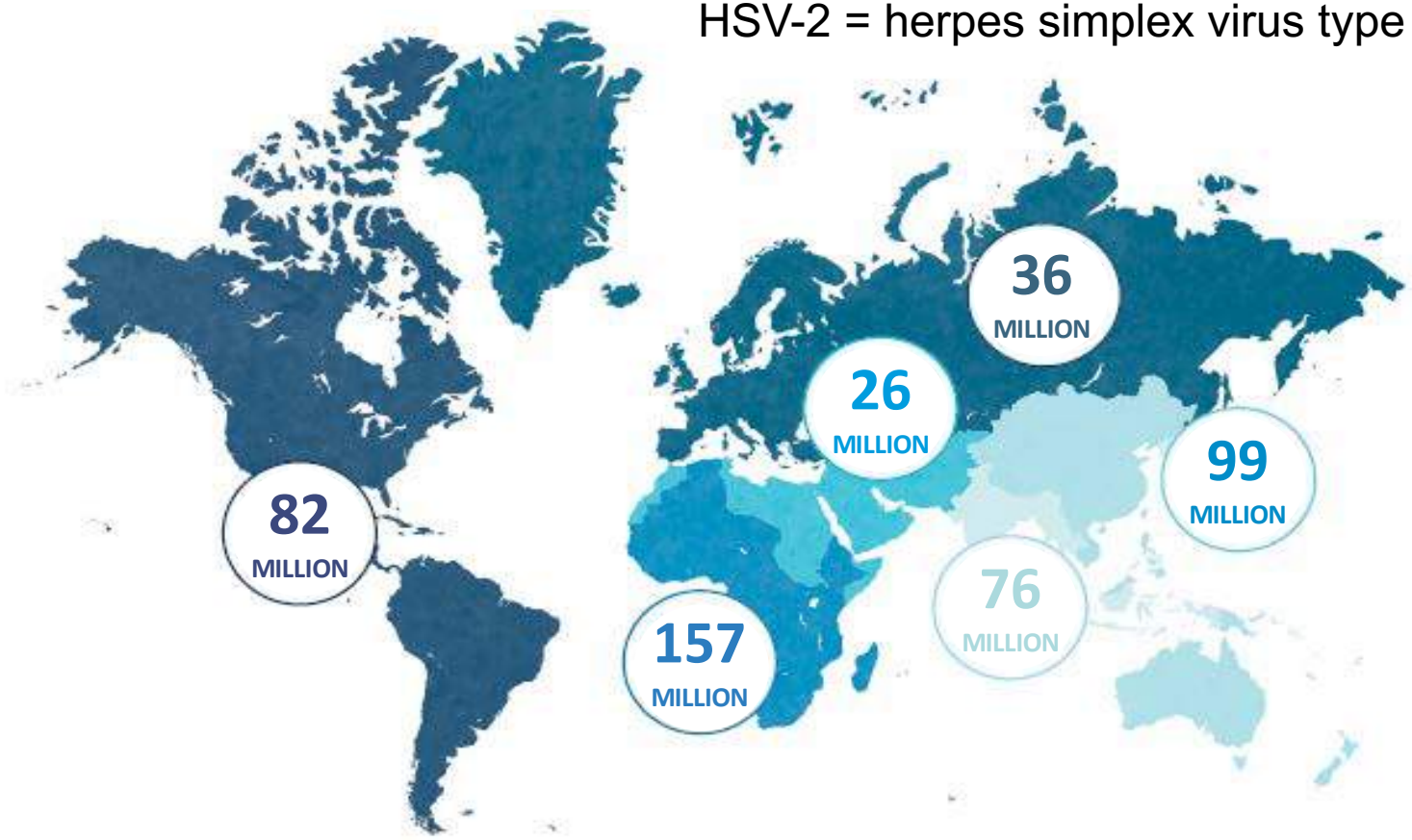

World Health Organization

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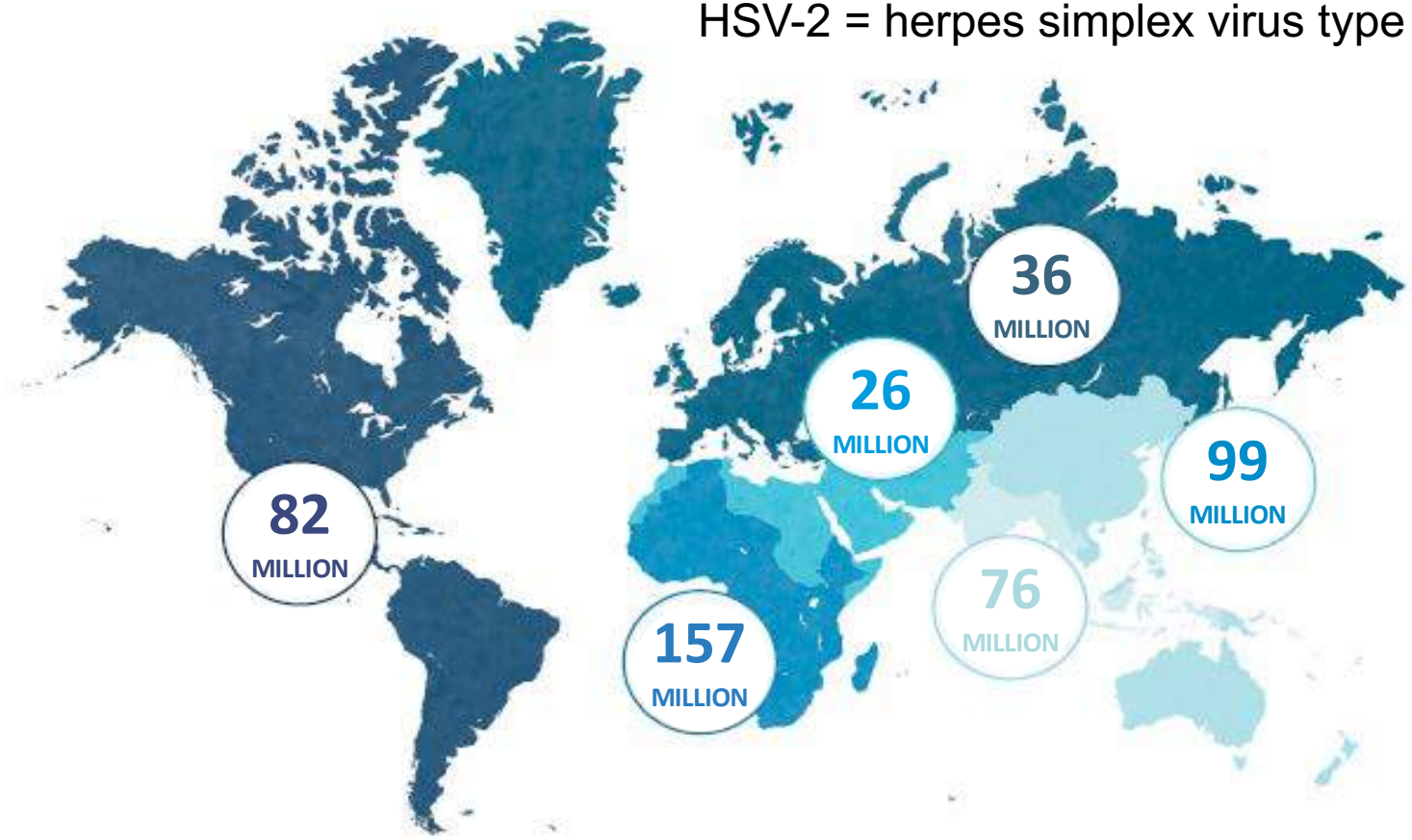

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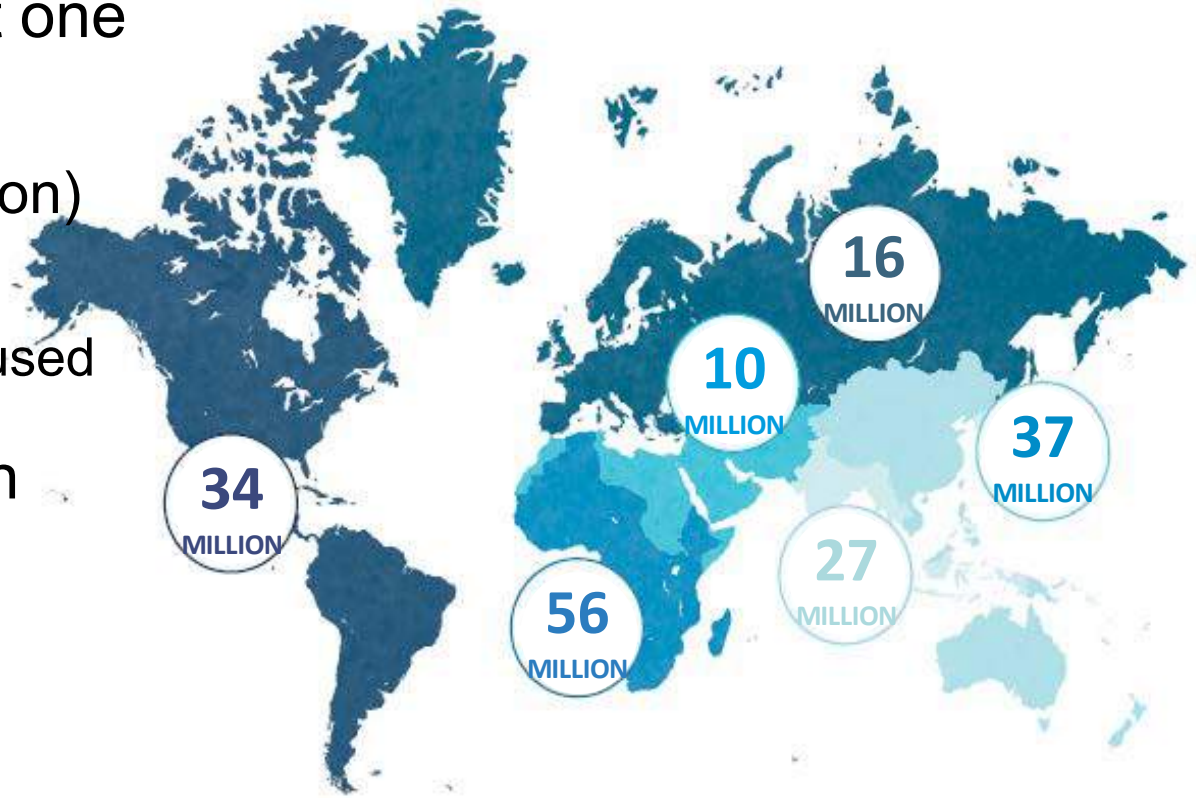

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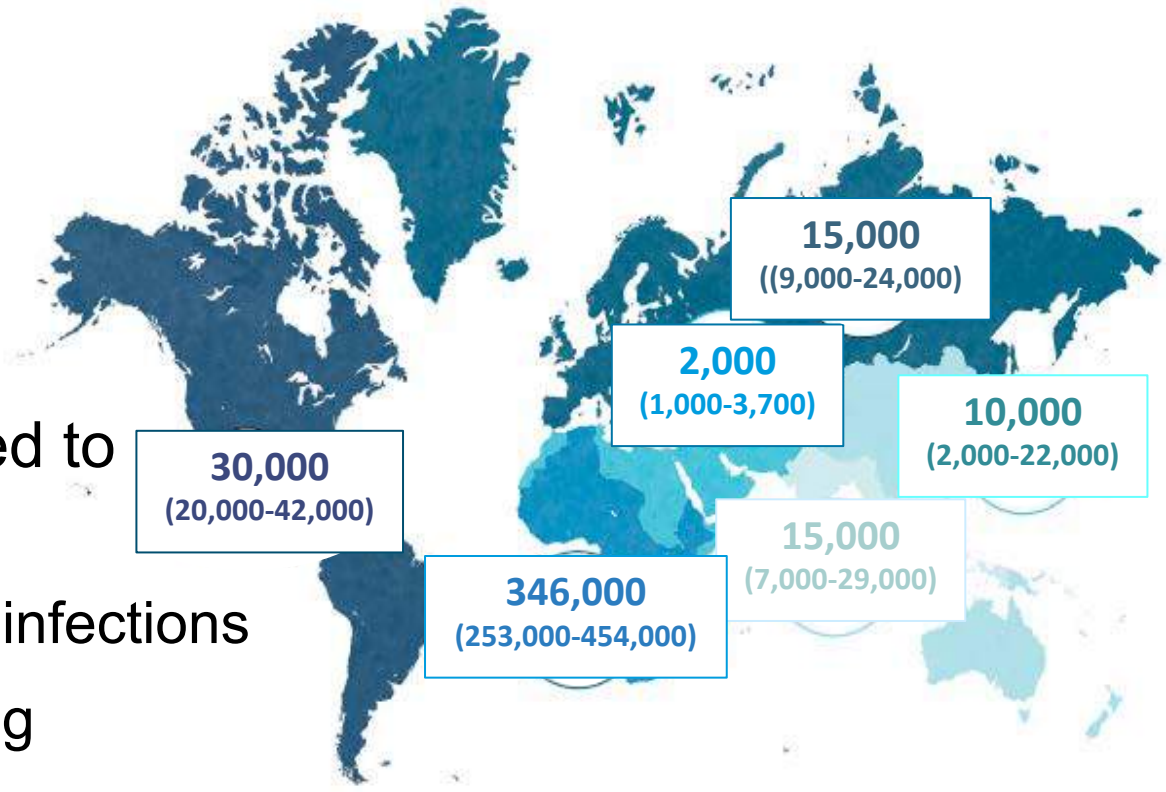

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World Health Organization

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Gonorrhoea vaccines: new activities

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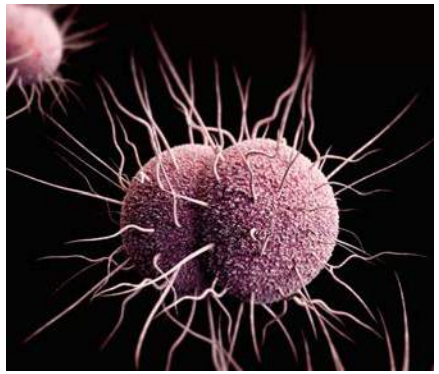

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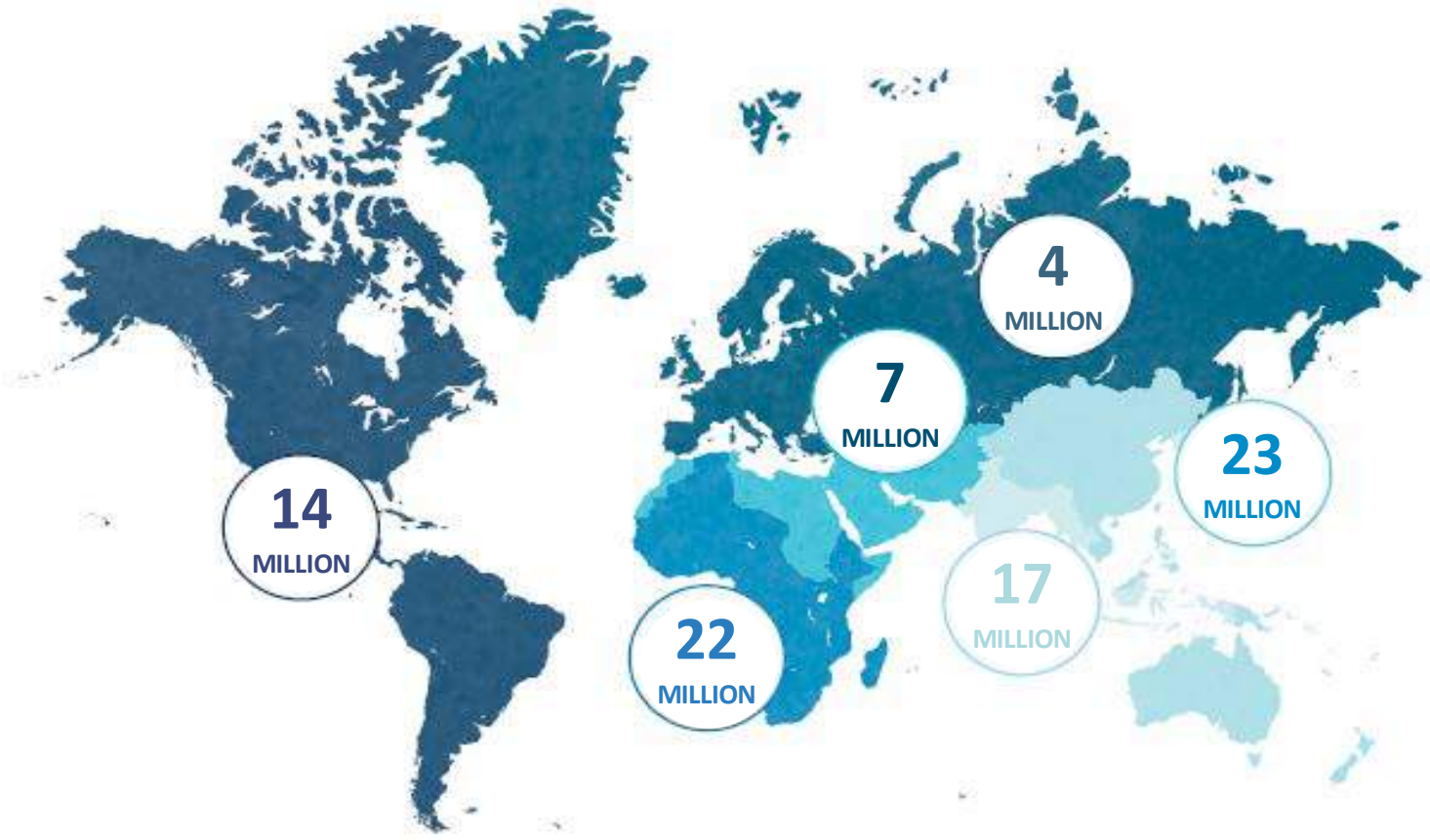

Untreated, can lead to:

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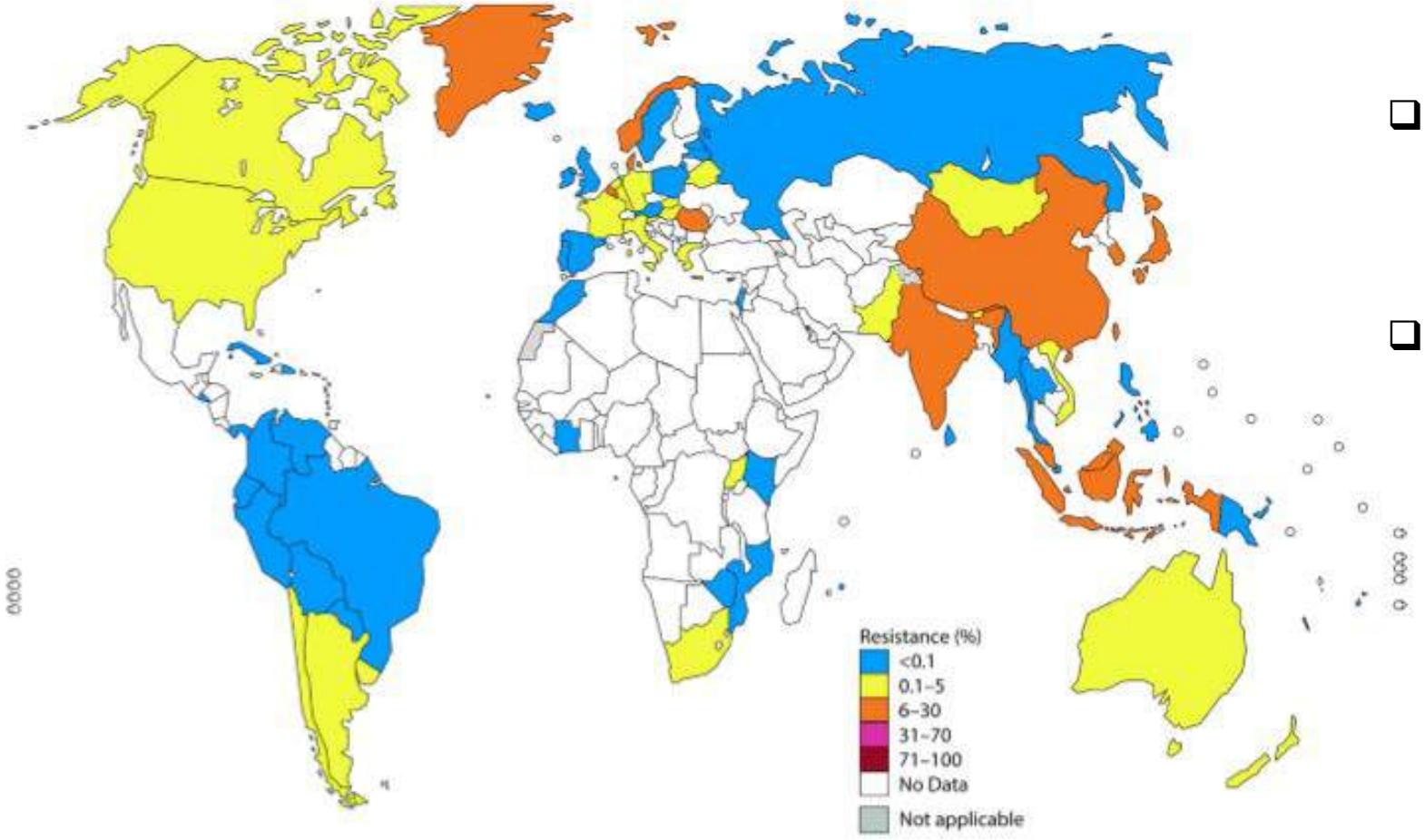
Gonorrhoea vaccine development increasingly important due to AMR



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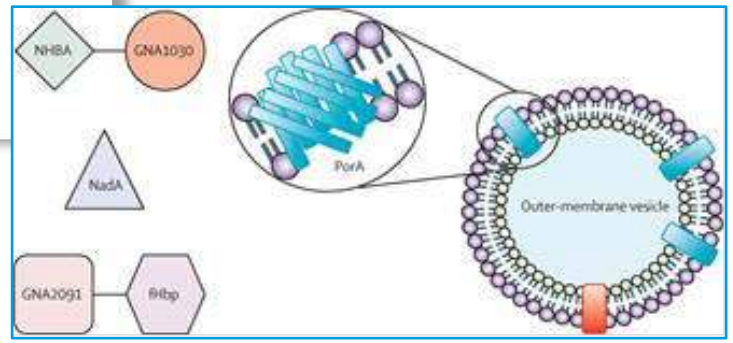

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Recent developments have jumpstarted interest in gonococcal vaccines

World Health Organization

- Molecular pathogenesis studies, advances in genomics, proteomics, immunoproteomics: range of candidates, most in preclinical phase

World Health Organization

- Main approaches
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    - **Meningococcal OMVs**
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World Health Organization

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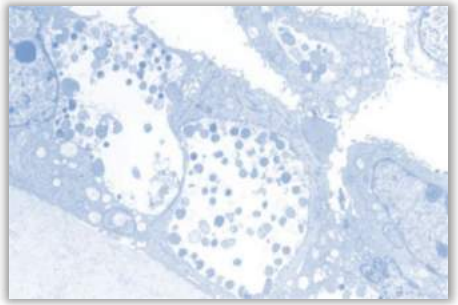

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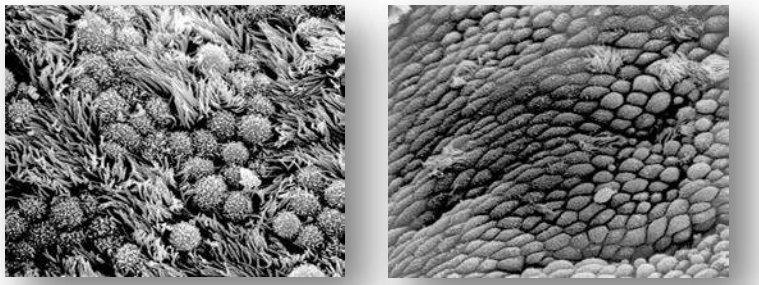

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Vaccines for sexually transmitted infections (STIs)

World Health Organization

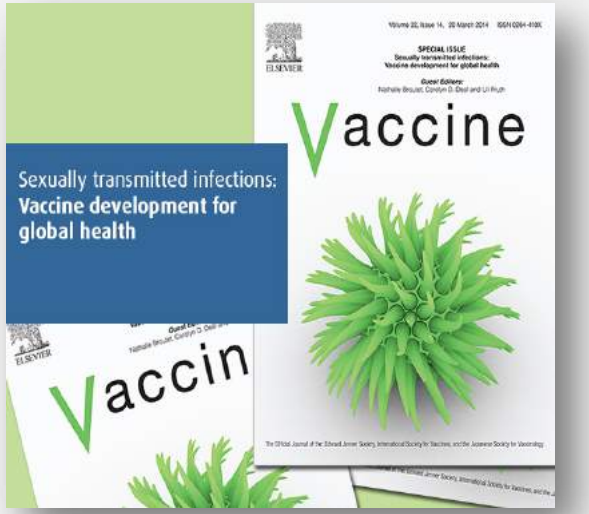
Outline

- STI vaccine roadmap
- HSV vaccines: progress and plans
- Gonorrhoea vaccines: new activities
- Chlamydia vaccines: update
- Opportunities for WHO engagement

STI Vaccine Roadmap

World Health Organization

- Global roadmap to advance STI vaccine development
- Critical next steps from pre-vaccine development through vaccine introduction



Vaccine 34 (2016) 2939–2947

Contents lists available at ScienceDirect

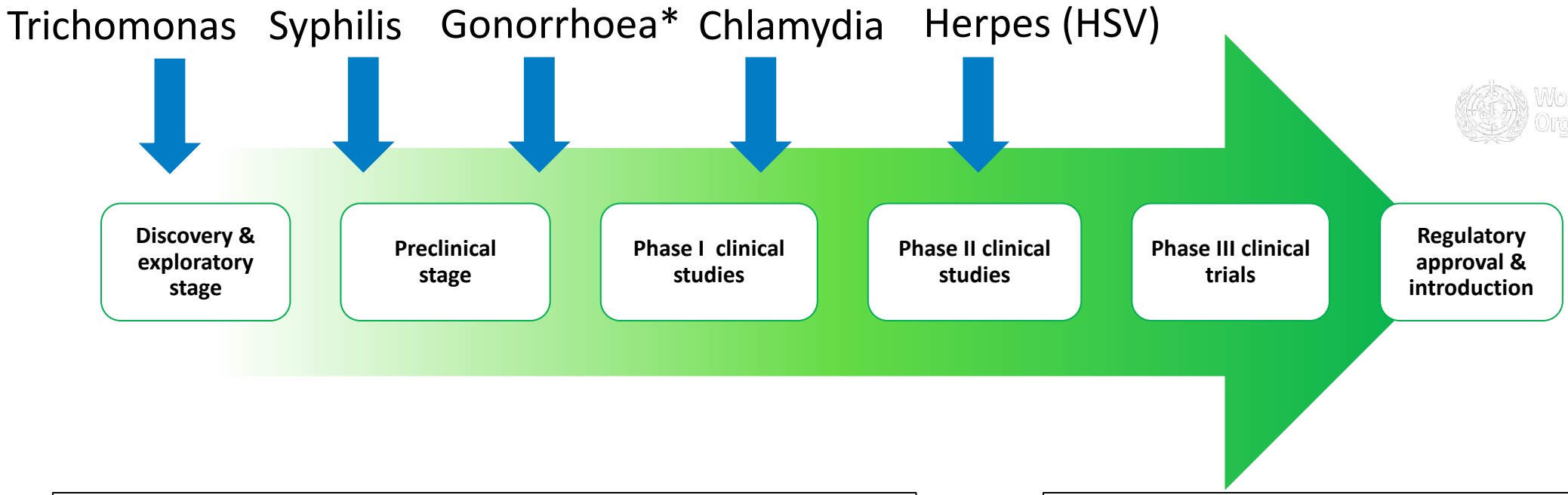
Vaccine

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

The global roadmap for advancing development of vaccines against sexually transmitted infections: Update and next steps

Sami L. Gottlieb[a,*], Carolyn D. Deal[b], Birgitte Giersing[a], Helen Rees[c], Gail Bolan[d], Christine Johnston[e], Peter Timms[f], Scott D. Gray-Owen[g], Ann E. Jerse[h], Caroline E. Cameron[i], Vasee S. Moorthy[a], James Kiarie[a], Nathalie Broutet[a]

Current status of the development pathway of STI vaccines



*Licensed *N meningitidis* B vaccine may also have some activity against *N gonorrhoeae*

HSV = herpes simplex virus
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HSV vaccines: progress and plans

World Health Organization

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World Health Organization

Genital ulcer disease

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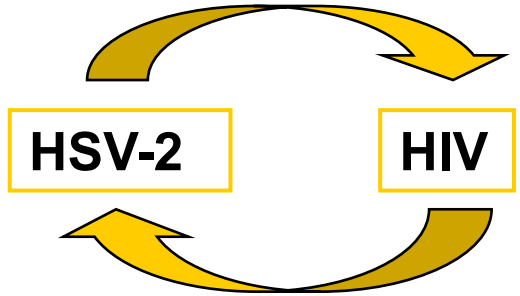

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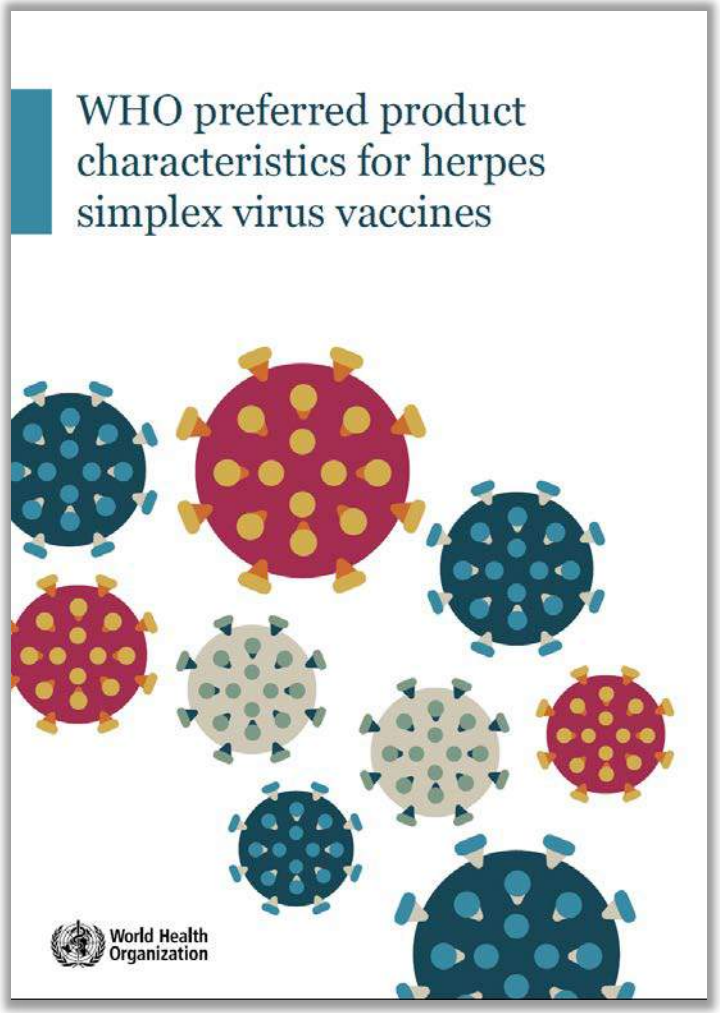

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Progress and next steps: HSV vaccine full public health value proposition

World Health Organization

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World Health Organization

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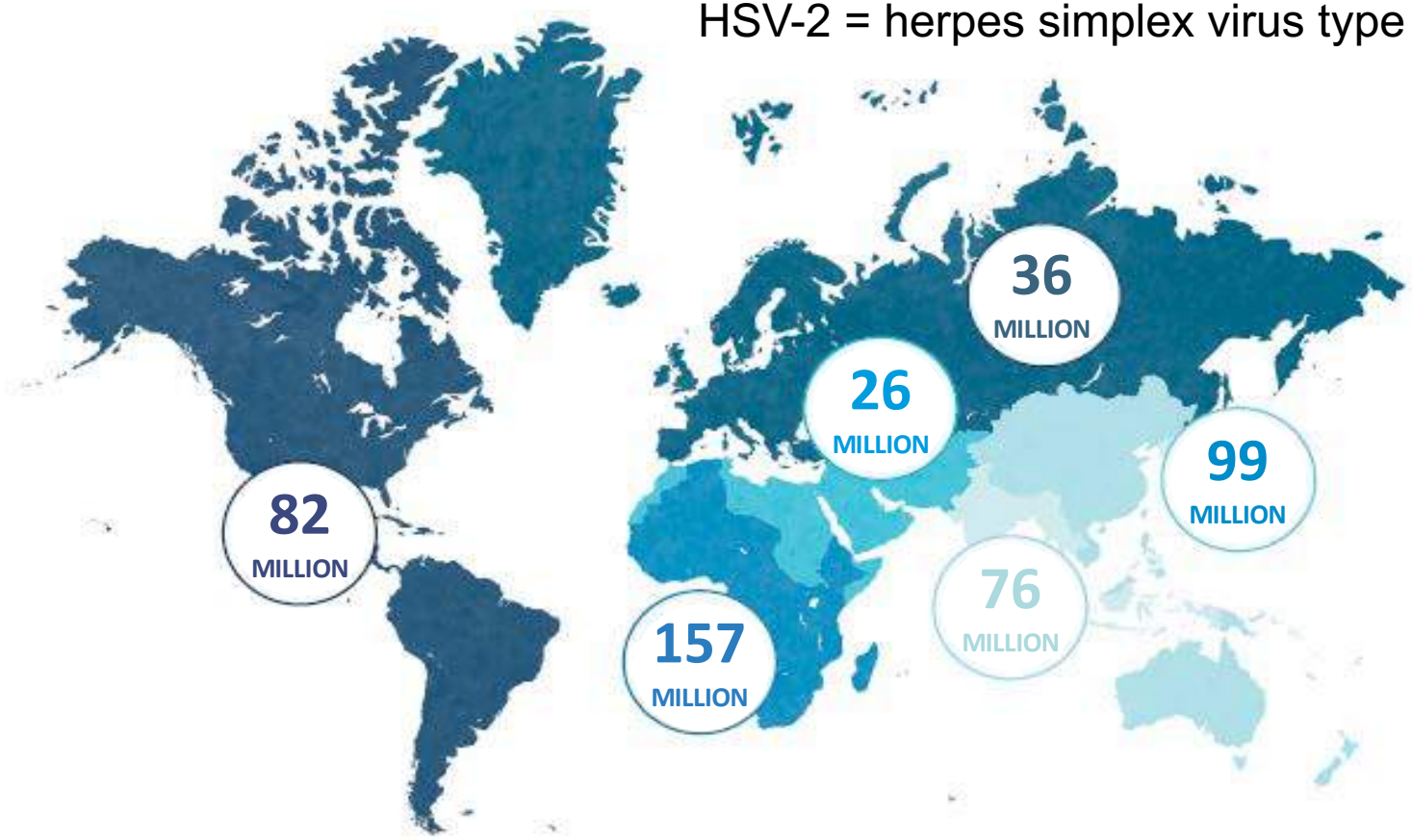

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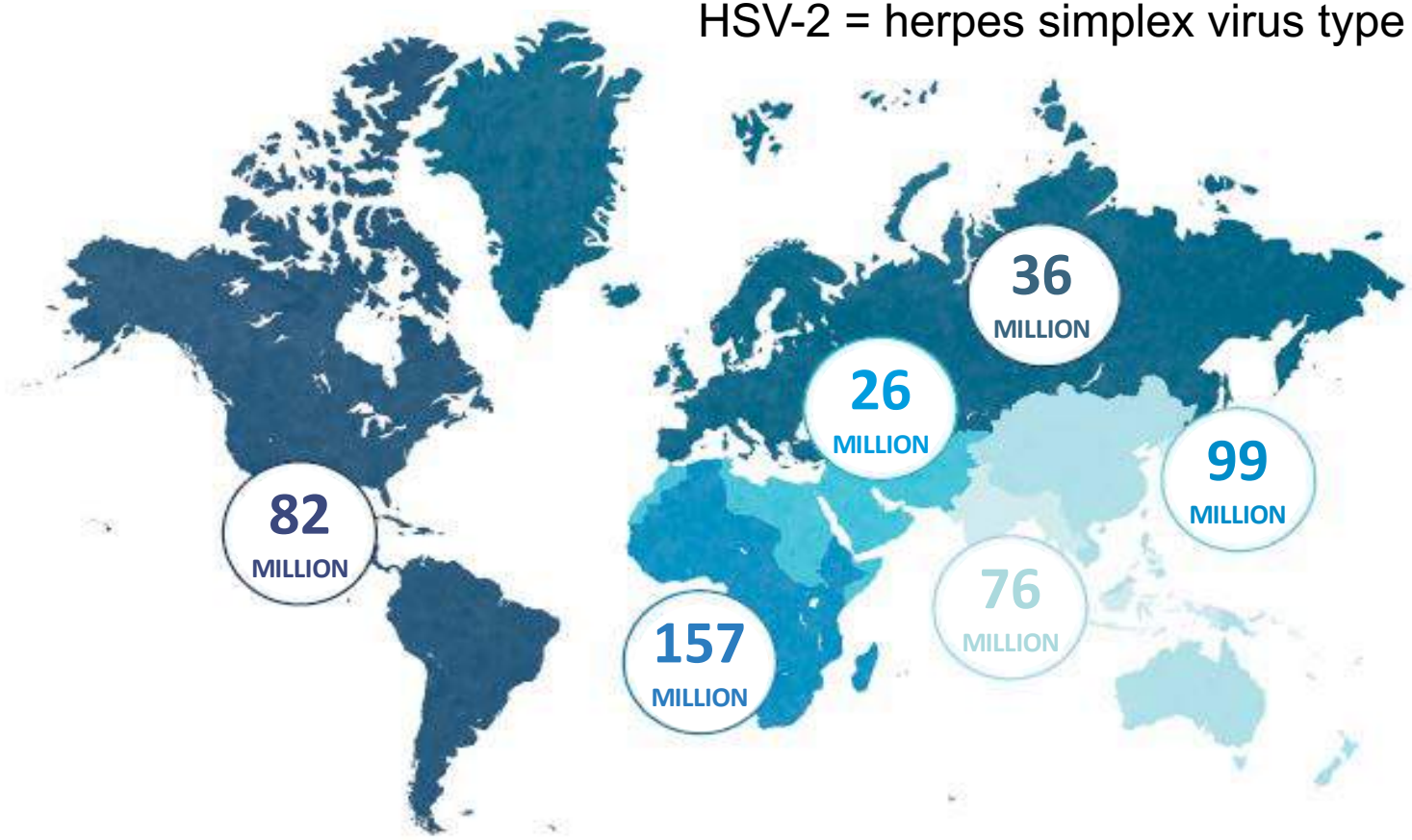

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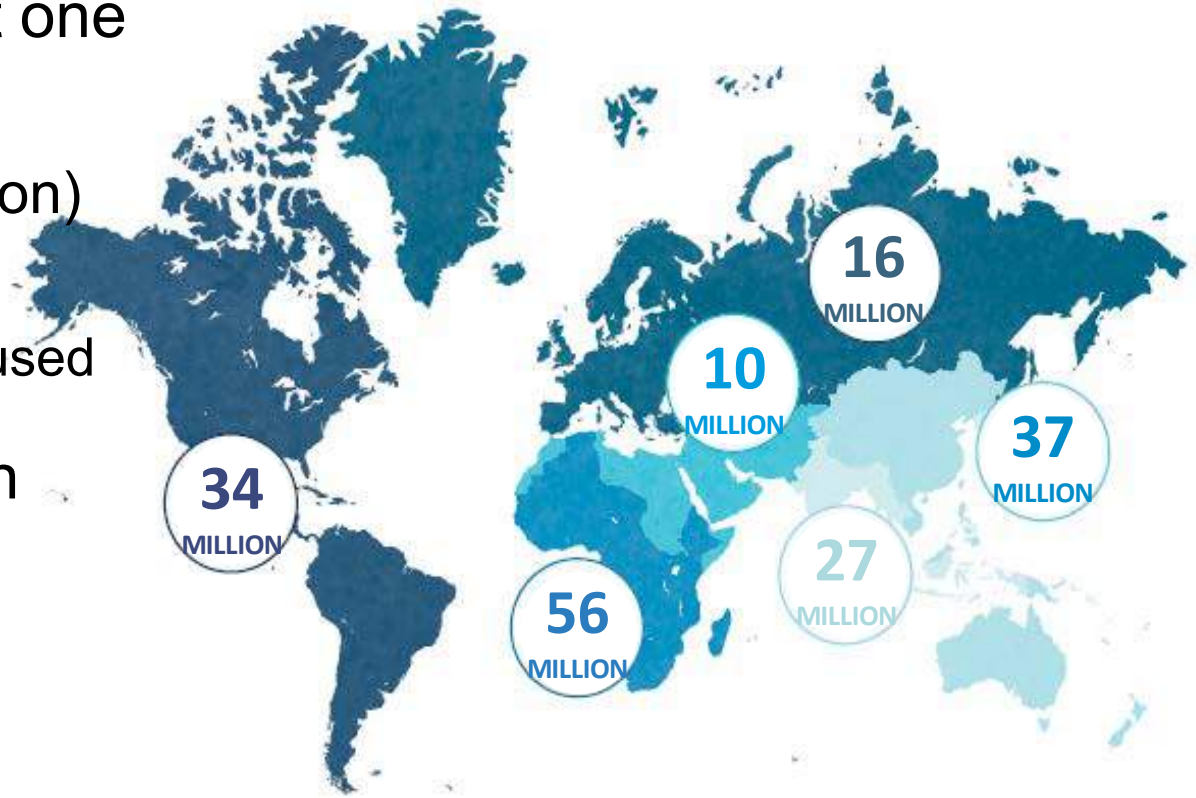

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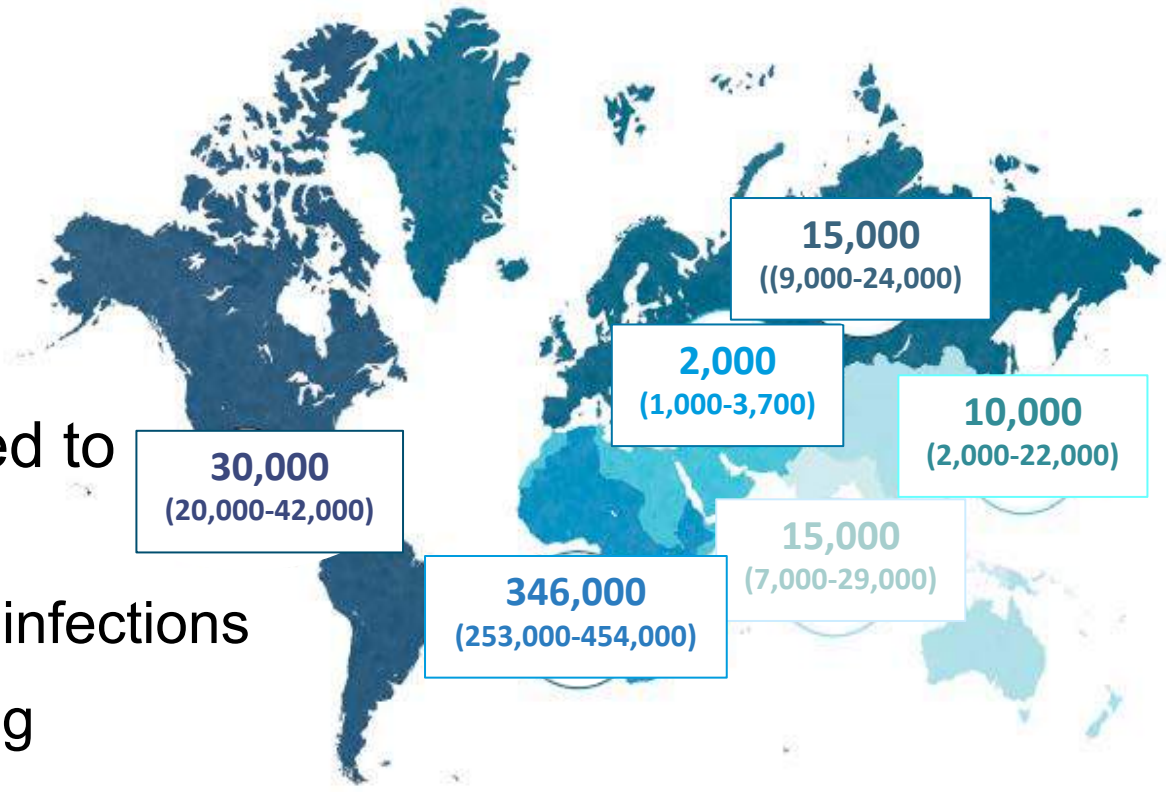

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Summary next steps: HSV vaccine

World Health Organization

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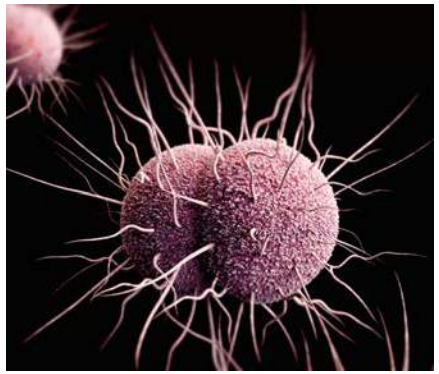

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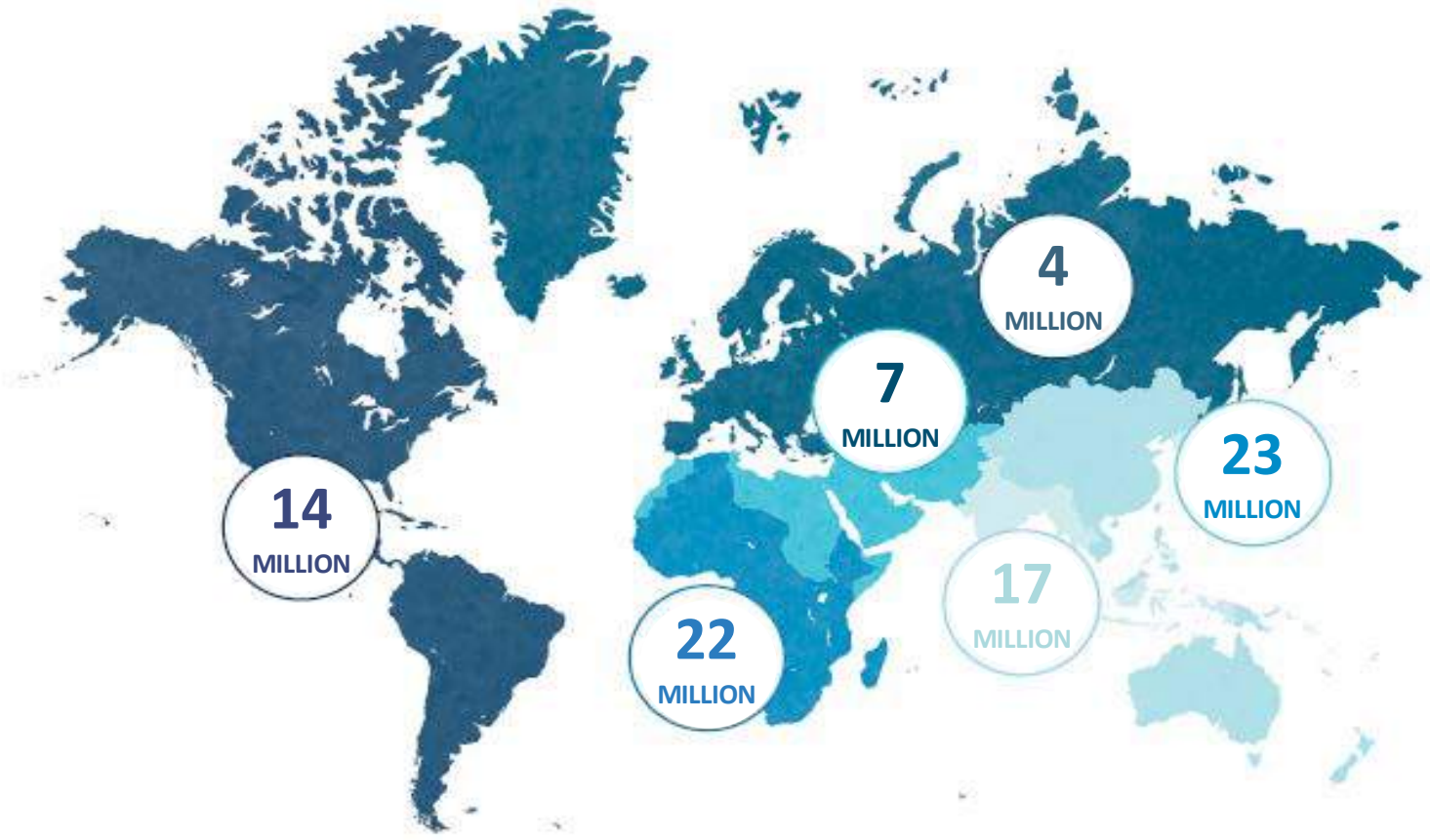

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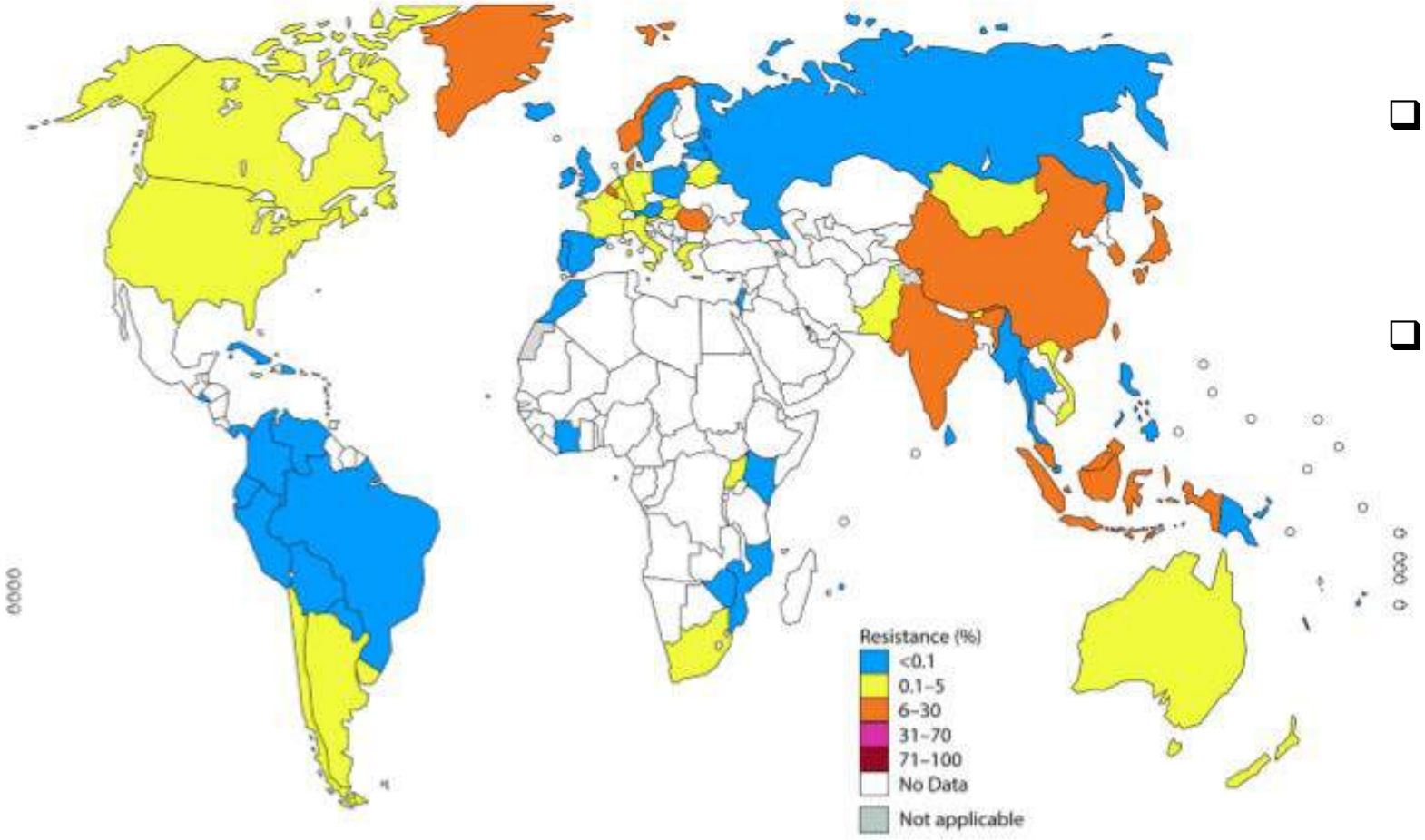

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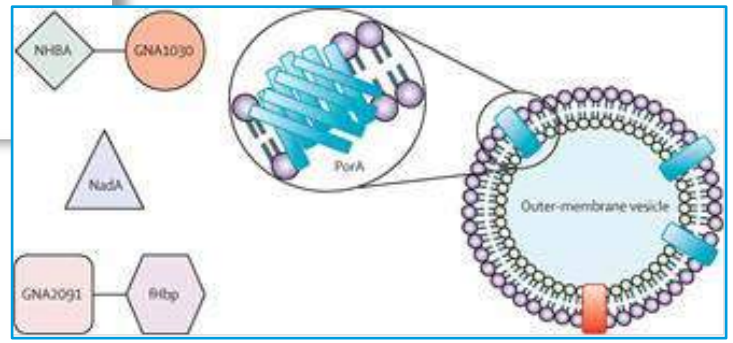

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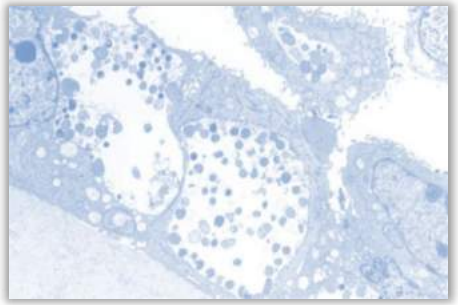

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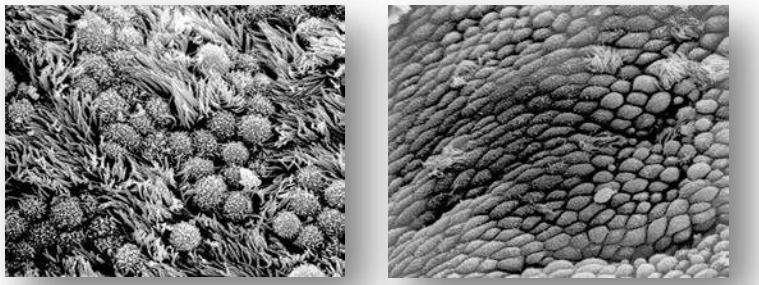

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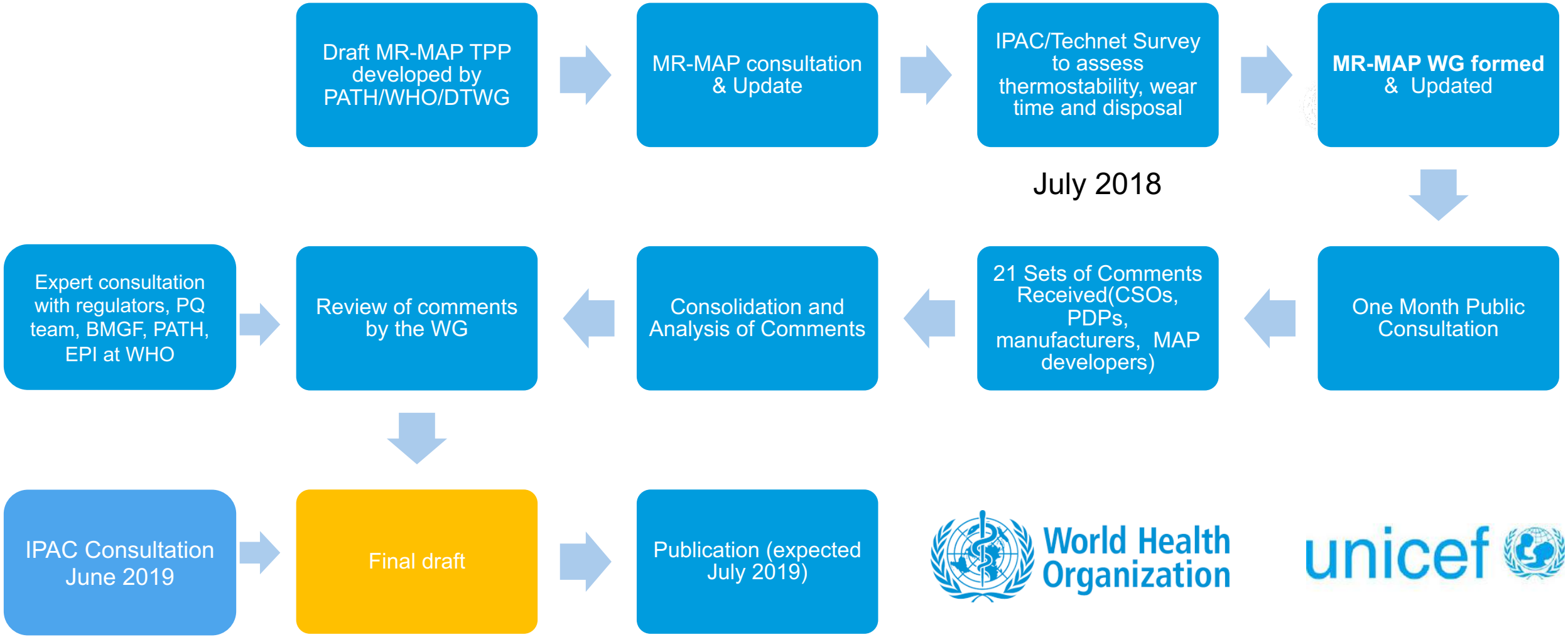
Vaccine delivery technologies:

Microarray patches

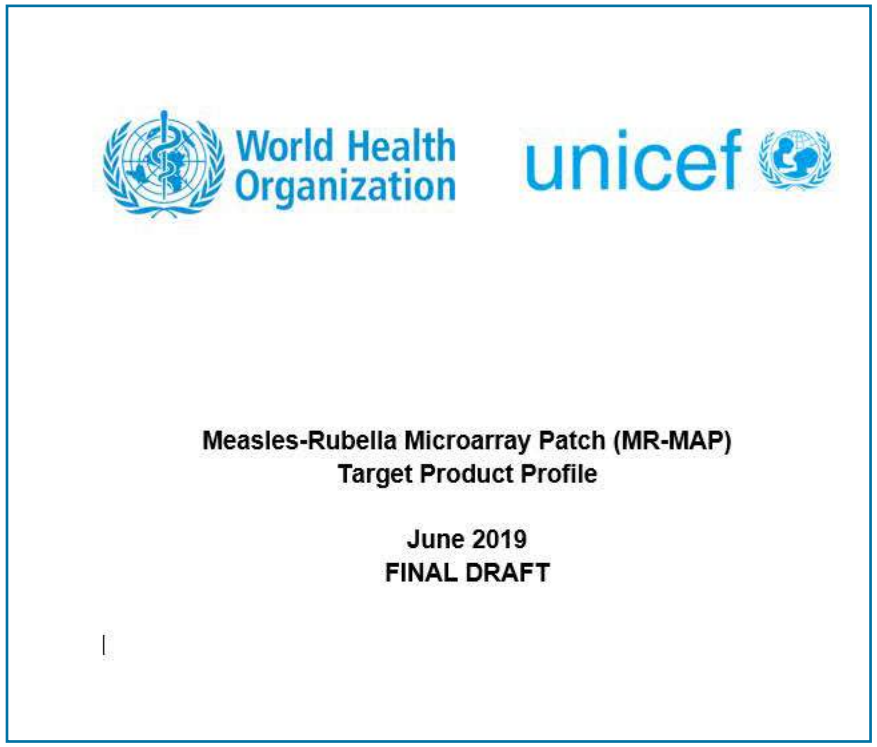
MR-MAP TPP development process



MR-MAP Working Group:

Measles/Rubella MAP working group:

- Robin Biellik
- David Durrheim
- Michael J.Free
- Martin I. Meltzer
- James Robinson
- Marion Wentworth
- Pieter Neels
- Mark Papania
- William (Bill) Moss
- Katrina Kretsinger
- Nicolas Peyraud
- David Robinson
- Darin Zehrung



- MR-MAP demand forecasting (CDC & Unicef)
- Integrated product development pathway
- Overview of the MR-MAP TSE R&D workshop
- Clinical and regulatory strategy to accelerated licensure…

Opportunities for WHO engagement

- PPCs: how to get them to key stakeholders and optimize impact
- Value propositions: which components and when to summarize in formal documents for different pathogens
- Prioritization and support of critical data and research needs
- How best to collaborate across different initiatives
  - AMR efforts for the same and different pathogens
  - Value propositions for the same pathogen across different interventions

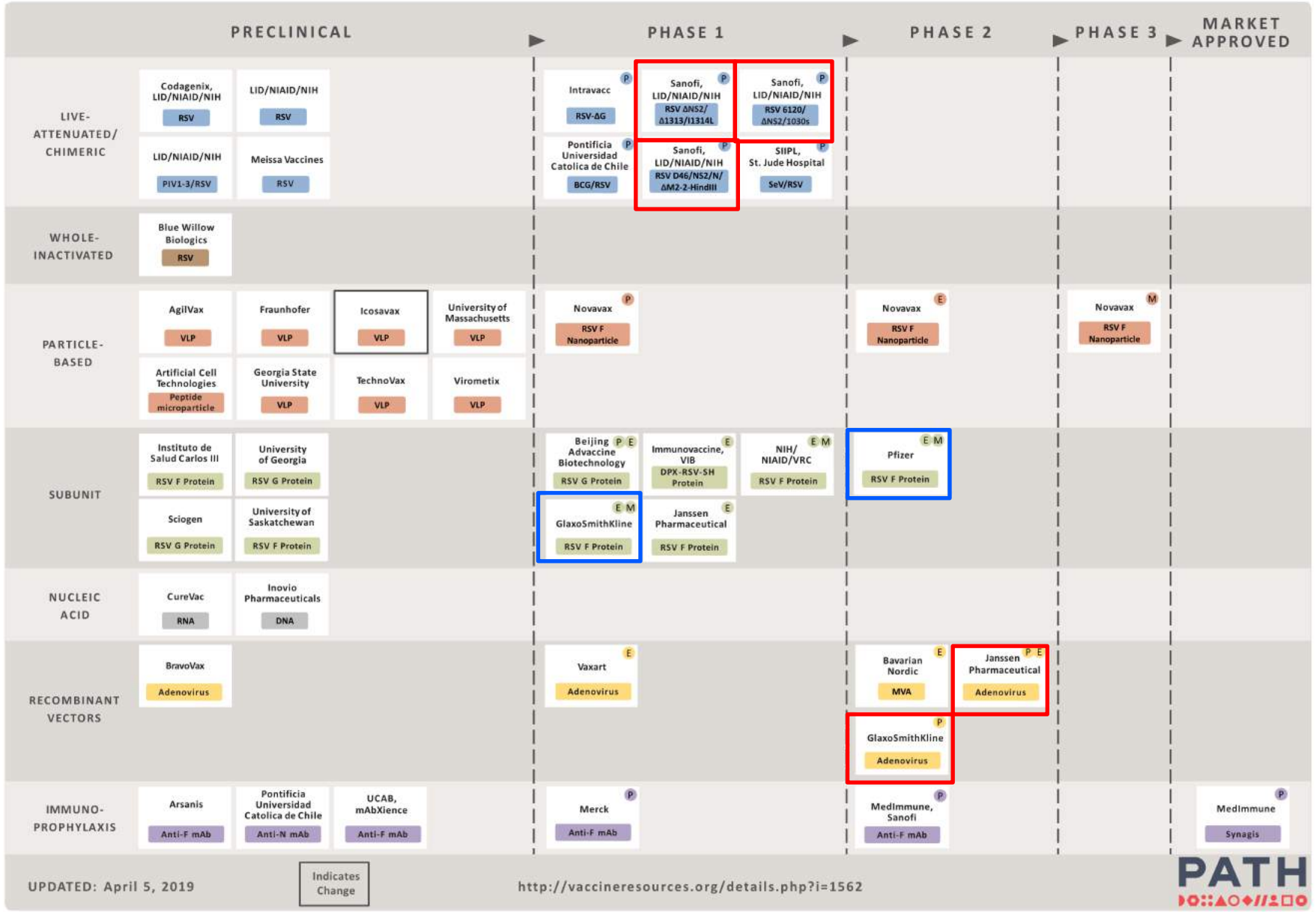
Update on RSV vaccine pipeline

R. Karron
27 June 2019

RSV Vaccine and mAb Snapshot

maternal pediatric

TARGET INDICATION: P =PEDIATRIC M =MATERNAL E =ELDERLY



RSV vaccines for maternal immunization: PPC excerpts

Parameter	Preferred Characteristic	Notes
Efficacy	Greater than 70% vaccine efficacy against confirmed severe RSV disease in the offspring, from birth to age 4 months (and preferably more).	A vaccine with 50% vaccine efficacy against confirmed severe RSV disease in the offspring, from birth to age 3 months, may be considered as acceptable for use. Proposed priority study endpoint case definitions have been published *(10)*. The dynamic of protection over time throughout infancy should be described, taking seasonality patterns into account. The vaccine efficacy against other endpoints of public health interest should also be evaluated, including: • non-severe RSV respiratory disease • recurrent wheezing, hyper-reactive airway disease and asthma • RSV-related morbidity in vaccinated women • reduction of antibiotic use in infants
Strain specificity	Vaccination protects against both RSV A and B subtypes.	

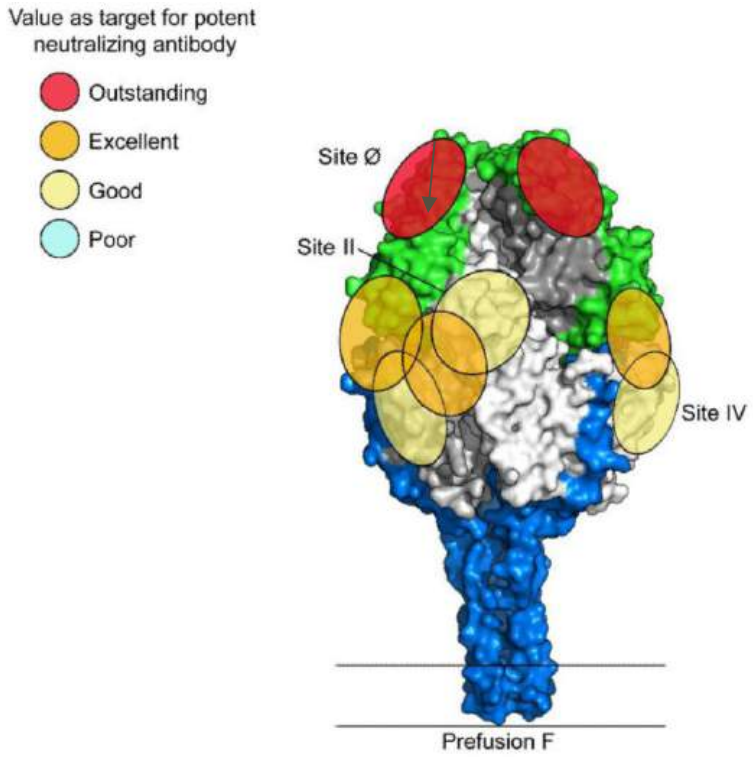
RSV vaccines for maternal immunization: PPC (2)

Parameter	Preferred Characteristic	Notes
Immunogenicity	Established correlate/surrogate of protection based on a validated assay measuring antibody levels in the mother and/or the neonate.	A detailed quantitative profiling of passively transferred antibodies, and relationship to timing of vaccination in pregnancy is desirable. Longevity of vaccine-induced maternal antibodies in infants should be characterized and the relationship to duration of protection should be investigated. The fine specificity of vaccine antigen neutralizing epitopes should be characterized, as they may have a significant influence on binding and functionality of the antibody induced. The generation of clinically relevant validated neutralization assay data, ideally using high-throughput formats, is an important goal. Quantitative assays measuring the ability of vaccine-induced antibodies to compete with monoclonal neutralizing antibodies (such as palivizumab or motavizumab) are interesting, but may not be reflective of all effector functions of vaccine-induced immunity, and should not replace the need to evaluate neutralization. The role of antibody transferred through breast-feeding should be investigated. The influence of maternal HIV infection and malaria in pregnancy should be evaluated.

GSK's maternal immunisation RSV candidate vaccine is being developed to provide passive protection to the newborn[1]

Purified recombinant F protein engineered to preferentially maintain its pre-fusion form:[1]

- Administered as a single dose during the third trimester of pregnancy, boosting pre-existing maternal immunity[1]
- Provides passive immunity to the newborn via placental transfer of anti-RSV antibodies[1]



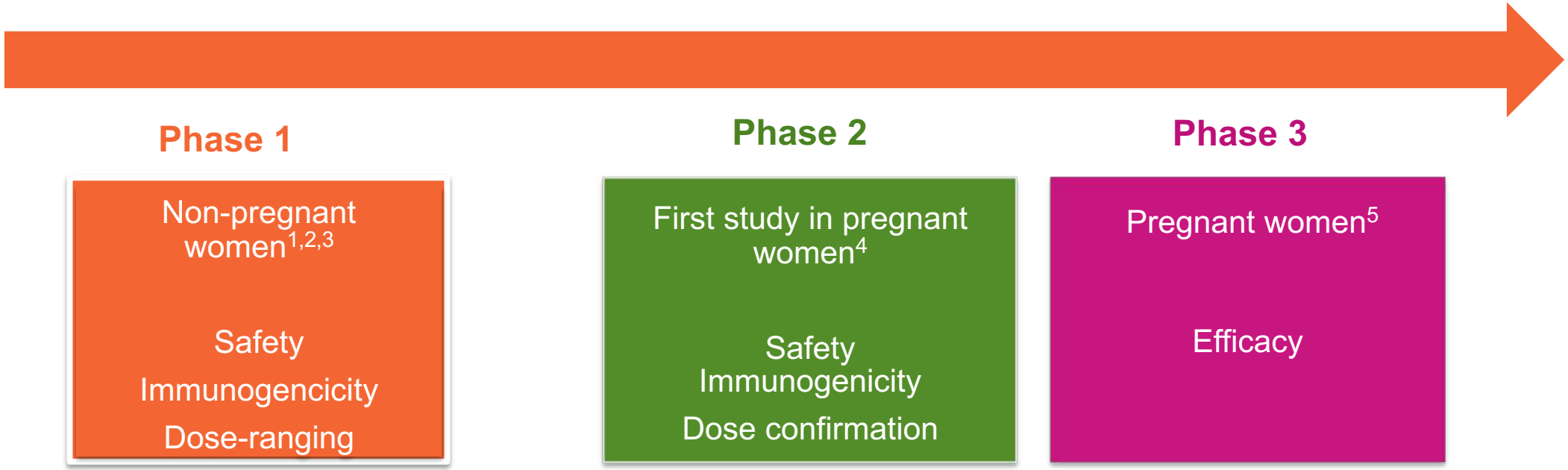
Native structure of prefusion protein[2] used to **engineer vaccine antigen**

Image of F protein reprinted from *Curr Opin Immunol*, Vol 35, Graham BS *et al*. Novel Antigens for RSV Vaccines. Pages 30–38. Copyright 2015, with permission from Elsevier

RSV, respiratory syncytial virus

1. Langley JM *et al. J Infect Dis* 2017;215:24–33; 2. Graham BS *et al. Curr Opin Immunol* 2015;35:30–38

Overview of clinical development for maternal RSV candidate vaccine



IDMC, Independent Data Monitoring Committee

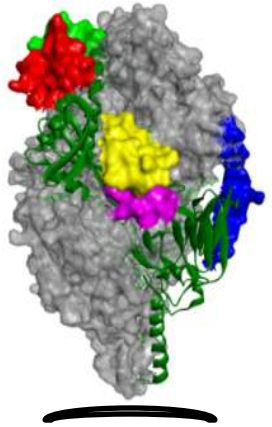
1. Langley JM *et al. J Infect Dis* 2016; doi: 10.1093/infdis/jiw453; 2. NCT02360475. https://clinicaltrials.gov/ct2/show/NCT02360475 (accessed June 2017); 3. NCT02753413. https://clinicaltrials.gov/ct2/show/NCT02753413 (accessed June 2017); 4. World Health Organization (WHO), 2017. International Clinical Trials Registry Platform: EUCTR2016-002733-30-GB. http://apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-002733-30-GB (accessed August 2017); 5. GSK. RSV vaccine product development overview. http://www.who.int/immunization/research/meetings_workshops/GSK_RSV_vaccdev_status_Dieussaert.pdf (accessed June 2017)

Important features of Pfizer's RSV vaccine candidate

VACCINE ANTIGEN

- Stabilized prefusion F with rigorously monitored conformation
- Sequence based on contemporary strains
- Elicits 50-fold higher NAb titers than postfusion F in NHPs
- Does not enhance respiratory pathology in cotton rats

Prefusion F



INDICATIONS

- **Maternal**
  - Immunize pregnant women to prevent RSV-associated lower respiratory tract illness (LRTI) in infants
  - Aim to protect infants from birth to 4-6 months of age
- **Older adult**
  - Prevent RSV-associated moderate to severe LRTI in adults ≥ 60 years of age
  - May be administered annually concomitant with flu vaccine

Maternal phase 2 study: description and objectives

- Pregnant women 18 to 49 years of age
- Multiple formulations
- Respiratory disease surveillance
- To be initiated in 3Q 2019
- Pfizer's RSV vaccine is being developed for maternal immunization globally

Description	**Phase 2 randomized, placebo controlled, observer-blind, dose-ranging**
Objectives	**Primary**: Safety and tolerability mother and infant **Secondary**: Immunogenicity • RSV neutralizing antibody titers in cord blood and infants • To describe rates of RSV positive LRTI in the study population • Follow for 12 months

GSK and Pfizer Maternal RSV vaccines in phase 1-2 development

- Contain stabilized versions of RSV F in the prefusion conformation
- Induce high levels of RSV neutralizing antibodies
- For both products, phase 2 trials in pregnant women scheduled to begin within the coming year

RSV vaccines for pediatric immunization: PPC excerpts

Parameter	Preferred Characteristic	Notes
Indication	Active immunization of infants, for prevention of RSV disease in infants and young children.	Preferred endpoint case definitions have been published *(10)*.
Target population	Infants, for co-administration with existing vaccines from the Expanded Program on Immunization.	HIV infection and mild/moderate malnutrition should not be a contra-indication to vaccination.
Schedule	The vaccination regimen should provide the earliest protection and longest duration of protection possible.	The optimal age schedule will depend on whether a maternal RSV immunization or infant RSV monoclonal antibody program is already introduced, in which case the infant vaccination schedule should aim to extend protection, as maternally-derived or monoclonal antibody levels wane. The development plan should assess interference between maternally acquired/monoclonal antibodies and infant vaccine immunogenicity and protection. The optimal age will depend on a balance between immunogenicity and whether or not interference is seen between paediatric vaccination and pre-existing circulating antibodies. Some vaccines may be less prone to interference from pre-existing antibodies than others, either because of the nature of the platform itself or based upon the route of delivery (e.g. mucosal rather than parenteral).

RSV vaccines for pediatric immunization: PPC (2)

Parameter	Preferred Characteristic	Notes
Vaccine platform and adjuvant requirement	A well characterized platform with existing favourable data on safety and immunogenicity in early life is preferred.	Adjuvant requirement should be investigated and justified if included.
Safety	Safety and reactogenicity at least as favourable as other WHO-recommended routine vaccines for use in the Expanded Program on Immunization Safety profile demonstrates no or only mild, transient reactogenicity and no serious adverse events related to vaccination No indication of ERD in vaccinated children.	In addition to typical toxicology evaluation of investigational paediatric vaccines, preclinical investigations should include the evaluation of the risk of post vaccination ERD. Safety in children should first be investigated in RSV-experienced subjects, after favourable evaluation in older subjects. As ERD has historically been associated with vaccination of children without past RSV exposure, progression to younger infants and children with no past RSV infection who are seronegative at screening should be done under intense safety surveillance. Paediatric vaccination studies should include high quality medical oversight, with independent unblinded continuous safety data review, allowing detection of cases of RSV disease with features of enhanced severity, and early trial termination accordingly. A small number of seronegative infants only should be included initially, to allow for faster enrolment when enough evidence is accrued about the lack of post-vaccination ERD occurrence. This should be tailored to the available evidence about the level of risk, which may be lower for some vaccine platforms than others.
Efficacy	Greater than 70% vaccine efficacy against confirmed severe RSV disease over at least one-year post-vaccination. Reduction in frequency and severity of RSV illness.	A vaccine with 50% vaccine efficacy against confirmed severe RSV, over at least one-year post vaccination, may be considered as acceptable for use. Proposed priority study endpoint case definitions have been published *(10)*. The dynamic of protection over time should be described, taking seasonality patterns into account. Protection over at least 2 years or successive RSV seasons, or more, would be preferred. The vaccine efficacy against other endpoints of public health interest should also be evaluated: • non-severe RSV respiratory disease, • hyper-reactive airway disease and recurrent wheezing in children, • reduction of antibiotic use. The demonstration of an effect of vaccination on RSV transmission, possibly requiring booster doses, would be of great public health interest, but may be left for evaluation in specifically designed post-approval trials.

GSK's paediatric candidate vaccine (ChAd155-RSV) uses a chimpanzee adenovirus vector to encode RSV proteins

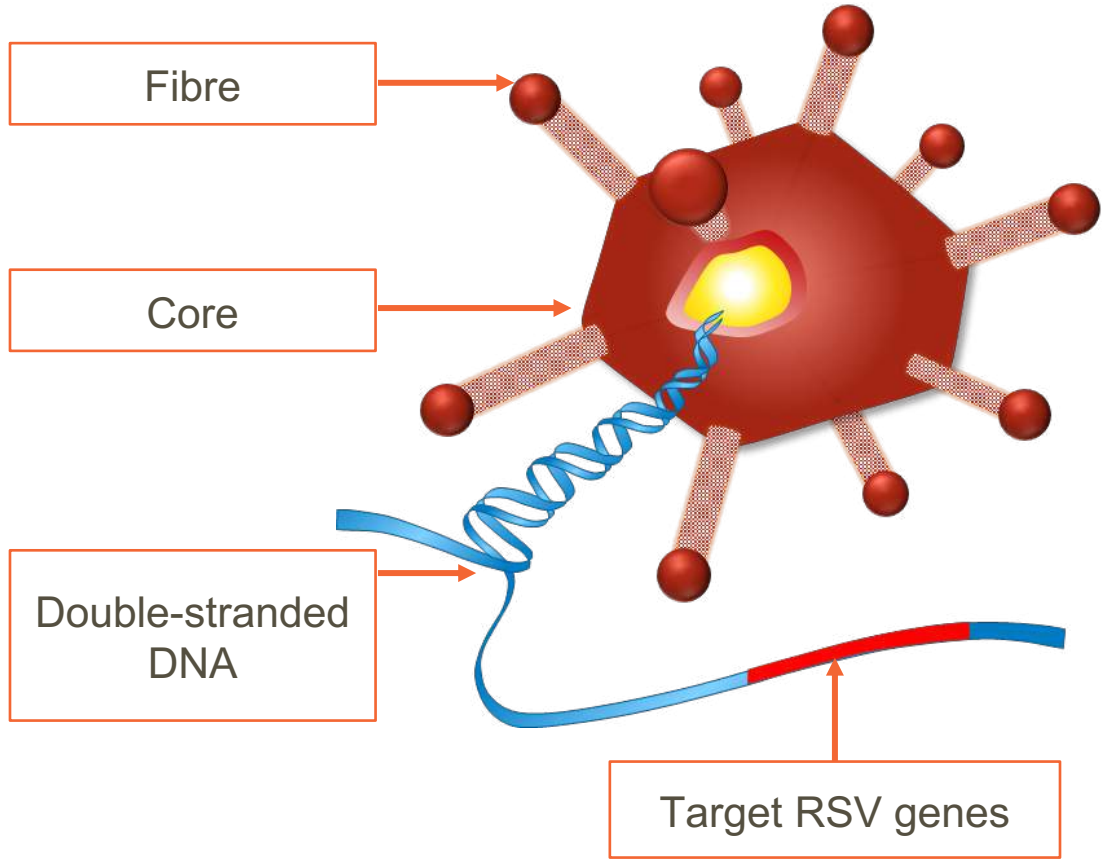
Chimpanzee-derived adenovector (ChAd155)

RSV proteins:

- Fusion protein F
- Nucleocapside protein N
- Matrix protein M2.1

ChAd155-RSV

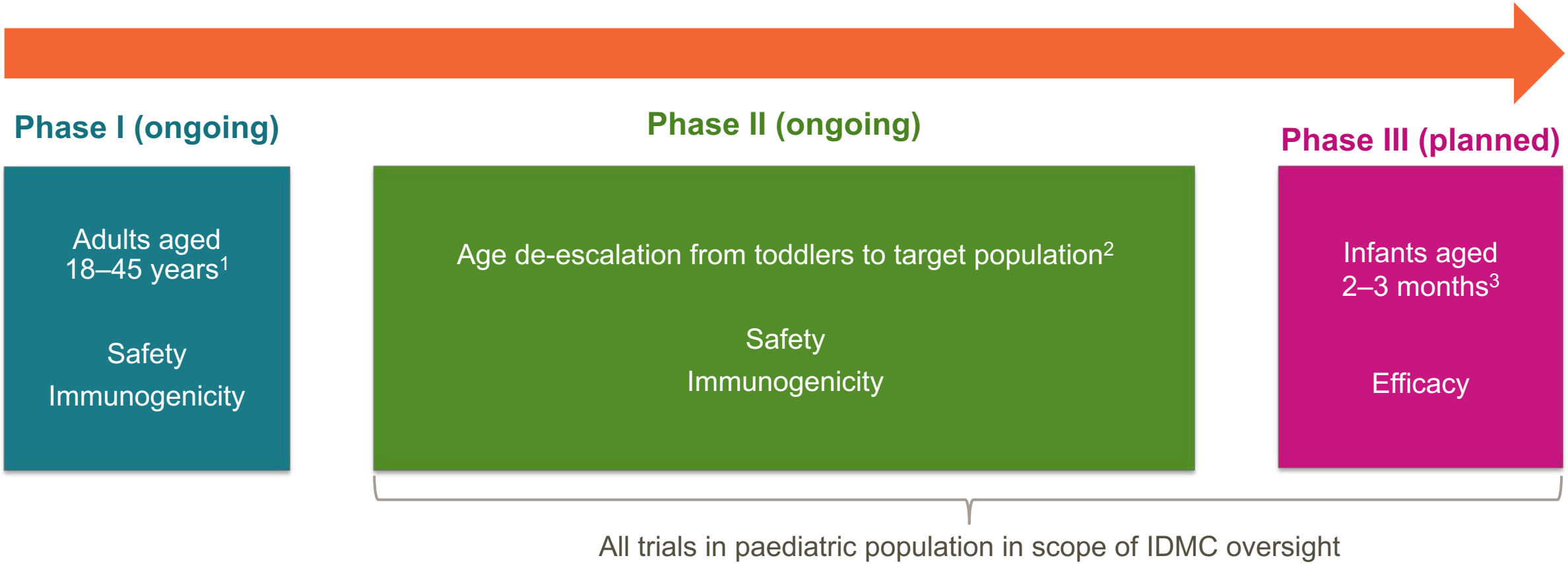
- ✓ Non-replicative
- ✓ F protein is a target for nAb production
- ✓ N and M2.1 proteins are a source of T-cell epitopes



nAb, neutralising antibody; RSV, respiratory syncytial virus

GlaxoSmithKline Biologicals, 2016. Summary notification information format for the release of genetically modified organisms other than higher plants in accordance with Article 11 of Directive 2001/18/EC. http://gmoinfo.jrc.ec.europa.eu/bsnifs-gmo/B-ES-16-07-en.pdf (accessed April 2018)

Overview of clinical development for paediatric RSV candidate vaccine



IDMC, Independent Data Monitoring Committee; RSV, respiratory syncytial virus

1. NCT02491463. https://clinicaltrials.gov/ct2/show/NCT02491463 (accessed April 2018); 2. NCT02927873. https://clinicaltrials.gov/ct2/show/NCT02927873 (accessed April 2018); 3. GSK. RSV vaccine product development overview. http://www.who.int/immunization/research/meetings_workshops/GSK_RSV_vaccdev_status_Dieussaert.pdf (accessed April 2018)

Overview of Clinical Development for Janssen RSV Junior Vaccine Ad26.RSV.preF

JR2001 Safety and immunogenicity	JR2002 Safety and immunogenicity	JR2003 Safety and immunogenicity	JR2004 Safety and immunogenicity	JR3001 Pivotal Efficacy
• Phase 1/2 in 12-24 Mo • RSV seropositive • 2 doses	• Phase 1/2 in 12-24 Mo • RSV seronegative • 3 doses • Follow-up 2 RSV seasons	• Phase 1/2 in 6-12 Mo • Follow-up 2 RSV seasons	• Phase 1/2 in 2-6 Mo • Co-administration with childhood vaccines • Follow-up 2 RSV seasons	• Phase 3 in 2-6 Mo
ongoing	*ongoing*	*planned*	*planned*	*planned*

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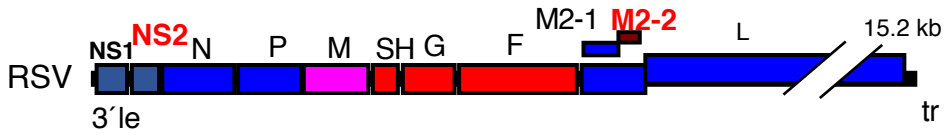
Live-attenuated RSV vaccine candidates

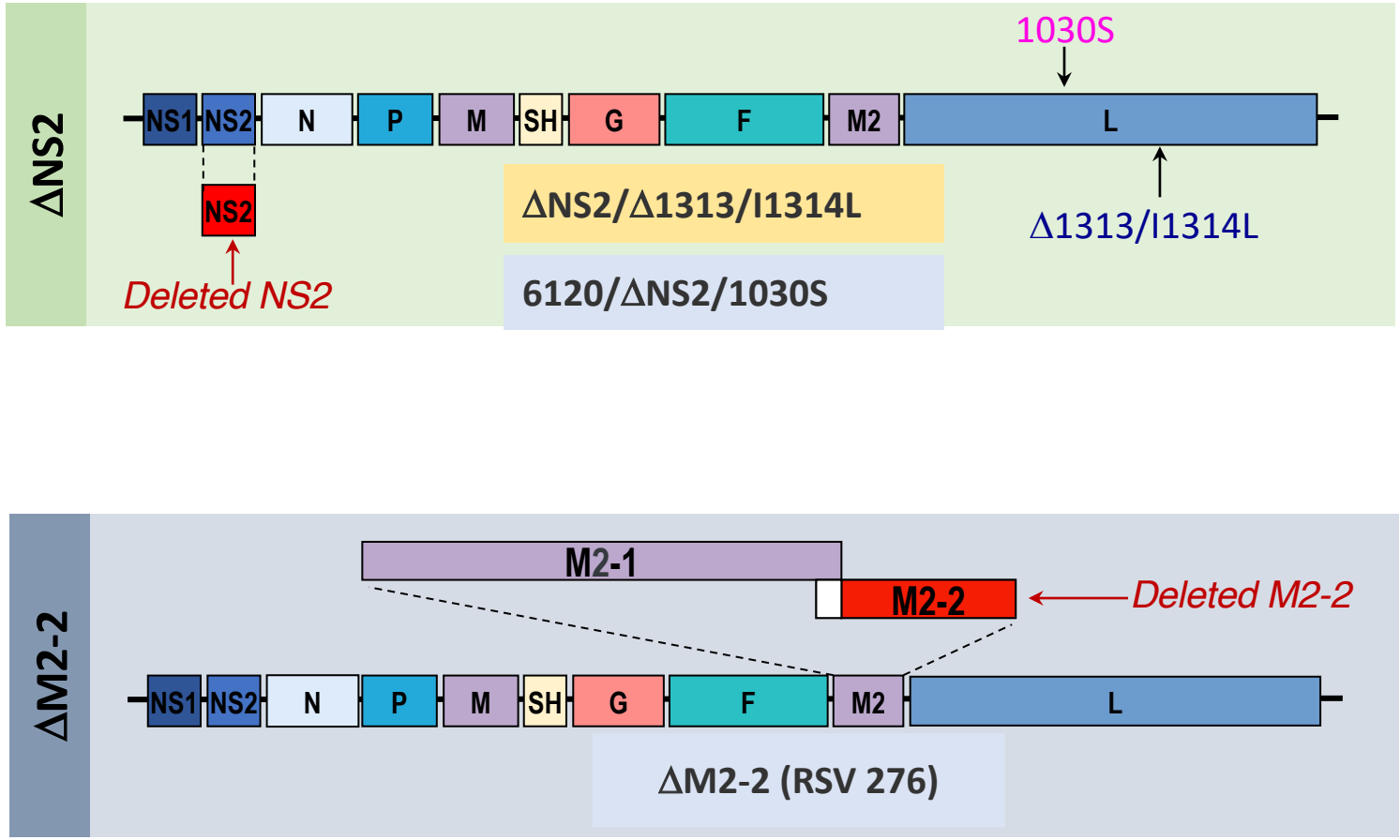
Deletion of non-essential accessory proteins to yield improved phenotypes:

- M2-2 : Up-regulation of antigen expression (ΔM2-2)

- NS2: Reduced viral suppression of host interferon responses (ΔNS1, ΔNS2)



Live-attenuated RSV vaccines in phase 1B/2 trials



Head-to-head comparison in RSV-naïve infants and children ages 6-24 mos:

ΔNS2/Δ1313/I1314L
6120/ΔNS2/1030S
RSV 276 (ΔM2-2 candidate)

NCT03916185

Pediatric RSV vaccines in phase I-II development

- Adenovirus vectored vaccines (GSK, Janssen) currently being evaluated in RSV-seronegative infants (GSK) and toddlers (Janssen)
- Live attenuated vaccines being evaluated in RSV-naïve infants and children ages [4] 6 -24 months. Head-to-head trial underway.

With thanks to colleagues at…

- GSK
- Janssen
- Pfizer
- NIH/Sanofi Pasteur

Update on WHO activities related to RSV preventive products

World Health Organization

Daniel Feikin, MD

Initiative for Vaccine Research/Immunizations, Vaccines and Biologicals/WHO

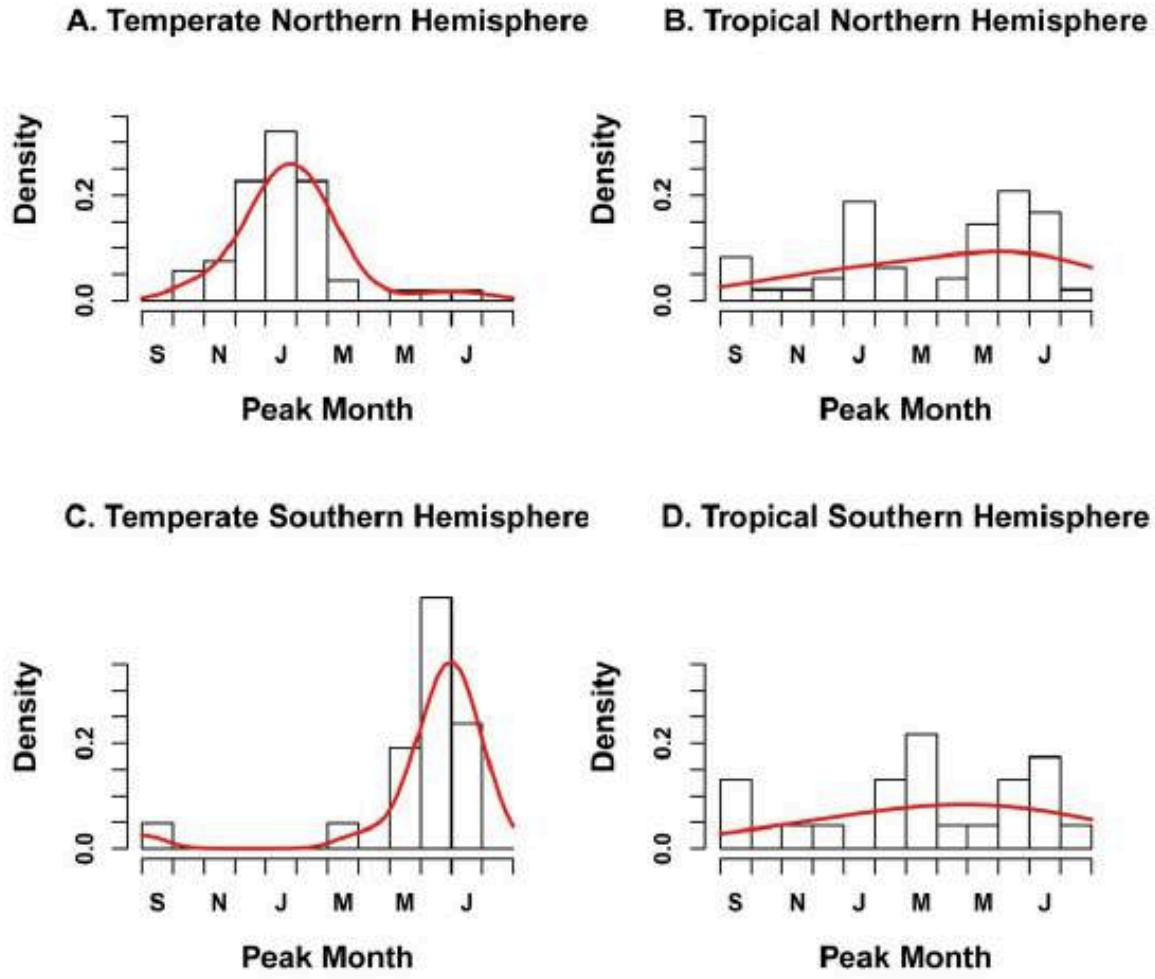
WHO RSV work: Topics of focus in last year

- Expanding RSV surveillance using the influenza surveillance platform
  - Led by Global Influenza Program
  - 2nd phase into 22 countries
- Development of Guidelines for Quality, Efficacy and Safety of RSV Vaccines
  - Led by Technology Standards and Norms
  - Template for PQ and LMICs market authorization

WHO RSV work: Topics of focus in last year

- Defining the causal role of RSV infection on wheeze/asthma
  - Meta-analysis
  - Expert consultation
  - Association consistently found in observational studies, not RCTs
  - Methodological biases common
  - Evidence is inconclusive in establishing a *causal* association
  - Prevention of severe, acute RSV disease remains highest priority for policy
  - Standardized best practices in future, including in clinical trials

Lack of RSV seasonality in tropics?



From: Bloom-Fesbach K, PlosOne 2013.

World Health Organization

Seasonality in LMICs is apparent in most places

Tropic of cancer

equator

Tropic of capricorn

Slide from Li You, Univ Edinburgh

World Health Organization

RSV Technical Advisory Group

- Distinct role from PDVAC
- Advice to IVB on issues related to RSV prevention research and policy
- Not a SAGE working group, but on the spectrum
- Topics in last year
  - Safety of protein-subunit vaccines in adults
  - Novavax maternal immunization phase III trial
    - Q1. How to consider one product in context of the pipeline of products?

Long-acting mAbs for RSV prevention

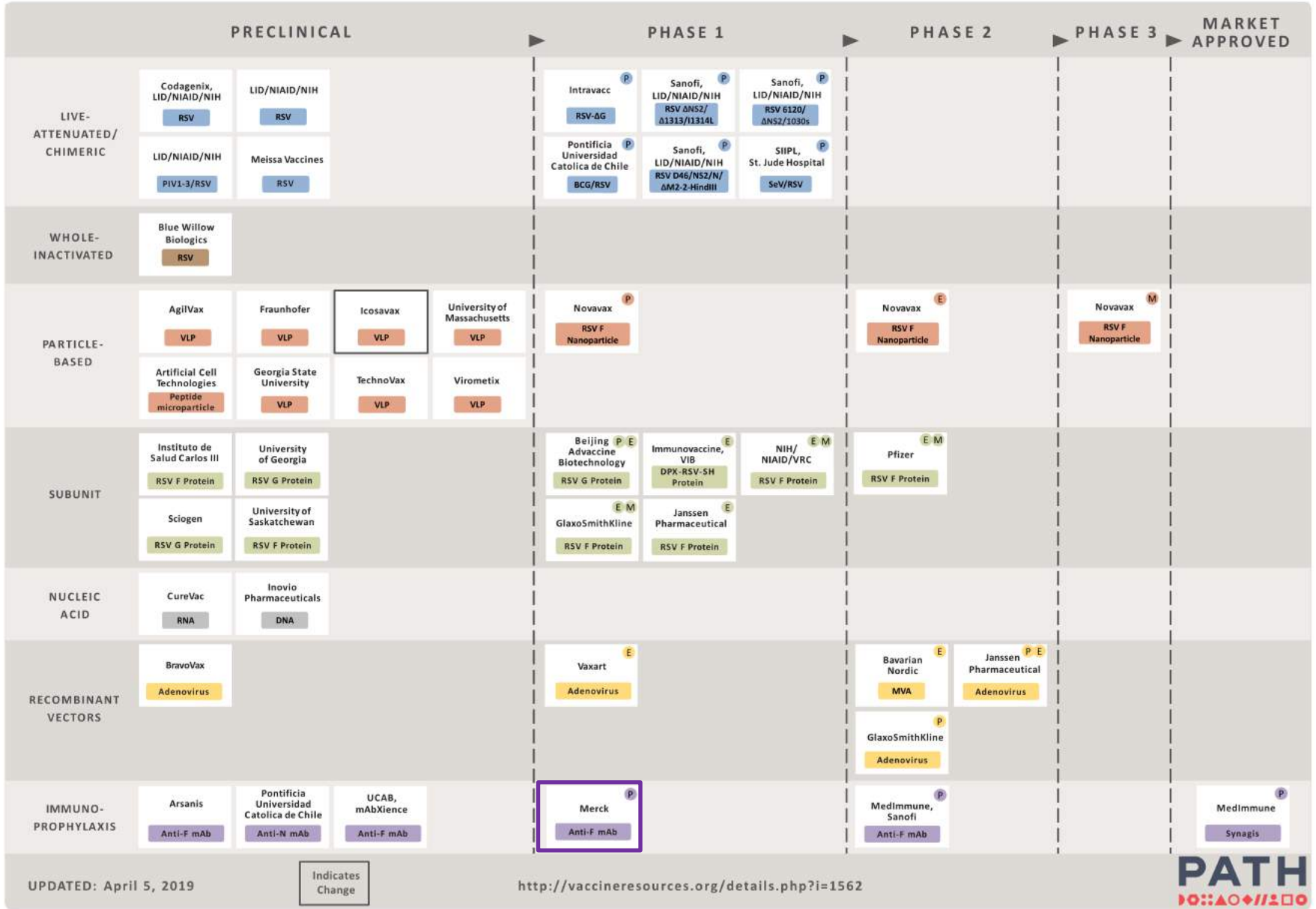
- Early draft of Preferred Product Characteristics
- Discussion with manufacturers
- Discussion about potential indications for use in LMICs
  - Targeted populations vs. all infants
  - Seasonal vs. year-round dosing
  - Q2. Cost an insurmountable barrier to general use?

Update on RSV mAb pipeline

R. Karron
27 June 2019

RSV Vaccine and mAb Snapshot

TARGET INDICATION: (P) =PEDIATRIC (M) =MATERNAL (E) =ELDERLY



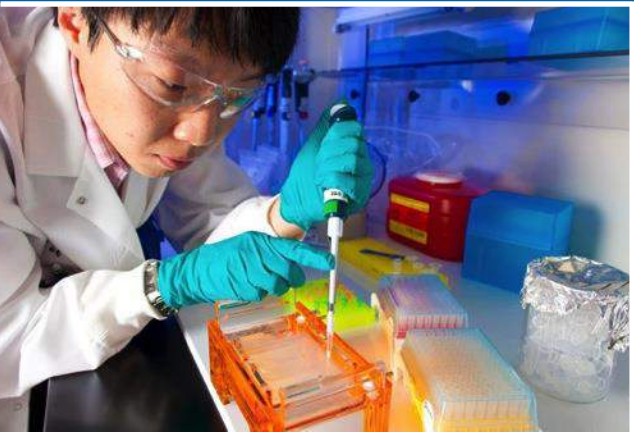
MK-1654 (Merck)

- Fully human neutralizing mAb that binds to site IV of the RSV fusion (F) glycoprotein
- Contains YTE mutation to extend half-life
- Well-tolerated in adults; median t ½ 77-86 days when administered IM[1,2]
- Clinical placebo-controlled trial of single ascending doses of MK-1654 in preterm (29-35 wk GA) and term infants ages 0-8 months (Chile, Colombia, S. Africa, Spain, USA) NCT03524118
  - Safety
  - PK and t ½
  - ADA

1. Maas et al ID Week 2018. 2. Aliprantis et al, ID Week 2018

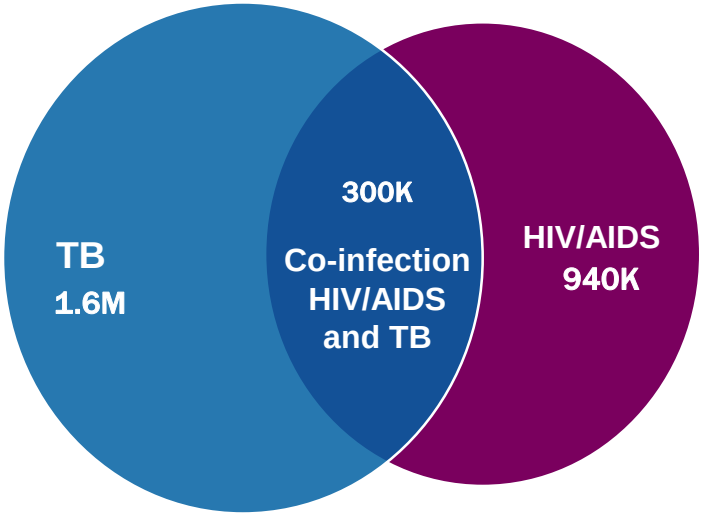
TB Vaccines:
Pipeline Overview and Status of Late-stage Candidates

Ann M. Ginsberg, MD, PhD
PDVAC
27 June 2019 / Geneva




New TB vaccines: a critical, unmet global health need

- 10M new TB cases in 2017
- 1.6M deaths
- >1/4 of all AMR-related deaths



Deaths in 2017

Source: WHO Global TB Report 2018

PROGRESS

Multiple Target Populations

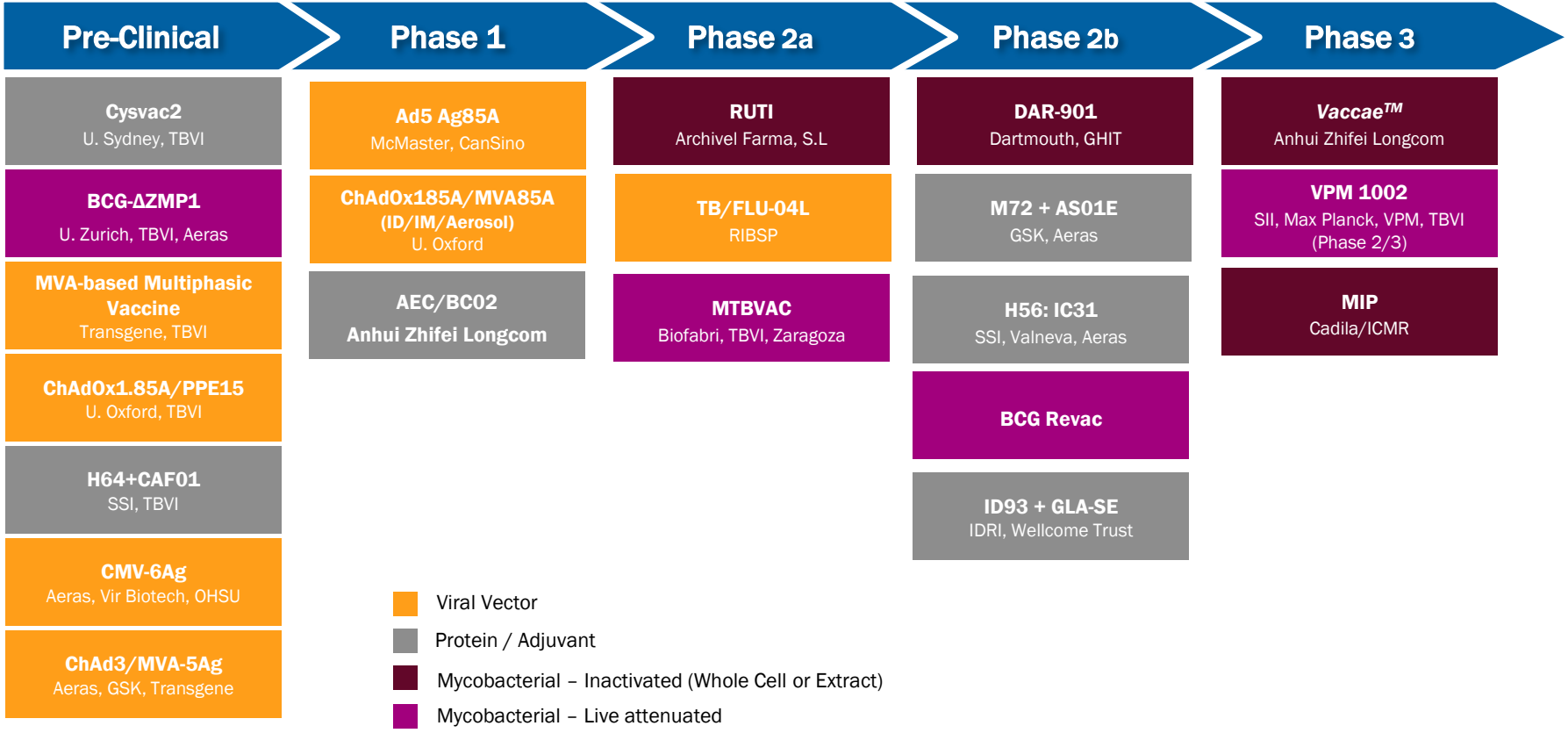
- Infants/children
- Adolescents/Adults
- TB patients – during or post-cure

Multiple Therapeutic Indications

- Prevention of Infection – e.g., infant BCG replacement with improved BCG*
- Prevention of TB disease
  - BCG replacement
  - BCG boost (proximal)
  - BCG boost (distal)
- Prevention of recurrent TB
- TB treatment shortening +/or increased cure rates (adjunct to treatment)

* Under discussion with regulators

Overview of Global Pipeline



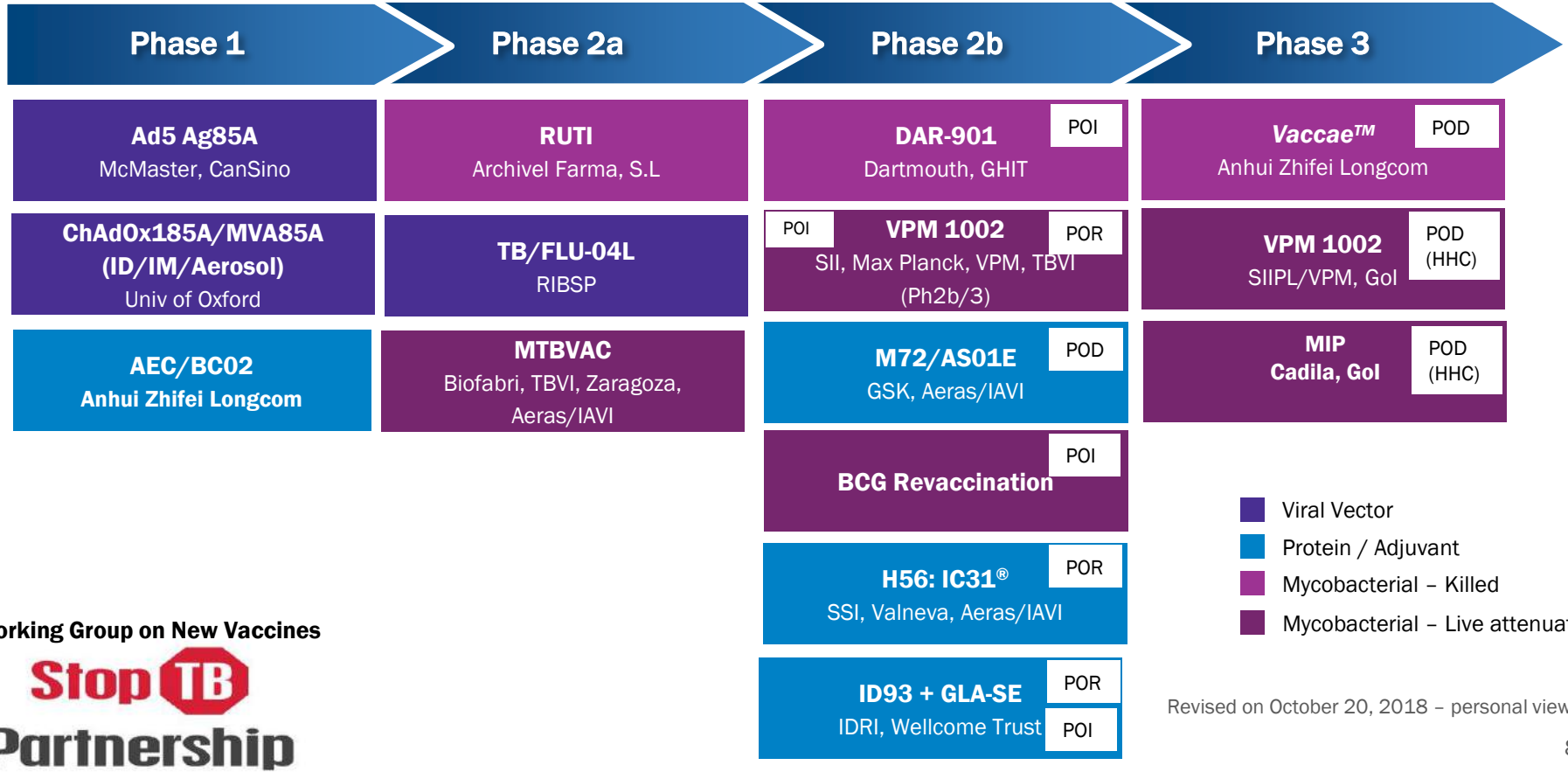
Candidates in preclinical development are representative and include those in the IAVI and/or TBVI portfolios that have completed Gate 1 as published in Barker L, Hessel L, Walker B, *Tuberculosis,* 92S1 (2012) S25–S29

Recent Progress in preclinical and translational science:

- Alternate Routes of Administration
  - iv BCG in mice[1] and NHP[2] – high levels of protection and evidence of role for trained innate immunity[3]
  - Phase 1 studies of aerosol delivery in humans[4]
- Novel vectors: e.g., CMV-TB (Picker/Aeras collaboration)[5]
- New tools – e.g.:
  - Bar-coded Mtb strains[6]
  - Controlled human infection models[7]
  - Biorepository to support correlates discovery

[1]Kaufmann E et al, Cell. 2018 Jan 11;172(1-2):176-190.e19. doi: 10.1016/j.Cell.2017.12.031. [2]Sharpe S et al, Tuberculosis (Edinburgh) 2016 Dec; 101: 174–190. [3]Cell Rep. 2016 Dec 6;17(10):2562-2571. doi: 10.1016/j.celrep.2016.11.011. [4]Manjaly TZR, PLoS Med. 2019 Apr 30;16(4):e1002790. doi: 10.1371/journal.pmed.1002790. eCollection 2019 Apr. 5Hansen SG et al, Nat Med.. 2018 Feb;24(2):130-143. doi: 10.1038/nm.4473. Epub 2018 Jan 15. [6]Martin CJ et al, Mbio. 2017 May 9;8(3). pii: e00312-17. doi: 10.1128/mBio.00312-17. [7]Minhinnick A et al, J Infect Dis. 2016 Mar 1;213(5):824-30. doi: 10.1093/infdis/jiv482. Epub 2015 Oct 8

Global Clinical Pipeline of TB Vaccine Candidates



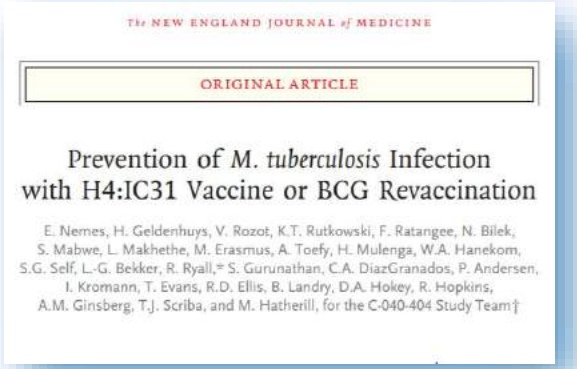
Working Group on New Vaccines

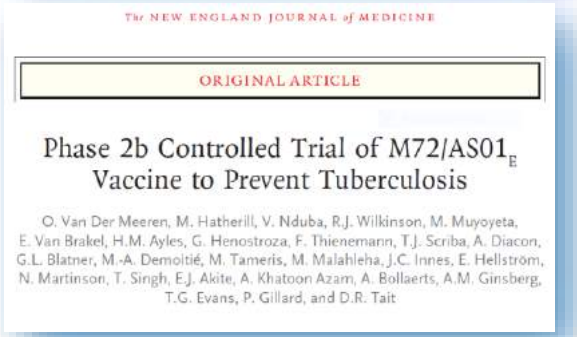
Stop TB Partnership

Revised on October 20, 2018 – personal view!

2018 – a Year of Unprecedented Progress

- New use for 98 year old current vaccine - protect high risk, uninfected populations from Mtb infection with BCG revaccination
- Proof of concept that a subunit vaccine (2 Mtb antigens plus adjuvant) can protect against TB disease
- First demonstration that a vaccine can protect Mtb-infected adults from developing TB disease
- First opportunity to discover correlates of protection and increase understanding of protective human immune responses





Phase II Prevention of Infection Trial H4:IC31 and BCG revaccination

Clinical Trial Sites:

SATVI and DTHF/Emavundleni

iavi

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Overview – First TB Vaccine POI Trial

Trial: NCT02075203

Objectives:

Phase 2 Proof of Concept Prevention of Infection study to evaluate safety, efficacy and immunogenicity

3 Study Arms:

- H4:IC31 (IM, 2 doses, 56 days apart)
- BCG revaccination (ID, 1 dose; SSI BCG)
- Placebo (saline; IM, 2 doses, 56 days apart)

Population:

- QFT*-negative adolescents (12–17y.o.)
- Western Cape, South Africa
- High risk of infection (~10% per year)

Design:

- Randomized (1:1:1)
- Placebo-controlled
- Partially blinded

Study Size:

N=990 (330/arm)

*QFT = QuantiFERON Gold In-Tube interferon gamma release assay

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POI Trial Results and Conclusions

Trial: NCT02075203

- Both H4:IC31® and BCG revaccination appeared safe and immunogenic
- Neither vaccine showed statistical significance in preventing initial infection (initial QFT conversion)
- BCG revaccination demonstrated statistically significant prevention of sustained infection (sustained QFT conversion): VE: 45.4%; p=0.01
- H4:IC31did not demonstrate statistically significant prevention of sustained QFT conversion: VE: 30.5%; p=0.08
- Biobank created and analysis plan being developed for discovery of candidate correlates of risk and/or protection against sustained infection

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satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE
DESMOND TUTU HIV FOUNDATION

First POI Trial: conclusions and next steps

BCG Revaccination

- Statistically significant protection against sustained infection
- Confirm then evaluate in Prevention of TB Disease trial
- Potential correlates of protection discovery

H4:IC31

- First signal of any protection against TB infection or disease in humans by a subunit vaccine
- Suggests benefit of studying other subunit vaccines
- Not being further developed

POI Trial Design

- Is feasible and may be useful tool for decision-making.
- Should be validated with a Prevention of Disease trial

Trial: NCT02075203

valneva

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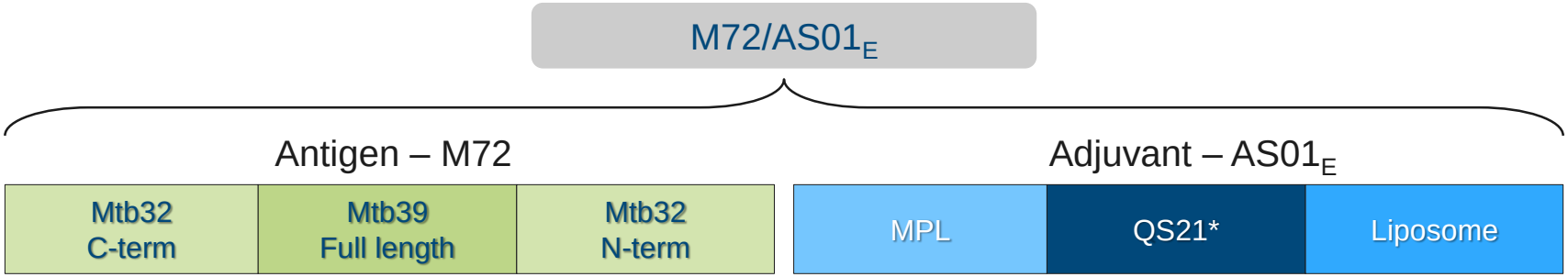
iavi

M72/AS01$_E$ Phase IIb Prevention of Disease Trial

Results of the primary analysis

M72/AS01$_E$ Candidate Vaccine

M72 antigens were initially identified in the context of controlled human infection



Determines specificity of the immune response[1]

- Recombinant protein comprising **full length Mtb39A** flanked by **inverted halves of Mtb32A**[1,2]
- Mtb 32A and 39A are highly immunogenic[2]
  - Genes present in virulent and avirulent strains of Mtb complex and in BCG[1]

Enhances the immune response to the antigen[2]

- Immunostimulants (MPL and QS21) in a liposome formulation[3]

1. BMC Immunol 2015;16:63; 2. J Immunol 2004;172:7618–28; 3. Hum Vacc Immunother 2014;10:2211–9.
2. AS01$_E$, Adjuvant System containing 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL [25 µg], produced by GSK), **Quillaja saponaria* Molina, fraction 21 (QS-21 [25 µg], licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation) and liposome.

M72/AS01$_E$ Candidate Vaccine

Goal: induce a robust Th1 CD4+ T cell response against Mtb antigens

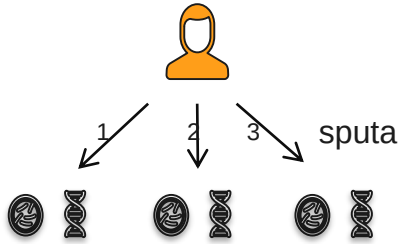
Clinical safety and immunological profiles to date

- Generally well tolerated although higher reactogenicity observed in patients with active tuberculosis
- High seroconversion rate & long lasting humoral response
- Poly-functional CD4 Th1 cells (IFNγ TNFα IL-2+)
  - 3 years persistence*
- CD8 Th1 cells
- IL-17-expressing CD4 T cells
- T cell responses in lung

Leroux-Roels, 2012; Montaya, 2013; Day, 2013; Tacher, 2014 ;
*Penn-Nicholson , 2015; Idoko, 2014; Kumarasamy, 2016; Gillard 2016; Van den Berg, 2018; Kumarasamy, 2018**

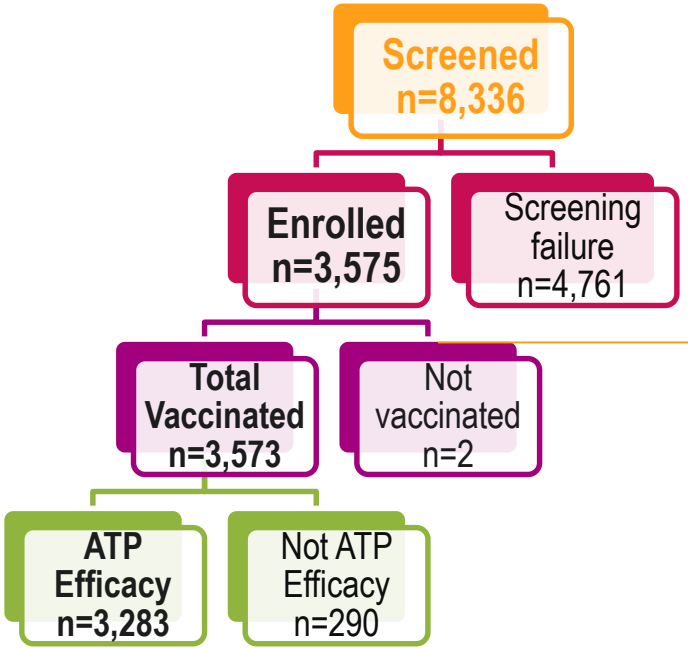
Phase IIb Study Design

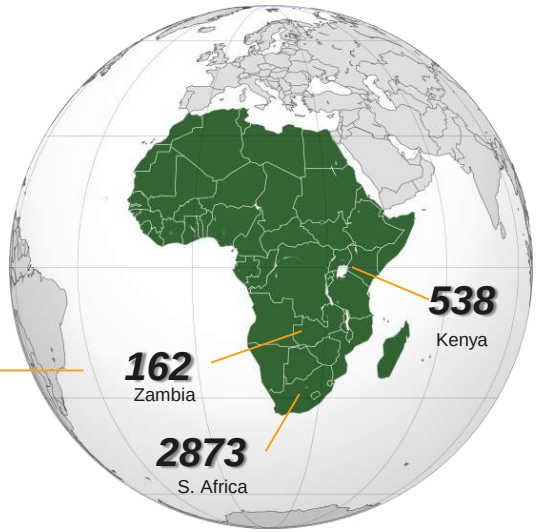
- Subjects
  - HIV negative healthy adults (18 - 50 years)
  - Negative sputum by PCR (Xpert MTB/RIF)
  - Mtb-infected: positive by QuantiFERON
- Design
  - Double-blind, randomized (1:1)
  - M72/AS01$_E$ or Placebo
  - 2 doses 1 month apart
- TB cases determination by
  - Active follow-up every 2 months either by calls, home visits or SMS
  - TB symptoms and bacteriological confirmation (3 sputum samples)
    - By PCR and/or MGIT culture
- 3 years follow up
  - Primary analysis at year 2
  - LSLV November 2018



Van Der Meeren et al., NEJM, 2018

Study Participants





Wikipedia, CC BY-SA 3.0

Trial sites:
KEMRI
CIDRZ
Zambart
SATVI
TASK
CIDRI
Aurum Inst.
Tembisa
Klerksdorp
BePart
Setshaba
PHRU

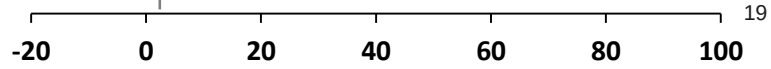
ATP : According To Protocol

Figure adapted from Van Der Meeren et al, presented at IDWeek, October 2018, San Francisco CA, Abstract 70677
http://www.idweek.org
Van Der Meeren et al., NEJM, 2018

All Efficacy Endpoints: primary analysis

Vaccine efficacy against TB for each case definition

Efficacy endpoints	TB diagnosis	HIV status	Sputum testing: Culture	Sputum testing: PCR	Sputum testing: Timing vs TB treatment start	Vaccine efficacy % (90% CI)	p-value
Case definition 1	**Pulmonary TB Clinical suspicion**	**HIV–**	**Any positive**			**54**	0.042
Sensitivity analysis	Pulmonary TB Clinical suspicion	HIV–	Any 2 positive		Before	70	0.017
Case definition 2	Pulmonary TB Clinical suspicion	HIV–	Any	Positive		58	0.051
Case definition 3	Pulmonary TB Clinical suspicion	HIV–	Any positive		Up to 4 weeks after TB treatment start	35	0.174
Case definition 4	Pulmonary TB Clinical suspicion	Any	Any positive			36	0.144
Case definition 5	TB diagnosed and treated by clinician	Any	Any	Any	Any	29	0.225
Modified case definition 5	TB diagnosed and treated by clinician	HIV–	Any	Any		28	0.267



N Engl J Med 2018, 379(17): 1621-34.

Vaccine Efficacy for Case Definition 1

Kaplan-Meier (ATP cohort for efficacy)

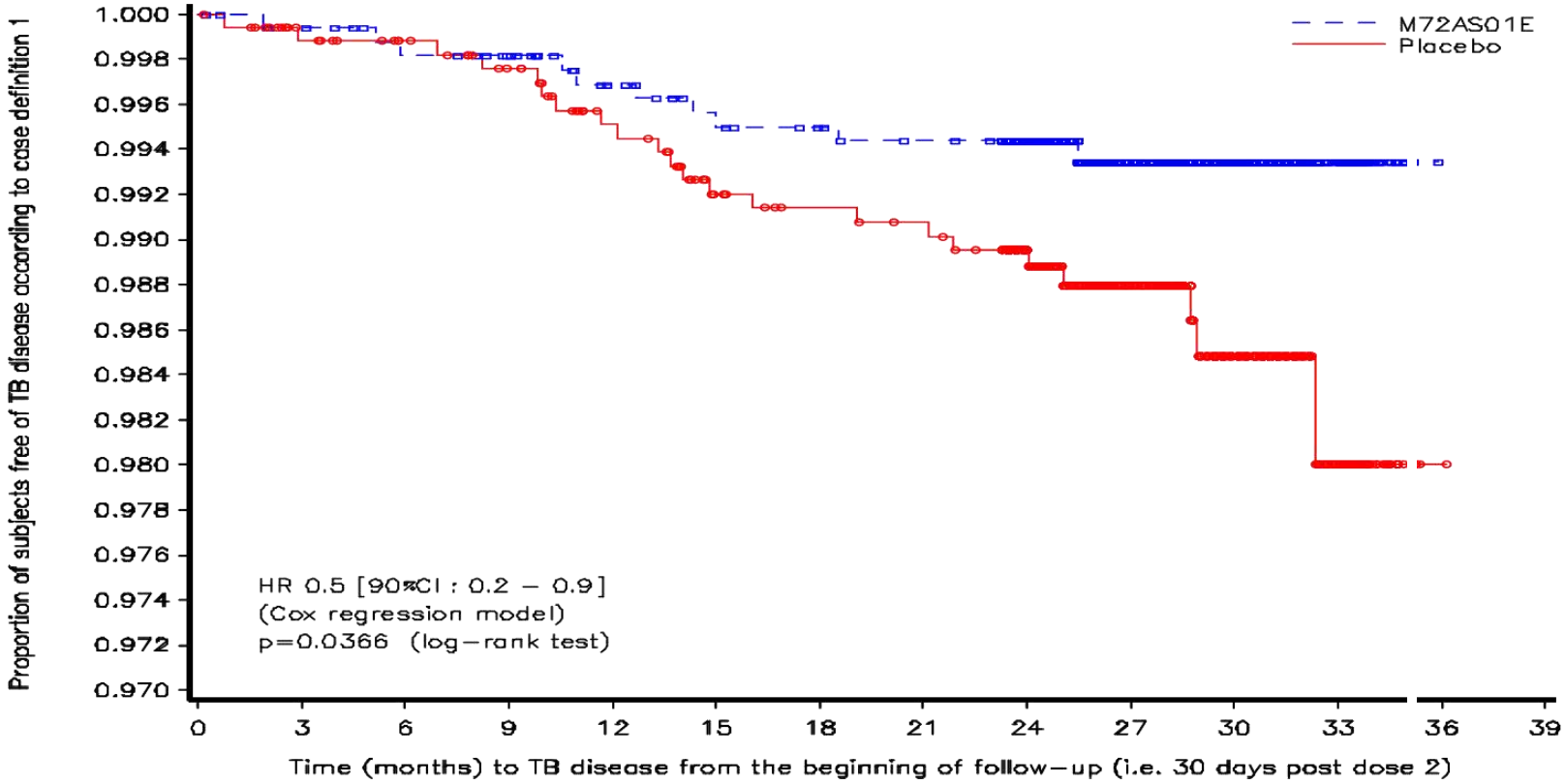


Figure adapted from Van Der Meeren et al, presented at IDWeek, October 2018, San Francisco CA, Abstract 70677

http://www.idweek.org

Van Der Meeren et al., NEJM, 2018

Conclusions and Next Steps

- M72/AS01$_E$ prevented TB disease in Mtb-infected adults
  - Efficacy of 54% [CI90% 14-75%, p=0.04] - primary endpoint met
  - Secondary endpoint met (VE of 58%; p=0.05)
  - VE calculated for the other case definitions ranged from 28-70%
  - Acceptable safety profile
- More research is warranted
  - End of study analysis
  - Aeras (now IAVI) Biobank to enable correlates discovery
- Next steps for M72 development are under discussion with key stakeholders and funders

Van Der Meeren et al., NEJM, 2018

Proof of Concept Study Acknowledgments

Study participants and their communities

Investigators and their teams

Mark Hatherill
Robert J. Wilkinson
Monde Muyoyeta
Nduba Videlis
Elana Van Brakel
Andreas Diacon
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Jennie Willson
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William Zonta

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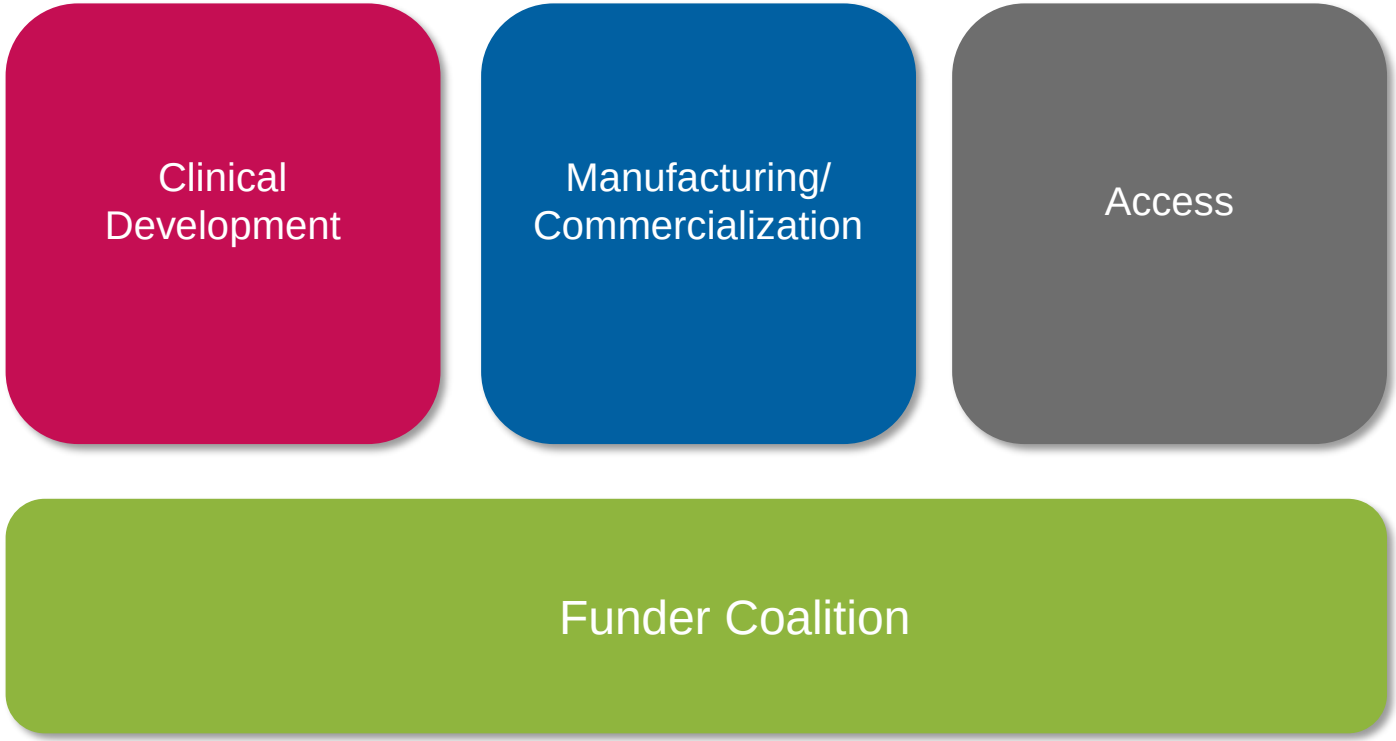
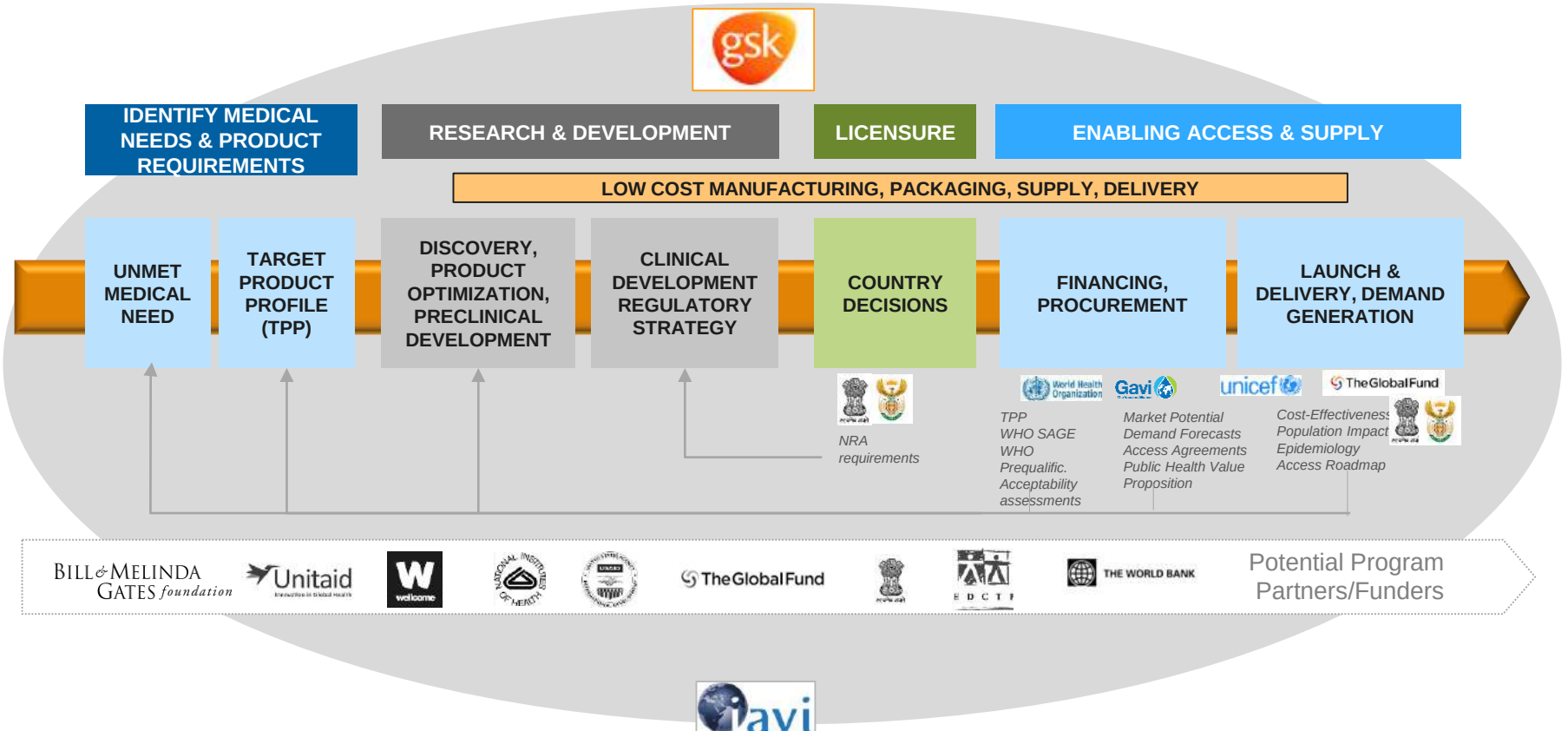
Aeras/IAVI (BMGF, DFID, DGIS, AusAID);
GSK

*Aeras TB vaccine clinical program was recently transferred to IAVI

A new model with novel partnerships and networks required to achieve ‘end-to-end’ program impact



A coalition of critical upstream and downstream partners will enable program funding, accelerated M72 development and rapid access



M72/AS01$_E$ Phase 2b development partner

International AIDS Vaccine Initiative

IAVI gratefully acknowledges the generous support provided by the following major donors

USAID FROM THE AMERICAN PEOPLE

PEPFAR U.S. President's Emergency Plan for AIDS Relief

BILL & MELINDA GATES foundation

THE WORLD BANK

Funded by the European Union

UKaid from the British people

CEPI New vaccines for a safer world

JAPAN

Ministry of Foreign Affairs of the Netherlands

MINISTRY OF FOREIGN AFFAIRS OF DENMARK DANIDA INTERNATIONAL DEVELOPMENT COOPERATION

Irish Aid An Roinn Gnóthaí Eachtracha agus Trádála Department of Foreign Affairs and Trade

सत्यमेव जयते Ministry of Science & Technology Government of India

amfAR, The Foundation for AIDS Research | Bill & Melinda Gates Foundation | The Buimerc Group | Broadway Cares/Equity Fights AIDS | The City of New York, Economic Development Corporation | Coalition for Epidemic Preparedness Innovations | European Union | Foundation for the National Institutes of Health | GlaxoSmithKline | Government of Japan | The Hearst Foundations | Irish Aid, Department of Foreign Affairs and Trade | Ministry of Foreign Affairs of Denmark | Ministry of Foreign Affairs of The Netherlands | Ministry of Science & Technology, Government of India | National Institute of Allergy and Infectious Diseases | Norwegian Ministry of Foreign Affairs | U.K. Department for International Development | The U.S. President's Emergency Plan for AIDS Relief through the U.S. Agency for International Development | The World Bank

And many other generous individuals and partners around the world

As of May 2018

Thank you

email: aginsberg@iavi.org

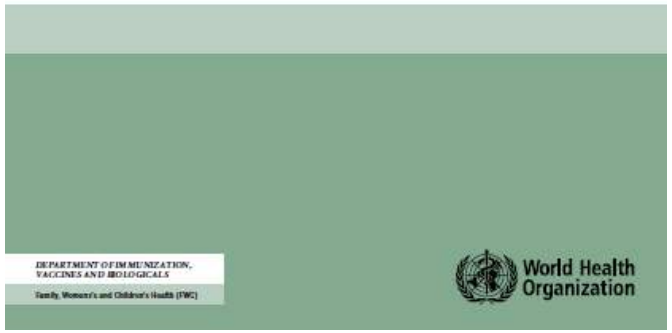
ANNEX

		LIC		LMIC		UMIC	
Duration (years)	VE(%)	% decrease in cases	CE vaccine price (USD)	% decrease in cases	CE vaccine price (USD)	% decrease in cases	CE vaccine price (USD)
5	40	24	1.30	24	3.45	17.5	6.97
	60	33	2.18	34	5.36	25	10.90
10	40	40	2.73	40	6.44	30	13.18
	60	52	3.98	53	9.04	42	19.95

Knight GM, Griffiths UK, Sumner T, et al. Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries. *Proceedings of the National Academy of Sciences of the United States of America*. 2014;111(43):15520-15525. doi:10.1073/pnas.1404386111.

New Tuberculosis Vaccines:

WHO IVR activities



Johan Vekemans, MD PhD

WHO Initiative for Vaccine Research

June 2019

TUBERCULOSIS in 2017

Estimated 10 million new cases and 1.6 million deaths. Over 90% in LMICs

Approximately 1/3 world infected with *Mycobacterium tuberculosis*

First cause of mortality in HIV

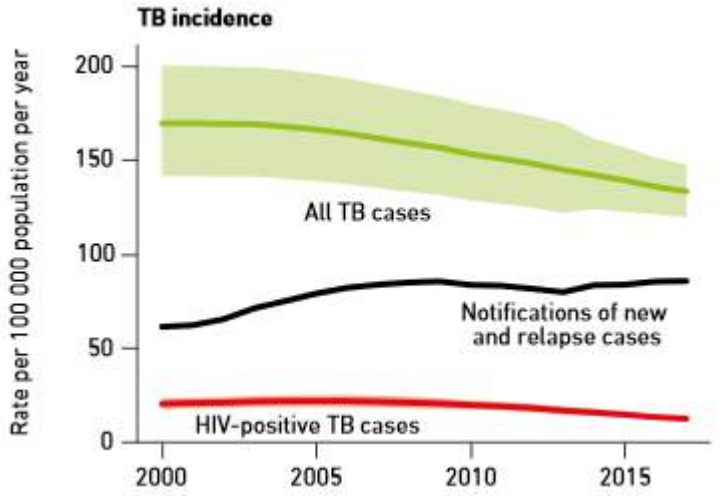
First cause of mortality due to AMR pathogens

estimated third of all deaths due to AMR pathogens

558 000 cases of DR-TB, of which 82% had MDR-TB and 6% XDR-T

End TB Strategy assumes new tools including vaccines will be available.

2035, reducing 90% of TB cases (from 2015)



WHO IVR recent activities

New TB Vaccines PPC published (prevention of TB in adults, in children)

New PPC being finalized : TB vaccine for improvement of TB disease treatment outcomes

Follow-up on new TB vaccine promising results: M72/AS01E

Upcoming: participation to a Technical R&D Roadmap

Full Public Value Proposition evaluation

New TB vaccine PPC

Two strategic priorities

New TB Vaccines for Use in Adolescents and Adults: Preferred Characteristics

World Health Organization

INDICATION

- Immunization for prevention of active pulmonary TB

World Health Organization

TARGET POPULATION

- Adolescents and adults. Proof of concept should prompt pediatric studies.

OUTCOME MEASURE AND EFFICACY

- 50% or greater efficacy in preventing confirmed pulmonary TB
- Protect both subjects with and without latent *Mtb* infection
- Protective in different geographical regions and latitudes

New TB Vaccines for Use in Adolescents and Adults: Preferred Characteristics

World Health Organization

SAFETY

World Health Organization

- Safety and reactogenicity profile should be favourable, similar to other current WHO-recommended routine vaccines for use in adolescents and adults

  - Mitigations to be considered given severity and major public health concern associated to TB

  - Safety should be favourable in particular risk groups (especially individuals living with HIV/AIDS)

New TB Vaccines for Use in Neonates and Infants: Preferred Characteristics

INDICATION

- Prevention of TB, including severe, disseminated, meningitis and pulmonary TB, in infants and young children

OUTCOME MEASURE AND EFFICACY

- Superior efficacy as compared to BCG alone

SAFETY

- Improved safety as compared to current BCG
- Demonstrated safety in HIV infected babies

New TB Vaccines : Preferred Characteristics

World Health Organization

DURATION OF PROTECTION

- Demonstrated efficacy over 2 years min to support initial policy decision
- Ten or more years of protection should be conferred after primary immunization
- Long-term follow-up studies will inform the duration of protection (post licensure)

World Health Organization

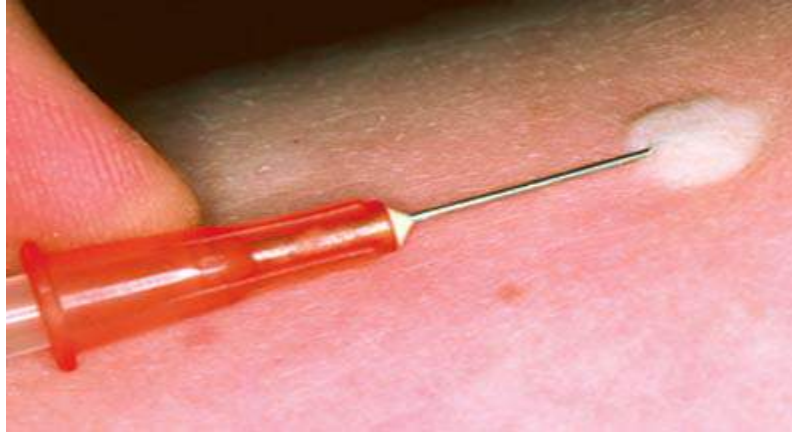
SCHEDULE

- A minimal number of doses and boosters required, no more than three doses for primary immunization. Long term follow-up studies, should determine the requirement for booster dose(s) – not more frequently than every 5-10 years

IMMUNOGENICITY

- Detailed characterization of immune responses
- Evaluation of association with protection ; identification of a correlates of protection
- The conservation of biological specimen for future use upon advances in technology and knowledge is encouraged

New TB Vaccines : Preferred Characteristics



PROGRAMMATIC SUITABILITY

- Innovation related to ease of administration and thermostability

VALUE PROPOSITION

- Evaluation of the vaccine impact on the TB epidemics in general, and on drug-resistant TB specifically, on co-morbidities (HIV), on health systems and the economy, is encouraged (role of modelling)

- The vaccine should be cost-effective and price should not be a barrier to access

Endpoints in TB Vaccine Trials:

Prevention of Mtb Infection (PoI - PPD skin test or IGRA conversion)

World Health Organization

Demonstrating biological effect with smaller sample size, cost, short duration

World Health Organization

Clinical significance? Prevention of disease not demonstrated

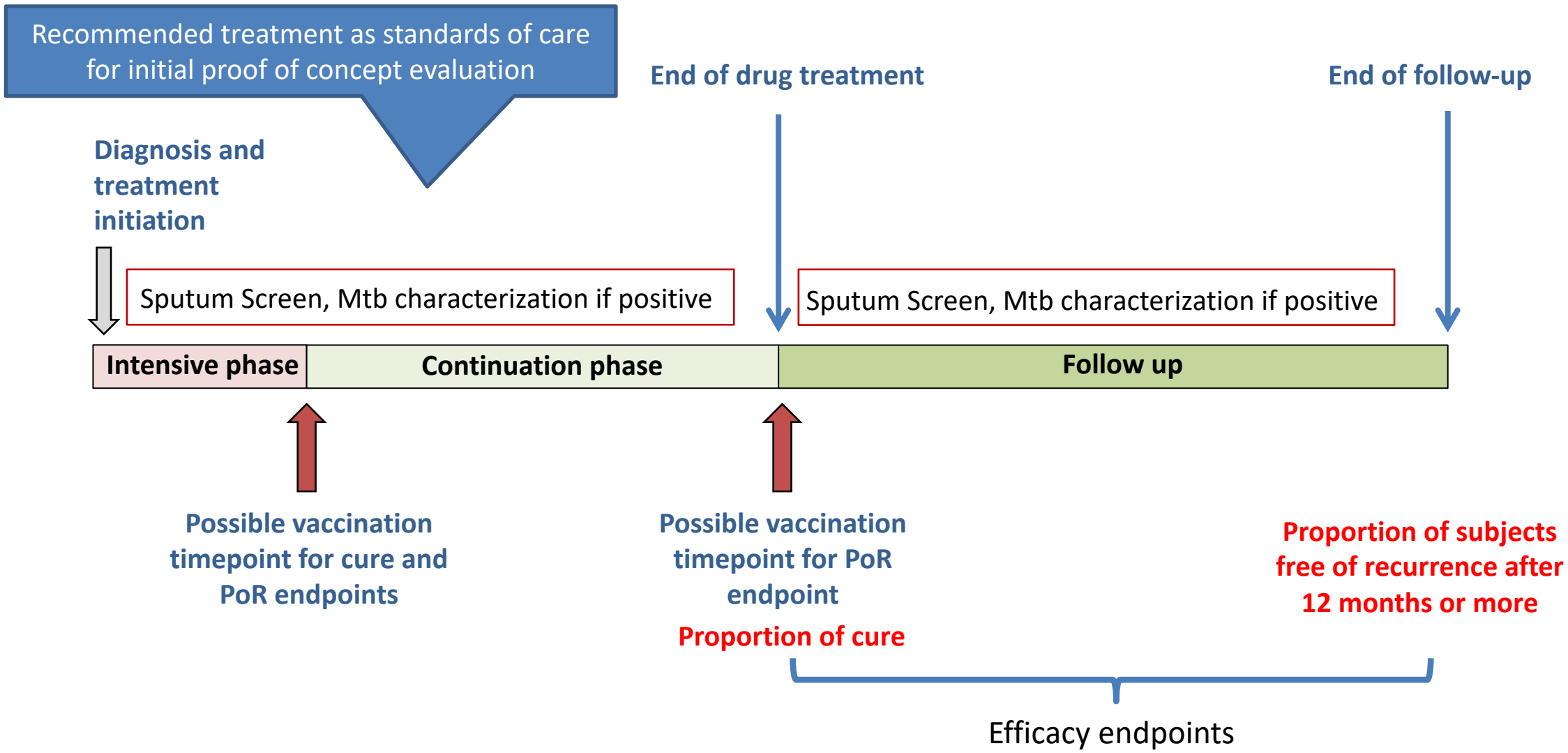
Risk of false negative result: a vaccine may be found not to prevent ‘immune take’ while successfully preventing progression to disease

Vaccines for improvement of TB treatment outcome

World Health Organization

- Aim to reduce treatment failure (increase cure rates), reduce frequency of relapse, simplify and shorten treatment regimen
- Specific interest in drug-R TB
- M72 results arguing in favour of feasibility
- Opportunity to also reduce progression to TB in recently exposed contacts, in TB infection test converters
- WHO PPC document under finalization

Vaccines for improvement of TB treatment outcome: PPC



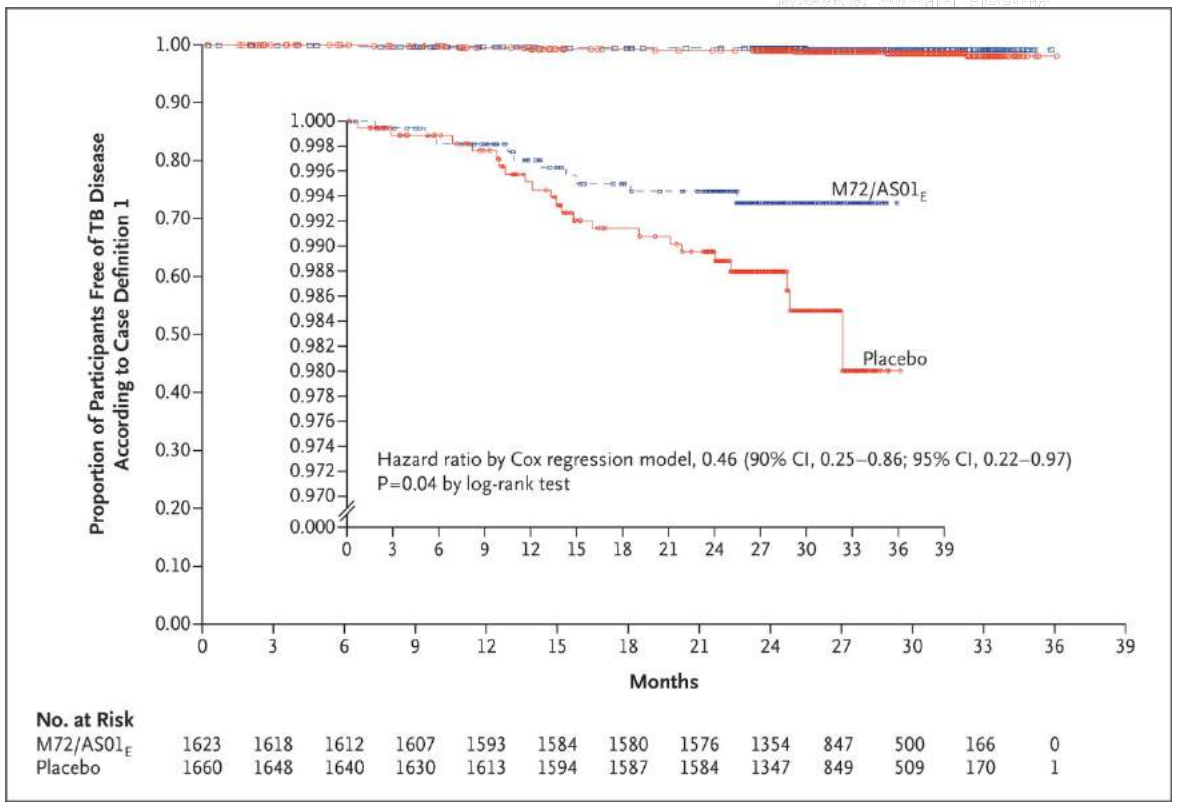
Phase 2b Efficacy study of GSK's Candidate TB Vaccine M72/AS01E in Adults with Latent TB Infection

World Health Organization

Vaccine	2-dose IM M72/AS01$_E$ (fusion protein Mtb32A, Mtb39A)
Sponsor	GSK (Aeras)
Population	3,500 IGRA+ adults
Endpoint	Incident, confirmed pulmonary TB
Site/s	South Africa, Kenya, Zambia

Favorable safety (some local and general reactogenicity)
VE over 2.3 years: 54% (90%CI 14-75%)
No indication of waning of protection (figure)
Data on additional 1 year FU awaited

Impact modelling estimates awaited



M72/AS01: WHO strategic vision

Progress the M72/AS01 candidate's evaluation with a sense of urgency

April 5th WHO consultation :

- GSK is seeking a partner/s to take license of M72 from GSK to develop, license, manufacture, be liable for, and supply M72 for the developing world (GSK will maintain proprietary control for the non-developing world)
- Limited number of doses currently available. Process improvement needed for Phase 3 material
- No established consensus on pathway forward and investments
- Willingness from many stakeholders to contribute. Need to ensure country perspectives are taken into account, countries contribute to the research agenda and resources
- Major risk of undue delays. Need for coordination and advocacy.

Preferred scenario, for discussion

Assuming 3rd year data confirm the results of 2 years follow-up:

- progression to Phase 3 trial in a population of teenagers/young adults in settings with high incidence
- accelerated licensure with narrow indication (prevention of pulmonary TB in young adults in high endemic settings)
- parallel proof-of-concept evaluation for other indications (HIV+, pediatric, contacts, PoR) and schedule optimization
- post-licensure investigations, country-led

Next steps for WHO

- Consultation on **clinical development pathway** to lay the way forward for future studies, in the context of potential use cases, trial designs, timeline, risks and opportunities

- Co-convene with Wellcome Trust a Funders' meeting to explore joint financing and innovative financial products to support development with and end to end perspective

- Development of a full **public health value assessment** for new TB vaccines

- Develop a **TB Vaccines R&D Technology Roadmap**

All activities to be conducted in close coordination with existing platforms (Global TB Vaccine Partnership)

Questions to PDVAC

Does PDVAC agree that the current level of evidence emerging from the Phase 2b M723/AS01E trial in Southern Africa justifies for WHO IVR to promote progression to Phase 3, based on the existing candidate product and schedule, with the intention to license the candidate vaccine for prevention of pulmonary tuberculosis in young adults in settings of high exposure?

Does PDVAC agree that finding the fastest feasible route to first licensure with subsequent expansion of indication constitutes an advisable product development strategy?

Burden of Disease for Enteric Pathogens.

World Health Organization

WHO Product Development for Vaccine Advisory Committee (PDVAC) Consultation, 26-28th June 2019

Holly Prudden, Birgitte Giersing, Mateusz Hasso-Agopsowicz

PD-VAC 2018 Recap and Recommendations

World Health Organization

Recap:

- ETEC remains a priority pathogen in LMICs and PDVAC will continue to advocate for, and support, the development of a vaccine. A key component of this effort should focus on improving the understanding and credibility of BoD estimates.
- Shigella remains a priority with primary goal to develop a safe, effective and affordable vaccines to reduce morbidity and mortality.

Model output	IHME (2013)	MCEE (CHERG, 2011)	IHME (2016)	MCEE (2016)
U5 Diarrheal Deaths Due to Pathogens:				Unpublished data, expected to show minor revisions in estimates associated with both pathogens.
Shigella:	33 400 (24900-43500)	28 000 (17000-71000)	99 680 (59550-161235)	
ETEC:	23 100 (17000-30000)	42 000 (20000-76000)	15 960 (4400-40300)	

Recommendations:

"To further investigate understanding and credibility of Burden of Disease estimates, through the formation of a joint IVIRAC/PDVAC independent working group to evaluate diarrheal burden models, and particularly to assess the level of uncertainty regarding ETEC mortality estimates."

Implementation of PD-VAC Recommendations

Formation of Expert Working Group (Summer 2018)

Participant	Affiliation
Ben Lopman	Emory, USA
Cherry Kang (PDVAC)	Translational Health Science and Technology Institute, India
Claudio Lanata (PDVAC)	Nutritional Research Institute, Peru
Mark Jit (IVIR-AC)	LSHTM, UK
Mark Riddle	Uniformed Services University, USA
Peter Smith (PDVAC)	LSHTM, UK
Robert Breiman (Chair)	Emory, USA
James Platts-Mills	University of Virginia
Virginia (Ginny) Pitzer	Yale University, USA
Wilfred Ndifon (IVIR-AC)	African Institute for Mathematical Sciences, South Africa

Organisation of Two Day Consultation with Modelling Groups (November 2018)

Observer: Laura Lamberti (BMGF)

WHO Secretariat: Birgitte Giersing (PDVAC sec), Raymond Hutubessy (IVIRAC sec), Holly Prudden, Mateusz Hasso-Agopsowicz

Purpose of Consultation

- To identify common assumptions and major differences between two burden models, focusing on global U5 mortality estimates.
- To identify recommendations/activities that may improve current inputs
- To identify recommendations/areas for further work to further increase the transparency and understanding of the global U5 mortality estimates
- To identify aspects that may inform and align future iterations of the models
- To draft a work plan over the next 12-18 months with the overall aim to better understand the BoD estimates of both groups

Key Lessons from Consultation

- IHME and MCEE produce different model estimates. This is particularly pronounced with respect to Shigella and ETEC.
- There are 3 broad levels at which differences in methodology may give rise to differences in estimates:
  - Differences in **model structure**
  - Differences in **methodology for processing the data**
  - Differences in **data quality**, inclusion and exclusion criteria

Recommendations

A work plan, with four corresponding workstreams* was formulated by the Working Group and both IHME and MCEE to explore methodological issues that explain the differences in estimates and address data gaps, which would improve overall understanding and quality of the modelling processes:

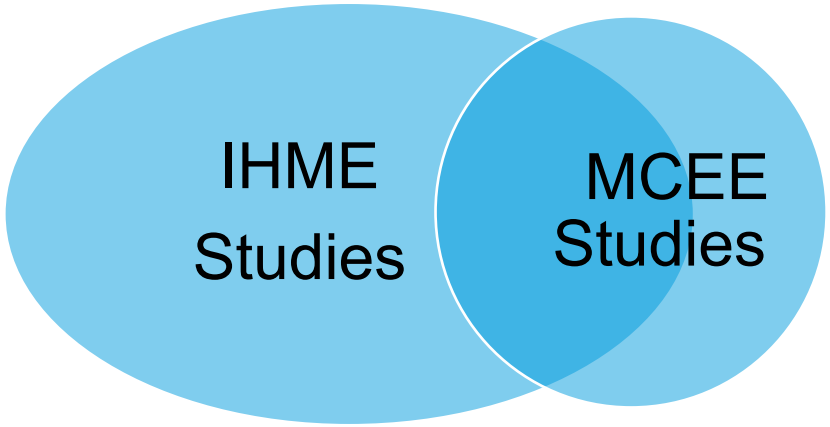
1. **Data Processing Exercise – a high level assessment of similarities and differences in study data.**
2. **Model Comparison Exercise – to address structural differences in models.**
3. **Data Quality Exercise – to improve understanding of the data utilised for modelling purposes.**
4. **Data Gaps – to identify and address areas of commonality where additional evidence may improve future estimates.**

Workstreams presented to IVIR-AC committee (March 2019) with endorsement of proposals and importance of this work

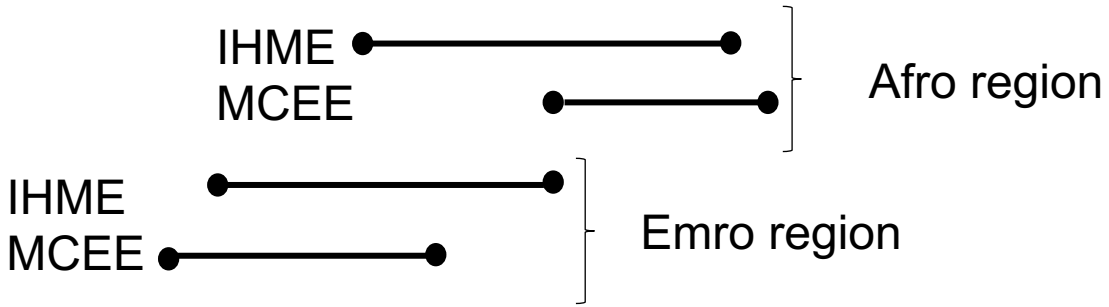
1. Data Processing Exercise

Purpose: A high-level assessment of differences in the studies used by each of the modelling groups.

Step 1: Identify which studies the groups have in common and those that are different.



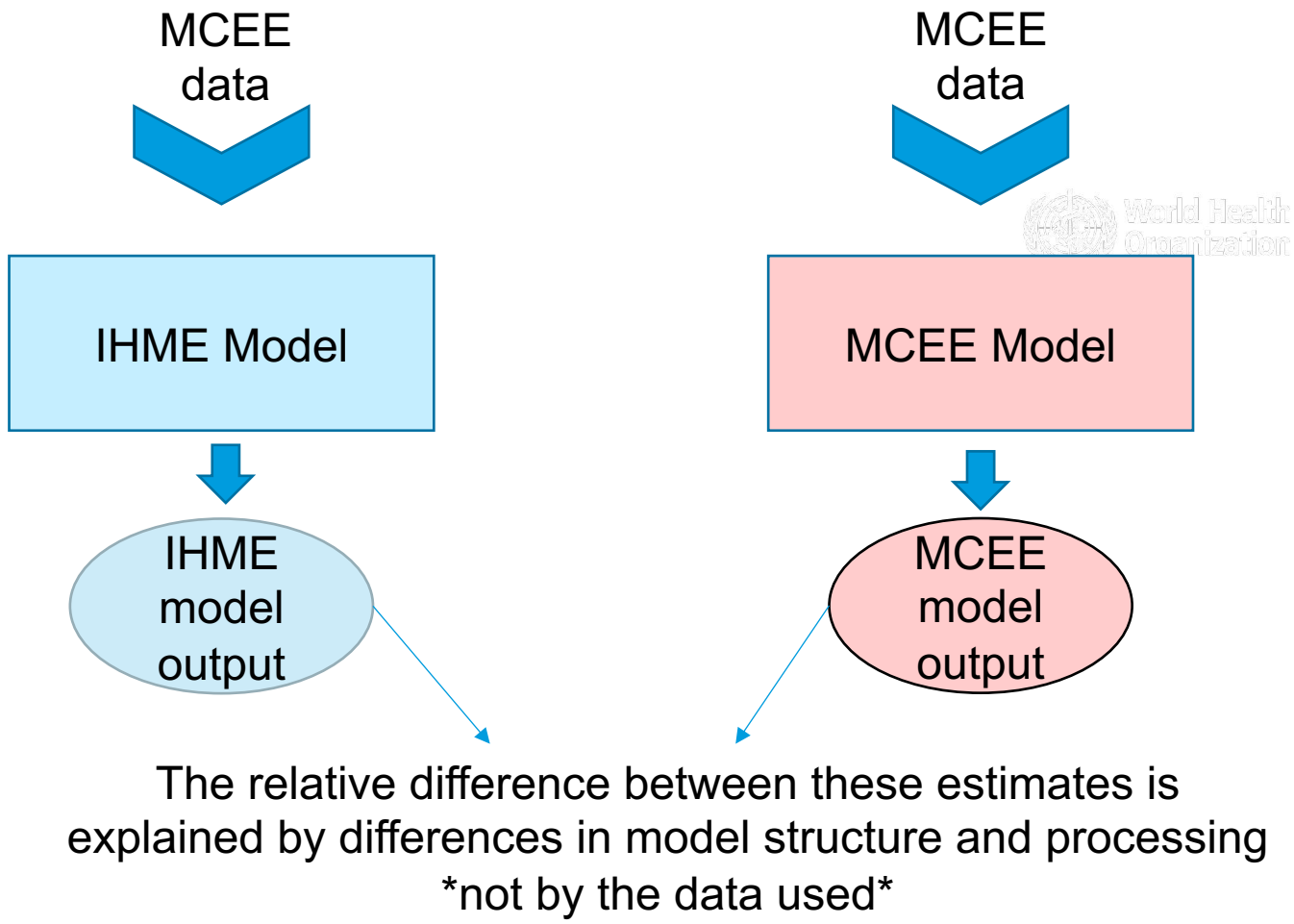
Step 2: Carry out a meta-analysis of the input data used by both groups (by region) to assess where fundamental differences may occur.



2. Model Comparison Exercise

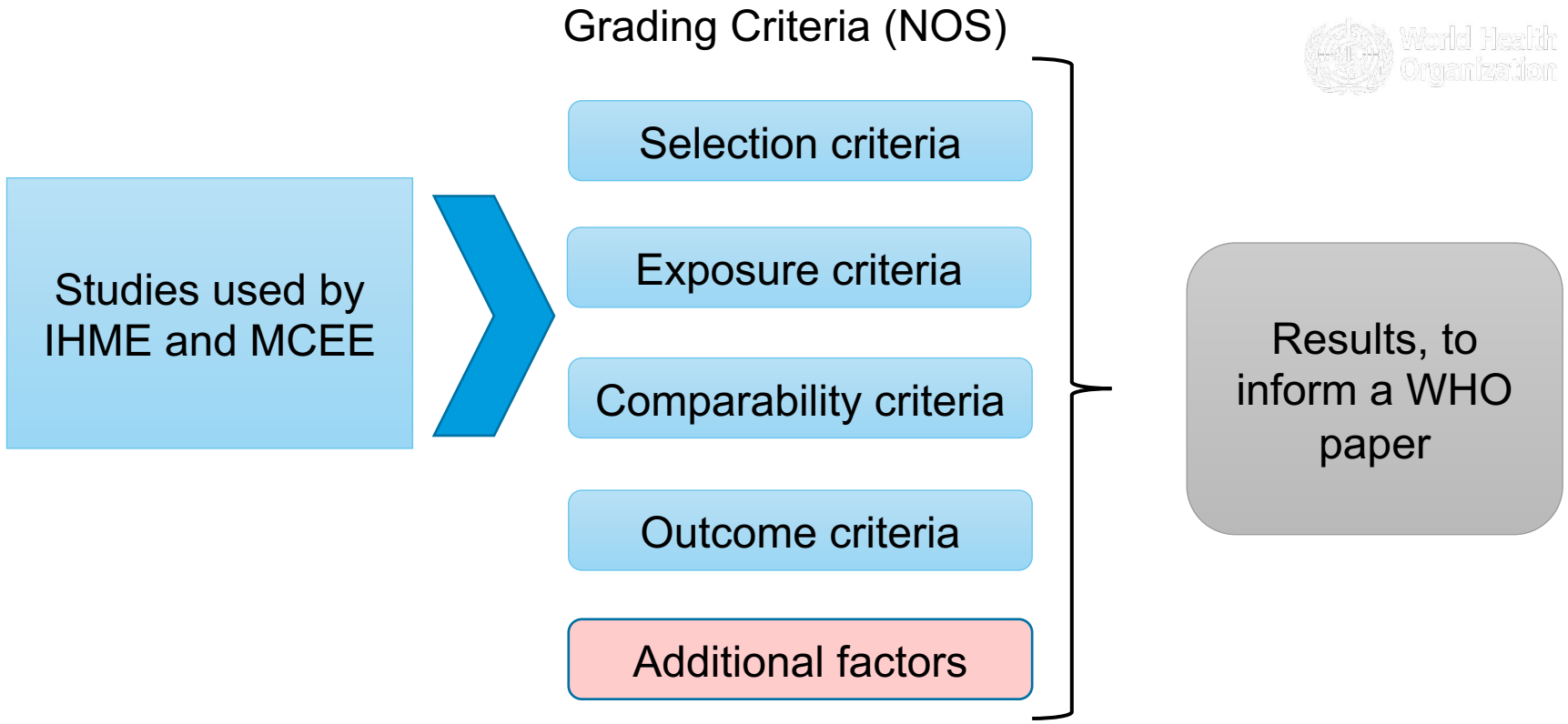
Purpose: To assess the relative differences in model outputs generated by both groups, when a common dataset is applied to both models.

Method: We will aim to utilise MCEE U5 data to generate the required outputs.



3. Data Quality Exercise

Purpose: To grade the quality of the data utilised by both groups using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies, to help inform the standard of data acceptable for estimating future modelling analysis on the burden of enteric disease.



4. Data Gaps

Purpose: To generate additional data through **systematic reviews** to provide the modelling groups with information to strengthen their approach.

Review 1: Update Odds Ratios (ORs) for the probability of detecting a pathogen, given diarrhoea. More evidence required on controls.

OR of presence of pathogen in cases	++++ (sufficient data)
OR of presence of pathogen in controls	+ (more data required)

Review 2: Assumption that case fatality rate (CFR) is the same for all pathogens. More information required to assess this assumption.

CFR → Assumed equal

Shigella	Norovirus
Rota	Salmonella
ETEC	Campylobacter

Work to date

Data Processing Exercise: - Initial comparison of data to identify differences between MCEE and IHME for six pathogens. - More thorough review planned and completion of meta-analysis.	**Data Quality Exercise:** - Grading analysis proposal generated and agreed upon with Working Group. Next step to share with groups. - IHME and MCEE studies extracted. Grading analysis to begin, early July.
Model Comparison Exercise: - Initial model input data compiled and shared. - U5 data for MCEE model generated and shared. - Call with IHME scheduled for next steps.	**Data Gaps Exercise:** - Criteria defined and agreed upon for systematic reviews. - Analysis commenced 24/06.

Other Key Outputs:

- Short report for (Nov 2018) meeting consultation completed and shared with meeting attendees.
- Full joint publication on meeting consultation pending submission.

Next steps

- Joint consultation publication submitted (journal tbc) July 2019.
- Publication of two separate systematic reviews.
- Joint publication, outlining proposed future methodology for recommended data used in generating enteric burden of disease estimates, summarising workstreams and key findings.


World Health Organization
Thank you

June 27, 2019

Trivalent Rotavirus P2-VP8 Subunit Vaccine and its Public Health Value Proposition

Product Development Vaccine Advisory Committee
World Health Organization

Stan Cryz, Alan Fix, Chris Gast, Jorge Flores,

Bill Hausdorff, Fred Cassels

NRRV Team

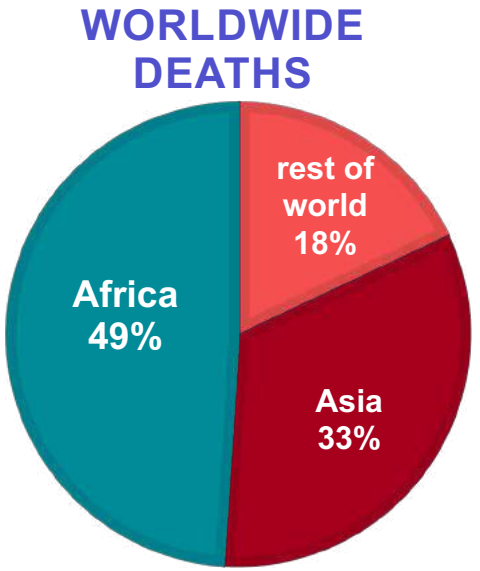
PATH

ROTAVIRUS DISEASE

Rotavirus remains a leading cause of severe diarrhea among children <5 yrs worldwide

- Current disease burden:

  >250 million cases of diarrhea annually
  129,000 diarrheal deaths in 2016
  (declined from >500,000 in 2000).



- Four live attenuated oral rotavirus vaccines: WHO PQ

  Rotarix, GSK; RotaTeq, Merck;
  Rotavac, Bharat; RotaSiil, Serum Institute.

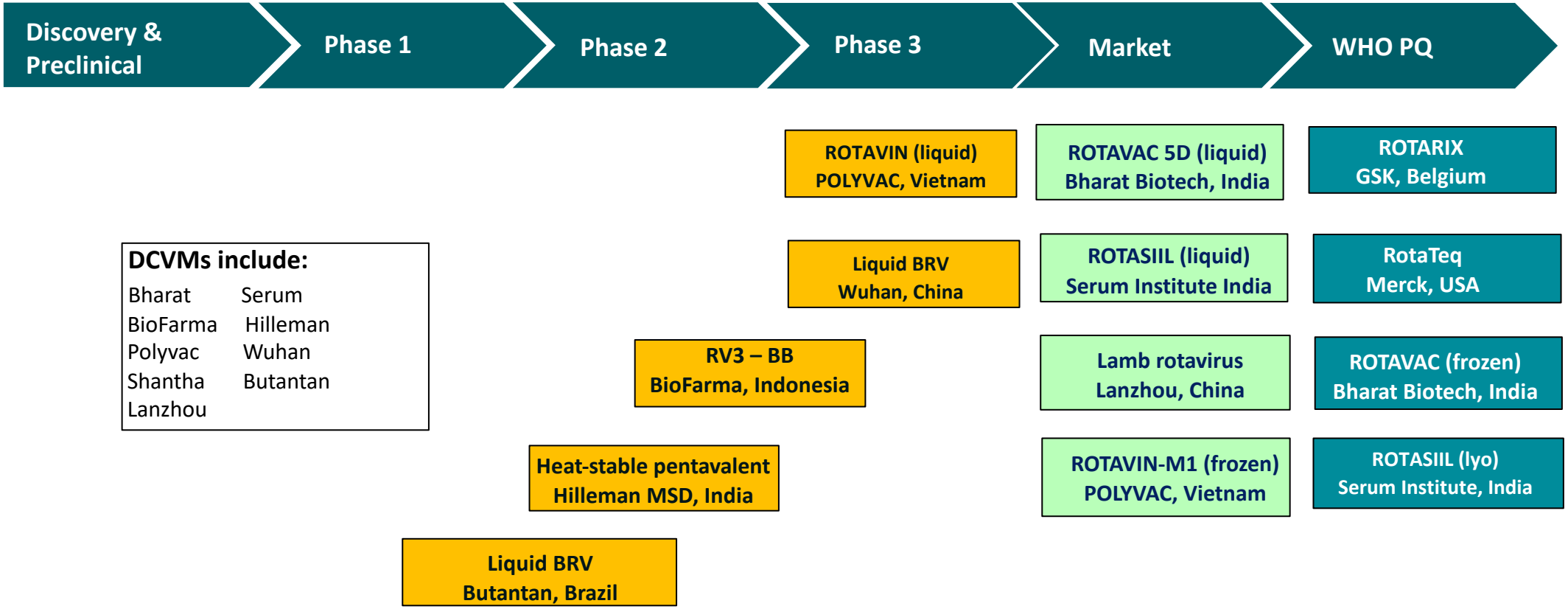
- Vaccination well established globally:
  - All settings observed a real impact (high, middle and low income settings)
  - Significant reduction in rotavirus related mortality, severe rotavirus diarrhea and all cause diarrhea in countries vaccine introduced.

Despite major progress, rotavirus disease continues to impact on child health.

1. Troeger et al Lancet ID 2018.

Slide Courtesy of Carl Kirkwood

Live Oral Rotavirus Vaccines



Rationale for Considering an NRRV Vaccine

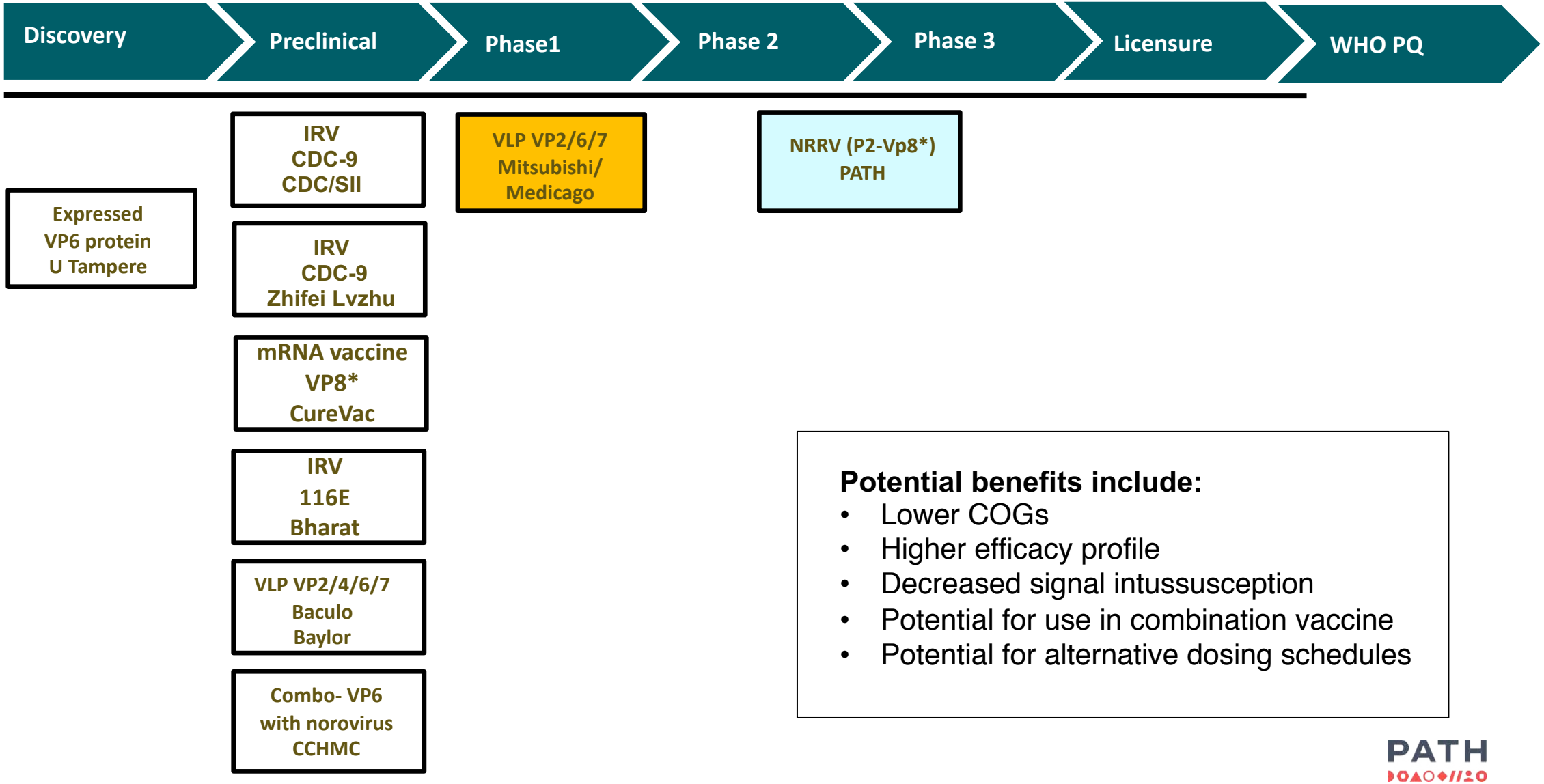
Limitations of current live oral rotavirus vaccines:

- Offer great benefit to populations in resource-limited countries but have reduced efficacy in those populations compared to other populations
  - Potential reasons include inference by maternal antibodies, coinfection with other pathogens, enteropathy, co-administration of OPV, nutrient deficiency and host genetics
- Cost compared to other EPI vaccines is high

NRRV candidates:

- Parenteral administration could avoid several intestinal barriers that oral vaccines must overcome, and thus may provide superior efficacy in target populations
- Projected to be relatively inexpensive (<<$1 per dose)
- May be added to EPI vaccines (co-formulated), facilitating delivery (and further decreasing cost)

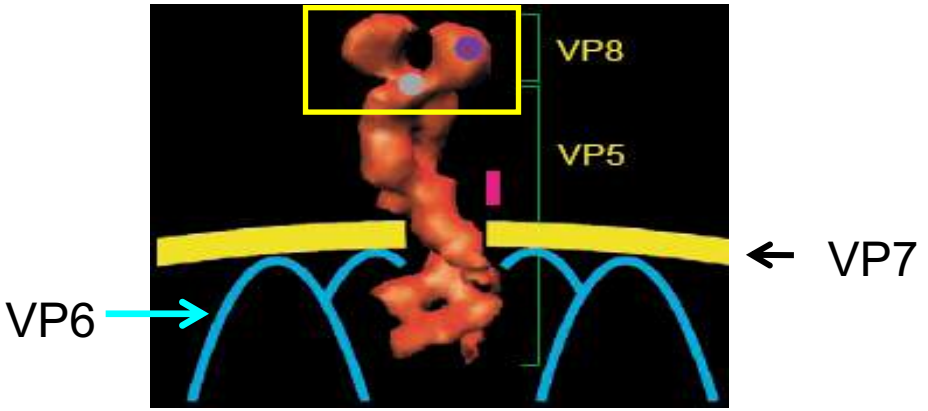
Next Generation Rotavirus Vaccines--Non Replicating



Potential benefits include:

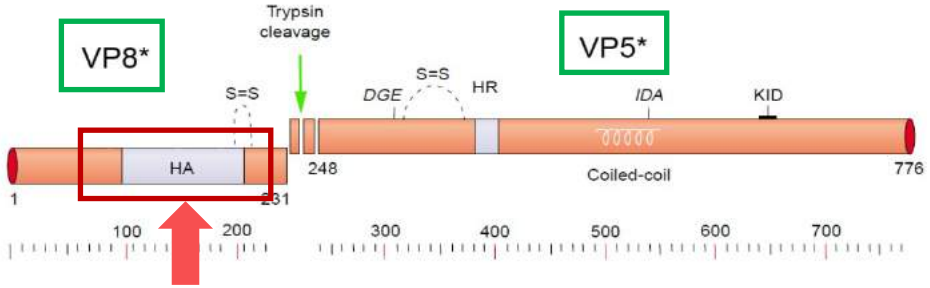
- Lower COGs
- Higher efficacy profile
- Decreased signal intussusception
- Potential for use in combination vaccine
- Potential for alternative dosing schedules

Characteristics of the P2-VP8 Subunit Vaccine



- Developed at US NIH by Dr. Yasutaka Hoshino
- Comprised of recombinant truncated VP8 ~ 21kDa
  - Expressed in *E. coli*
  - Simple three step column chromatography process
  - Liquid formulation, adsorbed to aluminum hydroxide

VP4



- The trivalent P2-VP8 subunit vaccine is made by combining three VP8 subunit proteins expressing P[4], P[6] and P[8] serotypes, each fused to the P2 T-cell epitope of tetanus toxin
- Elicits immunoglobulin G (IgG) and immunoglobulin (IgA) binding antibodies as well as rotavirus neutralizing antibodies in pre-clinical studies; protection from disease in neonatal piglet model
- No unexpected toxicity observed in GLP toxicology studies on rabbits and guinea pigs following administration of four doses (4 X human dose) of vaccine at two week intervals
- Two dose vial without preservative, each 0.5 ml dose contains 90 ug of antigen (30 ug per serotype)

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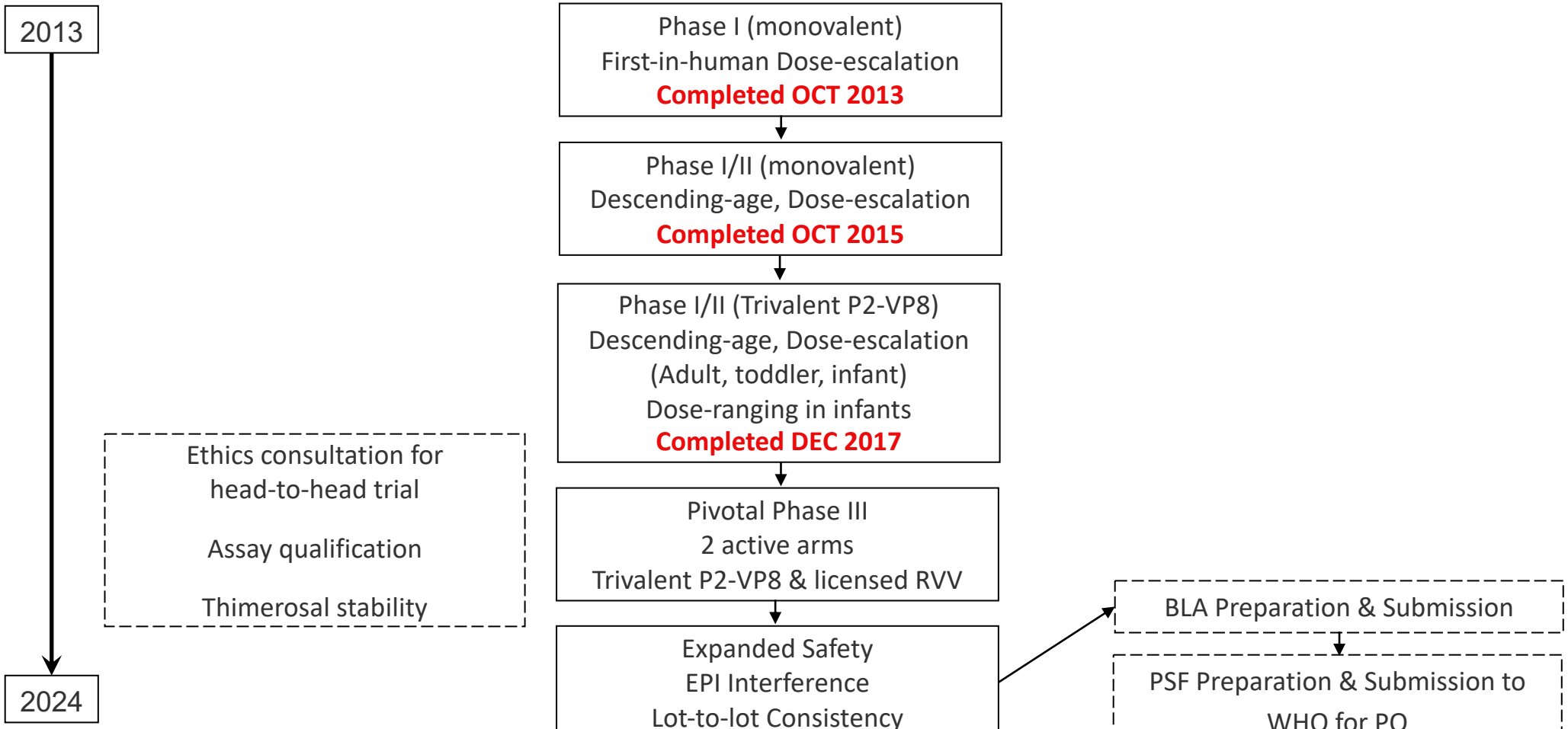
Target Product Profile (TPP)

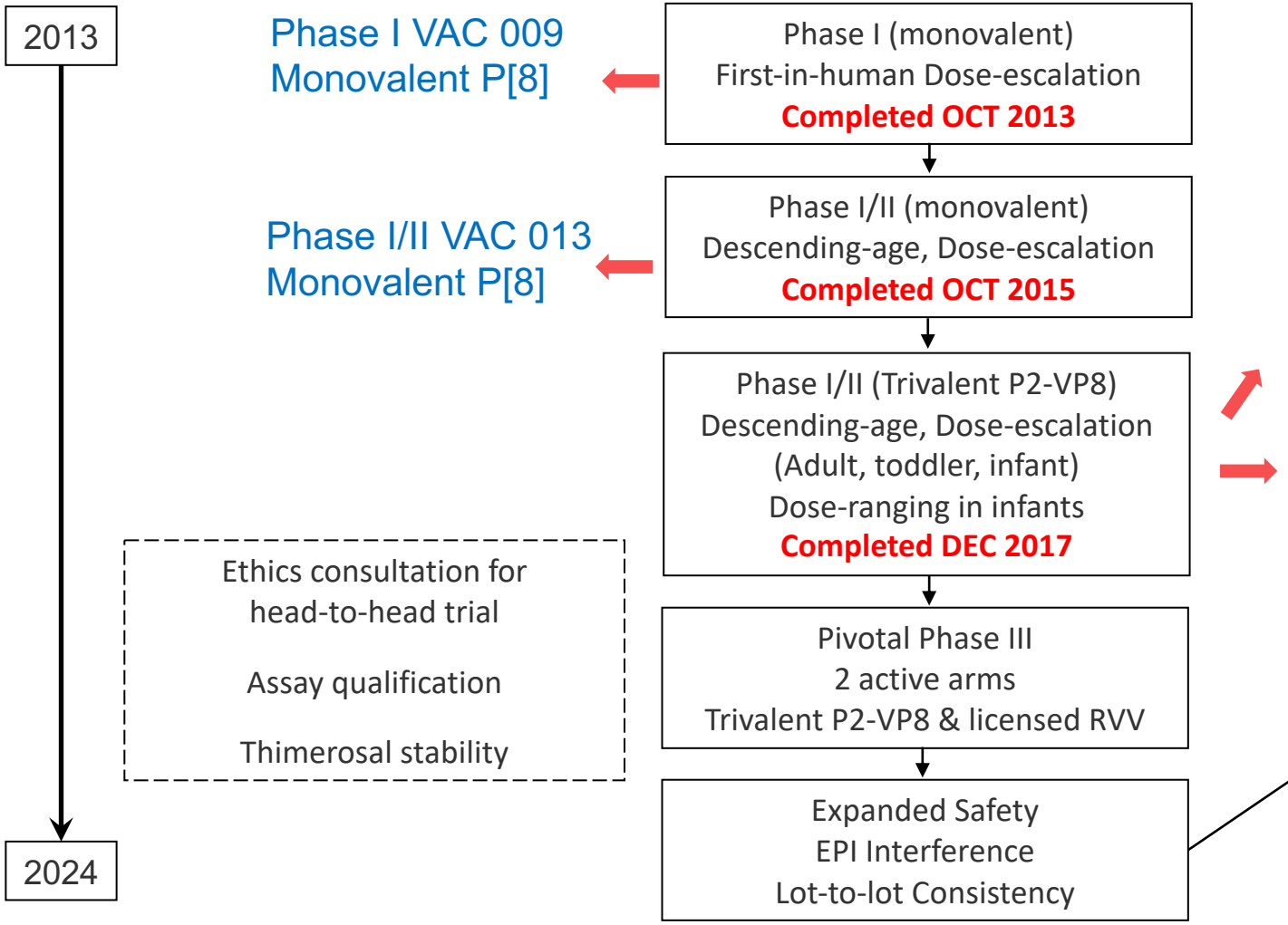
Attributes	
Indication	Prevention severe rotavirus gastroenteritis
Target Population	Infants (6-12 weeks old) during primary EPI series (for co-administration)
Route of Administration	IM
Presentation / Formulation	2 dose vial, liquid, 2-8 C. Formulated with aluminum hydroxide, ea 0.5 mL dose 90 ug P2-VP8 antigen (30 ug ea P[4], P[6], P[8])
Dosing Schedule	3 doses at 4 week intervals, starting 6-8 weeks of age
Vaccination strategy	Routine (+ penta/hexa)
Expected Efficacy	≥ 75% in Phase 3 trial
Price per Dose	~ $0.68 / dose
Manufacture	SK bioscience, Seoul, manufacturing stand-alone vaccine for Phase 3 trial. Additional manufacturing partner(s) envisioned for combination vaccine development.
Product Registration	Korea is anticipated first country of licensure (for export).
WHO Prequalification	Yes, 2H 2024
Manufacturing Capacity	65 million doses per year 2-dose presentation

End to End Clinical Development Plan

Preclinical 2010-2013



End to End Clinical Development Plan



Phase I/II VAC 041 Trivalent P[4], P[6], P[8]

- Safety & tolerability in South Africa healthy adults, toddlers, infants
- 15, 30, 90 ug IM 28 days apart
- Impact Vxn on shedding Rotarix

Results

- All dosage levels safe & well tolerated
- Robust anti-P2-VP8 IgG against all three P types
- Three doses better responses than two
- Significant decrease shedding Rotarix
- Greatest impact shedding with 90 ug dose (30 ug each serotype)

Assessment of Efficacy of the Standalone TV-P2-VP8

CVIA 061

A double-blind, randomized, active comparator-controlled, group-sequential, multinational trial to assess the safety and efficacy of a trivalent P2-VP8 subunit rotavirus vaccine in prevention of severe rotavirus gastroenteritis in healthy infants

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CVIA 061 Key Study Characteristics (1)

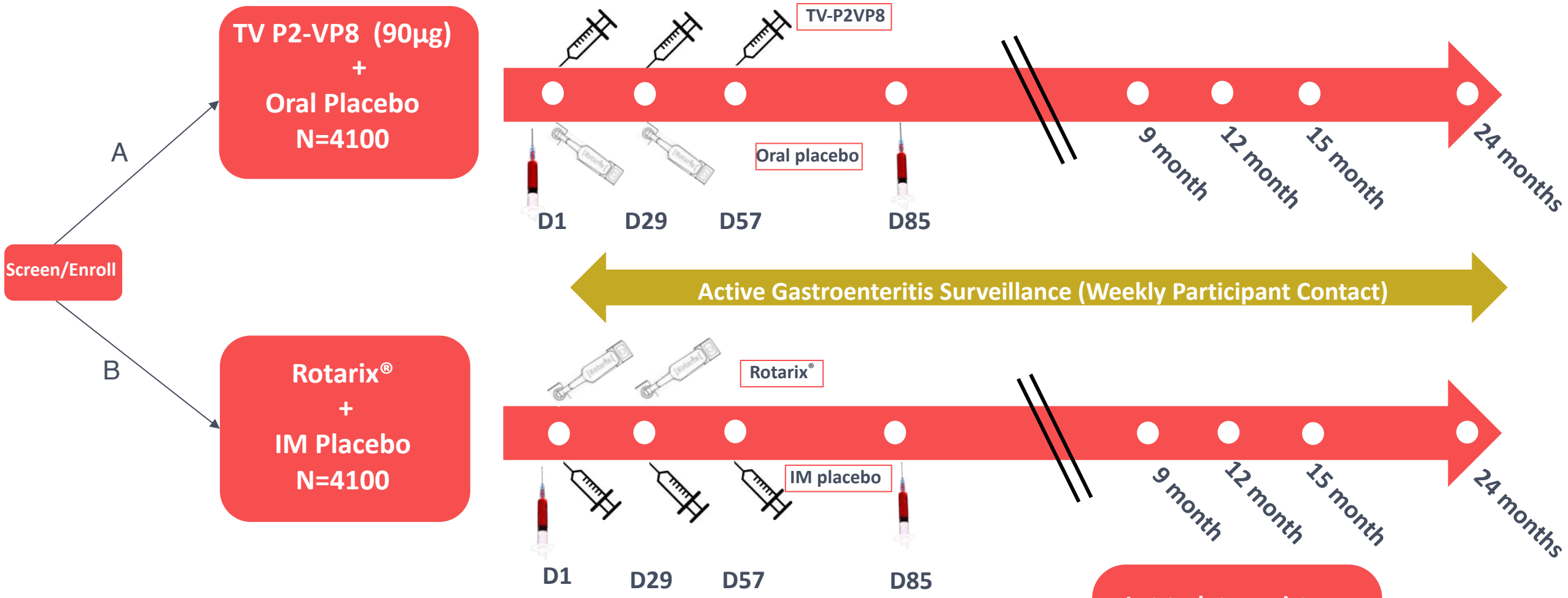
- Two arm, double-blind, group-sequential, double-dummy trial (1:1)
  - TV P2-VP8 vaccine
  - Rotarix
- Multinational
  - To include 3 countries in Africa and sites in India
- Dose-level/regimen: 3 monthly doses of 90 µg of TV-P2-VP8, administered monthly with EPI vaccines at 6, 10 and 14 weeks of age
- Follow-up through 2 years of age (unless futility criteria met)

CVIA 061 Key Study Characteristics (2)

- Group sequential trial with two stages
  - Stage 1 ~3,500 infants, with interim assessment of futility
  - Stage 2 – if do not meet futility criteria at interim analysis, proceed to enroll balance of full study population (~8,200)

- Assessment of lot-to-lot consistency of 3 lots of vaccine
- Exploration of immune correlates of risk
- Assessment of interference with response to EPI
- Anticipated initiation – Q3 2019

Double-Dummy Study Design



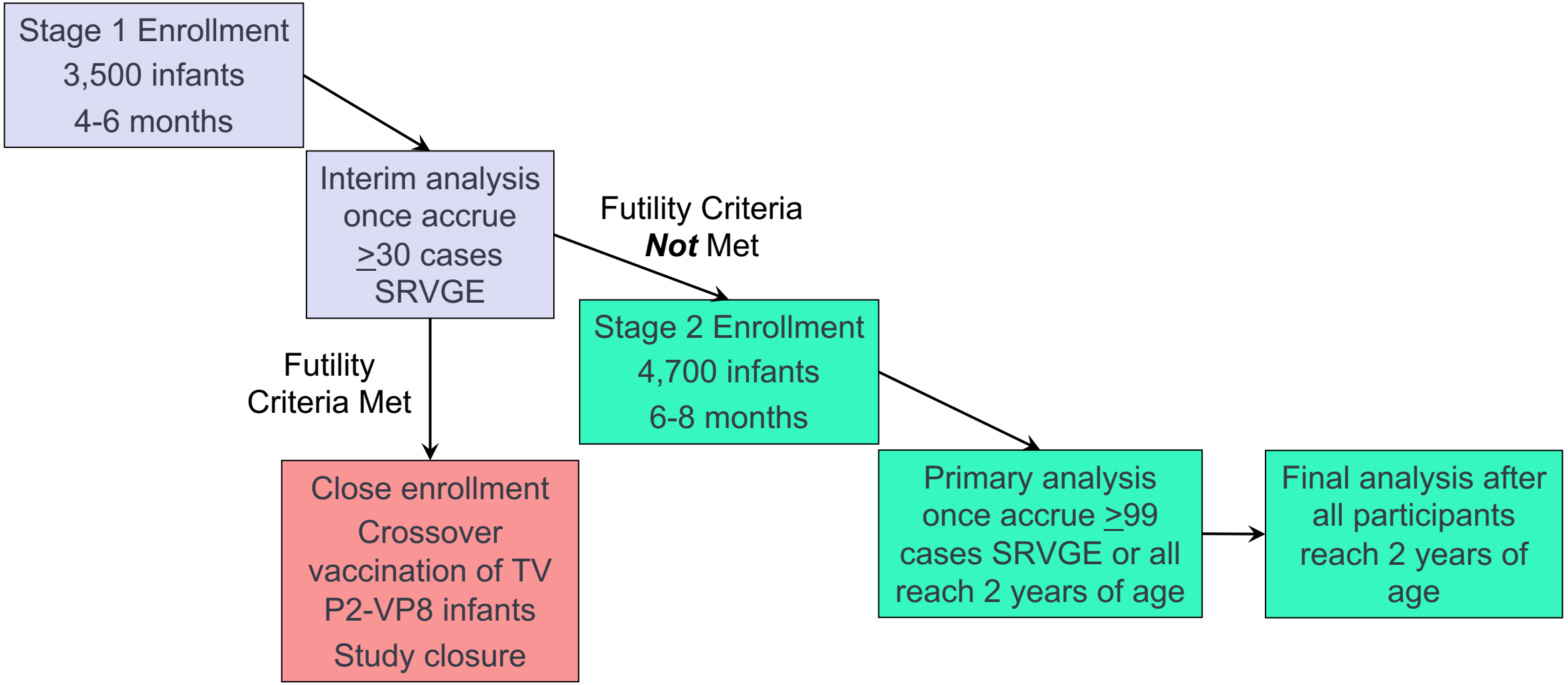
1st dose at 6-8 weeks of age; subsequent doses 4 weeks (28 days) later from previous dose

Oral placebo: ORS; IM placebo: Normal saline

Lot-to-lot consistency
N=1200; 400/lot

UIP Non-interference
N= 800; 400/group

CVIA 061 Study Outline



TV-P2-VP8 Future Development

- Assessment of efficacy of standalone vaccine
- Potential exploration of mixed regimens of live, oral RV vaccines and P2-VP8 vaccine
- Development of co-formulated vaccine, combining other EPI vaccines and P2-VP8 in a single injection
- Should efficacy results warrant, licensure and WHO prequalification of standalone and/or co-formulated vaccine for global availability

CENTER FOR VACCINE
INNOVATION AND ACCESS

Maximizing impact of Rotavirus vaccines: NRRV value proposition

Bill Hausdorff, PhD

Lead, Public Health Value Proposition

CVIA/PATH

Washington, DC

PATH

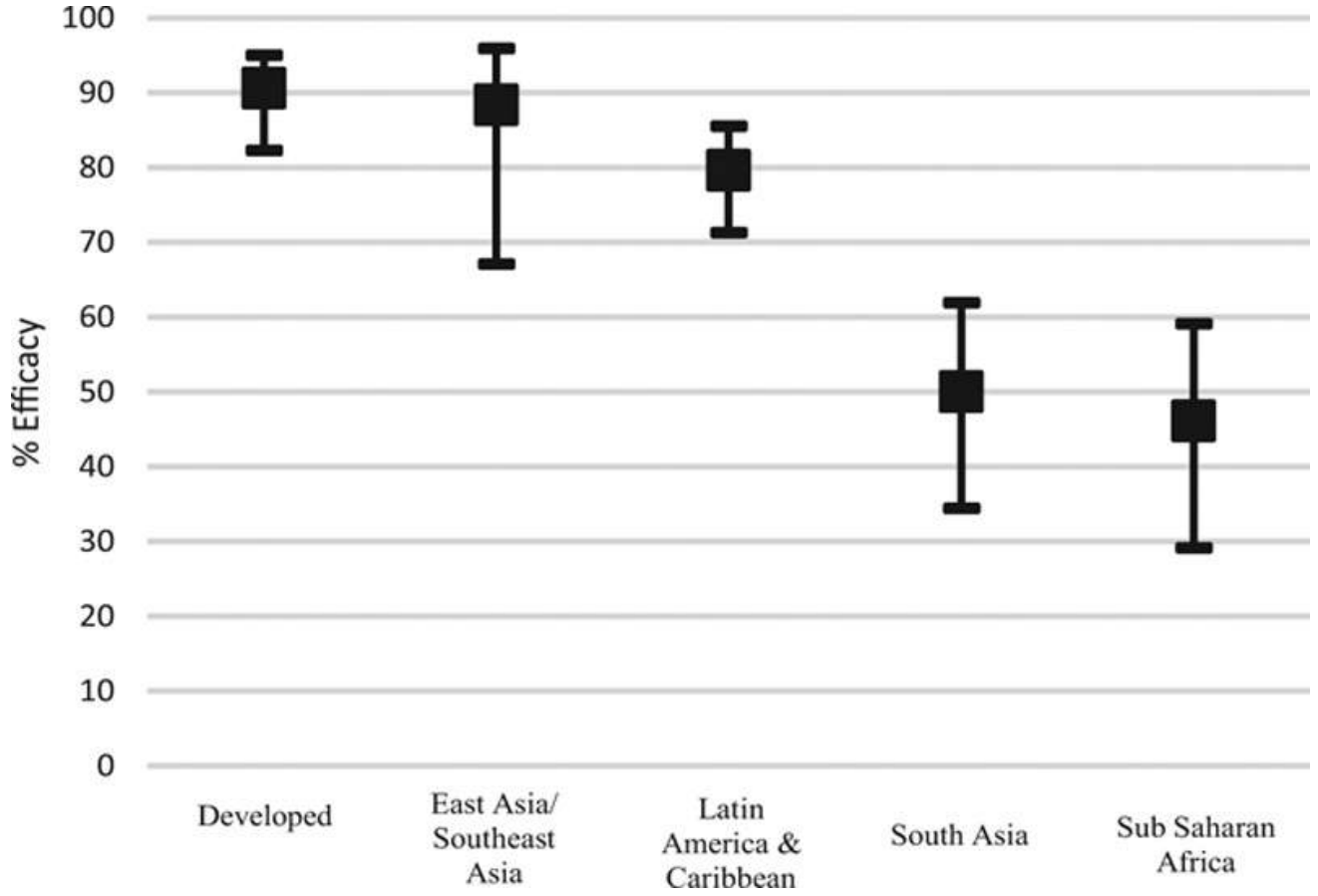
The solution to the problem is…

…a next generation, parenterally administered rotavirus vaccine!!

But what, exactly, is the problem?

Isn't THIS the problem?

NRRV should have intrinsically higher efficacy in primary series against severe disease in LICs.



Efficacy of live, oral rotavirus vaccination on severe rotavirus diarrhea, by region

Box represents percent efficacy; whiskers represent upper and lower bounds for the 95% confidence interval

Do we even need a Value Proposition?

A Systematic Review of the Effect of Rotavirus Vaccination on Diarrhea Outcomes Among Children Younger Than 5 Years
Lamberti, Laura M.; Ashraf, Sania; Walker, Christa L. Fischer; Black, Robert E. The Pediatric Infectious Disease Journal35(9):992-998, September 2016.doi: 10.1097/INF.0000000000001232

Wolters Kluwer
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Yet NRRV has several other potential advantages over live oral vaccines

- Lower cost of goods/dose
- Could form part of mixed schedule with oral vaccine for higher efficacy
- Could serve as a booster to oral vaccine to prevent waning in 2nd year of life
- Could be combined with DTP penta (or hexa) and/or IPV to minimize cold chain burden
- No intussusception

Which of these are “nice to have,” and which as “must haves”? Is higher efficacy itself a “must have”?

Alternatively, do we even have to choose among these advantages?

Yes. We have to make some choices. We can't do everything.

Choices shape clinical program & recommending body/market interest

Primary Theoretical Advantage	Clinical Endpoint Needed	Recommending Body/Market Implications
Higher VE in LICs	Demonstrate NRRV's clinical efficacy superiority	Strong selling point to SAGE & LICs but perhaps not to MICs?
Lower COGs/dose	Demonstrate efficacy non-inferiority	Do LICs care if GAVI is paying? Is current price an important barrier for MICs?
As part of mixed schedule or booster to counteract waning of current VE	No need to demonstrate any efficacy after primary series; need to demonstrate heightened efficacy after mixed/boost	COGs advantage lost; is preventing incremental late disease sufficiently interesting to SAGE & countries?
Combinable with DTP combos or IPV	Efficacy non-inferiority followed by work with one manufacturer to demonstrate immuno non-inferiority	Delayed time to market; plus would this allow single manufacturer to dominate DTP combo field?
No intussusception	Efficacy non-inferiority (impossible to demonstrate lack of intussusception pre-licensure)	Has US/Euro/Oz intussusception been a barrier to uptake in LICs or MICs? Is this a selling point?

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And alignment of key stakeholders' perception of the vaccine value is strongly desirable

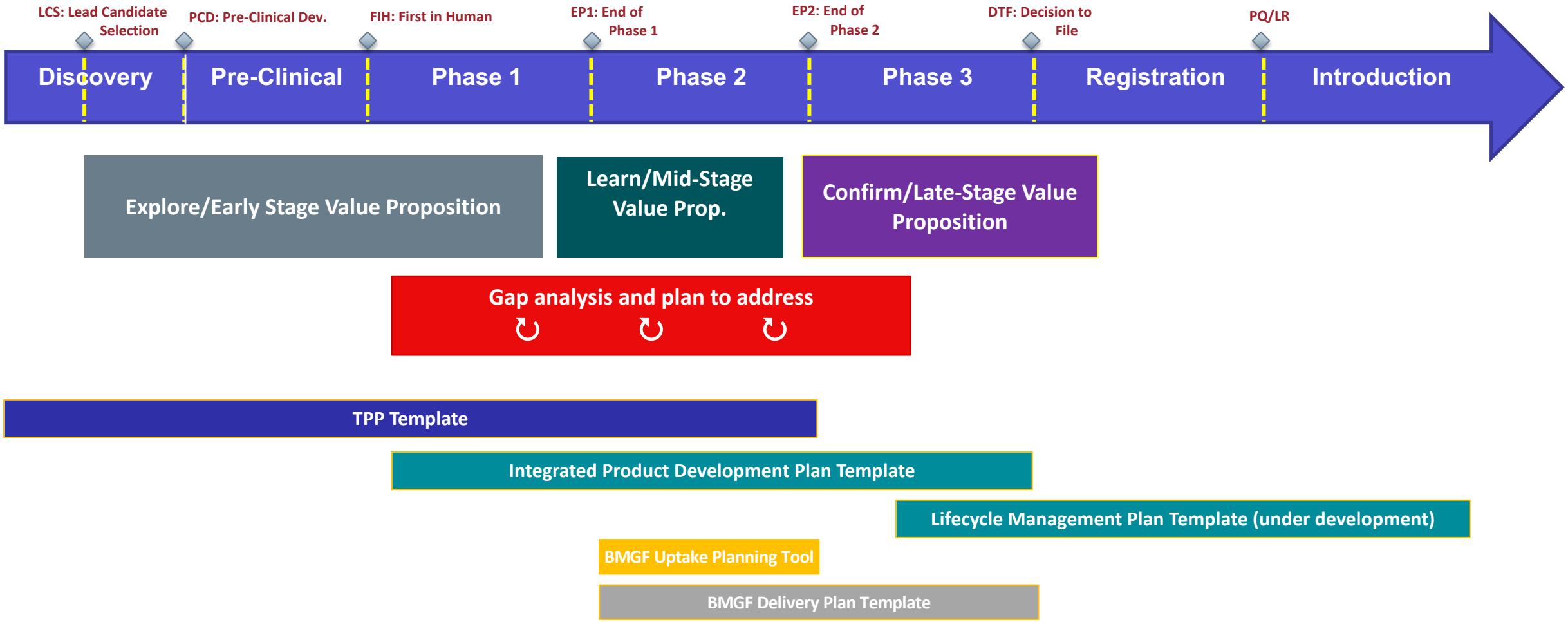
- PATH: Ensure clinical development program will deliver "actionable" results
- BMGF: mitigate risks and costs of programmatic twists and turns
- WHO SAGE: will ultimately want them to recommend it
- End Users (e.g., including NITAGs and EPI program mgrs): they will ultimately choose among multiple products, and perhaps even pay for it
- GAVI: will want GAVI to be planning to buy vaccine
- WHO PQ: need to ensure we've done what is necessary to satisfy
- Regulators: need to ensure they appreciate the purpose of the product
- Others?

Public Health Value Proposition

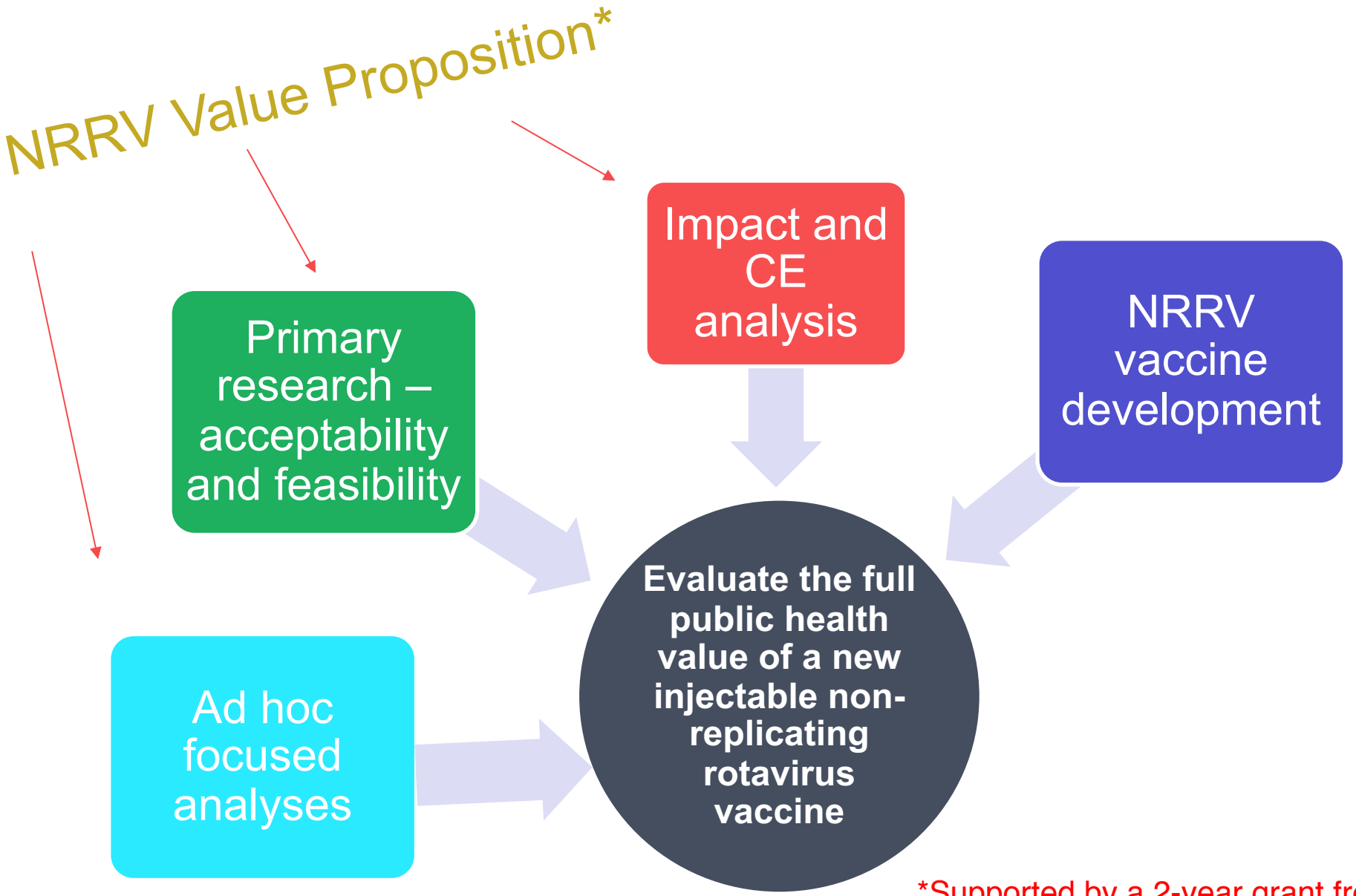
- **Critical, evidence-based process to ensure our efforts align with need and capacity for intended beneficiaries**
  - Communicate value using the lens of stakeholders
  - Consider alternative solutions available to beneficiaries
- **Inform planning for evidence generation during vaccine development**
- **Guide requirements for successful vaccine introduction**
  - Identify and develop information required to support policy recommendations and uptake

In current WHO lingo: “Full Public Health Value of Vaccines”

Value Proposition Develops Over Project Lifecycle and Complements Other Project Documents



PATH's Main NRRV Activities



*Supported by a 2-year grant from BMGF

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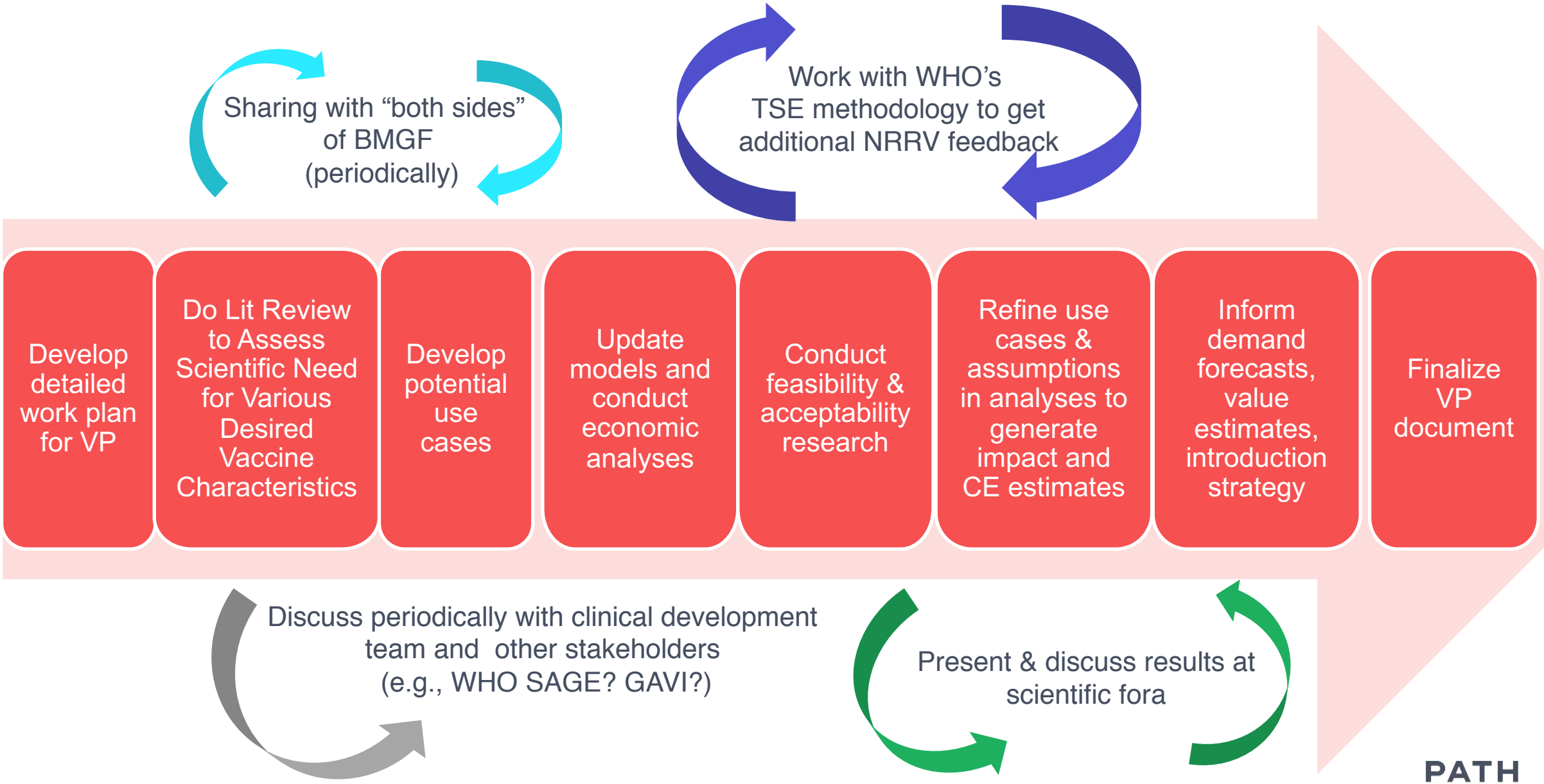
For NRRV, how are we going to do it? Project overview

How do we align with stakeholders? VP as a living document



Acceptability & feasibility of introducing NRRV

A Mixed-Method Study to Assess Future Demand

Overall objective: Ascertain country preferences for RV products including NRRV

Based on anticipated health or economic advantages, within a range of RV vaccine options and in different country contexts

Specific components:

- ***key informant interviews with global stakeholders***

- ***scenario-based interviews with national stakeholders***

  Sri Lanka, Myanmar, Malawi, Kenya, Ghana, Senegal, Peru

- ***semi-structured interviews with health providers administering vaccines***

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Development of RV vaccine use-case scenarios

Option 1: Oral Vaccine Scenario

Efficacy, storage, cost, presentation attributes of licensed LORVs, as well as RV3-BB (neonatal dose), are provided

Option 2: NRRV Scenario

NRRV as a co-administered intramuscular vaccine requiring three doses starting at 6-8 weeks during primary EPI series.

Efficacy may be higher or similar to LORVs

Cost and storage assumptions provided

May be standalone, part of a DTP-combination, and/or co-administered with LORVs

Essentially, a series of forced choices:

Which option would you prefer if NRRV looked like this? Or like this? Or this?

PATH

One early output of the NRRV Value Proposition

(Example of an Ad hoc focused analysis)

Critical assessment of the potential value of a booster dose of NRRV

The problem: Oral RV VE in some settings reported to wane by 20% or more in 2nd year of life (Rogawski JID 2018)

LORV Efficacy Study	Waning: Percent decrease between 1st and 2nd year efficacies
Madhi	36.9%
Armah & Tapia	35.1%
Colgate	42.2%
Armah & Sow	23.7%
Cunliffe & Madhi	31.8%
Average	**33.9%**

- Underlying explanation not clear
  - Could be waning immunological protection and/or a methodological artefact due to increased natural immunity in control group with age
- Could a heterologous booster dose of NRRV at 9 or 12 months be a solution?

Is this an important avenue of research to prioritize?

Value Proposition Approach: Slow down, take a critical look at the potential public health value of a Booster Dose

Results I

A significant portion of the "waning" would be "unfixable" by NRRV as it is due to age-related accumulation of naturally protected controls

Magnitude of natural protection estimated by looking at VE in efficacy trial controls who had experienced symptomatic RV episodes (Rogawski JID 2018)

Study	Waning: Percent decrease between 1st and 2nd year efficacies	How much higher 2nd year efficacy should be (based on symptomatic RV)	*Percentage of "waning" that is artefactual* (Hausdorff calculations)*
Madhi	36.9%	5.8%	*16%*
Armah & Tapia	35.1%	10%	*28%*
Colgate	42.2%	15.5%	*37%*
Armah & Sow	23.7%	14.8%	*62%*
Cunliffe & Madhi	31.8%	18%	*57%*
Average	**33.9%**	**12.8%**	***40%***

This percentage of artefactual waning likely underestimated, since (unmeasured) sub-clinical RV infection in controls further contributes to natural protection (Lopman JID 2018)

Results II

A highly effective NRRV booster dose at 9 or 12 mos. : too late for major incremental impact on RV mortality

(Model-based analysis by Burnett Vaccine 2017)

Estimates based on: RV mortality by age, plus assumption of 65% & 45% VE for LORV in 1st & 2nd yrs of life

NOTE: assumes all reported waning is due to immunological failure (i.e., not artefactual)

Other Assumptions

Waning can occur in abrupt step-wise fashion [highly unlikely], linearly, or logarithmically

In best case scenario, boosting increases VE by 50%

Region	Linear waning	Logarithmic waning
Deaths occurring in ABSENCE of boost despite high oral RV coverage		
Africa	62,466	62,382
Southeast Asia	28,507	27,838
Deaths preventable by 12 mo. booster increasing VE by 50% (%)		
Africa	2,658 **(4.3%)**	4,035 **(6.5%)**
Southeast Asia	2,153 **(7.6%)**	3,269 **(11.7%)**

A boost at 9 and/or 12 months is not likely to make a major impact because

1. a significant portion of “waning” appears artefactual

2. even a highly effective NRRV dose at 9 months would come too late to make a major impact, at least on RV mortality

Similar VE and epidemiological considerations would also greatly attenuate magnitude of impact on serious RV disease

A few conclusions

- The NRRV Value Proposition is already helping us to garner insights on where there is—and isn't—significant public health value for an effective next generation rotavirus vaccine
- The NRRV VP is most useful if it is
  - A critical, rather than promotional, assessment
  - Has outputs that are disseminated as they are generated to help inform strategy, clinical trial design, vaccine development rather than bunched together years later
- Tangible outputs include
  - Presentations at international meetings
  - Peer-reviewed publications
  - A summary report

Variety of expertise utilized to develop NRRV Value Proposition

PATH	• Overall guidance; use case scenario development; cost-effectiveness analyses; vaccine stakeholder and user interviews; project management
London School of Hygiene and Tropical Medicine	• Contribute to use case scenario development and undertake impact and cost-effectiveness modeling
Linksbridge SPC	• Contribute to use case scenario development, demand forecasting, market analytics and ensuring alignment between feasibility and acceptability research and market analysis needs; technical content and perspective, market analysis in final report
Vaccine Developer	• Awareness of and input into Value Proposition
In-country partners	• Conducting some of the stakeholder surveys & interviews

Plus potentially: WHO (TSE), others?

Collaborators/Funding

-Commercial Manufacturing Partner: SK Bioscience, Seoul, South Korea

-Serological Analysis: Cincinnati Children's Hospital Medical Center: Serology

-Biochemical/Biophysical Characterization of Vaccine Antigens: Kansas University

-Phase I/II Clinical trials:

Johns Hopkins University, Baltimore MD USA

South African Clinical Research Centers:

RMPRU, Soweto / Shandukani, Johannesburg / FAMCRU, Tigerburg

-Phase III Clinical trial:

Africa:

CIDRZ, Lusaka, Zambia / Dodowa Health Research Center, Ghana / MLW, Blantyre, Malawi

India:

CHRD-SAS, New Dehli / KEM Hospital Research Centre, Pune / NICED, Kolkata

Funding Provided by Bill and Melinda Foundation


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Paratyphoid vaccine development

CONFIDENTIAL

Andrew J Pollard

Typhoid

Typhoid vaccines

SAGE noted the continued high burden of typhoid fever and the alarming increase in antimicrobial resistance of *Salmonella* Typhi (*S.* Typhi) in low- and middle-income countries. SAGE re-emphasized the importance of programmatic use of typhoid vaccines for controlling endemic disease. Following review of the available data, SAGE recommended the introduction of typhoid conjugate vaccine(TCV) for infants and children over 6 months of age as a single dose in typhoid endemic countries. Introduction of TCV should first be prioritized to countries with the highest burden of disease or a high burden of antimicrobial resistant *S.* Typhi. SAGE also recommended catch-up vaccination wherever feasible, with priority for catch-up in the youngest age groups (up to 15 years of age), depending on local epidemiology.

Typhoid vaccination is recommended in response to confirmed outbreaks of typhoid fever. Typhoid vaccination may be considered in humanitarian emergencies depending on risk assessment in the local setting.

WHO prequalification Jan 2018

WHO SAGE recommendations Oct 2017

Gavi funding Nov 2017

TyVac

UOXF, UMB

UOXF | UMB

Nepal	Bangladesh	Malawi
20,000	>58,000	28,000
Buddha Basnyat Shrijana Shrestha	John Clemens Firdausi Qadri	Melita Gordon

BILL & MELINDA GATES foundation

Interim analysis

2019 BMGF/WELLCOME *SALMONELLA* CONVENING: *SALMONELLA PARATYPHI*

London, May 1, 2019

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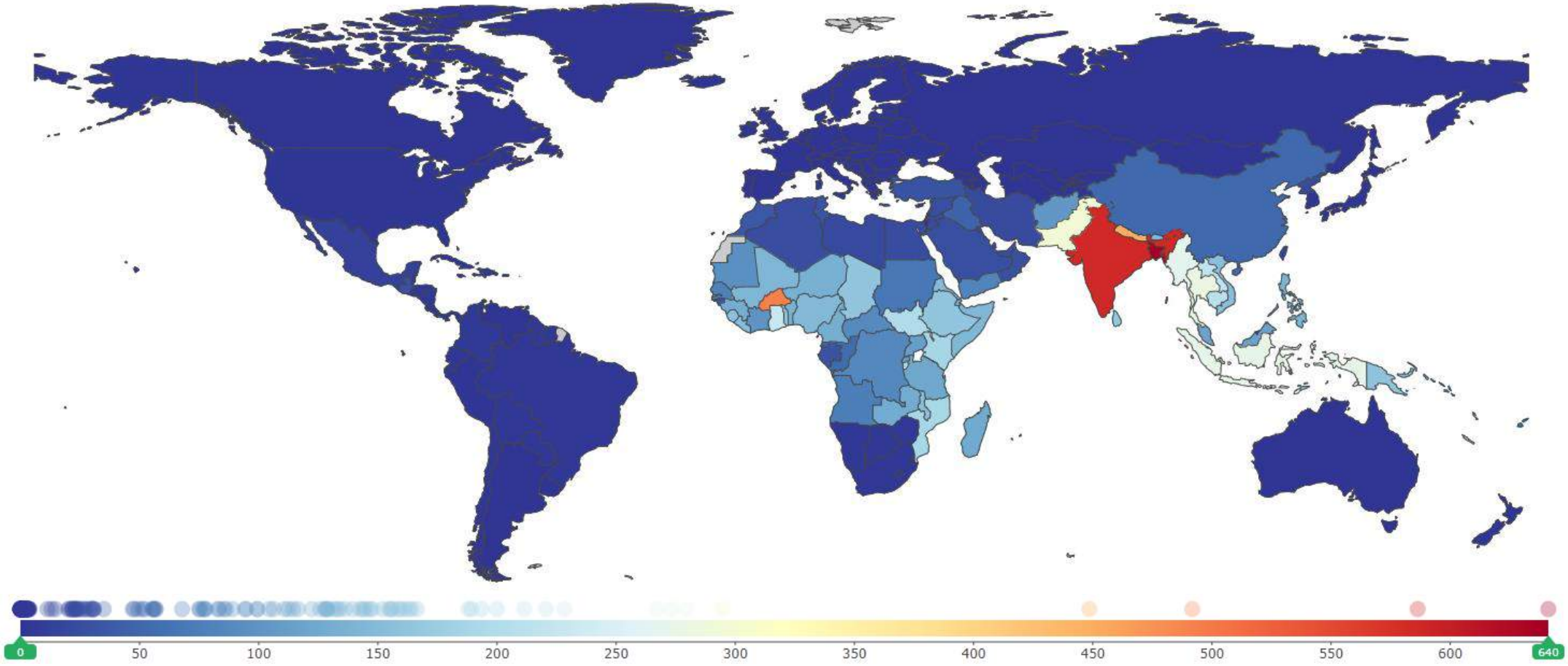
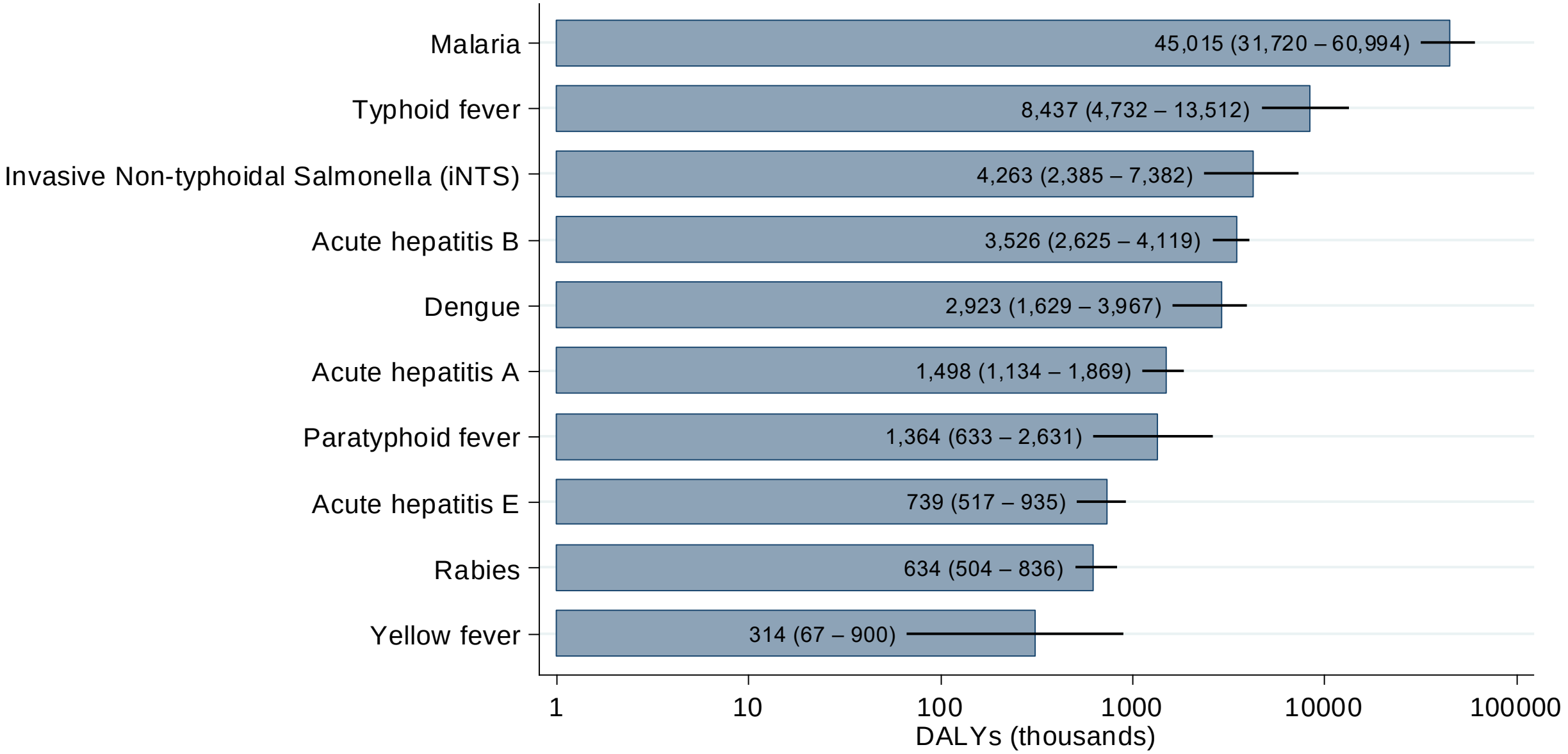
Typhoid & paratyphoid incidence rates per 100,000, age-standardized, 2017



14.3 million (12.5 – 16.3) cases in 2017

Paratyphoid, global estimates by year (thousands)

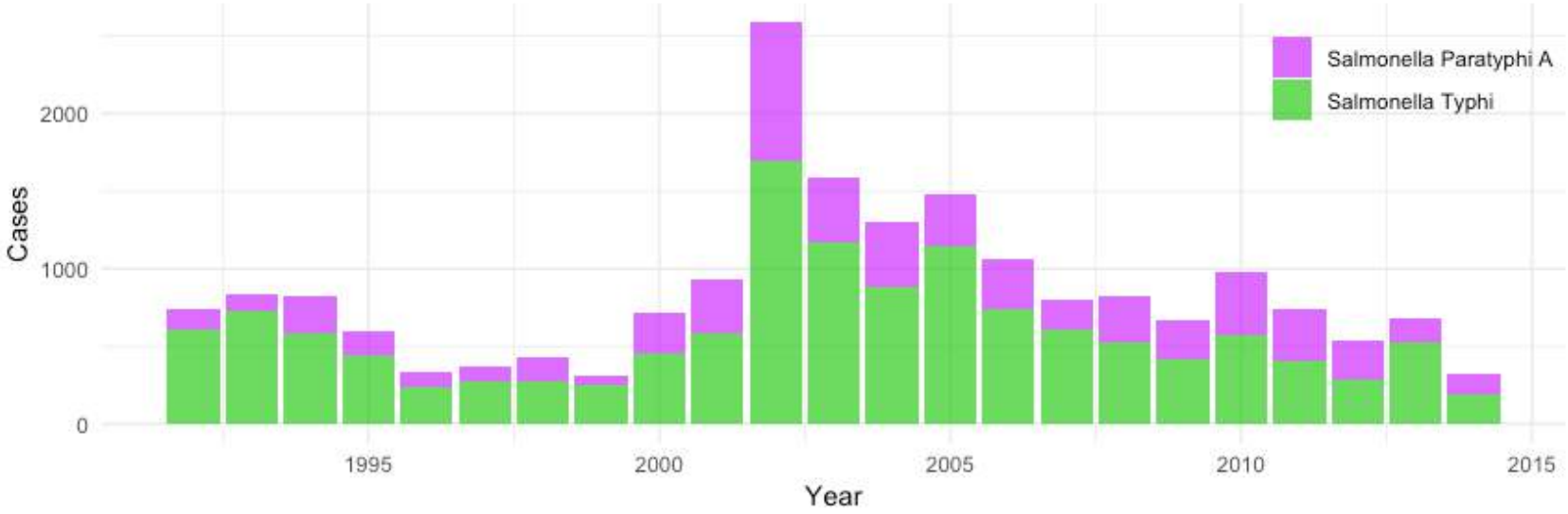
Year	Incidence	Deaths	YLDs	YLLs	DALYs
1990	5,508 (4,233 – 7,086)	28.5 (12.7 – 56.7)	15.0 (9.4 – 22.6)	2,071 (913 – 4,172)	2,086 (925 – 4,184)
1995	5,139 (3,963 – 6,543)	27.3 (12.4 – 53.8)	14.0 (8.8 – 21.0)	1,977 (888 – 3,912)	1,991 (897 – 3,926)
2000	4,698 (3,640 – 5,953)	25.2 (11.5 – 49.9)	12.9 (8.1 – 19.5)	1,817 (835 – 3,600)	1,830 (846 – 3,611)
2005	4,232 (3,311 – 5,327)	23.0 (10.5 – 45.3)	11.6 (7.3 – 17.3)	1,649 (756 – 3,259)	1,661 (764 – 3,273)
2010	3,794 (2,992 – 4,739)	20.9 (9.5 – 40.6)	10.4 (6.7 – 15.5)	1,477 (670 – 2,862)	1,487 (684 – 2,875)
2017	3,397 (2,666 – 4,184)	19.1 (8.7 – 37.3)	9.4 (5.9 – 13.9)	1,354 (622 – 2,620)	1,364 (633 – 2,631)

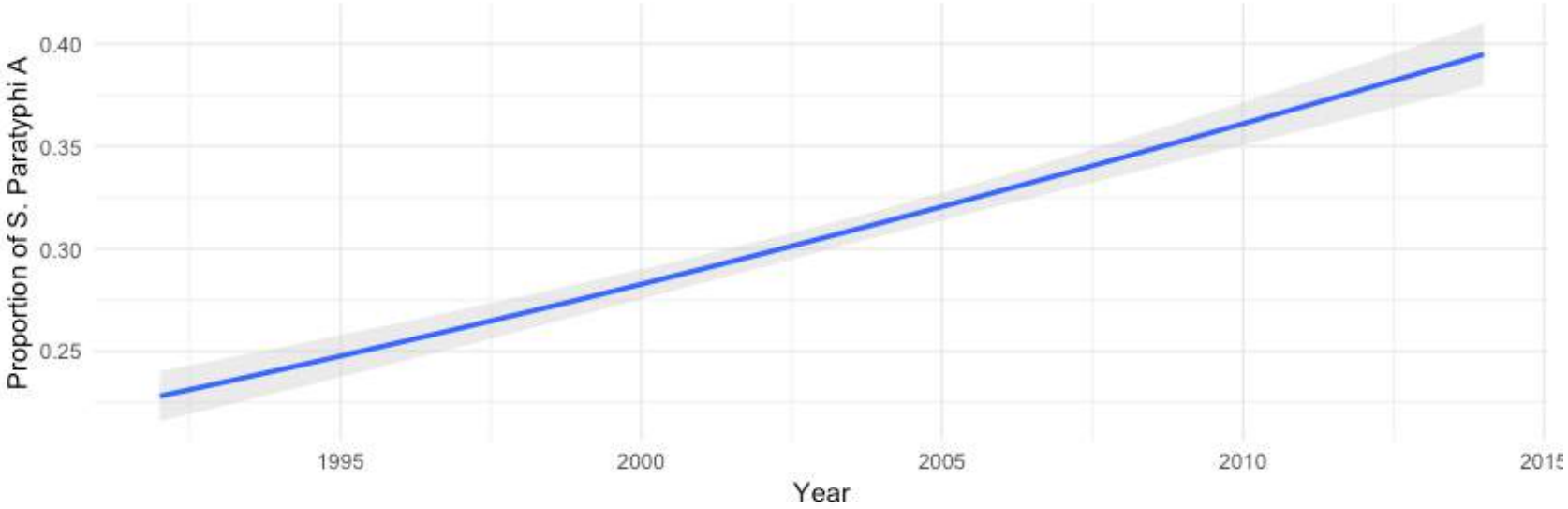

Malaria
45,015 (31,720 – 60,994)
Typhoid fever
8,437 (4,732 – 13,512)
Invasive Non-typhoidal Salmonella (iNTS)
4,263 (2,385 – 7,382)
Acute hepatitis B
3,526 (2,625 – 4,119)
Dengue
2,923 (1,629 – 3,967)
Acute hepatitis A
1,498 (1,134 – 1,869)
Paratyphoid fever
1,364 (633 – 2,631)
Acute hepatitis E
739 (517 – 935)
Rabies
634 (504 – 836)
Yellow fever
314 (67 – 900)
1
10
100
1000
10000
100000
DALYs (thousands)

Variation

- Time
- Vaccination
- Geography
- Age

Variable incidence of *S.* Paratyphi A over time





Nepal

In Patan, Nepal, proportion of SPA doubled from 1992 to 2014

Adapted from data by Zellwegger et al, *PLoS NTDs,* 2017

Shifting burden related to vaccination?

- Schwartz et al found that the whole cell (TAB) vaccine in travelers to Nepal was 95% protective against Typhi and 72-77% against Paratyphi (small numbers)

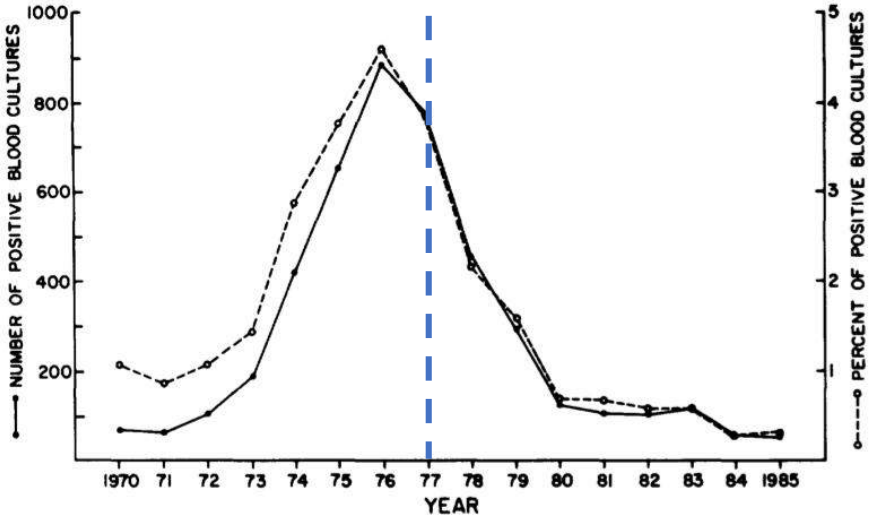


Figure 2, *left*. Total number of blood culture–confirmed cases of typhoid fever expressed as the number and percentage of the total number of blood cultures obtained at Siriraj, Chulalongkorn, and Bamrasnaradura hospitals in Bangkok, Thailand, 1970–1985.

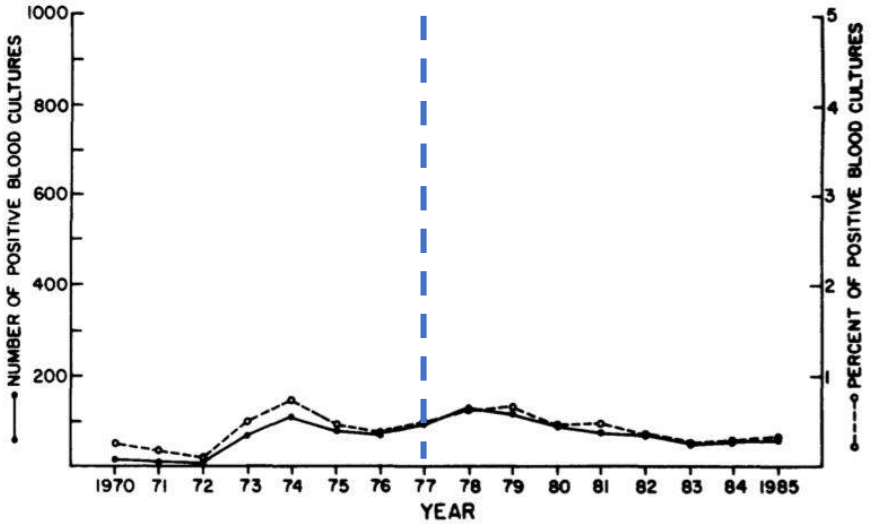


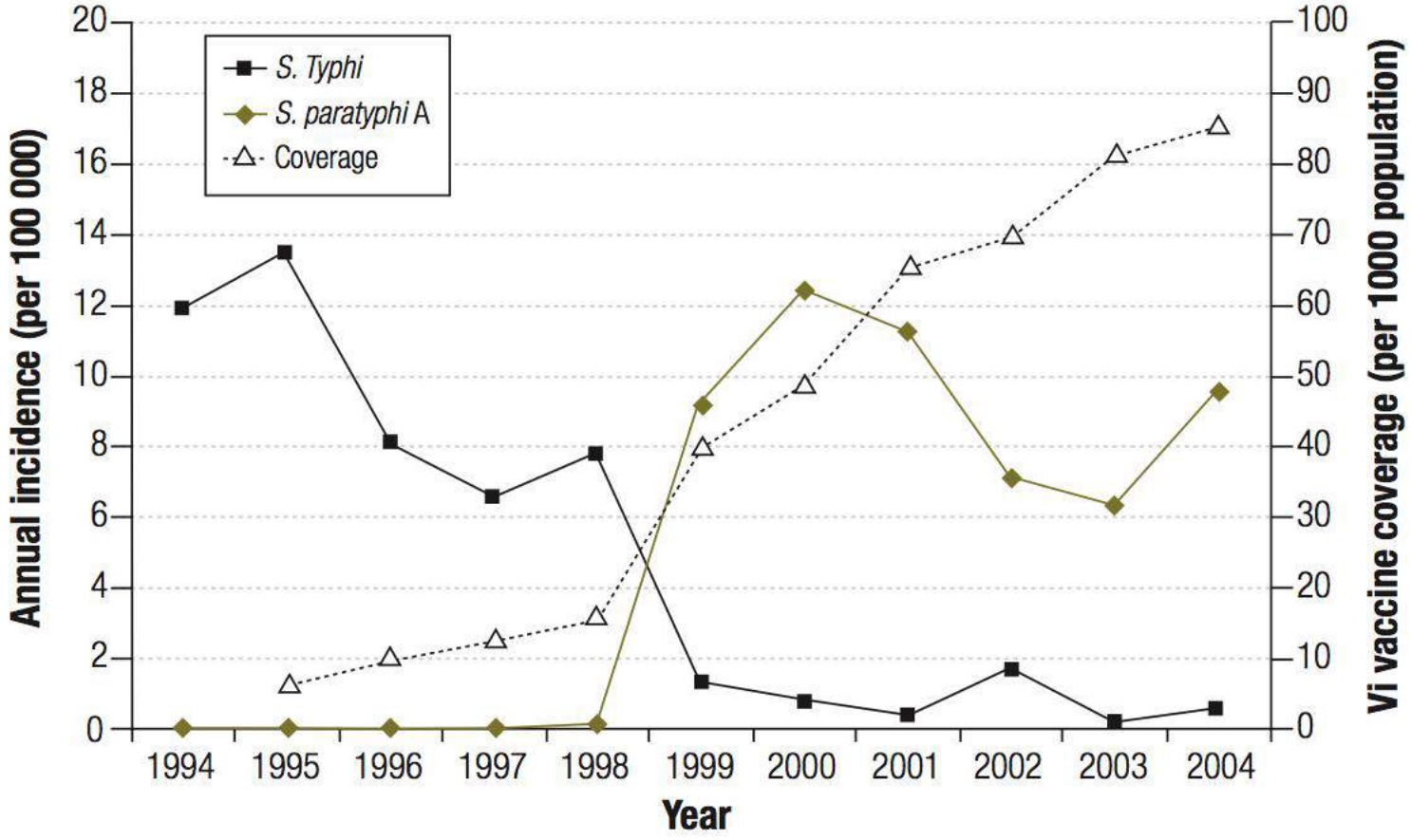
Figure 2, *right*. Total number of blood culture–confirmed cases of paratyphoid fever expressed as the number and percentage of the total number of blood cultures obtained at Siriraj, Chulalongkorn, and Bamrasnaradura hospitals in Bangkok, Thailand, 1970–1985.

Typhi:Paratyphi ratio declined from 9.9 : 1 to 0.9 : 1

Schwartz et al, *Ann Int Med* 1990
Bodhidatta et al, *Rev Inf Dis*, 1987

Shifting burden related to vaccination?

Fig. 2. **Estimated *Salmonella typhi* and *Salmonella paratyphi* A incidence with cumulative Vi polysaccharide immunization coverage in Guangxi province, China, 1994–2004**



Dong et al, *BWHO* 2010

Summary

- *S.* Paratyphi A shares many similar genomic features to Typhi, has adapted to human hosts, and causes similar clinical syndrome
- Overall, the relative burden of SPA as a cause of enteric fever has been increasing in South Asia, though not uniformly
- Vaccination against *S.* Typhi *may* accelerate this shift (Thailand, China)
- AMR remains a major threat, including potential for XDR and Azithromycin resistance

Paratyphoid Vaccine

- Generally lower incidence than *S*. Typhi
- Variable by geography
- Standalone vaccine unlikely to be used for population control
- Bivalent typhoid-paratyphoid attractive for comprehensive control of enteric fever

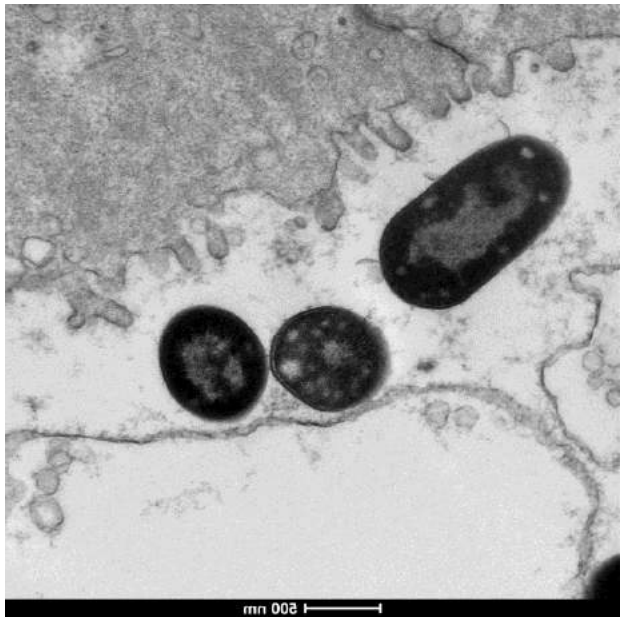
Bivalent typhoid-paratyphoid

- Live attenuated vaccines (CHIM in 2019 (UMB/Bharat), Prokarium)
  - License on basis of VE in CHIM
  - Plus field immunogenicity

- Conjugates (Vi-conjugate + LPS conjugate Bio-E)
  - License on non-inferiority to licensed typhoid vaccines (on immunogenicity)
  - Added potential of paratyphoid component from field immunogencity plus evidence of protection in CHIM

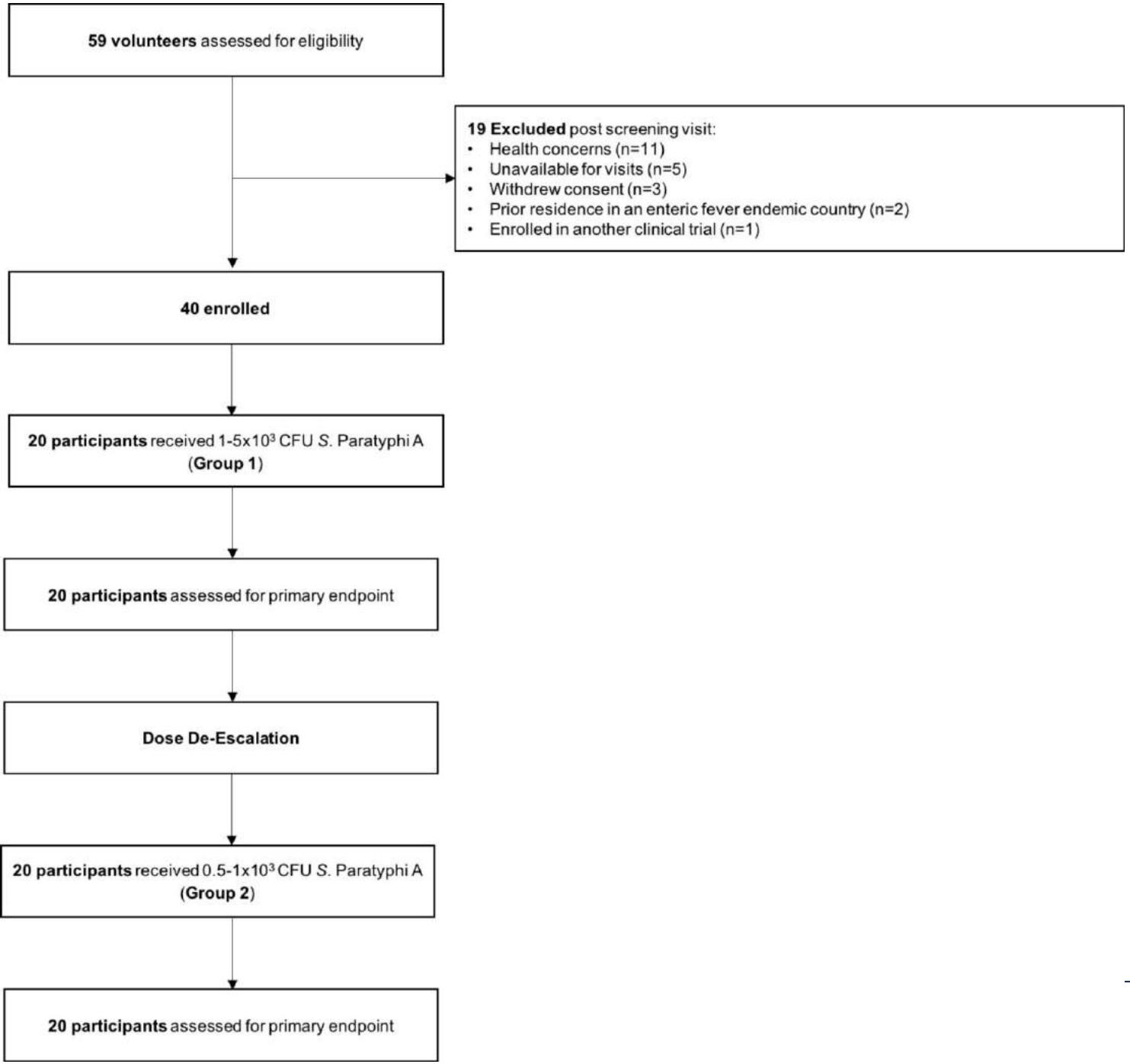
- Paratyphoid efficacy trials probably not feasible
  - 100,000-250,000
  - supporting data for paratyphoid component from CHIM

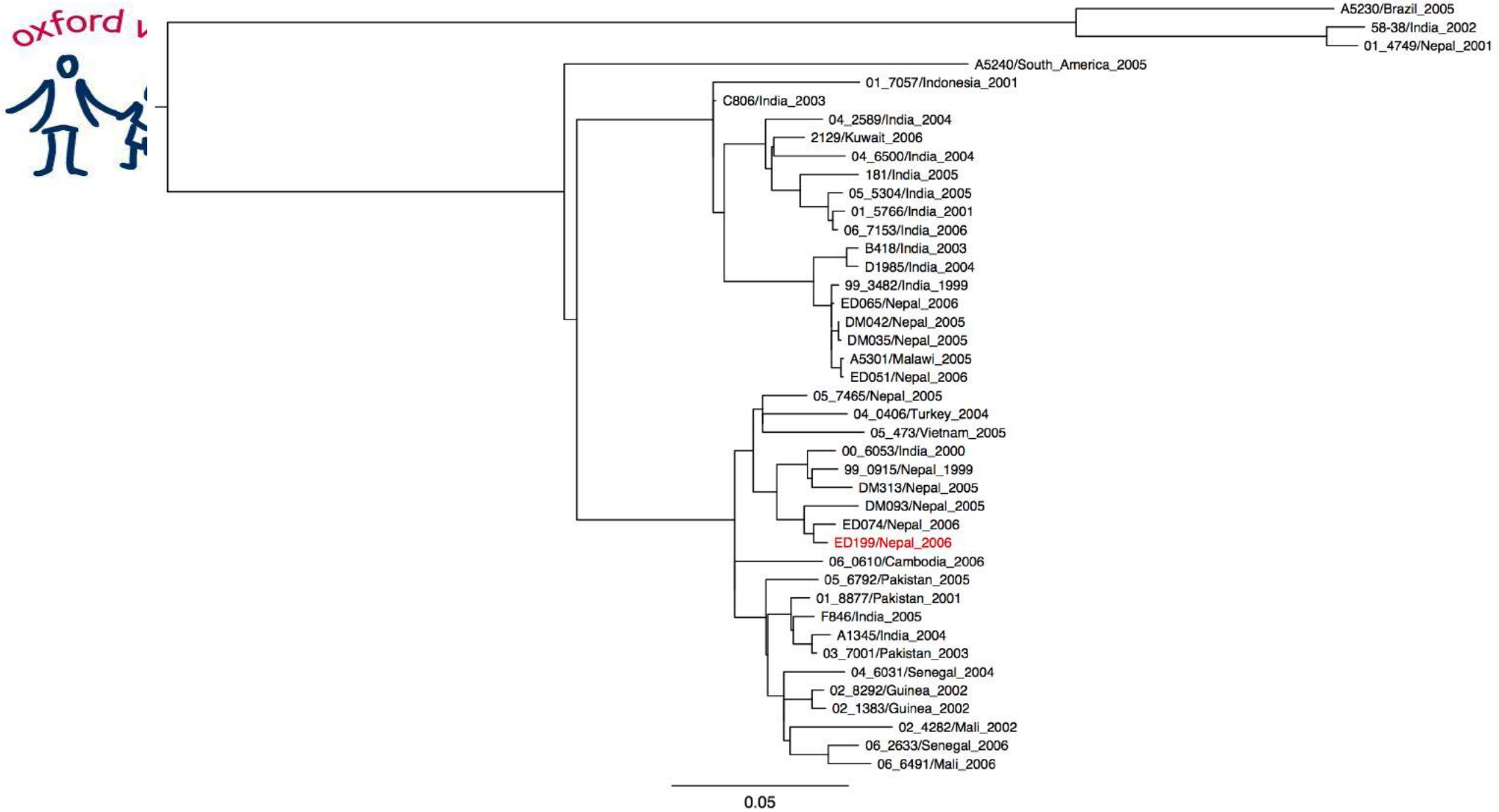
S. Paratyphi A (NVGH308)



Paratyphoid CHIM

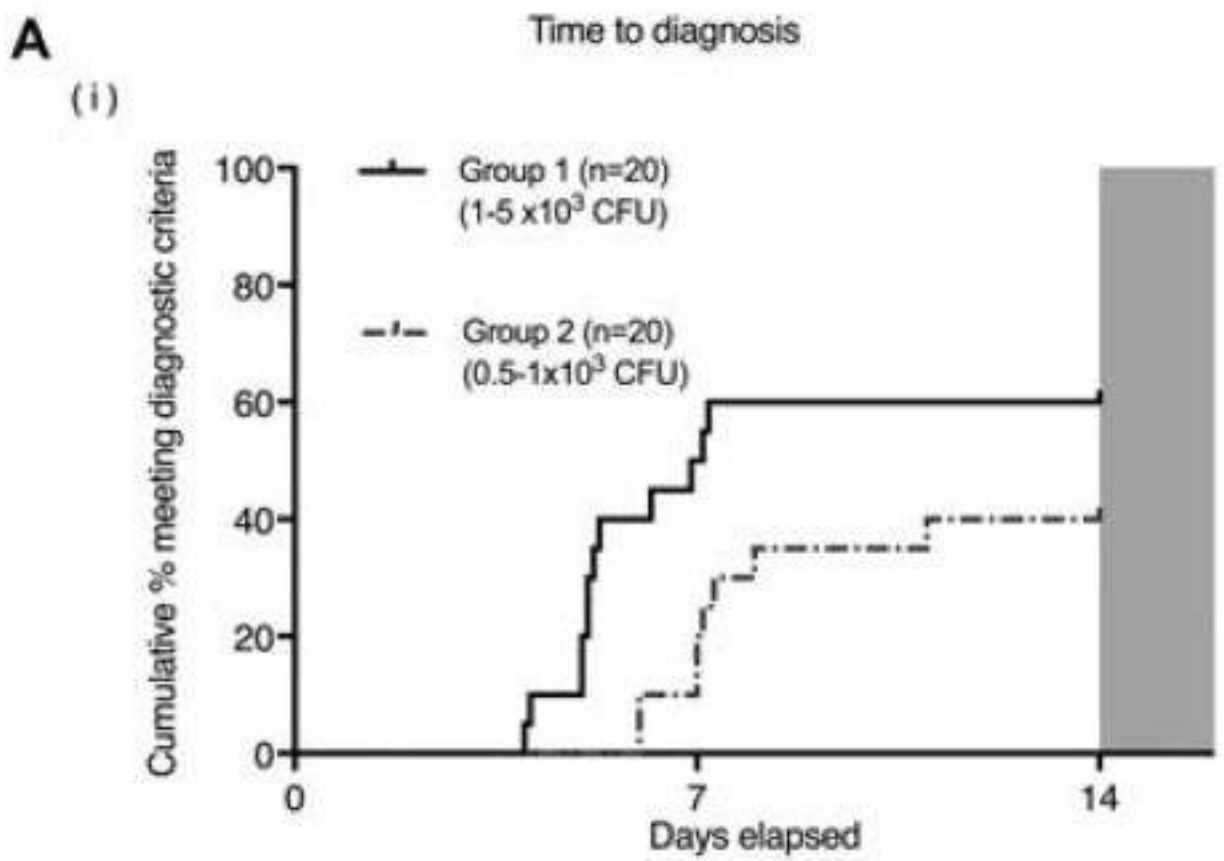
Andrew J Pollard FMedSci


59 volunteers assessed for eligibility
19 Excluded post screening visit:
• Health concerns (n=11)
• Unavailable for visits (n=5)
• Withdrew consent (n=3)
• Prior residence in an enteric fever endemic country (n=2)
• Enrolled in another clinical trial (n=1)
40 enrolled
20 participants received 1-5x10³ CFU S. Paratyphi A (Group 1)
20 participants assessed for primary endpoint
Dose De-Escalation
20 participants received 0.5-1x10³ CFU S. Paratyphi A (Group 2)
20 participants assessed for primary endpoint


A5230/Brazil_2005
58-38/India_2002
01_4749/Nepal_2001
A5240/South_America_2005
01_7057/Indonesia_2001
C806/India_2003
04_2589/India_2004
2129/Kuwait_2006
04_6500/India_2004
181/India_2005
05_5304/India_2005
01_5766/India_2001
06_7153/India_2006
B418/India_2003
D1985/India_2004
99_3482/India_1999
ED065/Nepal_2006
DM042/Nepal_2005
DM035/Nepal_2005
A5301/Malawi_2005
ED051/Nepal_2006
05_7465/Nepal_2005
04_0406/Turkey_2004
05_473/Vietnam_2005
00_6053/India_2000
99_0915/Nepal_1999
DM313/Nepal_2005
DM093/Nepal_2005
ED074/Nepal_2006
ED199/Nepal_2006
06_0610/Cambodia_2006
05_6792/Pakistan_2005
01_8877/Pakistan_2001
F846/India_2005
A1345/India_2004
03_7001/Pakistan_2003
04_6031/Senegal_2004
02_8292/Guinea_2002
02_1383/Guinea_2002
02_4282/Mali_2002
06_2633/Senegal_2006
06_6491/Mali_2006
0.05

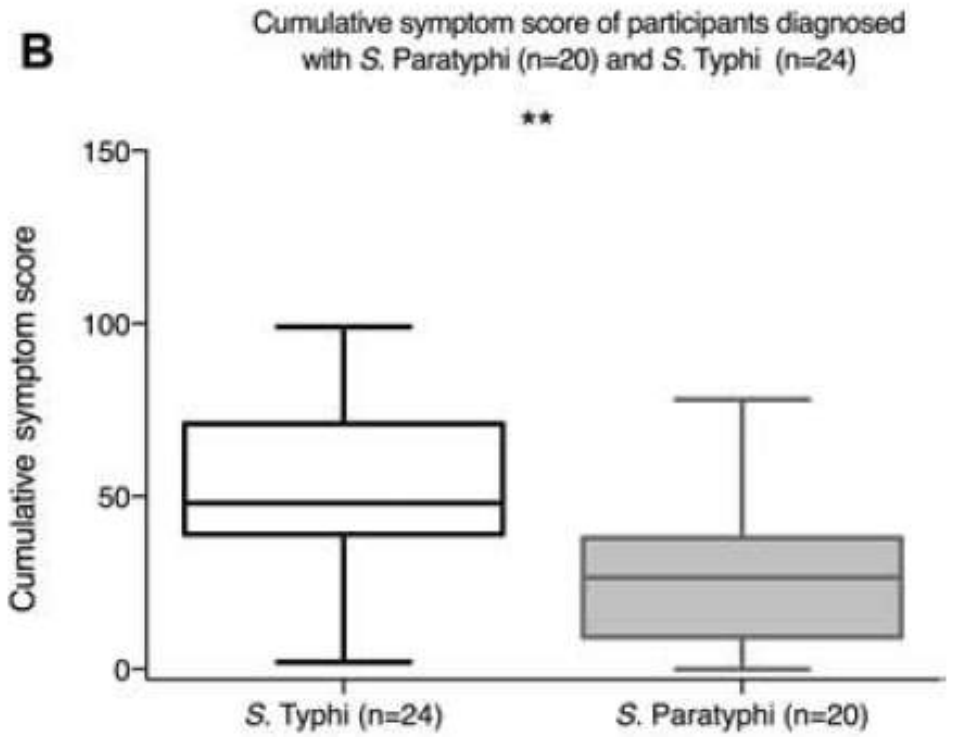
Paratyphoid attack rates

Composite diagnosis



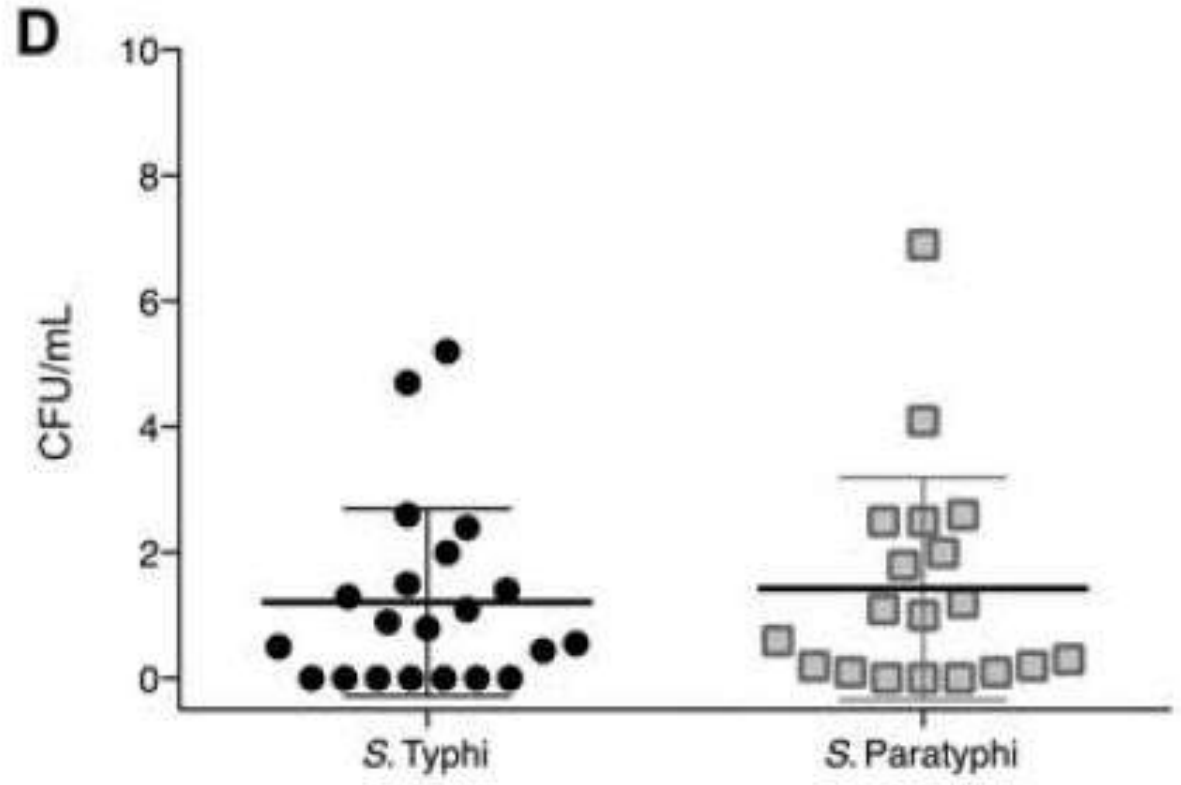
Dobinson et al, 2017

More symptomatic with S Typhi

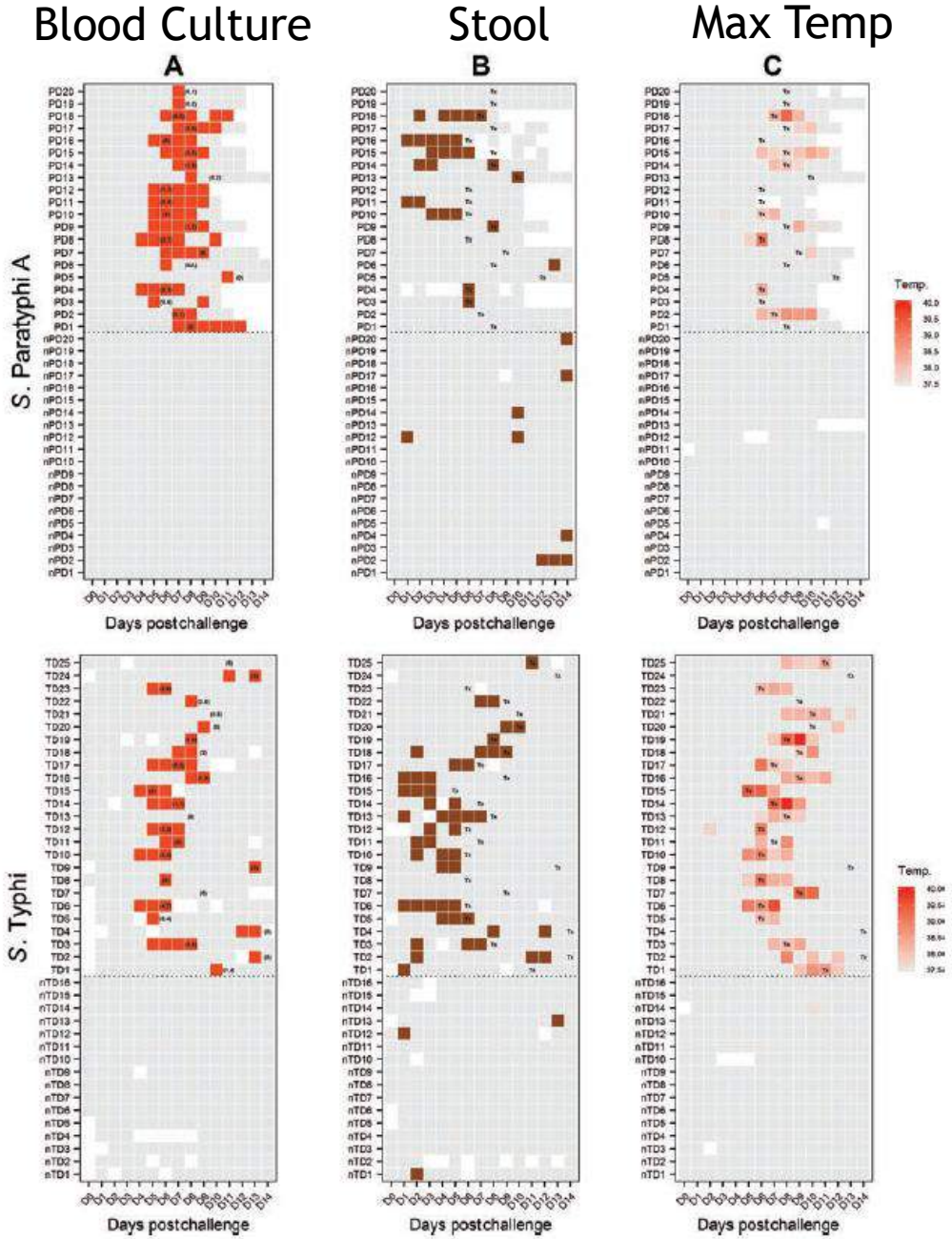


Dobinson et al, 2017

S Typhi vs S Paratyphi CFU



Dobinson et al, 2017



Dobinson et al, 2017

Acknowledgements

- Cal Maclennan, BMGF
- Jeff Stanaway, IHME
- Jason Andrews, Stanford
- Jacob John, CMC, Vellore
- Vikram Paradkar, Bio-E
- Laura Martin, Audino Podda, Rino Rappuoli, GSK
- Mike Levine, CVD
- TyVAC team

INVASIVE NON-TYPHOID SALMONELLA VACCINES

WHO Product Development for Vaccines Advisory Committee
26-28 June 2019

Cal MacLennan, Duncan Steele

Confidential and proprietary data

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INTRODUCTION AND OBJECTIVES

Background

- WHO SAGE recommendation for use of typhoid conjugate vaccines (October 2017)
- WHO pre-qualification of the Typbar TCV vaccine (Bharat Biotech) (December 2017)
- GAVI-supported implementation of TCV
- **Increasing global interest in the development of broadly-protective vaccines against *Salmonella* disease, particularly invasive *Salmonella* disease**

Co-interest from

- Wellcome Innovations and Vaccines
- BMGF Enteric and Diarrheal Disease
- National Institute of Allergy and Infectious Diseases
- Initiative for Vaccine Research, WHO

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SCIENTIFIC CONSULTATION ON PAN-SALMONELLA APPROACHES, LONDON. MAY 2019

Broad aims of a scientific consultation hosted by Wellcome Trust and BMGF

- Examine the case to support the development of broadly-protective *Salmonella* vaccines
- Review the current status of **paratyphoid A** and **iNTS** vaccine development
- Discuss how to advance broadly-protective *Salmonella* vaccines, including identification of knowledge gaps and potential pathways towards licensure

- Disease burden

  Discussion - strength of case for vaccine need, data gaps, plan to address
- Vaccines in development

  Discussion - comparison of approaches, clinical trials considerations
- Pathway to licensure, value proposition, CHIM, assays & standards, regulatory considerations

  Discussion - pathway feasibility, data gaps, regulatory engagement

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INTRODUCTION AND OBJECTIVES

Two potential combination *Salmonella* vaccines

1. ‘Enteric fever vaccine’
   - To include coverage of *S*. Paratyphoid A
   - Potentially most plausible in combination with Typhoid Conjugate Vaccine as a bivalent vaccine
   - Coverage South/South-East Asia

2. ‘Invasive non-typhoidal Salmonella’ (iNTS) disease
   - *S*. Typhimurium and *S*. Enteritidis
   - Coverage Sub-Saharan Africa
   - Is a trivalent combination vaccine plausible including TCV and *S*. Typhimurium and *S*. Enteritidis?

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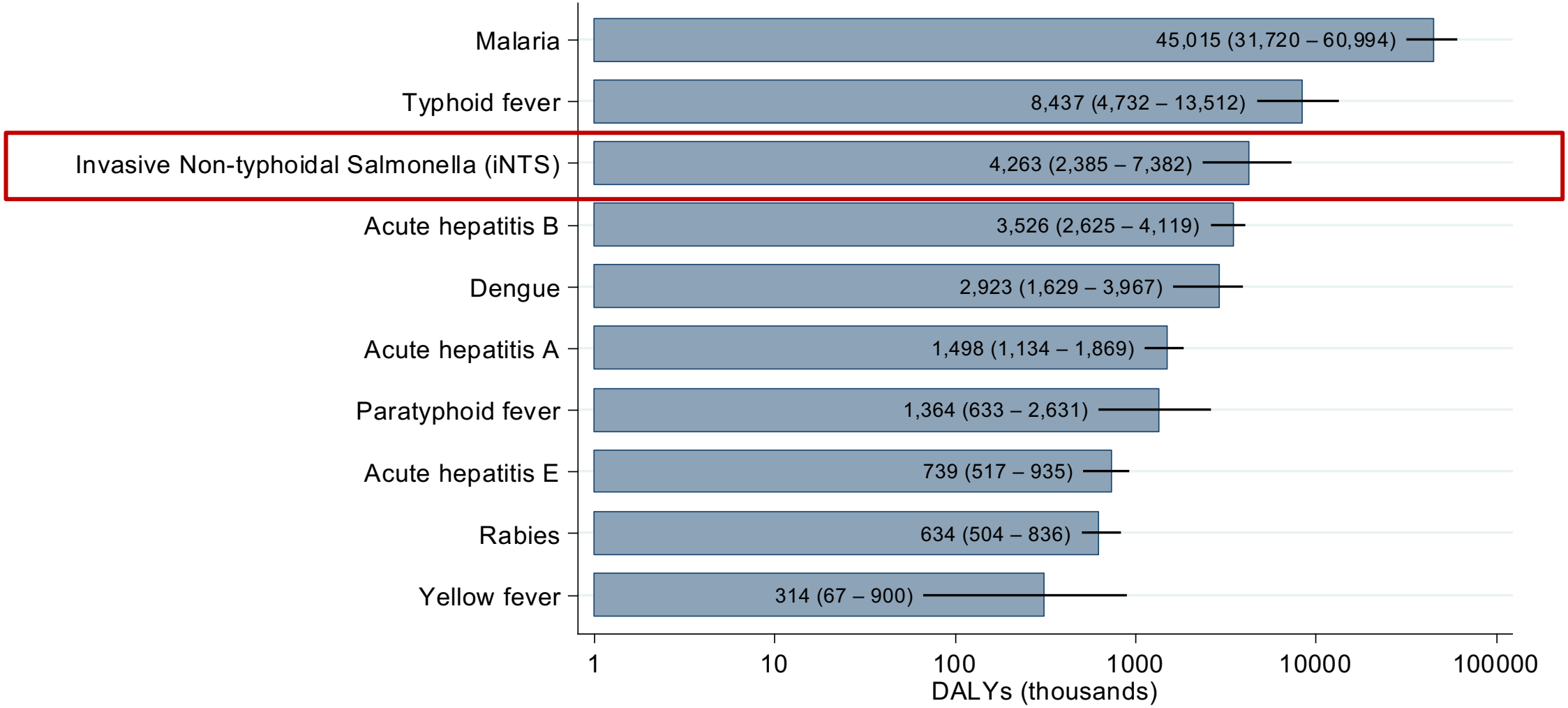
THE CASE


Malaria
45,015 (31,720 – 60,994)
Typhoid fever
8,437 (4,732 – 13,512)
Invasive Non-typhoidal Salmonella (iNTS)
4,263 (2,385 – 7,382)
Acute hepatitis B
3,526 (2,625 – 4,119)
Dengue
2,923 (1,629 – 3,967)
Acute hepatitis A
1,498 (1,134 – 1,869)
Paratyphoid fever
1,364 (633 – 2,631)
Acute hepatitis E
739 (517 – 935)
Rabies
634 (504 – 836)
Yellow fever
314 (67 – 900)
1
10
100
1000
10000
100000
DALYs (thousands)

MEDICAL NEED FOR A BIVALENT iNTS VACCINE

- The burden of iNTS disease, caused by *Salmonella* Typhimurium and *Salmonella* Enteritidis, is a serious public health concern in Sub-Saharan Africa.
- 600,000 to 3.4M cases of iNTS disease occurred globally in 2010*. >50% of cases of iNTS disease occur in Sub-Saharan Africa. Case-fatality rates commonly reported at ~15-20%
- ~622,000 cases estimated in 2017 (490,000 – 800,000). ~68,000 deaths in 2017**
- High prevalence of iNTS disease seen in children under 3 years of age
- Clinical presentation is most commonly with fever alone: diagnosis not usually possible
- Diagnosis requires blood culture facilities that are uncommon in Sub-Saharan Africa
- Antimicrobial drug resistance to iNTS isolates, including MDR, is common. Emergence of fluoroquinolone and ceftriaxone resistance makes treatment increasingly difficult
- Effective methods for disease control as improvement to water supply and sanitation is lagging and cost prohibitive in endemic countries

*Ao et al, 2015; **GBD, 2017

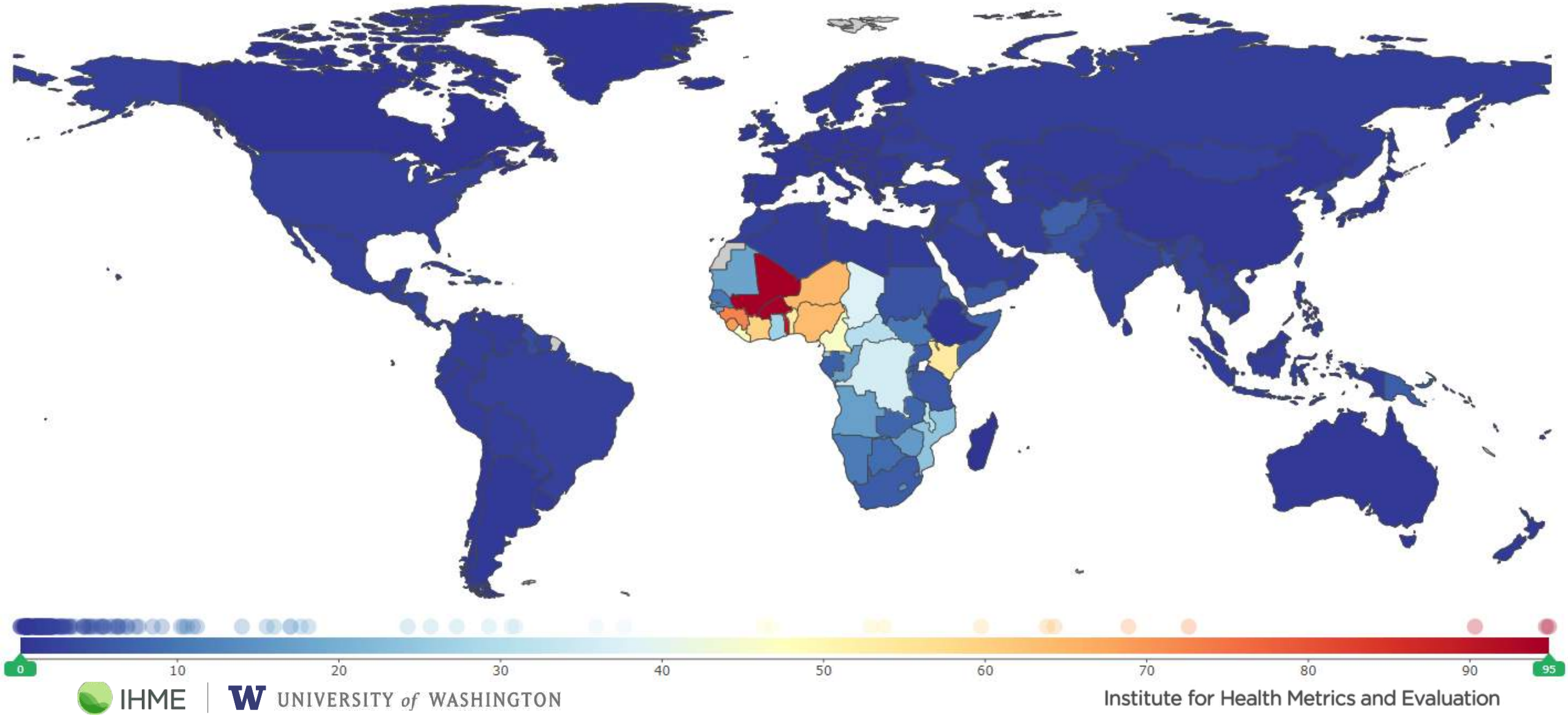
RESULTS: COMPARING GBD AND OTHER PUBLISHED ESTIMATES

- Two previous studies reported iNTS burden estimates, and both produced estimates for the year 2010:

Study	Estimated cases, 2010	Estimated deaths (thousands), 2010
Ao *et al*, 2015	3.4 million (2.1 to 6.5)	681.3 (415.2 – 1,302)
GBD 2017	622 thousand (490 to 800)	67.6 (39.2 – 110.0)
Kirk *et al*, 2015 (WHO FERG)	597 thousand (?)	63.2 (39.0 – 94.2)

Ao *et al* include deaths for which HIV is underlying cause
Kirk *et al* exclude such deaths

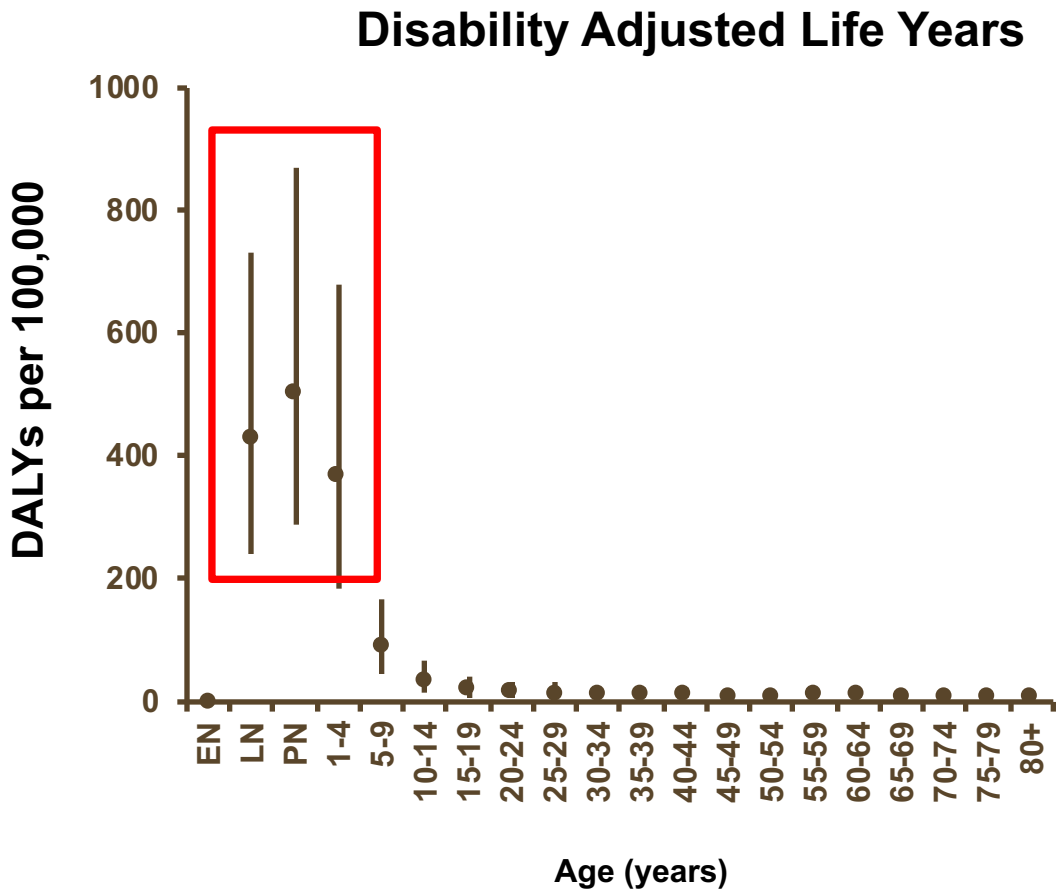
iNTS INCIDENCE RATES PER 100,000, AGE-STANDARDIZED, 2017

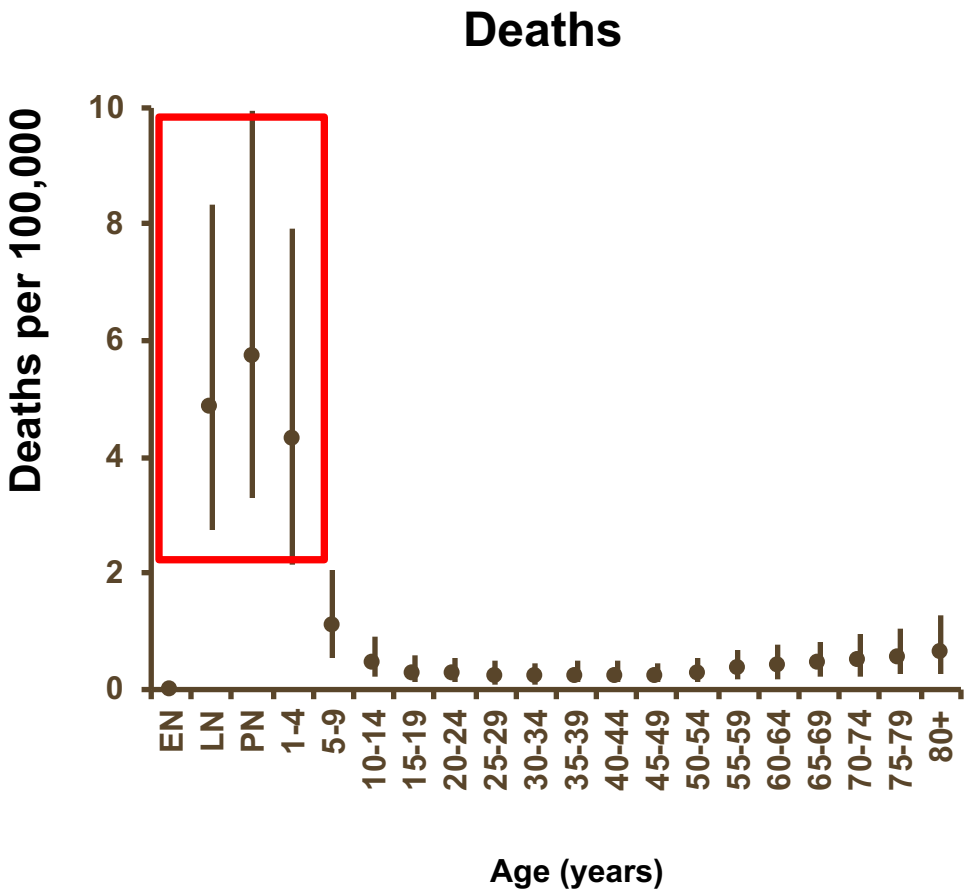


IHME | UNIVERSITY of WASHINGTON

Institute for Health Metrics and Evaluation

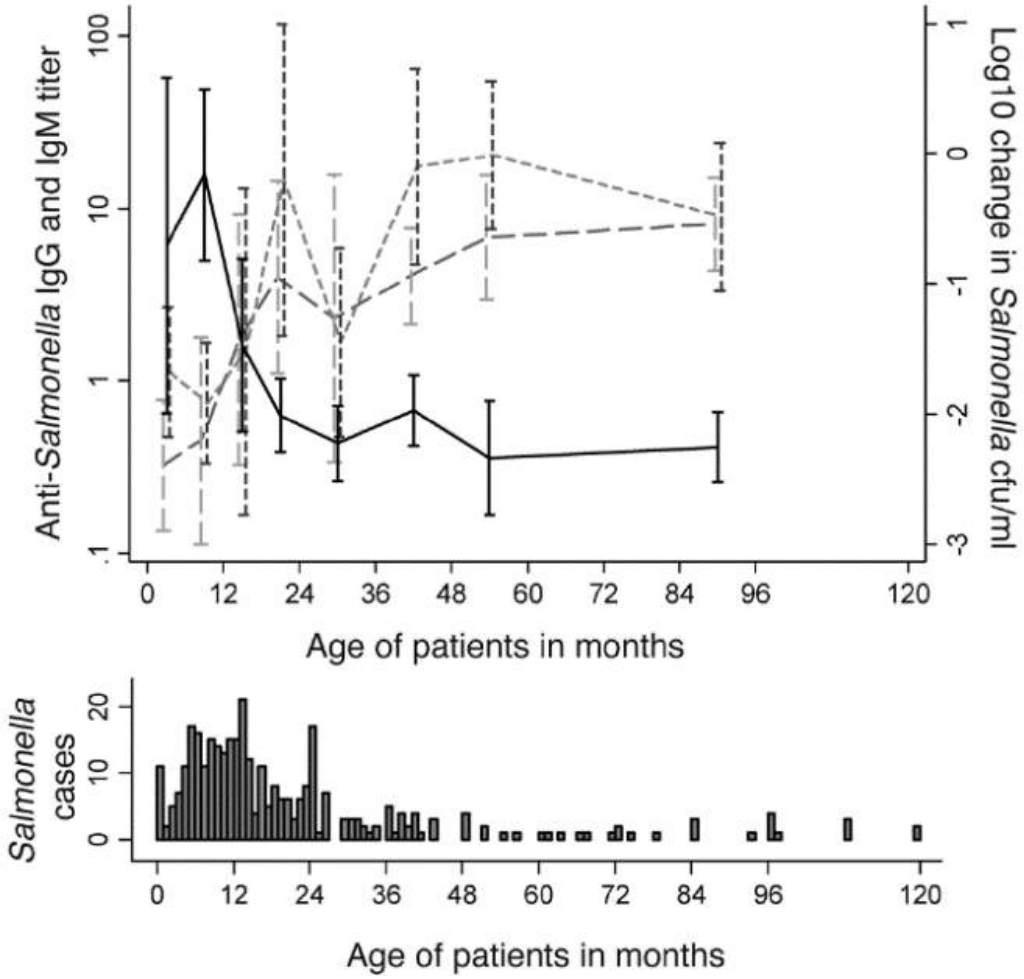
NON-TYPHOIDAL *SALMONELLA* INVASIVE DISEASE DALYS AND DEATHS BY AGE, WORLDWIDE, GLOBAL BURDEN OF DISEASE 2017





http://vizhub.healthdata.org/gbd-compare/

A ROLE FOR ANTIBODIES IN IMMUNITY TO iNTS DISEASE IN AFRICAN CHILDREN



Acquisition of bactericidal antibodies inversely corresponds to age at which African children are susceptible to iNTS disease

nature Vol 452|3 April 2008

RESEARCH HIGHLIGHTS

IMMUNOLOGY

Antibiotic antibodies

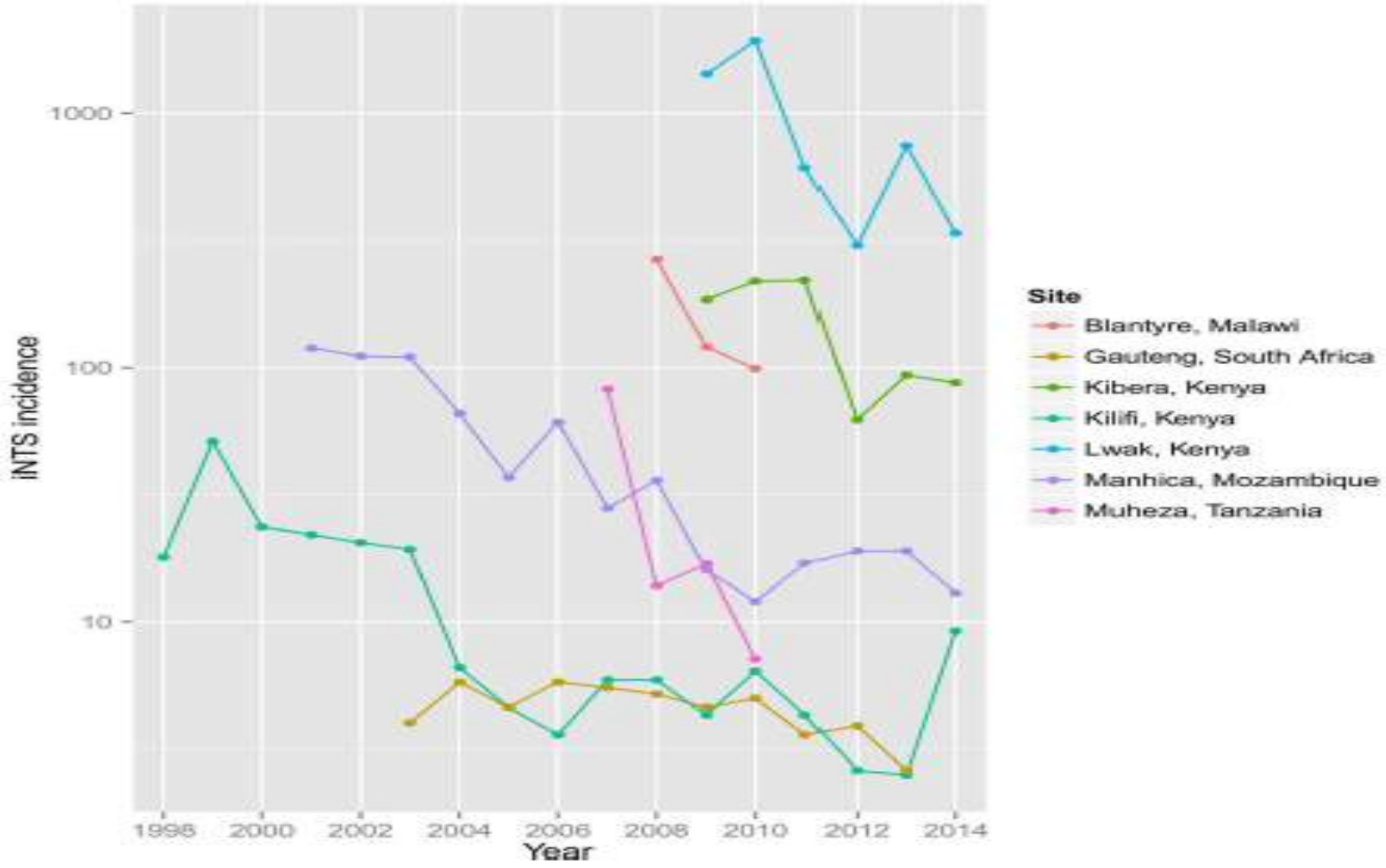
J. Clin. Invest. doi:10.1172/JCI33998 (2008)

The discovery of functional antibodies against strains of *Salmonella* that do not cause typhoid raises hopes that a vaccine can be developed. In Africa, such strains kill up to 24% of infected children in communities in which appropriate antibiotics and blood-culture facilities are available.

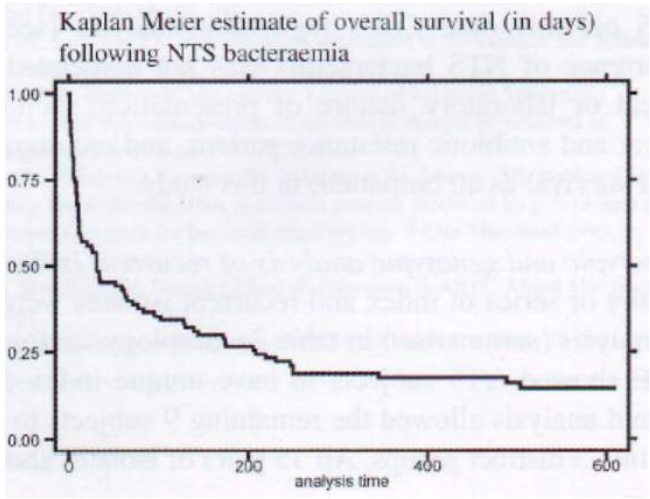
…AND THE ARGUMENTS AGAINST

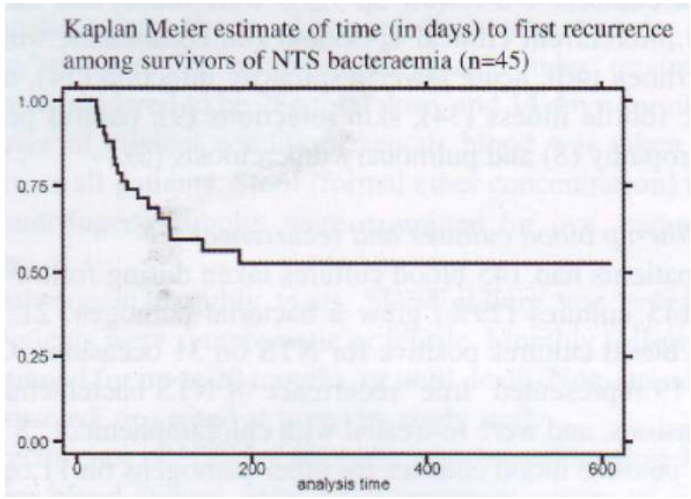
- iNTS disease incidence appears to be falling in some settings
- Complexity due to co-dependence of iNTS disease on co-morbidities - that are potentially preventable (malaria) and treatable (HIV infection)
- Complexity due to co-dependence of iNTS disease on co-morbidities - disparity in key mechanisms of immunity with different co-morbidities (malaria, HIV infection, malnutrition)
- Crowded EPI schedule at point where the vaccine is most likely needed (infants at 6/10/14 weeks)
- Lack of commercial incentive – diseases of the most vulnerable populations
- Large financial/time commitment required before efficacy read out – phase 3 field study required, as there is no CHIM available

VARIATION IN INVASIVE NON-TYPHOIDAL SALMONELLA DISEASE INCIDENCE IN AFRICA OVER TIME



HIV AND iNTS DISEASE





2000 → 2010

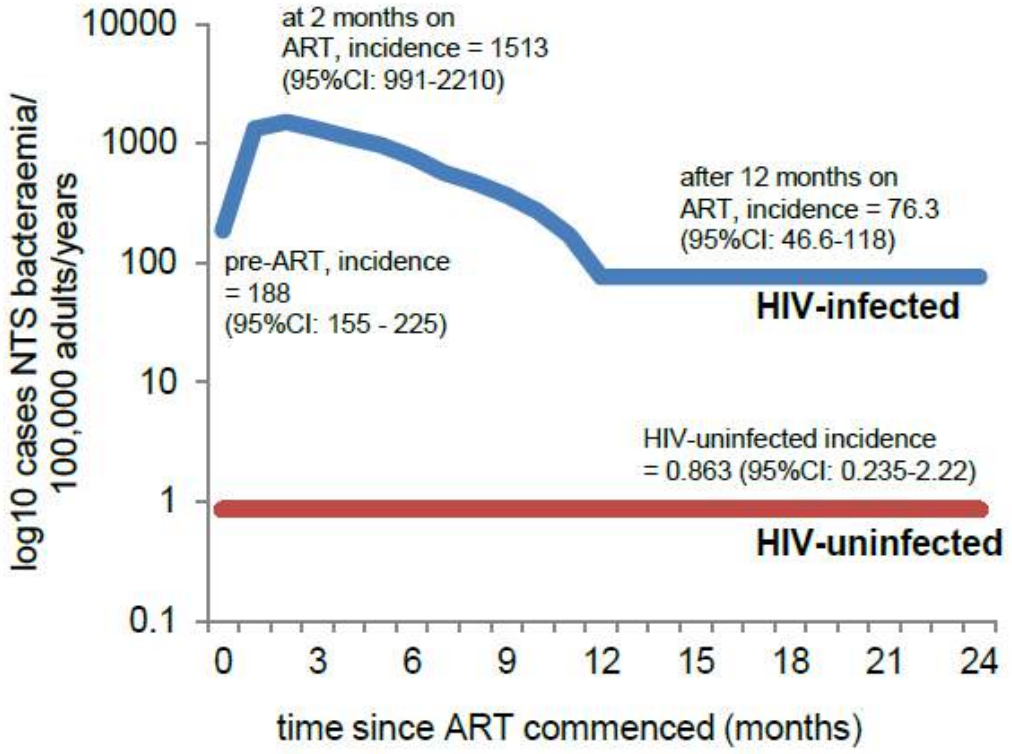
2004
ART
roll-out

Figure 1. Changing susceptibility to NTS bacteraemia with ART among HIV-infected Africans

A.Estimated minimum incidence of NTS bacteraemia in Malawi in relation to time on ART*

(*figure kindly prepared by Dr Nick Feasey, collaborator*)

*based on data from Feasey NA et al, PLoS One 2014, assuming a 50% blood culture sensitivity rate to detect NTS bacteraemia



THE VACCINE CANDIDATES

Name	Description	Developer	Stage of development	References
O:4,5/O:9-flagellin	O:4,5/O:9 Conjugate	University of Maryland	Preclinical	50,69
O:4,12-TT	O:4-TT Conjugate	NIH	Preclinical	51
Os-po	O:4-porin Conjugate	National Bacteriology Laboratory, Stockholm	Preclinical	146
O:4,5/O:9-CRM_{197}	O:4,5/O:9 Conjugate	NVGH	Preclinical	145
WT05	Live attenuated	Microscience, Wokingham Berkshire	Phase 1	147
CVD 1921 and CVD 1941	Live attenuated	University of Maryland	Preclinical	148
S. Typhimuirum ruvB mutant	Live attenuated	Seoul National University	Preclinical	149
Salmonella hfq deletion mutant	Live attenuated	Indian Institute of Science Bangalore	Preclinical	150
SA186	Live attenuated	Istituto Superiore di Sanità Roma	Preclinical	151
MT13	Live attenuated	KIIT University Odisha	Preclinical	152
Various	Live attenuated, DNA adenine methylase mutants	University of California, Santa Barbara	Preclinical	153,154
Various	Live attenuated, regulated delayed attenuation	Arizona State University	Preclinical	155-157
Porins	*S.* Typhimurium porins	National Bacteriology Laboratory, Stockholm	Preclinical	146
OmpD	Outer membrane protein	University of Birmingham, UK	Preclinical	73
S. Typhimurium and *S.* Enteritidis GMMA	Generalized Modules for Membrane Antigens	NVGH	Preclinical	65,158,159

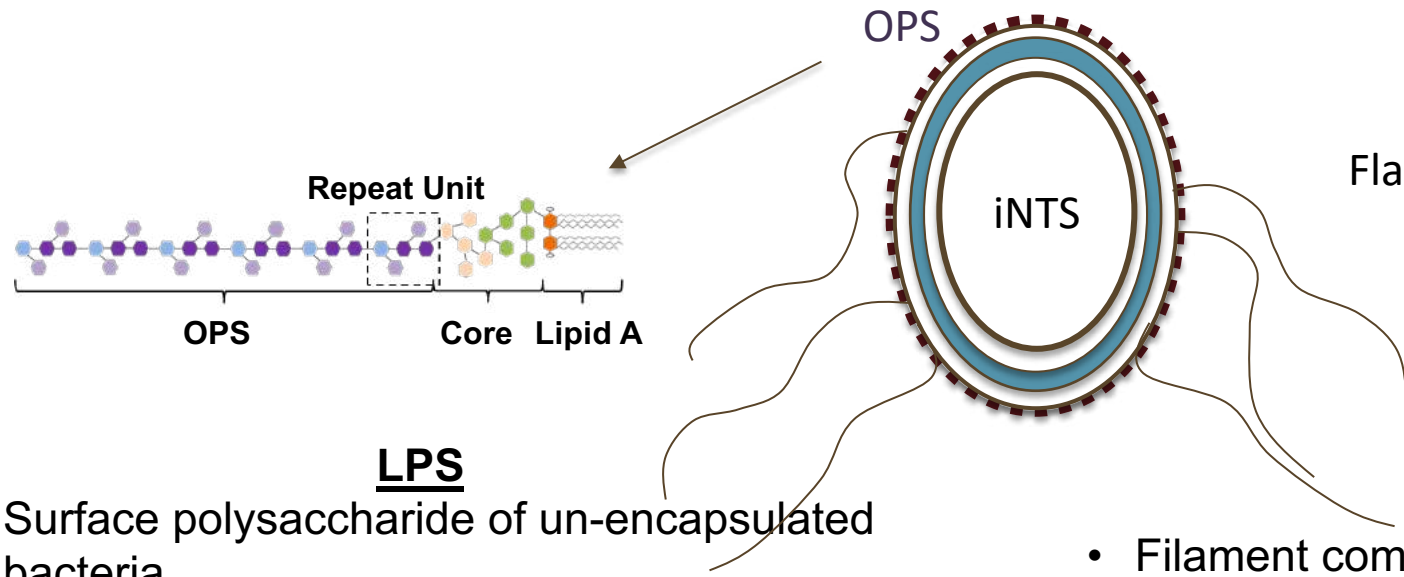
*an exhaustive list, particularly of all candidate vaccines in preclinical studies, is beyond the scope of this review

Bharat Biotech, Hyderabad, India

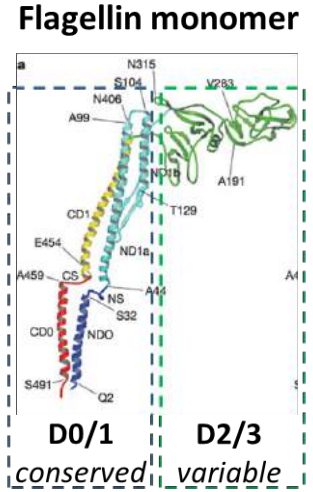
Bio E, Hyderabad, India

MacLennan CA, et al. Hum Vaccine Immunother 2014

LIPOPOLYSACCHARIDE (LPS) & FLAGELLA



Flagella →



Namba, 2003

LPS

- Surface polysaccharide of un-encapsulated bacteria
- Conserved core PS (species)
- OPS structure defines serotype:
  - *S*. Typhimurium (serogroup B)
  - *S*. Enteritidis (serogroup D)
- Anti-OPS antibodies bactericidal, protect in animal models

Flagella

- Filament comprised by multimer of single flagellin protein
- Multiple types -- variable epitopes define serovar
- Anti-flagellin antibodies have functional bactericidal activity, protect mice against invasive infection [Ramachandran et al., PLoS One 2016]

➢ **CVD iNTS vaccine: Core-OPS conjugate with phase 1 flagellin protein (FliC)** [Simon et al., I&I 2011; Baliban et al. PLoS NTD 2017, Baliban et al. PLoS NTD 2018]

(Slide courtesy of Rafi Simon)

A VACCINE TO PREVENT INVASIVE *SALMONELLA* DISEASE INCLUDING NTS AND TYPHOID FEVER IN SUB-SAHARAN AFRICA

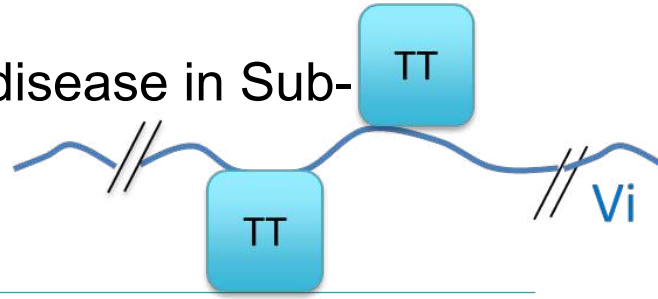
- **Need a single combination vaccine** to cover main NTS serovars: *S*. Typhimurium and variants (I:4,[5],12:i), *S*. Enteritidis & *S*. Dublin)

- **Vaccine must be compatible with the Expanded Programme on Immunization (EPI) schedule** for sub-Saharan Africa

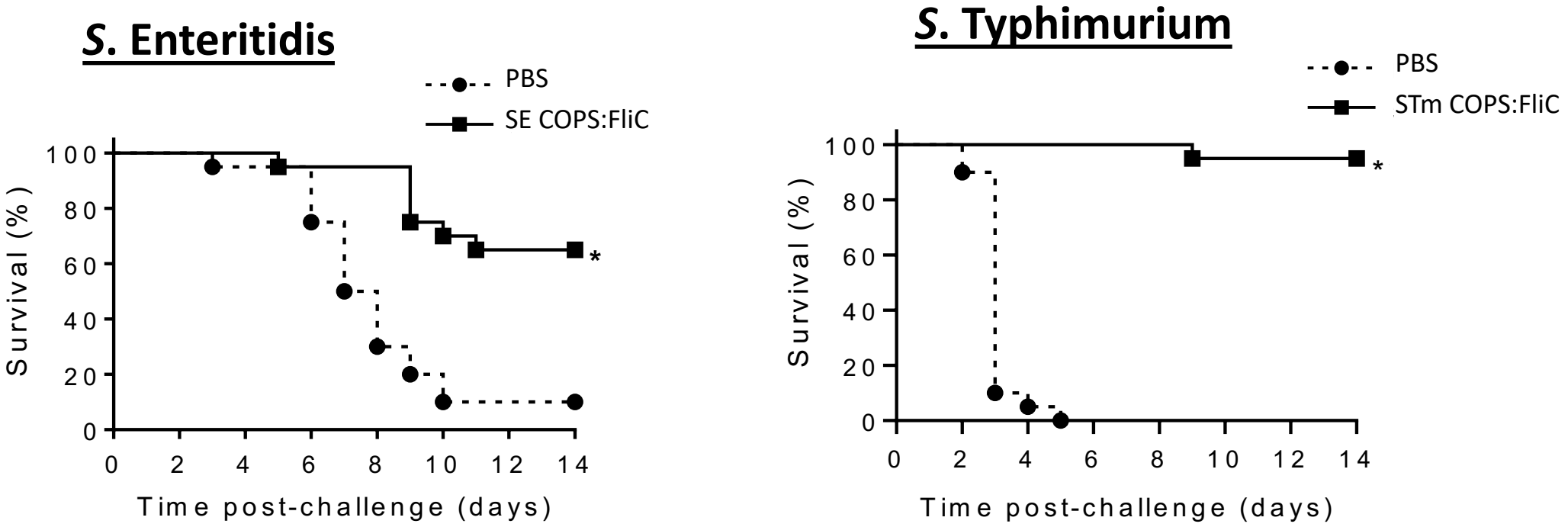
Attenuated engineered *Salmonella* mutants:

- Increase the **occupational safety** of large-scale fermentation in the industrial setting
- **Increase the yield** of COPS (hapten) and flagellin subunits (carrier protein)
- Conjugates made this way have a **lower cost of goods**

- **Tri-valent** parenteral conjugate vaccine to prevent invasive Salmonella disease in Sub-Saharan Africa with the pre-qualified Typbar TCV.



PROTECTION AGAINST FATAL INFECTION WITH MALIAN *S.* ENTERITIDIS (R11) OR *S.* TYPHIMURIUM (D65) BLOOD ISOLATES IN MICE IMMUNIZED WITH THE HOMOLOGOUS PATHOGEN MONOVALENT COPS:FLIC VACCINES



Immunization: D0, D14, D28 with 2.5 µg conjugate polysaccharide or PBS
Challenge: IP infection at D56 with 1 x 10^6 CFU *S.* Enteritidis R11 (IP LD50 = 2 x 10^5) or 5 x 10^5 CFU *S.* Typhimurium D65 (IP LD50 = 2 x 10^4); *P<0.0001 (log-rank)

(Slide courtesy of Rafi Simon)

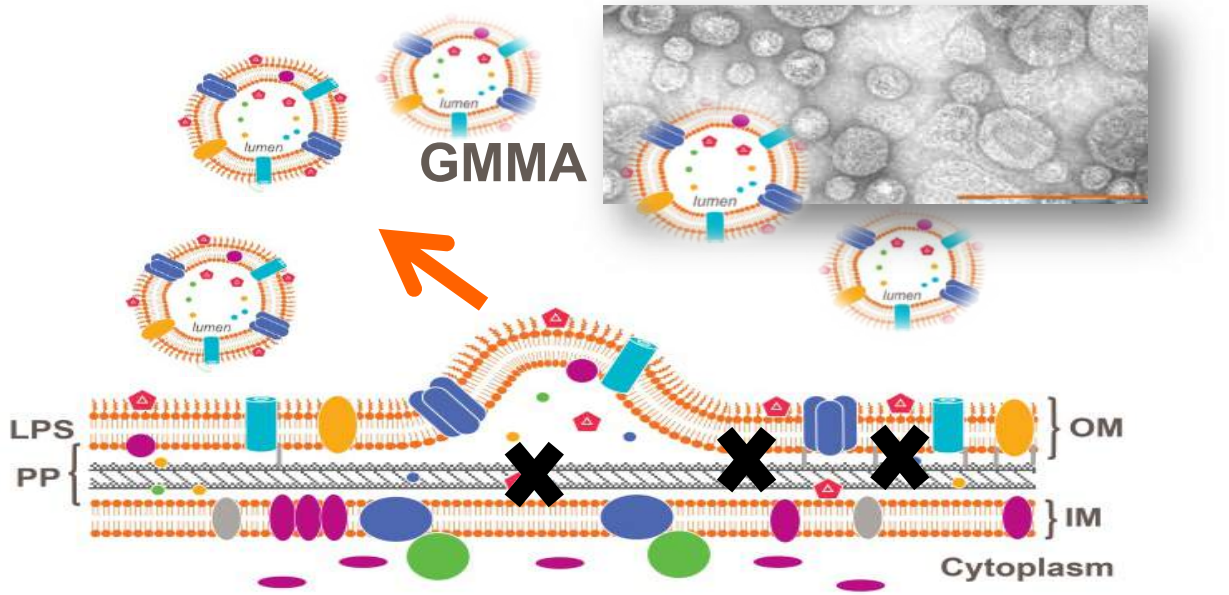
PROPOSED CLINICAL DEVELOPMENT

- **Phase 1 safety** and immunogenicity study of bivalent and trivalent vaccines and placebo 4-fold increases in serum anti-COPS, anti-Vi and homologous anti-FliC IgG antibody
- Step-wise **age-descending (down to infants 6 weeks of age) Phase 2 study** of Trivalent Conjugate Vaccine in 2 field sites in sub-Saharan Africa with iNTS burden and pre-licensure vaccine trial experience
- **Non-inferiority trial** with EPI vaccines used in Africa in relevant target age groups
- Phase 2 safety/immunogenicity in HIV-positive children
- **3-lot consistency trial** (for reactogenicity and immunogenicity) of vaccine versus placebo (3 vaccinees:1 placebo)
- **Large-scale randomized, controlled efficacy trial** of the Trivalent Conjugate Vaccine to be performed at multiple sites in Africa with iNTS burden and pre-licensure trial experience

CVD

GVGH'S INTS VACCINE APPROACH

GMMA (Generalized Modules for Membrane Antigens) Technology



Genetic modification to break links between outer and inner membrane and peptidoglycan to induce continuous **over-blebbing**

- Source of outer membrane
- Compartment containing immunogenic antigens
- Avoid side effects of whole cell bacteria vaccines
- Antigens presented in their natural environment and conformation, mimicking surface of the bacterium
- No additional chemical treatment needed
- Naturally adjuvanting

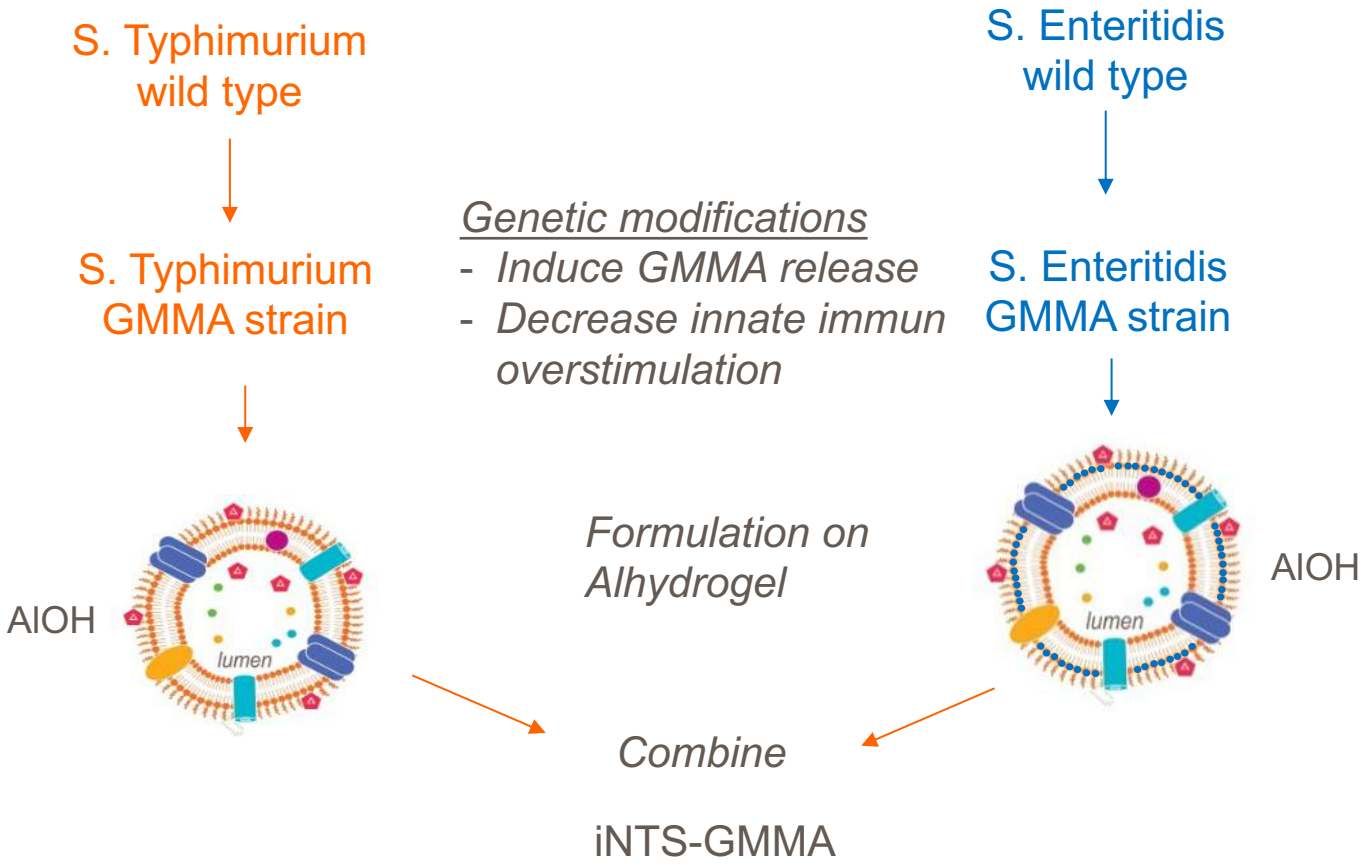
(Slide courtesy of Oliver Koeberling)

2-COMPONENT iNTS-GMMA VACCINE

GMMA from *S.* Typhimurium (STm) and *S.* Enteritidis (SEn)

iNTS-GMMA vaccine approach

- 2-component vaccine containing GMMA from *S.* Typhimurium and *S.* Enteritidis formulated on Alhydrogel

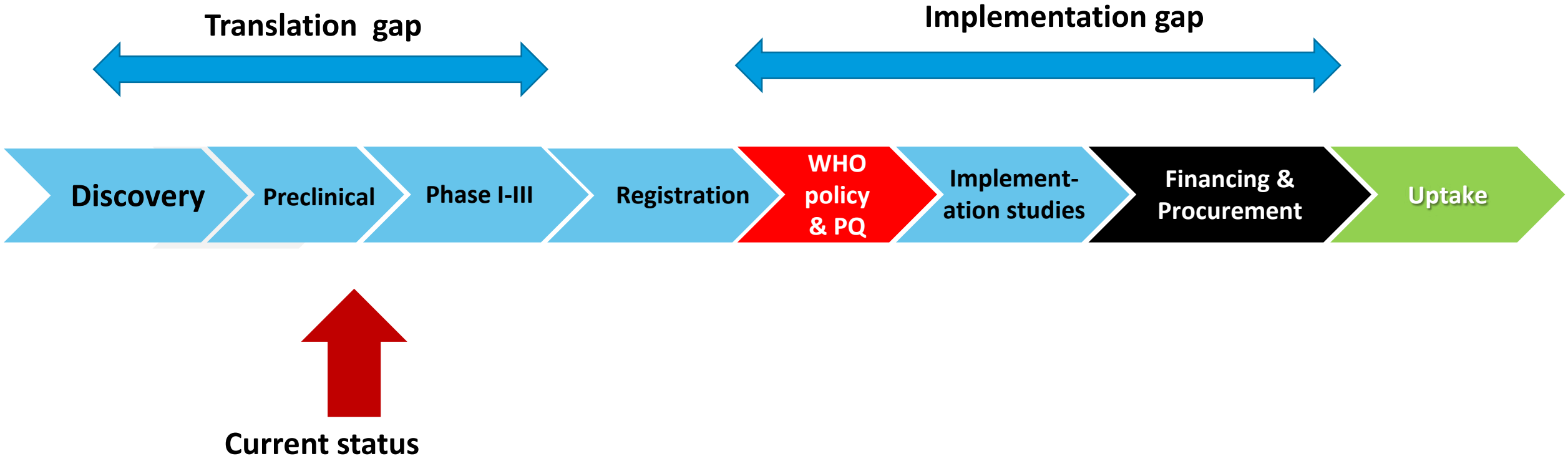


(Slide courtesy of Oliver Koeberling)

SUMMARY

- A comprehensive preclinical data package for the iNTS-GMMA vaccine in place demonstrating iNTS-GMMA
  - Immunogenicity in mice and rabbits
  - Manufacturability
  - Stability
- iNTS-GMMA project is at the stage to proceed with early clinical development

WHAT IS THE PATH FORWARD FOR UPTAKE OF AN INTS VACCINE…AND GAPS



(Slide courtesy of Birgitte Giersing WHO)

CONCLUSIONS FROM *SALMONELLA* CONVENING: iNTS

- Early stage with more questions and several unknowns
- Value proposition will need to evaluate iNTS/NTS, HIV-/HIV+, mortality, DALYs
- Epidemiology gap – incidence, shedding; is there an opportunity to explore in the RTS,S malaria vaccine pilot introductions in Africa
- Risk factor attribution needs further evaluation
- Reservoirs, sources, and modes of transmission need to be elucidated
- Clinical trials to target population are key next step
- Trial design and endpoints – carriage/shedding, immune indices
- iTPP - age of administration, combination – TCV (others)
- COPs examination of existing data & sero-epidemiology

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WHAT COULD ACCELERATE THE PATHWAY FORWARD?

- Early proven immunogenicity in the target population
- Availability of a Correlate of Protection
- Availability of a Controlled Human Infection Model (CHIM)
- Potential tethering to Typhoid Conjugate Vaccine – this seems unlikely given the differences in epidemiology and likely immunization scedules
- Value proposition
- Impact on carriage/shedding of NTS

- Early engagement with regulators

IMMUNOGENICITY STUDIES IN TARGET POPULATION

Are candidates sufficiently immunogenic to confer protection in LMIC children?

- No iNTS vaccine has been tested to date in the target population: young infants in LMICs
- Must evaluate immunogenicity in this target population, as soon as safety has been established in naive adults
- Requires a safety and immunogenicity study in descending age groups (to 6 weeks old) in LMICs.

- For a first iNTS vaccine: need for field data for safety and efficacy

SUMMARY

- A strong case for iNTS vaccine development, but community needs to be aware of detractors in addition to lack of a commercial driver
- No candidates currently in clinical development, but promise of two:
  - UMD/Bharat Biotech bivalent O-antigen/flagellin conjugate, and
  - GVGH/GSK bivalent vesicle vaccine First-in-Human studies in coming year
- Pathway potentially long without a clear Correlate of Protection to link immunogenicity to efficacy, or a Controlled Human Infection Model to give an early indication of efficacy


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