Group B streptococcus vaccine R&D

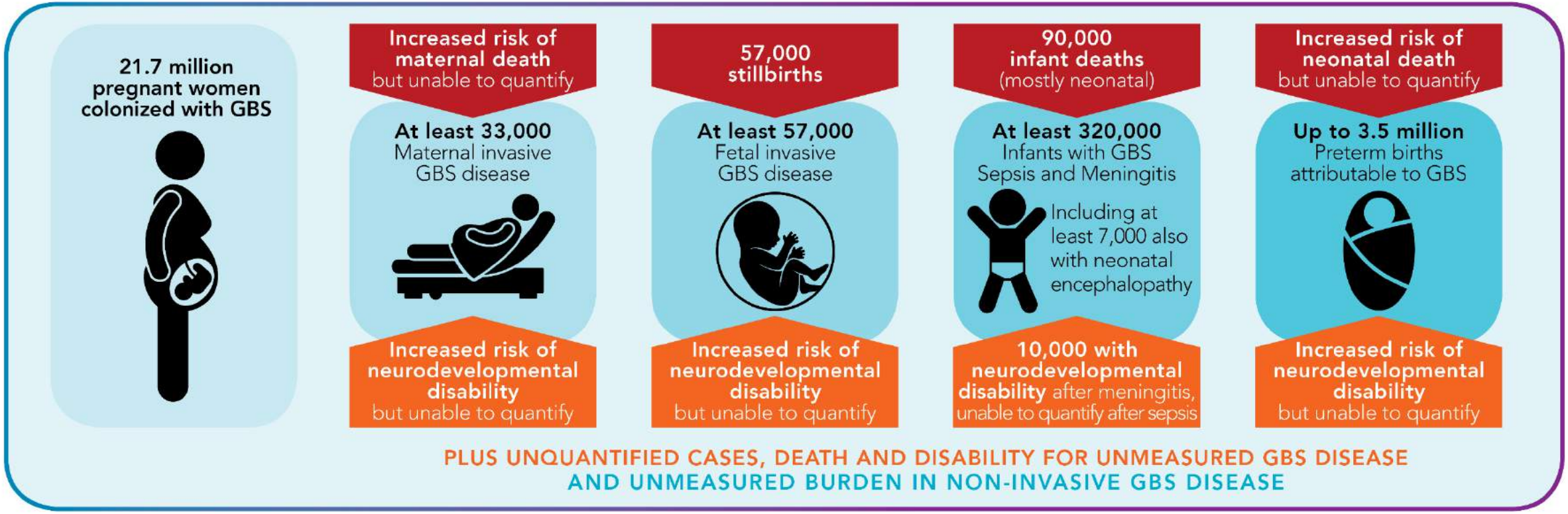
Update on WHO IVB activities

PDVAC

June 2019

World Health Organization

Why pursue a maternal GBS vaccine?



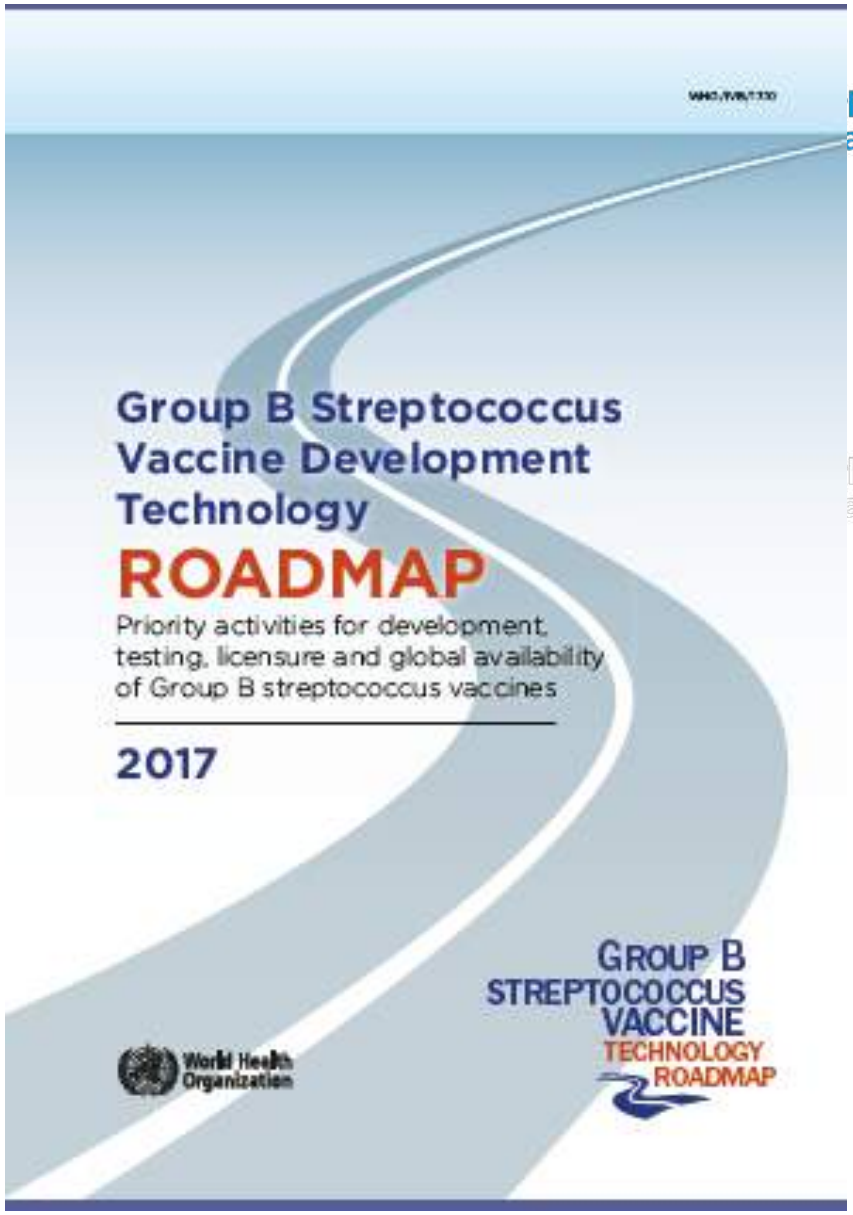
Estimates of the Burden of Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children. Seale AC et al. Clin Infect Dis. 2017

GBS vaccine R&D: current focus of WHO action

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

WHO Preferred Product Characteristics for Group B Streptococcus Vaccines

World Health Organization



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

GBS vaccine development status

Former front-runner: Phase I/II using trivalent protein conjugate polysaccharide :

- >75% of women had >4-fold rise in specific IgG ; mother-infant IgG transfer rates 50-80%
- **Lower IgG response: HIV-infected mothers; women with no baseline antibody**
- No benefit from use of alum

- **Back to formulation**

New front-runner: 6-valent protein conjugate polysaccharide vaccine in Phase 1/2a

- BMGF support

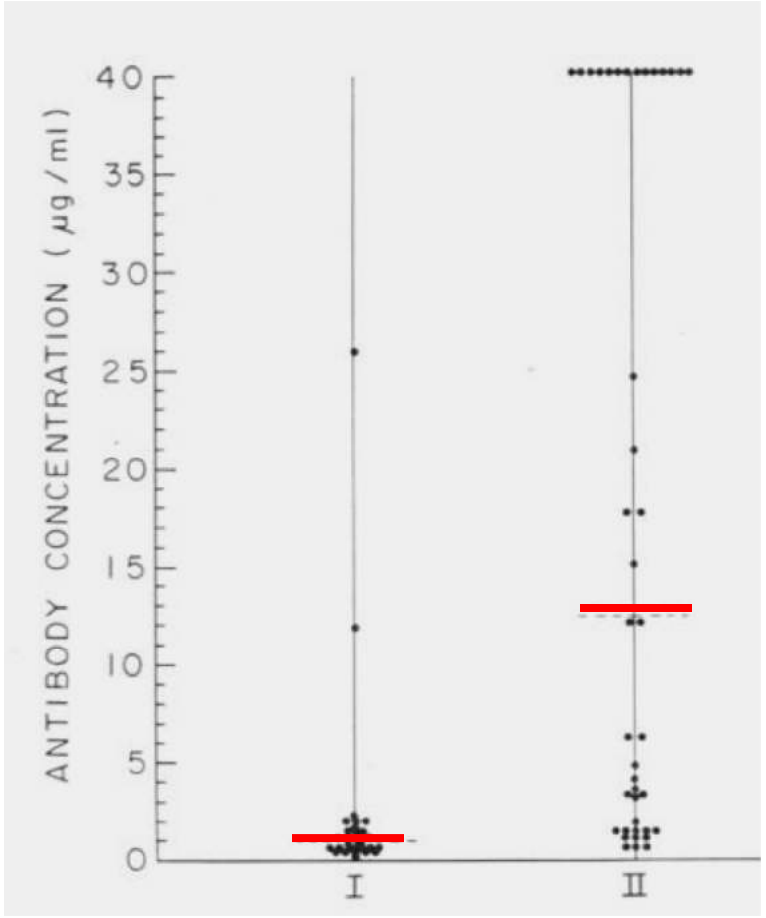
Mixture of 2 fusion proteins of the Alp-protein family, produced in E.coli, in alum.

- Phase 1, 2 dose schedule

Partnership with PATH aiming to produce low cost protein conjugate polysaccharide vaccine (preclinical)

Maternal antibodies to capsular polysaccharides reduces infant disease risk

Maternal antibody, GBS III CPS, µg/mL



Infant Disease

Infants Exposed

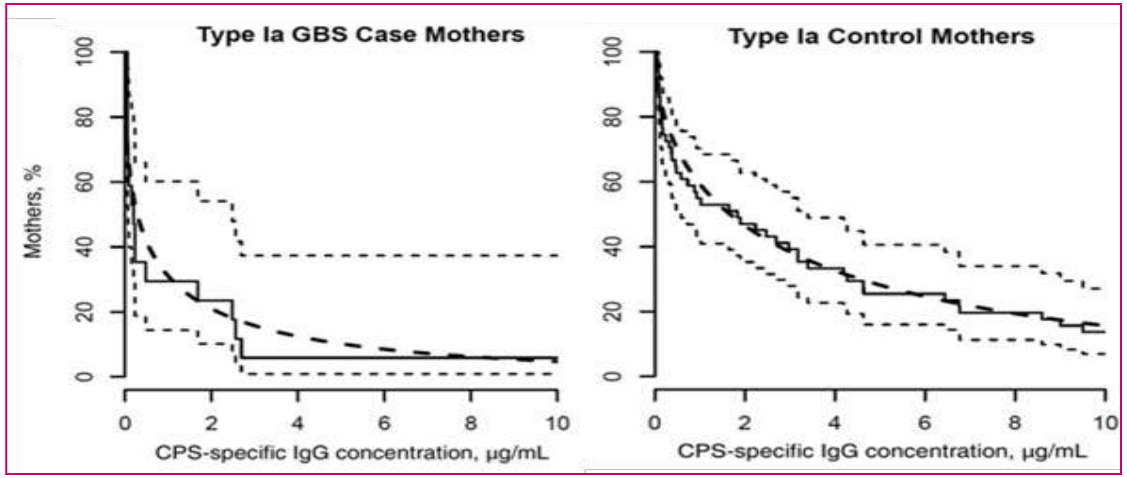
(*P* <.001, Mann-Whitney U test)

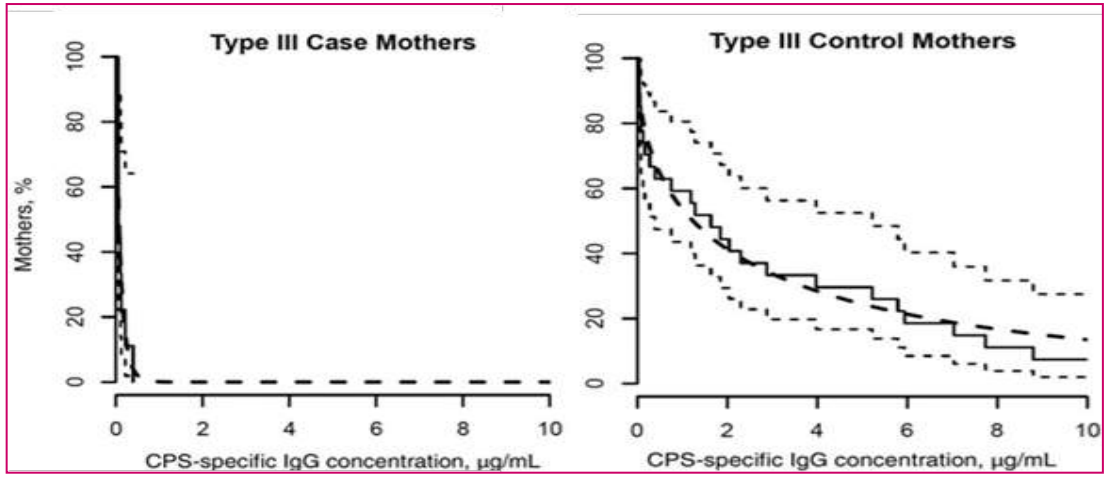
Baker CJ et al. *J Clin Invest* 1977;59:810.

Maternal antibodies to capsular polysaccharides reduces infant disease risk

High maternal IgG levels specific to the GBS capsular polysaccharide (CPS) associated to reduced risk of newborn infection in humans

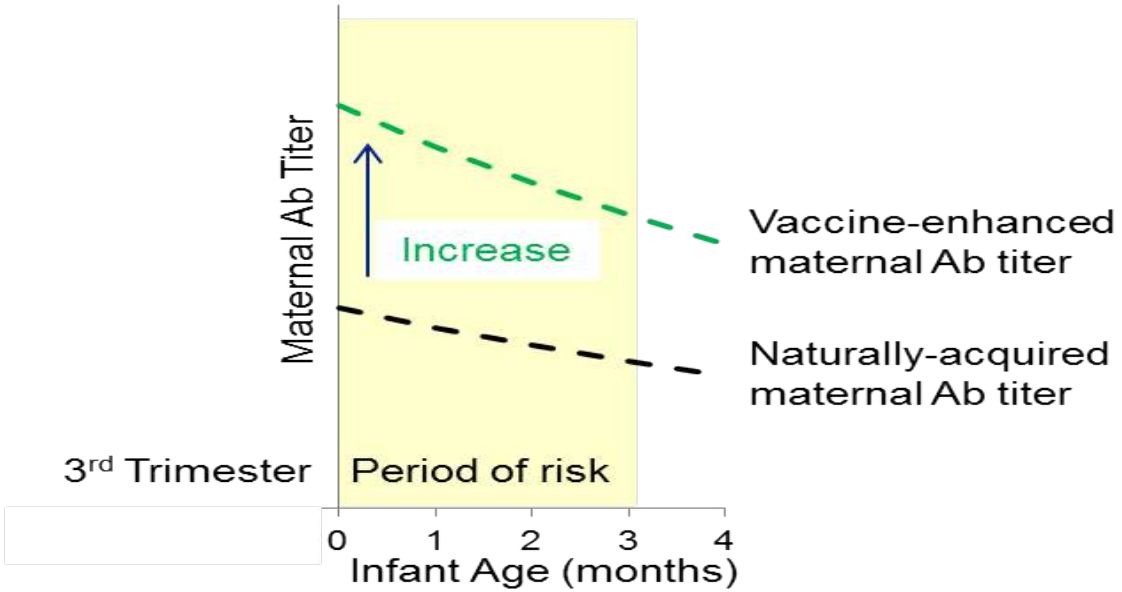
Percentage of mothers of infected (cases) or non infected babies (controls) with CPS–specific IgG serum concentrations ≥ to the value shown on the horizontal axis[4]





1) Baker & Kasper NEJM 1976; 294:753-756 ; 2) Lin et al. JID 2001 184:1022-1028; 3) Lin et al. JID 2004;190:928-934; 4) Baker et al. JID 2014;209:781–8

Maternal immunization may protect offspring through materno-fetal antibody transfer



Role of correlates of protection

Acknowledging the challenge of a 'classical pathway' including RCT demonstration of efficacy against invasive GBS bacterial disease clinical endpoint, in the context of favourable access to standards of care

Total number of pregnant women required in a placebo-controlled trial to demonstrate the efficacy of a GBS vaccine candidate against a defined disease endpoint.

Projected VE (LL 95% CI of 25%)	Expected disease rate in placebo recipients (cases per 1000 livebirths)			
	2.0	1.0	0.5	0.1
80%	30,000	62,000	122,000	620,000
60%	90,000	180,000	360,000	1,804,000

Assumptions: 80% power, P<0.05 for significance, 1:1 vaccine:placebo allocation, 15% loss to follow-up, 90% cases eligibility for inclusion as per primary case definition, 95% matching between vaccine and circulating types.

Vaccine 37 (2019) 3190–3198

Contents lists available at ScienceDirect

Vaccine

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

The role of immune correlates of protection on the pathway to licensure, policy decision and use of group B *Streptococcus* vaccines for maternal immunization: considerations from World Health Organization consultations

Johan Vekemans [a,*], Jonathan Crofts [b], Carol J. Baker [c], David Goldblatt [d], Paul T. Heath [e], Shabir A. Madhi [f], Kirsty Le Doare [e], Nick Andrews [g], Andrew J Pollard [h], Samir K. Saha [i], Stephanie J. Schrag [j], Peter G. Smith [k], David C. Kaslow [l]

- GCP quality research centres, diverse geographical areas, **baseline epi data, high standards** procedures, standards of care defined
- High quality **standard immune assays**, measuring bactericidal activity in serum, are developed. Supportive animal model data
- **Sero-epidemiological studies** based on predefined study protocols (timepoints, endpoints, various settings) and analysis plans (threshold or continuous model) define the relationship between antibody concentrations and disease risk (natural exposure)
- Estimates of effects are produced (aggregate across serotypes/strains and when possible, serotype/strain specific). Interaction factors characterized
- **Maternal vaccination trials:** favorable safety, immunogenicity (serotype/strain specificity, bactericidal activity) characterized in details.
- **Success criteria are pre-defined:** vaccination induces antibody levels above protective thresholds in a high, predefined proportion of recipients (or alternative robust statistical estimates based on continuous models). Aggregate estimates of effects are produced, serotype/strain specificity is investigated. Antibody persistence is demonstrated, beyond the period-at-risk. Pre-defined success criteria are passed. Factors affecting immunogenicity and antibody transfer are characterized.
- **Conditional licensure** based on indirect evidence : post-licensure Phase 4 effectiveness agreement
- **Plans for confirmatory evaluation of public health impact** based on consensus study design are developed early and **financed**.
- **Post-licensure pilot implementation studies** are conducted without delays, **leading to policy decision for wide-scale use**, country processes start, and procurement is ensured by public health agencies, informed by implementation science and analyses of full public vaccine value.

Role of correlates of protection

Ongoing sero-epidemiologic studies

Derived estimates of association between antibody levels and protection, in context of natural exposure

(US, RA, , UK, Uganda)

Coordination work :

- analytical methods
- Assay standardization

Assuming favorable safety

Vaccine immunogenicity studies

Next step: develop a predefined analysis and decision framework

Towards WHO assay standards: WHO Norms and Standards

World Health Organization

World Health Organization

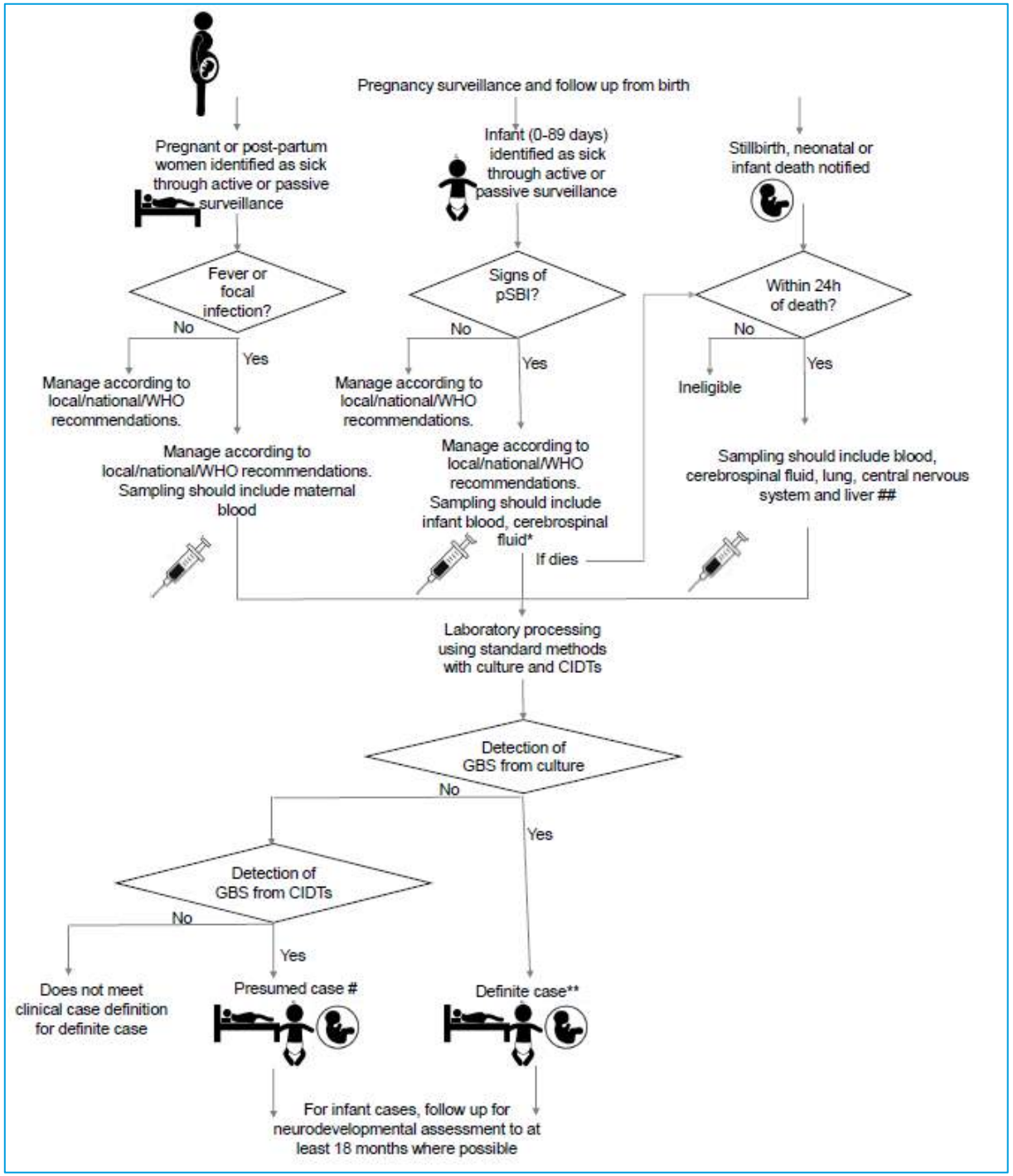
Endpoints:
case definitions and ascertainment

Built on a consensus building consultation process

Seale et al. Submitted to Vaccines

Projected to be of use for epidemiology studies, vaccine trials, surveillance activities

Background to surveillance standards



The Defeating Meningitis by 2030 roadmap sets out a global strategy to achieve

Our vision

Towards a world free of meningitis

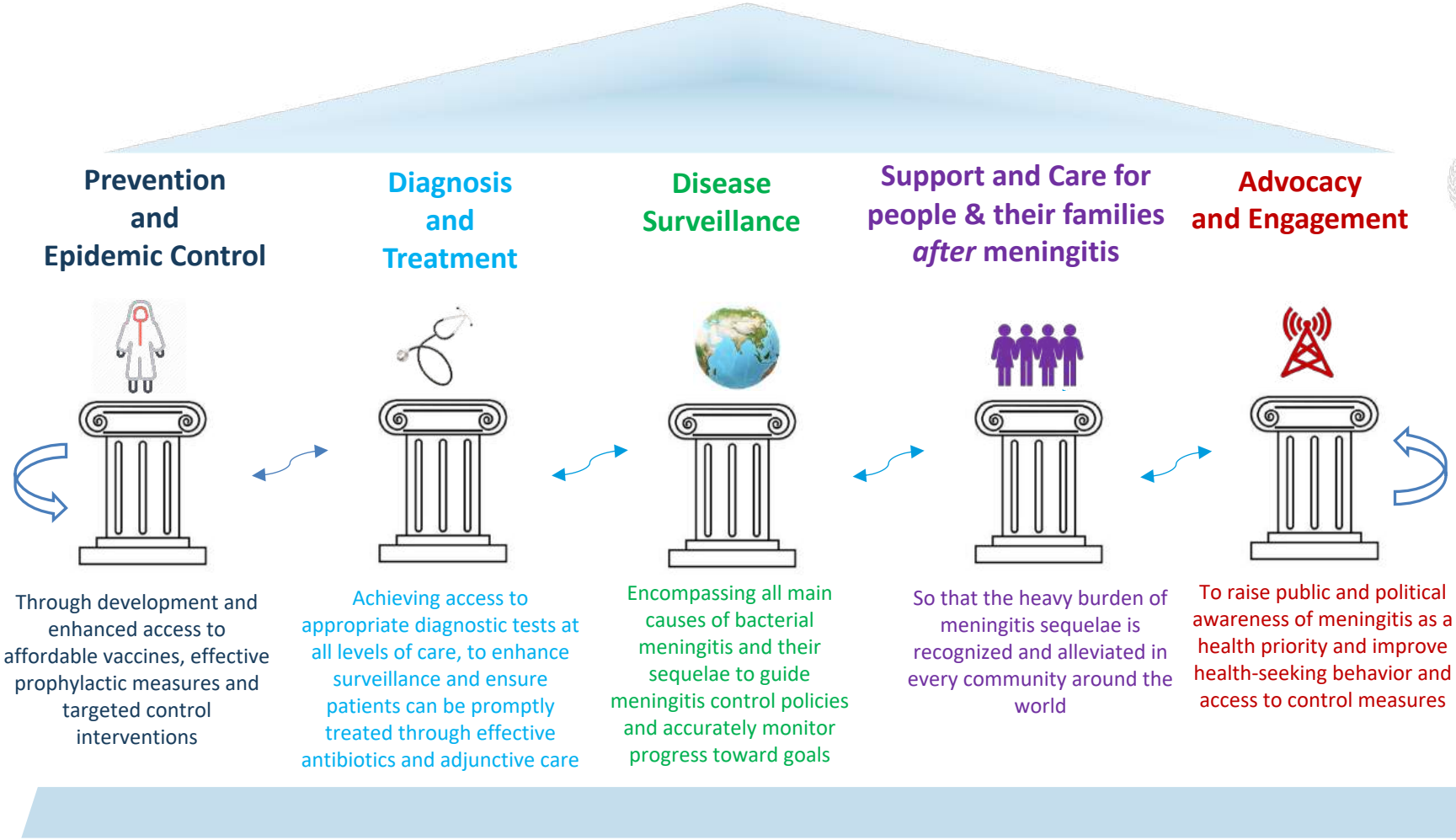
Proposed visionary goals to be achieved by 2030:

- Eliminate bacterial meningitis epidemics
- Reduce cases and deaths from vaccine-preventable bacterial meningitis*
- Reduce risk of disability and improve quality of life after all causes of meningitis

** Global and regional targets to be agreed*

Five pillars for the global roadmap

to achieve the overall goals of the strategy



The strategic goals, milestones and priority activities will be tailored to the context of each region

Updated WHO Vaccine Preventable Disease Surveillance Standards

- 20 VPDs based on available vaccines, current thinking in the field, and latest laboratory techniques
- Modular document with easy to use web-interface
- Last version from 2003—now regular updates without waiting 15+ years!
- English and French version available online in September 2018: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/standards/en/

Summary of updated WHO minimum recommended VPD surveillance standards

World Health Organization

Country commitment	Nationwide, case-based with laboratory confirmation of every case	Nationwide, aggregate with laboratory confirmation of outbreaks	Sentinel, case-based with laboratory confirmation of every case	Other (e.g. VPDs have different minimum standard of surveillance based on context)
Surveillance commitment in every country	• Measles • Poliomyelitis	-	-	• Neonatal Tetanus (no lab confirmation)
Surveillance commitment varies by country	• Diphtheria • Meningococcus • Rubella	• Hepatitis A • Hepatitis B • Mumps	• Congenital rubella syndrome • *H. Influenzae* • Influenza • Japanese encephalitis • Pertussis • Pneumococcus • Rotavirus • Typhoid	• Cholera (event-based) • HPV (surveillance not recommended) • Non-neonatal Tetanus (no lab confirmation) • Varicella (no lab confirmation) • Yellow fever (pending)

http://www.who.int/immunization/monitoring_surveillance/burden/vpd/standards/en/

GBS surveillance standards

- Same format as WHO VPD surveillance standards—1st chapter for disease with vaccine in development
- Will likely have much in common with surveillance for pneumococcus, but
  - GBS causes stillbirths and disease in very young neonates
  - Consider surveillance in pregnant women
  - GBS surveillance may need large birth cohort and defined catchment area
- WHO and CDC are leading the development of these surveillance standards
  - Will create expert working group
  - Face-to-face meeting end 2019 / early 2020

WHO and LSHTM collaboration to develop a public health value proposition for GBS vaccine

PDVAC meeting
June 2019

Dr Philipp Lambach
Raymond Hutubessy

World Health Organization

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GBS value proposition - Project goals

Develop and widely disseminate a comprehensive value proposition for Group B Streptococcus (GBS) vaccination for pregnant women (LMICs and HICs as integral part of market)

The value will be expressed by articulating the preventable burden of disease, estimating expected costs/gains from vaccinating pregnant women, feasibility considerations

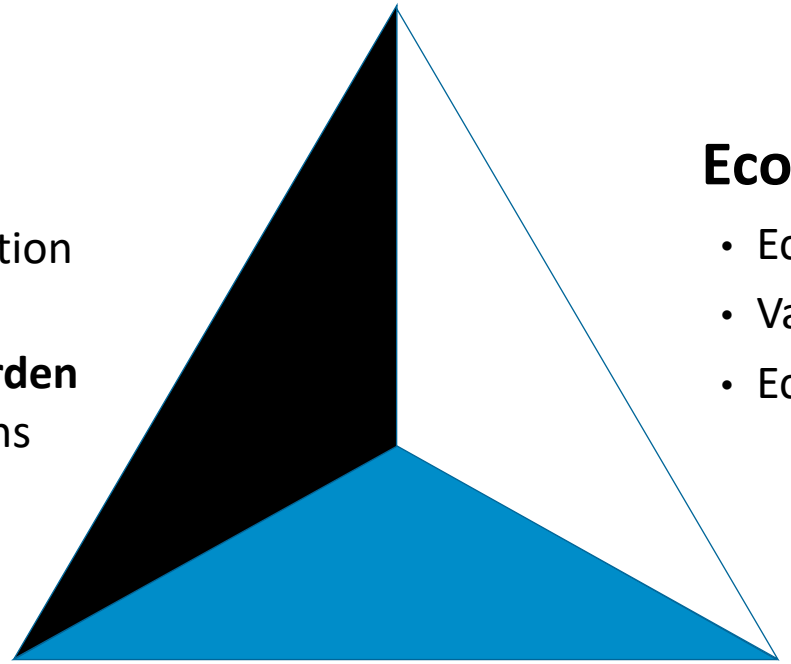
Data generated, tools developed and analyses shall

- Inform investments into full development of candidate vaccines
- Advance R&D and planning of public health implementation in routine programs
- Highlight major data gaps to inform future vaccine introduction in low resource countries

Project components / Workstreams (WS)

Disease burden (WS 1)

- **Medical need** for maternal immunization against GBS at global level
- **Quantification of MI preventable burden** of disease under different assumptions



Economic analyses (WS 2):

- Economic burden of disease
- Vaccine cost effectiveness
- Economic impact

Operationalization issues (WS 3):

- Vaccination schedule
- Service delivery
- Uptake
- M&E

WS 1: Burden of disease (BoD) and medical need

World Health Organization

Objectives:

- **Burden:** To assess the complete burden GBS disease
- **Serotypes:** To describe GBS serotypes by region (country if enough data)
- **Intrapartum antibiotic prophylaxis:** To estimate GBS disease burden preventable with IAP, implications for antibiotic use and potentially AMR
- **Vaccine impact:** To estimate GBS disease burden preventable by vaccination in pregnant women
- **Data gaps:** To synthesise data gaps regarding burden assessment and programmatic tracking

Outputs

- Revised analyses of cases, deaths, disability, socio-economic outcomes
- Generation of DALYs
- Will inform economic analyses

WS 2: Economic evaluations

Objectives:

- Estimate cost of illness and cost of immunization programs (building on Workstream 1)
- Estimate global impact of maternal GBS vaccination on disease, deaths, antibiotic consumption and resistance
- Conduct economic evaluation to assess the cost-effectiveness, return on investment, budget impact, extended cost-effectiveness and producer/consumer surplus of maternal GBS vaccination

Outputs

- Estimates based on a range of health economic evaluations to understand the value of a GBS vaccine targeting pregnant women from the perspective of the research and development community, funders and countries

WS 3: Operationalization of GBS vaccination programmes

Objectives:

Evaluate the potential impact of vaccine introduction on standard medical practice based on

- factors that may influence adoption and effectiveness of vaccination during pregnancy
- capacity of existing service delivery models

Research areas/questions:

- Vaccination schedule (repeat dose administration and optimal vaccination timing during pregn.)
- Service delivery (integration into/optimal delivery by EPI/ANC)
- Uptake (acceptance by pregnant women, HCW)
- Planning and conducting monitoring and evaluation (coverage monitoring)

Output

- Written summary of findings (report)

WHO Product Development for Vaccines Advisory Committee (PDVAC), Geneva, 26-28 June 2019

Economic considerations to inform the GBS vaccine global investment case

Mark Jit[1,2,3]
on behalf of the GBS maternal vaccine value proposition consortium

[1]London School of Hygiene & Tropical Medicine
[2]Modelling and Economics Unit, Public Health England
[3]School of Public Health, University of Hong Kong

Overview

Developing a value proposition for maternal GBS vaccination
(November 2017 – October 2020; no cost extension to March 2021)

Workstream 1
Burden of GBS disease and medical need for a vaccine

Joy Lawn
Anna Seale
Artemis Koukounari
Proma Paul
Fiorella Bianchi-Jassir

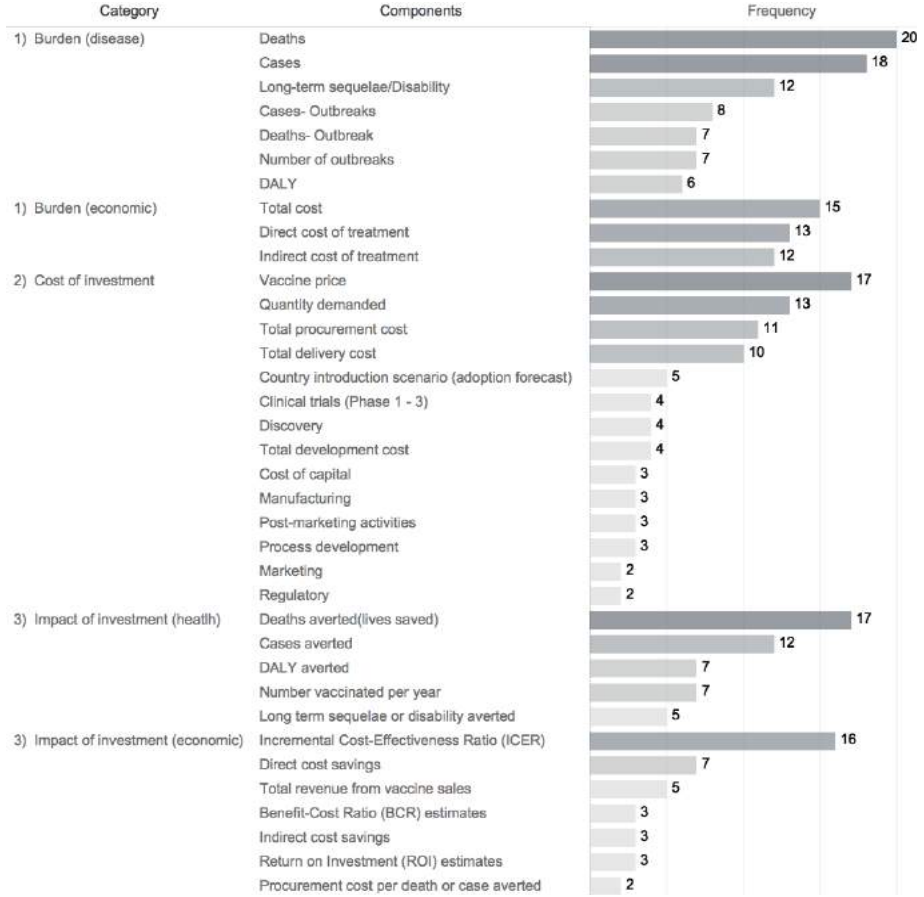
Workstream 2
Economic evaluations of maternal GBS vaccination

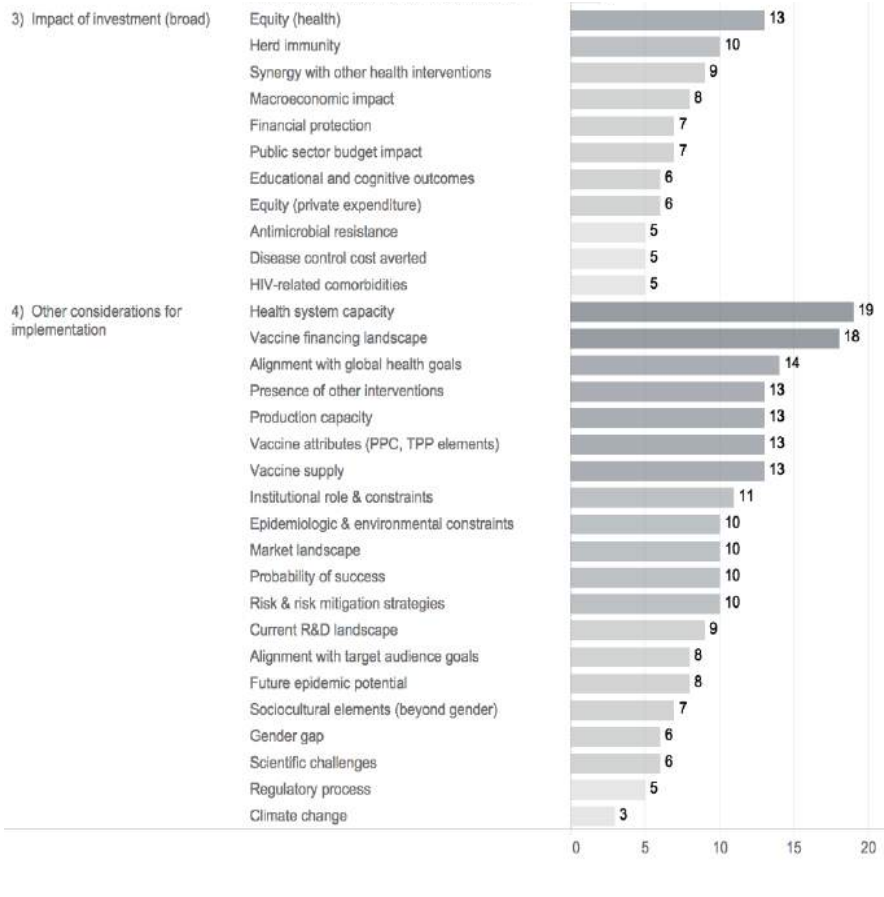
Mark Jit
John Edmunds
Simon Procter
Artemis Koukounari
Raymond Hutubessy

Workstream 3
Operationalisation of GBS vaccine implementation

Philipp Lambach
Emily Wootton
MMGH consultants

Systematic review of 24 investment cases of vaccines

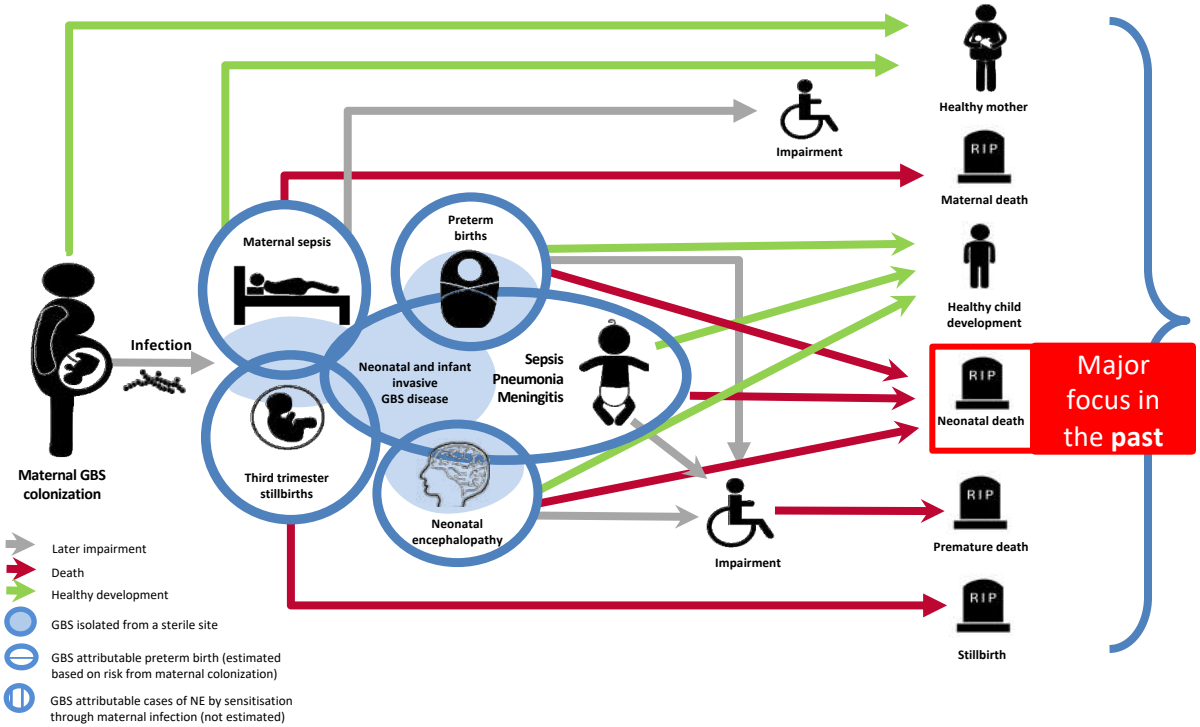




Sim SY et al. Value in Health; *in press*.

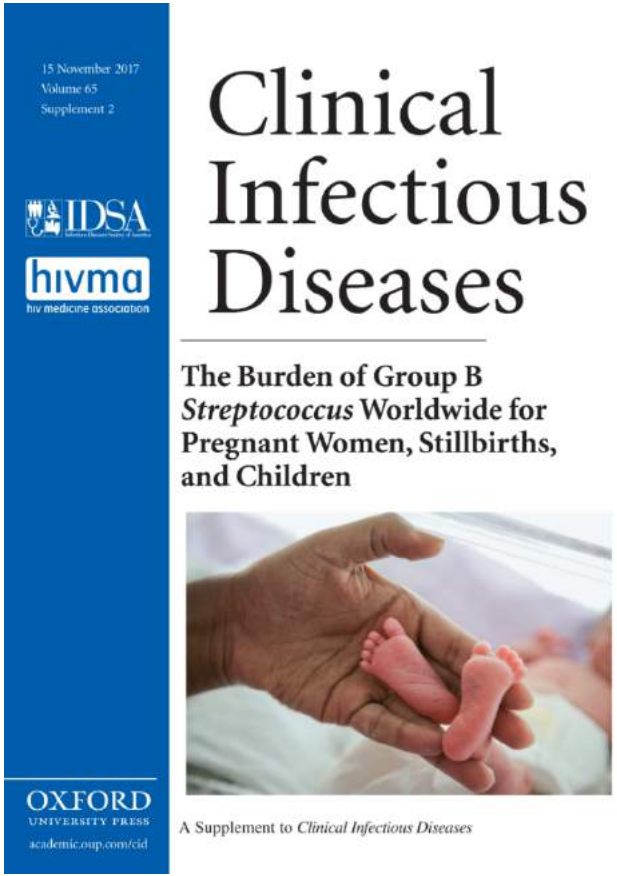
Counting the cost and health impact of GBS

What outcomes of GBS should be included?



NOW
Maternal, perinatal and child outcomes including cases, deaths and disability

Lawn JE, et al *Clinical Infectious Diseases*. 2017;65(S2):S89-99
Slide from Joy Lawn

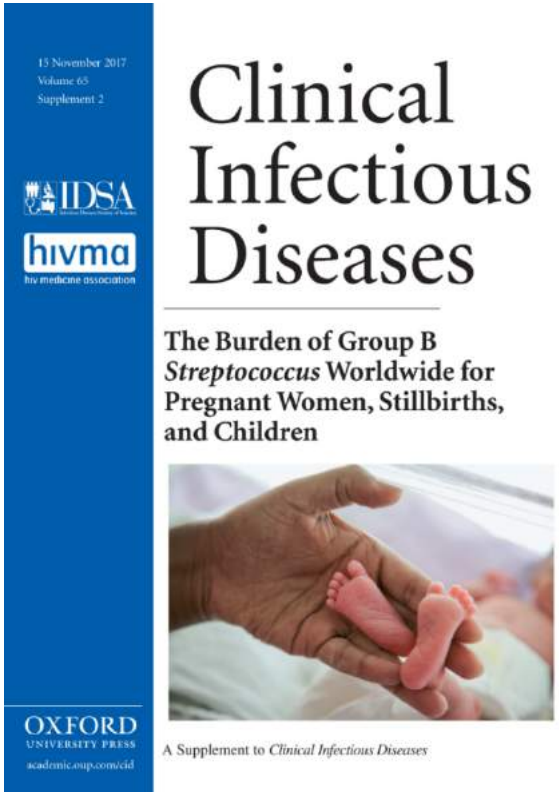


This work was supported by a grant to the London School of Hygiene & Tropical Medicine from the Bill & Melinda Gates Foundation (2015-2017).

Editors: Joy E Lawn, Anna C Seale.

Lead authors: Joy E Lawn, Neal Russell, Jennifer Hall, Anna C Seale, Fiorella Bianchi-Jassir, Kirsty Le Doare, Lola Madrid, Maya Kohli-Lynch, and Cally J Tann.
Expert Advisory Group: Ajoke Sobanjo-ter Meulen, Carol Baker, Claire Cutland, Craig Rubens, Johan Vekemans, Linda Bartlett, Paul Heath, Shabir Mahdi, and Stephanie Schrag.

11 papers, collaboration of 103 authors from over 30 institutions coordinated by the London School of Hygiene & Tropical Medicine



What was new?

- Worldwide reach from almost 100 countries and all regions (translated from ~20 languages)
- All relevant outcomes: cases, deaths and disability for pregnant women, stillbirths, and children
- Data inputs at least doubled compared with previous databases
- Investigator groups bringing important unpublished datasets – notably for stillbirths and regarding hypoxic ischaemic encephalopathy in neonates with GBS infection

Top data gaps

- Geographic: Limited representation from low- and middle-income countries
- Burden: **Long-term impairment outcomes,** stillbirth data (especially from Asia), attributable risk of GBS to preterm birth
- Economic: **Very limited cost of illness data**

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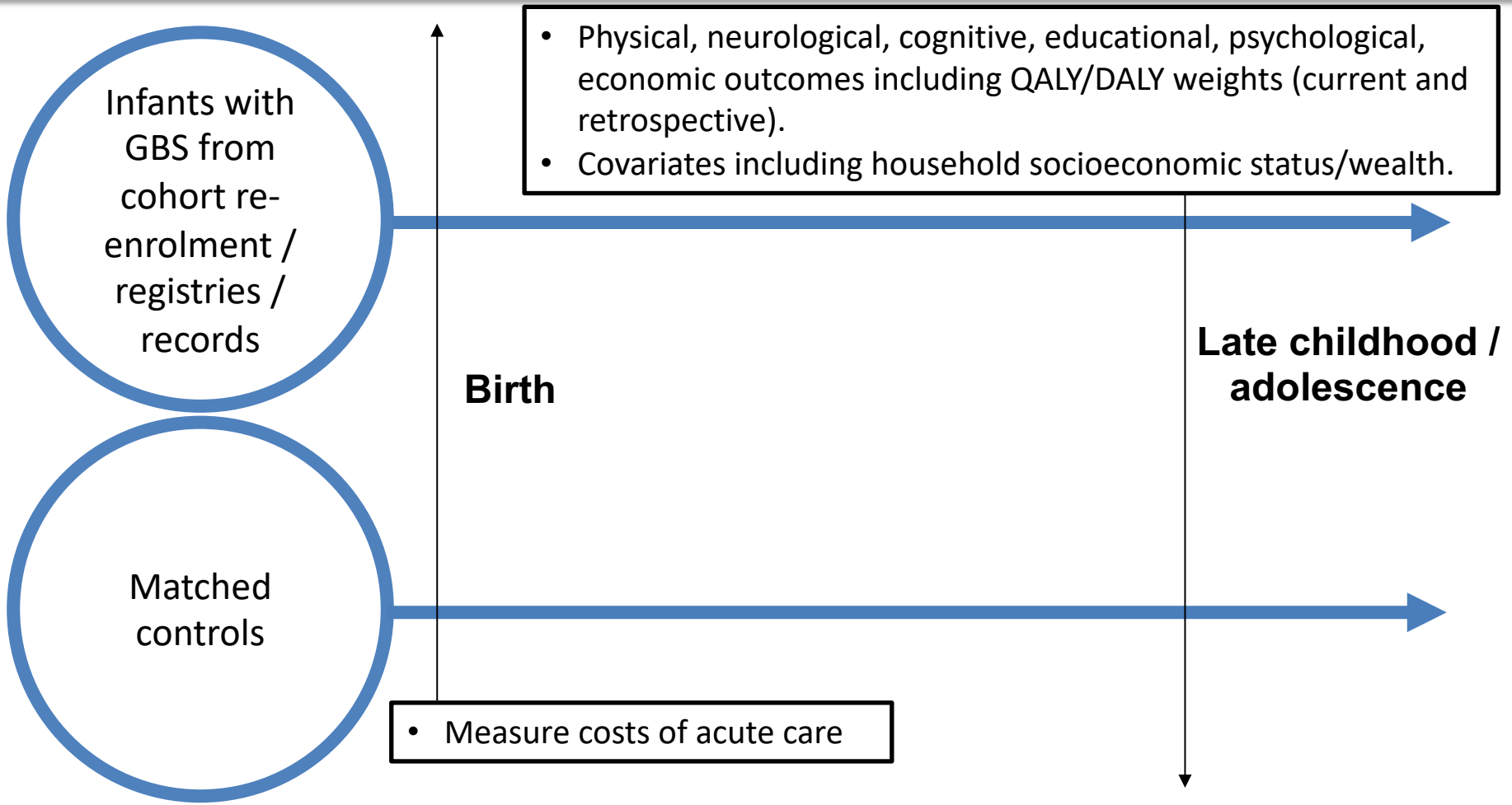
Capturing long-term outcomes



Capturing long-term health and economic outcomes

Study design	Country	Site/Facility type	Age at follow-up
Cohort re-enrolment	Argentina	Public hospitals	3-7 years
	India	Academic and referral hospital	18 months -15 years
	Kenya	County hospital	3-10 years
	Mozambique	District hospital	3-17 years
	South Africa	Academic hospital	3 years and approx. 6 years
Cross-sectional study on costs of acute care	India	Academic and referral hospital	Not applicable
	Kenya	County hospital	
	Mozambique	District hospital	
	South Africa	Academic hospital	
Electronic cohort	Denmark	Linked national database	Up to 23 years
	Netherlands	Linked national databases	Up to 30 years

Outcomes of immunisation programmes: paradigm shifts

From “narrow” to “broad” impacts
Jit et al. 2015

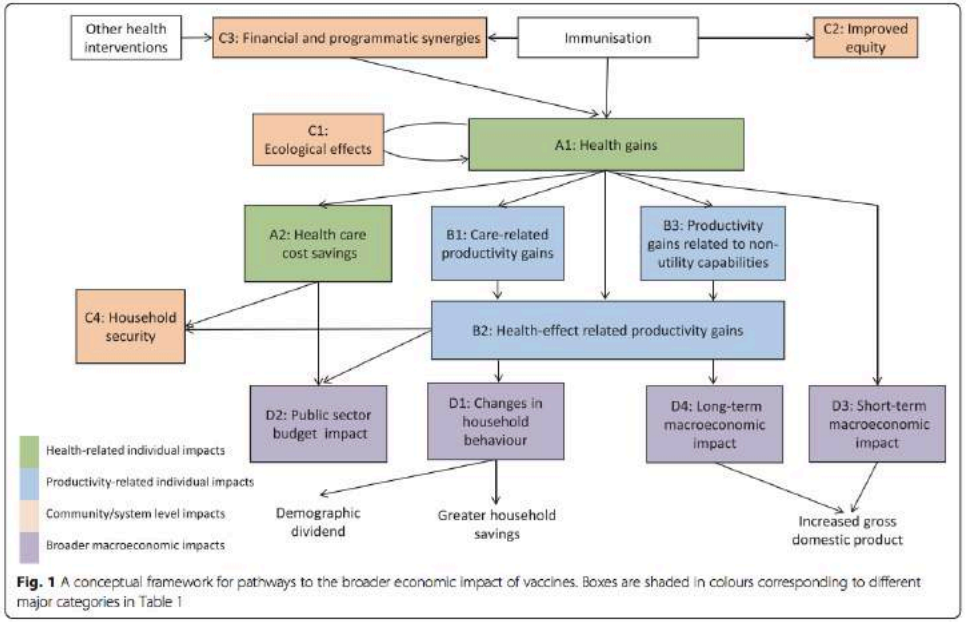


Fig. 1 A conceptual framework for pathways to the broader economic impact of vaccines. Boxes are shaded in colours corresponding to different major categories in Table 1

From “the brick wall” to “the other side”
Gessner et al. 2017

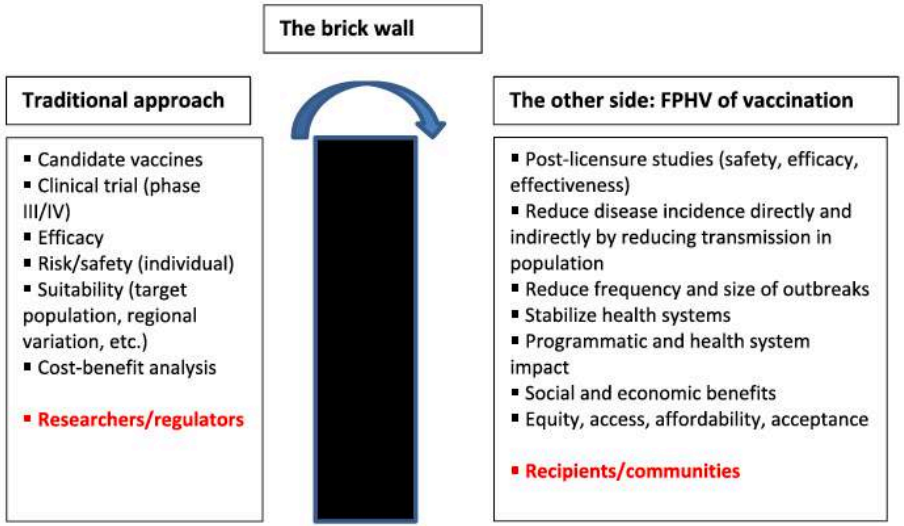


Fig. 2. The brick wall: Moving from vaccines to vaccination.

Sources:
Jit M et al. The broader economic impact of vaccination: reviewing and appraising the strength of evidence. BMC Medicine 2015; 13:209.
Gessner B et al. Estimating the full public health value of vaccination. Vaccine 2017; 35:6255.

Multiple analyses: a consequentialist framework

Cost-effectiveness	• Maternal GBS vaccination costs $100 per DALY averted and $200 per case avoided.
Threshold cost	• Maternal GBS vaccination is cost-effective at $2/dose.
Return on investment	• Maternal GBS vaccination brings $2 in economic returns per $1 invested.
Budget impact	• Maternal GBS vaccination will cost $10m in the year of introduction, and $5m a year thereafter.
Extended cost-effectiveness	• Maternal GBS vaccination prevents twice as many deaths and thrice as many cases of catastrophic expenditure in Q1 compared to Q5.
Global surplus	• Development of a GBS vaccine is worth $20bn to manufacturers, $100b to HICs and $75bn to LMICs.
Antibiotic resistance	• Maternal GBS vaccination reduces prescribing by 25%, the proportion of resistant carriers by 15% and the cost of resistance by 10%.

Addressing multiple audiences

Translation gap

Bench research → Clinical studies

Audience: research funders

Key requirements:

- Value of information
- Cost-effectiveness
- Broader return on investment
- Economic surplus

Marketing gap

Clinical studies → Licensure and market access

Audience: manufacturers

Key requirements:

- Market shaping
- Appropriate price range
- Financial return on investment

Implementation gap

Licensed vaccine → Population programme

Audience: donors and countries

Key requirements :

- Cost-effectiveness and budget impact within basic benefits package
- Equity (extended CEA)

Progress to date

Workstream 1
Burden of GBS disease and medical need for a vaccine

- Systematic review of GBS serotype distributions
- Protocol for cohort re-enrolment / electronic database review
- Ethics submitted for all study sites
- Framework for Bayesian synthesis of burden of disease evidence

Workstream 2
Economic evaluations of maternal GBS vaccination

- Systematic review of acute costs of neonatal sepsis and meningitis
- Review of costs of maternal vaccine delivery
- Protocol for collecting acute costs and long-term utilities
- Design of vaccine impact model (decision tree)

Workstream 3
Operationalisation of GBS vaccine implementation

- Expert group agreed on research questions on operationalization of GBS vaccination in countries
- Maternal immunization data repository (situation analysis and identification of factors affecting of GBS vaccination during pregnancy)

Additional information needed for the investment case

- What is the best approach to take to estimate the cost of pre-clinical and clinical research to bring a vaccine to licensure?
- What is the best way of estimating the risk of failure for a vaccine candidate at different phases of development and market access? (e.g. pre-clinical, phase I, phase II, phase III, post licensure)
- What are key information sources for insight on intended business strategy and market sector for vaccine candidates? (e.g. public/private, high/middle/low income countries, pricing, % revenue from markets etc.)
- What are key sources of information about the marginal cost of vaccine production for a pipeline vaccine?
- How would a vaccine manufacturer estimate its return on investment (i.e. total revenues over the lifetime of the vaccine until the patent expires/total costs of development, production and marketing)
- What sources of financing for (i) vaccine development and (ii) vaccine production do you think will exist? Eg. private sector purchase, public sector purchase, pooled procurement (PAHO/Gavi/other), innovative financing mechanisms, advance market commitments etc.

We would be highly appreciative of any information that PDVAC members may have – please get in touch with Mark Jit in person or at mark.jit@lshtm.ac.uk.

Questions for PDVAC

- Does PDVAC have any feedback and recommendations about the strategic directions and ongoing investigations for the investment case?

- Does PDVAC have any insight about additional key information sources, contacts and/or stakeholders that may be relevant to these investigations?

CEPI

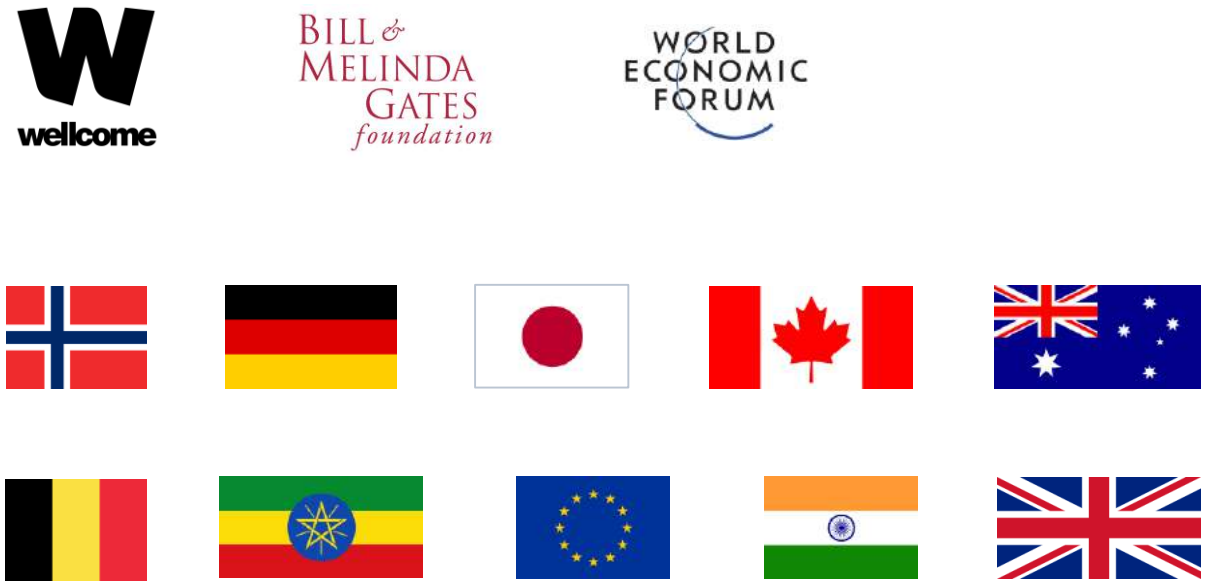
Development of vaccines for endemic response

Status of vaccine and manufacturing platform development

Melanie Saville, Director Vaccine Development

PDVAC, 28 June 2019

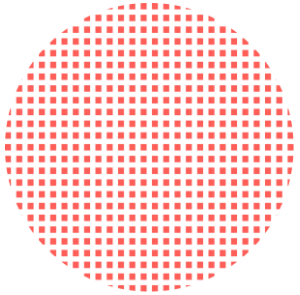
Our global partners



Our mission

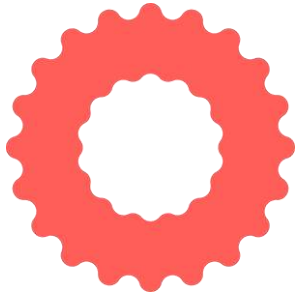
CEPI accelerates development of vaccines against emerging infectious diseases and enables equitable access to these vaccines for affected populations during outbreaks

Our strategic objectives



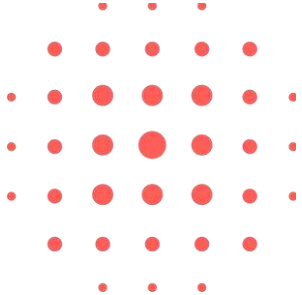
Preparedness

Advance access to safe and effective vaccines against emerging infectious diseases



Response

Accelerate the research, development and use of vaccines during outbreaks

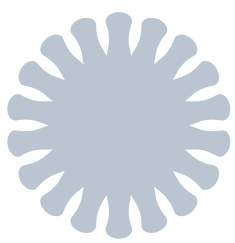


Sustainability

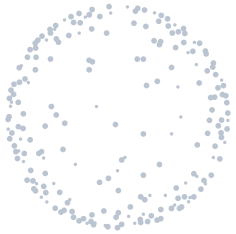
Create durable and equitable solutions for outbreak response capacity

A sustainable partnership

CEPI's initial priority pathogens

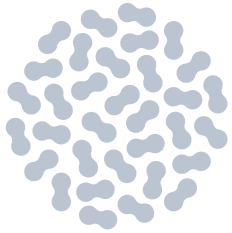


MERS

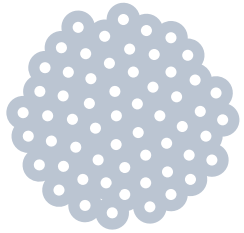


Lassa

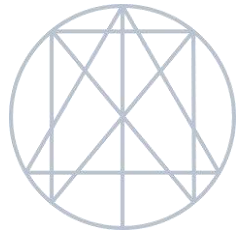
Nipah



Chikungunya



Rift Valley fever



Disease X

Integrated product development plans build on WHO TPP where available

Partnership agreements signed

Priority Pathogens

Disease	Lassa and MERS	Lassa and MERS	Lassa	Nipah	Lassa	MERS	Lassa, MERS, and Nipah	Nipah	Chik
Technology	Measles vector	DNA	rVSVΔG	rVSVNC4 ΔG	Protein sub-unit	MVA	ChAdOx	Measles vector	Measles vector
Investment (up to)	$37.5 M	$56.0M	$54.9 M	$25.0 M	$36.0 M	$36.0 M	$19.0M	$30 M	$21 M

Rapid response Platforms

Disease	Rabies, flu & Marburg	RSV, flu & MERS	Rabies, Yellow Fever & Lassa
Technology	Self-amplifying RNA	Molecular clamp	RNA
Investment (up to)	$8.4M	$10.6M	$34M

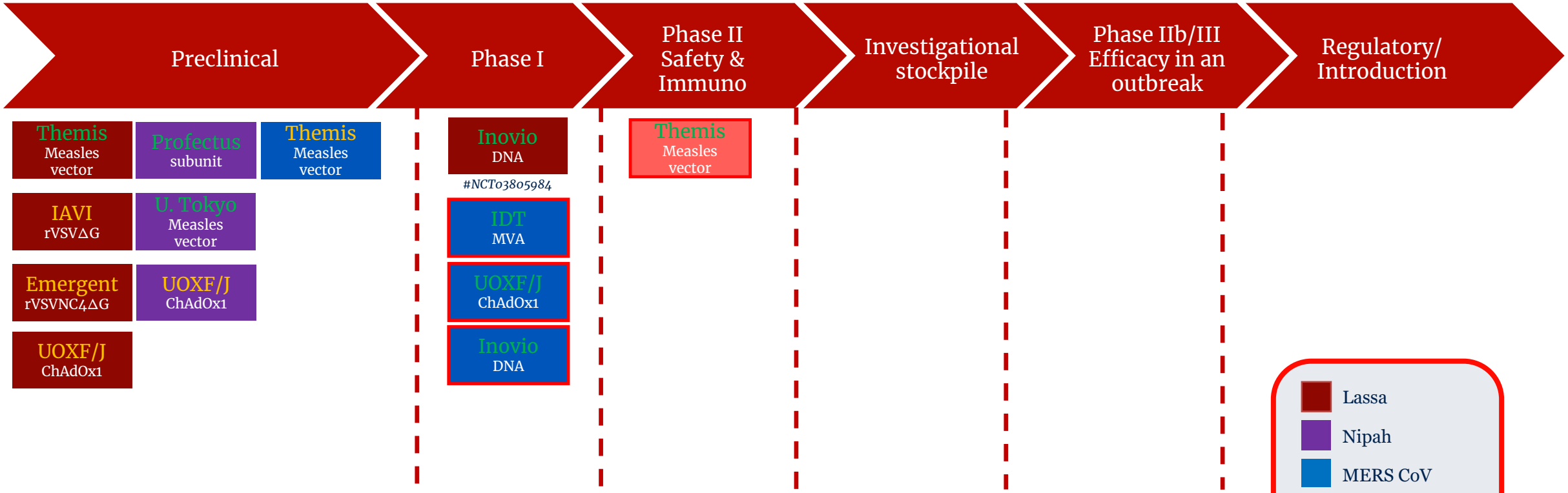
As of 28th June 2019

Note: *This is publicly announced funding. Some of these have options for further investment*

CEPI priority pathogen portfolio

Priority pathogens: CEPI funds late preclinical through phase II S&I and investigational stockpile generation

The diagram indicates where the projects are in the development process



Additional Chikungunya and Rift Valley Fever vaccine candidates will be announced shortly

Ebola

- Investments in clinical trials to support licensure

CEPI

As of 28th June 2019

Lassa portfolio – Vaccine profiles

	Themis	Inovio	IAVI	Emergent Biosolutions	Oxford Janssen
Technology	Measles virus Live rep	DNA + Electroporation	rVSVΔG Live replicating	rVSVNC4ΔG Live replicating	Chimp Adeno Rep incomp
Lassa transgene Josiah strain	GPC + NP	GPC	GPC	GPC	GPC
Project status	Preclinical	Phase I[1]	Preclinical Historically protection observed in NHP[2]	Preclinical	Preclinical

[1]NCT 03805984
[2]Geisbert et al PLOS Medicine 2005

MERS-CoV portfolio - Vaccine profiles

	Oxford/Janssen	IDT	Themis	Inovio
Technology	Chimp Adeno Rep incompetent	MVA Rep incompetent	Measles virus Live replicating	DNA + Electroporation
MERS transgene	Spike	Spike	Spike	Spike
Project status	Phase I study ongoing[1] (different cell line)	Phase I study ongoing[2] (different cell line)	Preclinical	Phase I data with IM injection[3]. Phase I/II ID ongoing in Korea[4]

[1]NCT03399578
[2]NCT03615911
[3]NCT02670187
[4]NCT03721718

Nipah Portfolio: Vaccine Profiles

	University of Tokyo	Profectus Biosciences	University of Oxford
Technology	Measles virus Live replicating	Recombinant subunit Alum	Chimp adeno Repl. incompetent
Nipah transgene	Glycoprotein	Hendra Glycoprotein	Glycoproten
Project status	Pre-clinical protection data in Syrian hamster and AGMs [1]	Pre-clinical PoC and tox. study performed[2]	Pre-clinical protection in Syrian hamster[3]

[1]Yoneda et al PlOS one, 2013
[2]Bossart et al Sci Transl Med, 2012
[3]Van Doremalen et al PLOS neg trop dis 2019

Data Package and Future Gaps

What we will get from CfP1 – funded

Data package resulting from the development plan in the contracted IPDP.

Non-Clinical: Data in relevant animal model

- Protection data (Challenge model)
- Cross reactivity and protection data across different virus clades
- Define correlates of protection (humoral and cellular immunogenicity)
- Phase I enabling toxicology data

Clinical Data: Phase I/Phase II data

- Safety database of 400-600 subjects receiving investigational vaccine (largely/all adult population)
- Humoral and cellular immunogenicity data
- Data to justify Dose and schedule

Manufacturing

- Clinical trial material
- A developed GMP manufacturing process suitable for phase I/II material that can be scaled to produce 100,000 doses
- Targeting temperature storage of DP at -20oC or 2-8oC
- Investigational stockpile
- A stockpile of 100,000 doses based on the phase I/II manufacturing process to be used in large clinical trials in an outbreak situation
- Formulation and presentations to be agreed with key stakeholders including regulators

What we need for future licensure – not funded

Additional work needed to fully meet WHO TPP/licensure data needs

Non-Clinical: Data in relevant animal model

- Reproductive toxicology (timing still under discussion)
- Full characterization and stability data on consistency lots

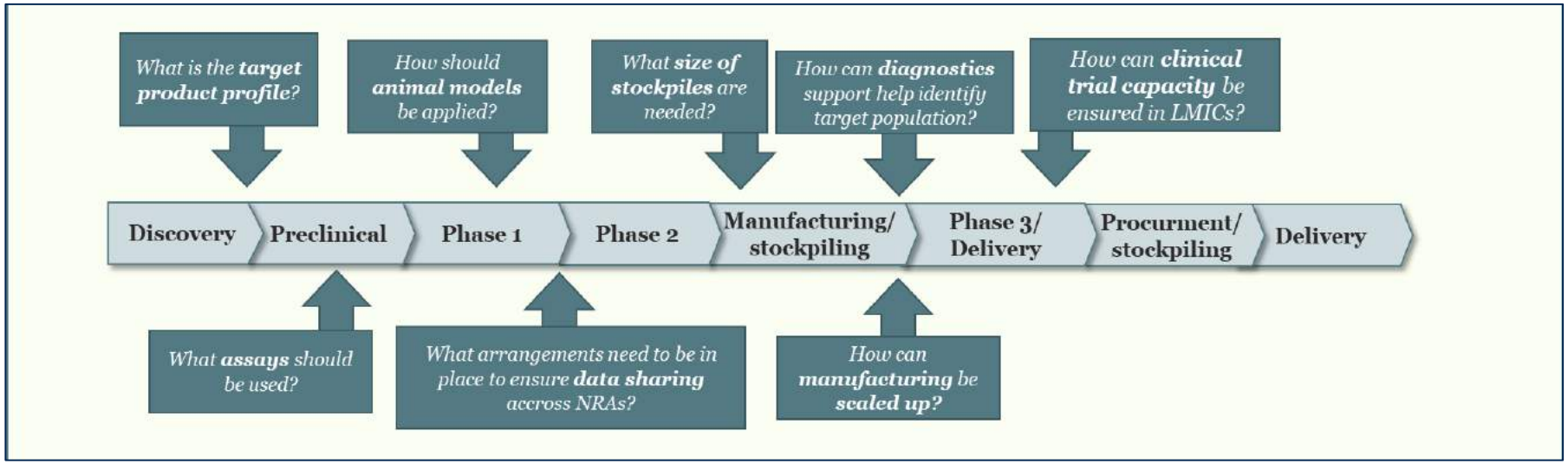
Clinical Data

- Vulnerable populations
  - Few developers are advanced enough to conduct clinical trials in children in the 5 yr period
  - Data in pregnant women
  - Data in immunocompromised
- Augmenting safety database
- Demonstration of efficacy if feasible (or effectiveness post approval)

Manufacturing

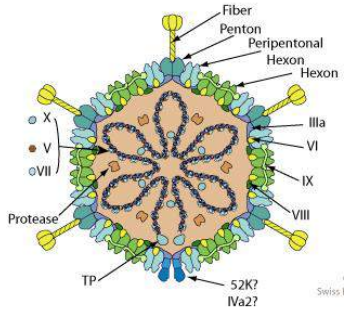
- Potential further scaleup
- Validation of manufacturing process
- Demonstration of lot to lot consistency
- Continued formulation development for enhanced stability
- Sustainable manufacturing strategy -
- Potency assay development and release testing under emergency conditions

Cross-Cutting Investments



Options

- Fund & manage
- Co-fund
- Facilitate



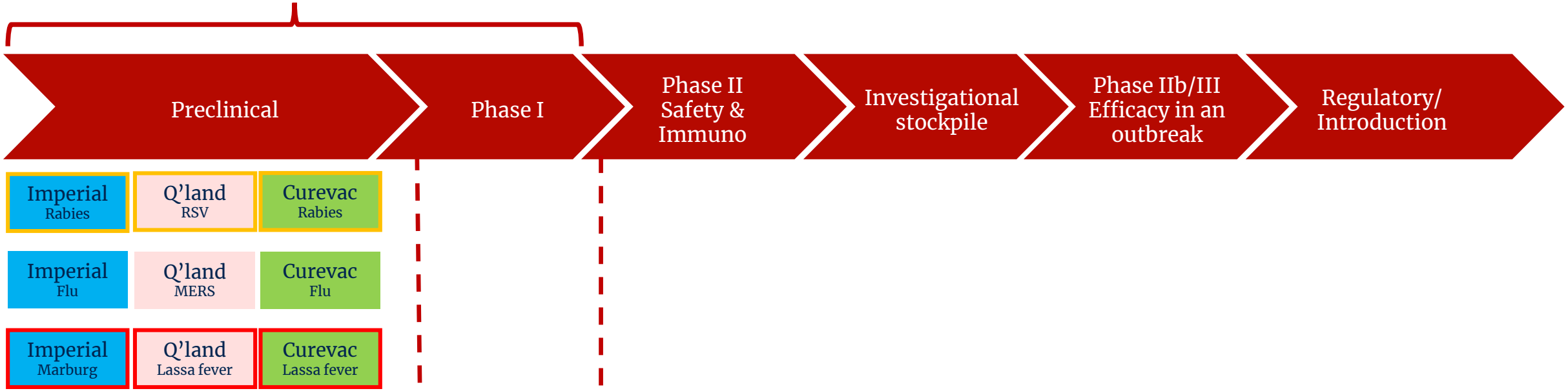
CEPI

Rapid response platform technologies

- CEPI supports development of vaccine platform technologies that can be rapidly deployed against known and newly emerging pathogens, to limit or prevent future outbreaks of known or new diseases.
- Projects must demonstrate:
  - Safety and immunogenicity
  - Validation of the platform using 3 pathogens (2 with known correlates of protection & validated animal model; 1 from the WHO priority pathogen list)
  - Manufacturing performance characteristics
  - 16 weeks for development of vaccine for a new pathogen (up to phase I)
  - 6 weeks to clinical benefit after 1st dose
  - 8 weeks to produce 100,000 doses after go-decision

CEPI rapid response (CfP2) portfolio

The diagram indicates where the projects are in the development process



Rapid response platform technologies

- Novel vaccine platform technologies capable of producing vaccine within 16 weeks are being funded
- Three candidates will be tested for each technology
- All three will undergo preclinical testing
- Only two of these will enter Phase I clinical trial
- One of the clinical candidates must be on the WHO Priority Pathogen Blueprint list

Imperial
Self-amplifying RNA

Queensland
Molecular clamp

Curevac
RNA

Preclinical only

Priority pathogen

As of 28th June 2019

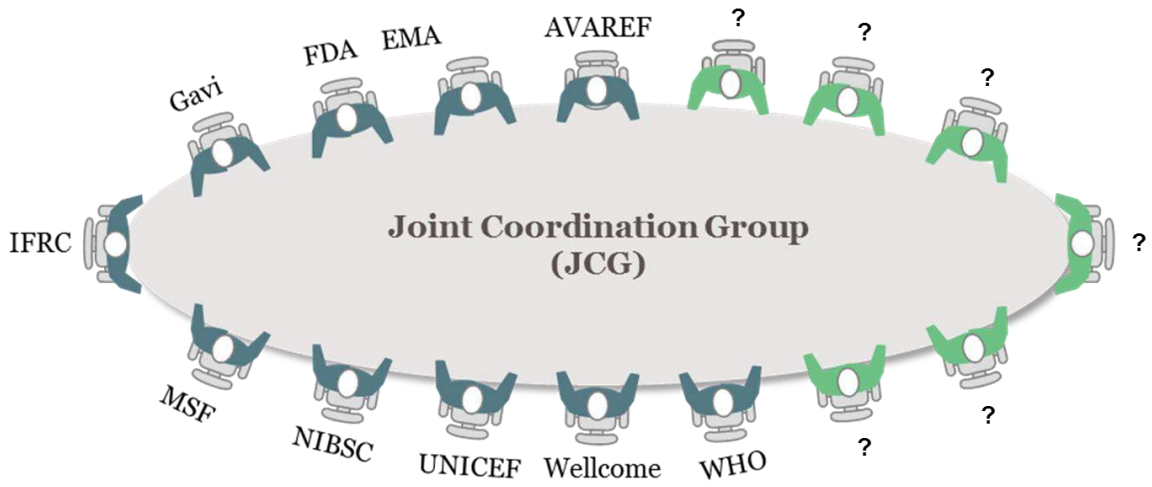
CEPI

Joint Coordinating group

Permanent members

comprised of:

- Multilateral institutions
- Regulatory agencies
- Procurement agencies
- Responders



Additional time-bound members, as needed:

- National regulatory agencies
- National institutes of public health
- National research agencies
- +++

Assays and standards

Regulatory steering committee

Sustainable Manufacturing

Conclusions

- We are investing in a range of vaccine candidates for 5 priority pathogens
  - The first 5 year funding will take the most promising candidates through phase II and manufacture of an investigational stockpile
- We are investing in rapid response platforms to accelerate vaccine development for pathogen X
- We have a number of cross cutting enabling science projects to accelerate vaccine development
- We are engaging key stakeholders and working our way through challenges to pass through the 2 valleys of death

Thank You

CEPI

FEB-2019

The Need for Novel Vaccine Delivery Approaches

Product Development for Vaccines Advisory Committee Consultation | June 28, 2019

Mark Papania, M.D. MPH

Measles Elimination Team

Global Immunization Division, CDC

Coverage and Equity- Reaching the “Hard to Reach”

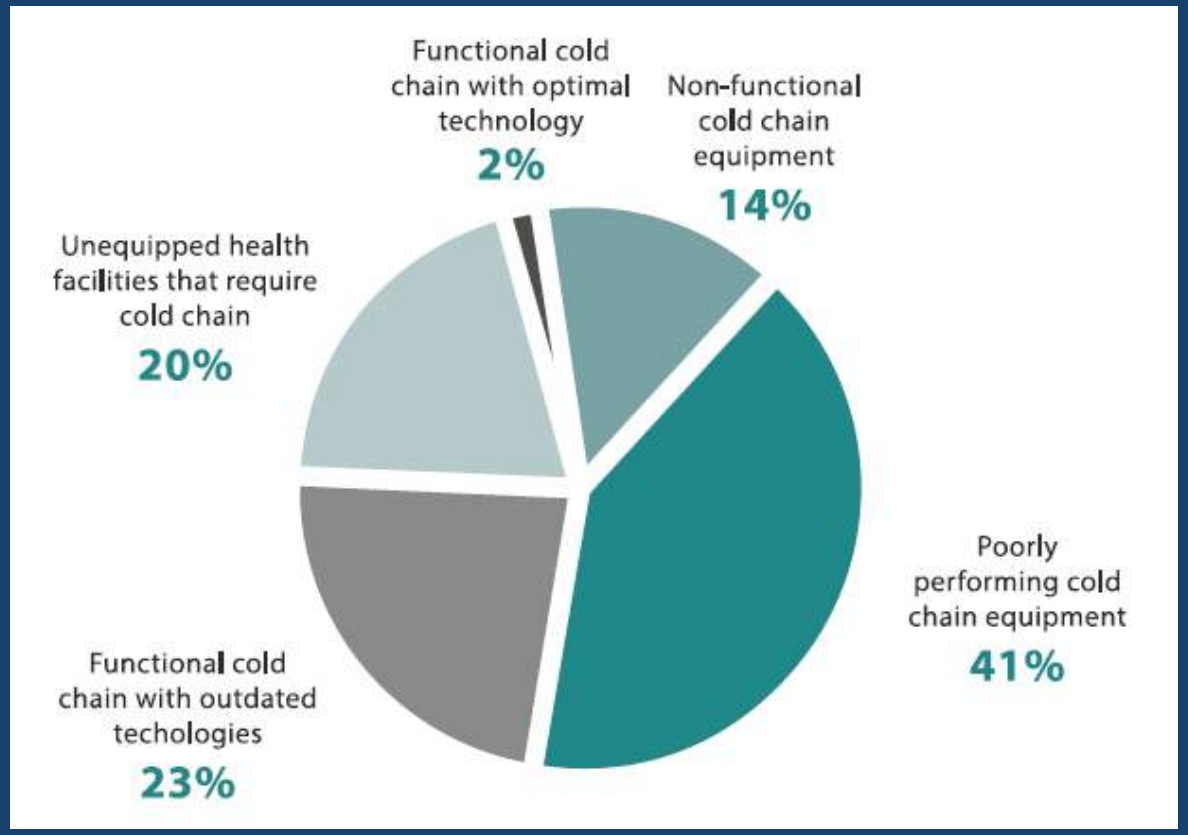
- Global coverage for well established vaccines stagnant at 85% for decades
- Roughly 20 million infants unvaccinated every year. Accumulates because for most vaccines there is no catch-up vaccination
- Bridging the gap between the current status and the coverage and equity goals “Everyone, Everywhere” will require new solutions and significant investment
- Potential Solution: Novel vaccine delivery approaches may improve coverage by lowering hurdles to access

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Logistical Hurdles Impede Immunization Coverage and Equity- Reaching the "Hard to Reach"

1. Cold chain issues
2. Packaging issues
3. Onsite reconstitution and filling
4. Needle issues

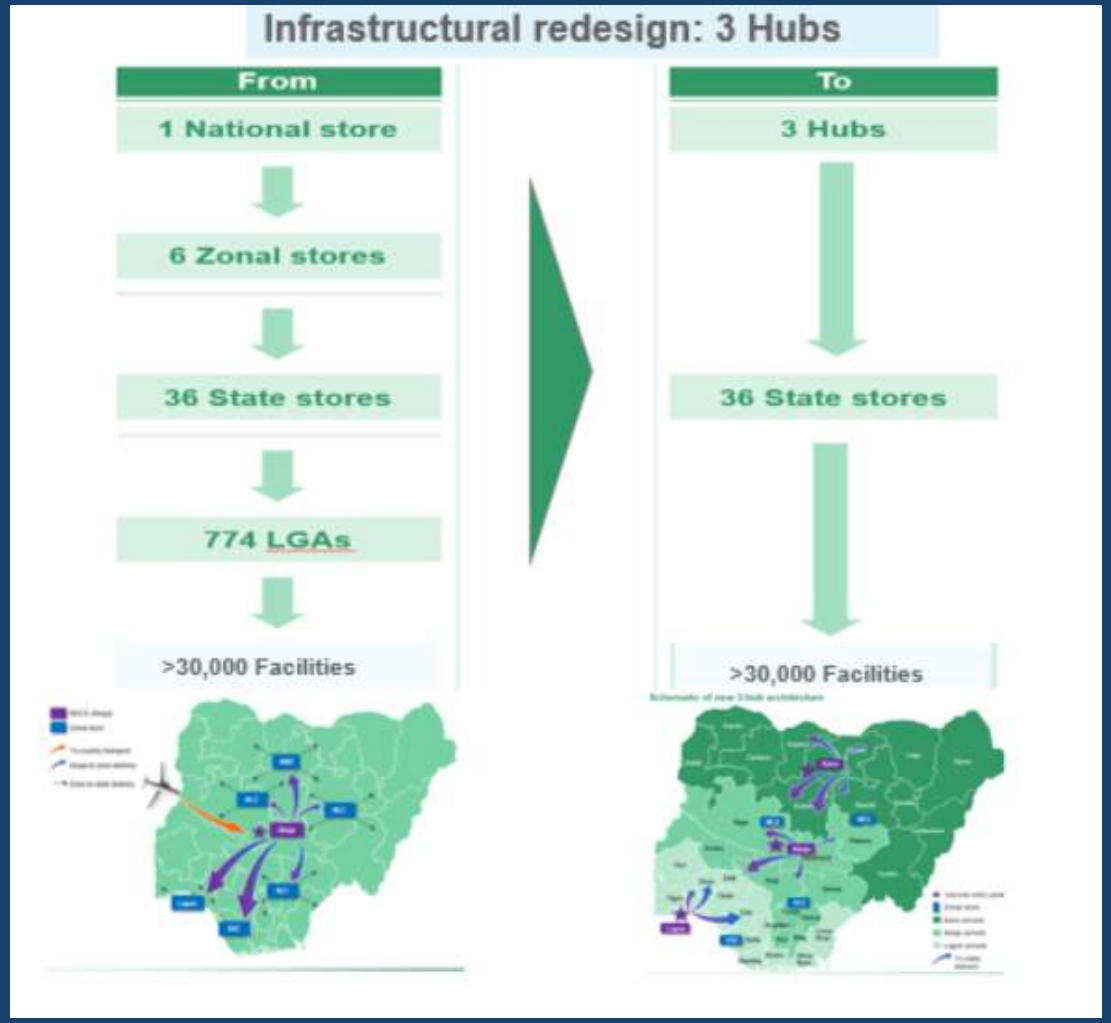
Cold "Ball and" Chain Issues: Inadequate cold chain storage, Nigeria 2019



Cold chain equipment status in low- and lower-middle-income countries in 2014 (n = 57).
http://www.who.int/entity/immunization/programmes_systems/supply_chain/EVM-JS_final.pdf Source: UNICEF/WHO 2016 Joint Statement on effective vaccine management (EVM).

- Need for end to end refrigeration hampers vaccine delivery in many settings
- Only 29% of GAVI countries met minimum temperature control standards (2013)
- Cold chain issues account for a significant proportion of immunization costs
- Last mile delivery requires heroic effort

Cold Chain Issues:
Inadequate cold chain storage, Nigeria 2019



- 59% of wards in Nigeria are currently CCE unequipped
- 48% of available CCE are not functional
- 93% of service points in Nigeria have <8hrs of grid power supply
- Total CCE improvement costs (10 years) $151,171,651
- > 30,000 Health Care Facilities

Can taking vaccine out of the cold chain improve coverage?

- Monovalent Hepatitis B vaccine (HepB) is heat stable, making it suitable for storage outside cold chain (OCC) at 37 C^{o} for 1 month
- In the Solomon Islands, 13 facilities maintained monovalent HepB birth dose (HepB-BD) OCC for up to 28 days
- Among facility and home births timely HepB-BD coverage increased from 30% to 68% and from 4% to 24%, respectively.

Hurdles to Immunization: Packaging Issues

- Multi-dose packages significantly less expensive per dose
  - SII measles 10 dose vial $0.24/dose vs. 5 dose vial $0.32/dose (66% higher)
- Limited cold chain capacity a factor in vial choice
- HCW have to choose between wasting vaccine and missing opportunities to vaccinate

Hurdles to Immunization: Onsite Reconstitution and Filling

- Use of wrong diluents can be fatal
- Contamination can also result in multiple deaths
- Complexity of onsite reconstitution and filling increases vaccinator skill level required
- Multi-dose vials increase risk
- Perfect Storm on the horizon when vaccine associated deaths feed the “anti-vax” movement

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Hurdles to Immunization: Needle Issues

- Needle fears are a barrier to immunization in children and adults*
- Needle stick injury dangerous and costly
- Reuse potential (if not auto-disabling (AD) syringe)
- Injection requires highly skilled vaccinators
- Safe disposal of sharps is costly

* Taddio et al Vaccine 2012

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Potential Solutions for Immunization Hurdles

- In theory - ideal vaccines would be thermostable, unit dose, needle free and not require reconstitution
- Need to work with customers to develop vaccine delivery solutions that meet needs and willingness to pay
- *How likely are we to provide needed vaccines to "Everyone, Everywhere" if we do not find solutions to improve access?*

Questions to PDVAC

- What is the role of PDVAC in the area of vaccine delivery technologies, in parallel with VIPS and as VIPS concludes?
  - Work with immunization programs to define full marginal value and prioritize delivery characteristics and technologies according to value for new and existing vaccines?
  - Develop guidance for delivery characteristics and innovations similar to PDVAC priority pathogen specific vaccines?
  - Incorporate delivery considerations into priority antigen specific guidance to encourage integration of delivery considerations early in vaccine development?

Catch 22

Not now!

Vaccines in development are in a race to get to market.

Incorporating new delivery technologies can add complexity and increase the time to market.

Too late!

Difficult to prioritize vaccine delivery technologies for vaccines already in use.

Thanks

VIPS - Vaccine Innovation Prioritisation Strategy

(focusing on vaccine product attributes)

Marion Menozzi-Arnaud, Gavi

Birgitte Giersing, WHO

June 2019

Presentation objectives

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

- Update PDVAC on the progress of VIPS
- Share initial high-level outcomes of the first prioritisation phase

VIPS: Vision and goal

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

VISION

- **Innovation** is one of the **Alliance priorities** for shaping markets to the benefit of Gavi-supported countries
- In this strategic period, the Alliance aims to pursue a common agenda of **driving vaccine product innovation to better meet country needs** and **support Alliance goals on immunisation coverage and equity**

GOAL

- **Prioritise innovations in vaccine product attributes** to provide greater clarity to manufacturers and partners to make investment decisions

Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

VIPS is a close Alliance-wide collaboration effort

World Health Organization

Gavi The Vaccine Alliance

unicef

BILL & MELINDA GATES foundation

PATH

CLINTON HEALTH ACCESS INITIATIVE

VIPS also relies on a Steering Committee: an independent and expert advisory body

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

17 experts bring the following expertise:

- **National immunisation programme** financing and implementation
- **Coverage and equity** barriers and challenges
- Infectious disease **epidemiology** / **vaccine-preventable disease control**
- **Health impact analysis** / modelling
- **Vaccine** innovations, **R&D**, upstream product development.

9 members are also PDVAC or IPAC members to ensure alignment.

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VIPS includes two analytical and prioritisation phases

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Phase I – Initial prioritisation of innovations

From December 2018 to June 2019

- Under **Phase I,** innovations will be analysed in terms of:
  - Their **characteristics and potential public health value;**
  - Their **potential 'breadth of use'** (applicability to several antigens) based on technical feasibility.

Phase II – Final prioritisation of innovations paired with antigens

From July 2019 to December 2019

- **In Phase II,** the prioritised innovations in Phase I will be paired with antigens in scope of VIPS for **further detailed analyses and prioritisation**.

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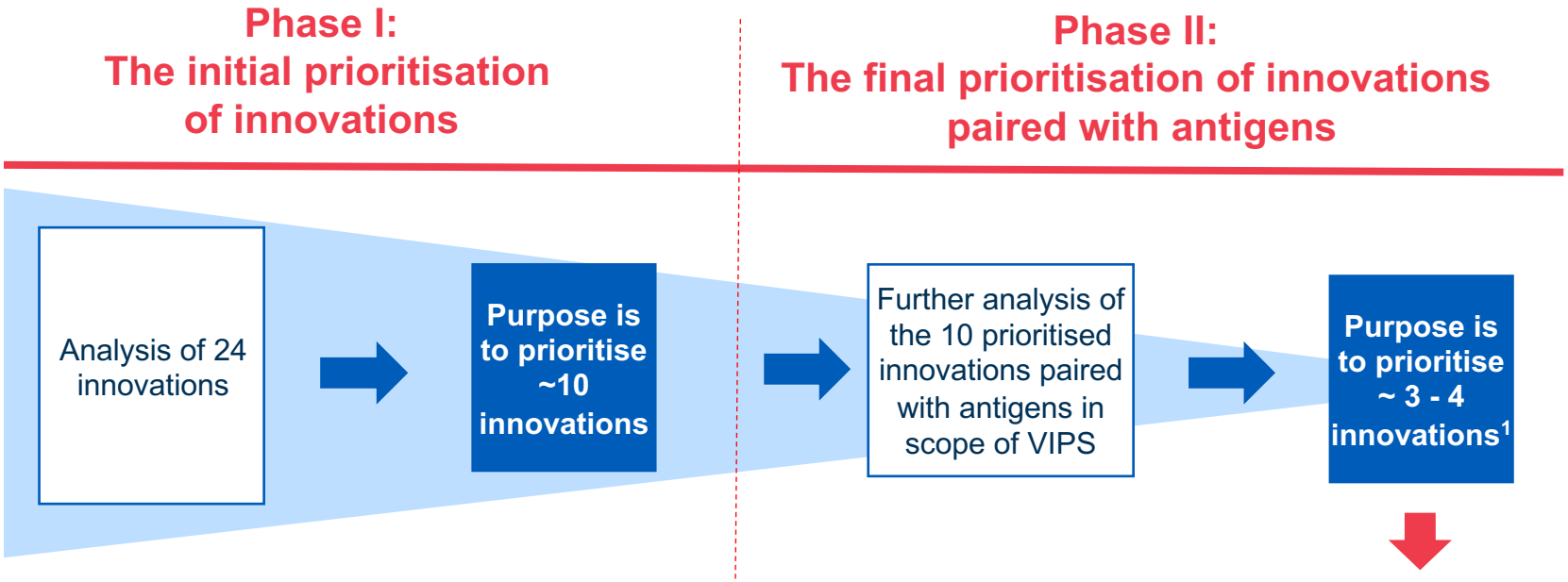
Overall prioritisation 'aim' and VIPS deliverables

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

We are here



A report will be published, with the aim to send signals to innovation developers, vaccine manufacturers and partners on most valuable innovations, rationale and recommendations for next steps and to inform the research agenda

(both Phase I and II outcomes will be communicated at the same time)

[1] Purpose is to prioritise innovations "themselves", "as platforms", however if relevant it will be signaled for which individual antigens/vaccines or types of vaccines the innovation is seen to be most valuable.

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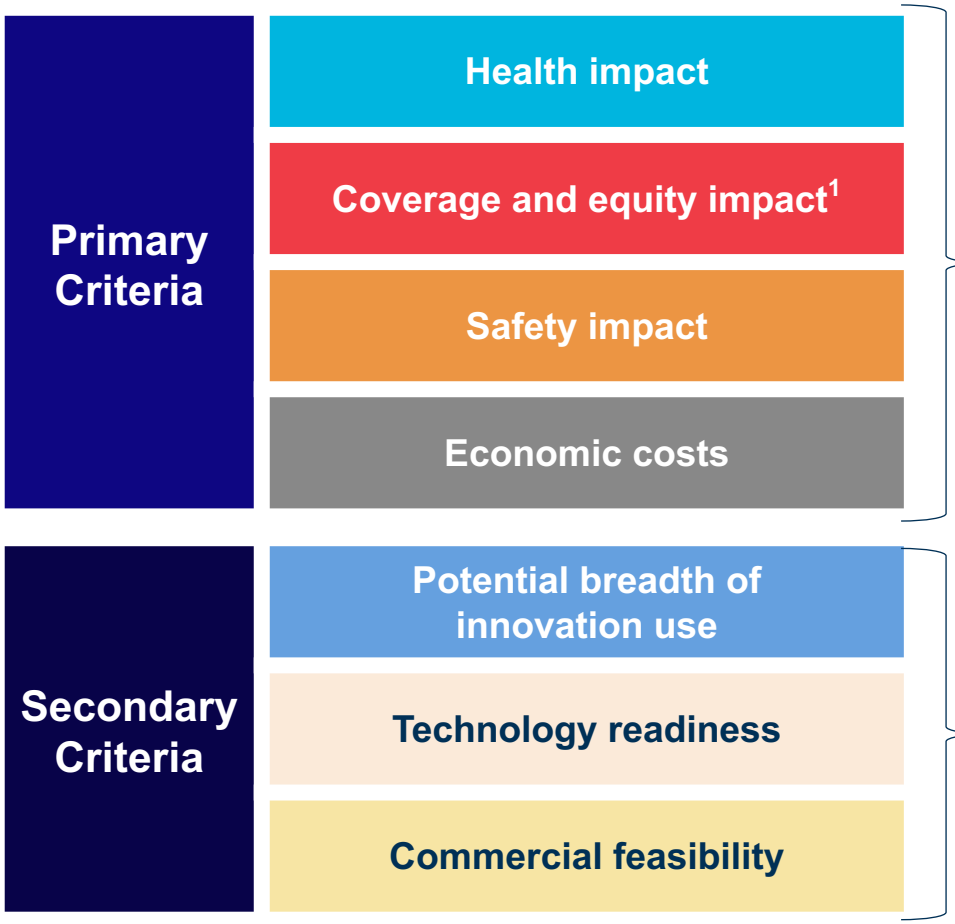
Under Phase I, 24 innovations have been assessed

Innovation Category	Innovation type
Primary vaccine container (without delivery device)	Blow-fill-seal (BFS) primary containers
	Dual chamber vials
Integrated primary container and delivery technology	Compact prefilled auto-disable devices (CPAD) – 3 subtypes
	Single-chamber cartridge injectors
	Dual-chamber delivery devices
	Microarray patches (MAP) – 2 subtypes
	Prefilled polymer BFS dropper/dispensers
	Prefilled dry-powder intranasal devices
	Solid-dose implants (with applicator)
	Sub-lingual dosage forms
	Oral fast-dissolving tablets

Innovation Category	Innovation type
Delivery technology (not pre-filled)	AD sharps-injury protection (SIP) syringes
	Disposable syringe jet injectors (DSJI) – 2 subtypes
	ID syringes – 3 subtypes
Formulation	Heat stable/controlled temperature chain (CTC) qualified liquid formulations
	Heat stable/ CTC qualified dry formulations
	Freeze damage resistant liquid formulations
Packaging and safety	Bundling devices
	Reconstitution vial adapters
	Plastic needles (for reconstitution)
Labelling	Freeze indicator on primary vaccine container
	Combined Vaccine vial Monitor (VVM) and Threshold Indicator (TI)
	Barcodes
	Radio Frequency Identification (RFID)

VIPS evaluation framework includes primary and secondary criteria – both will support the prioritisation exercise



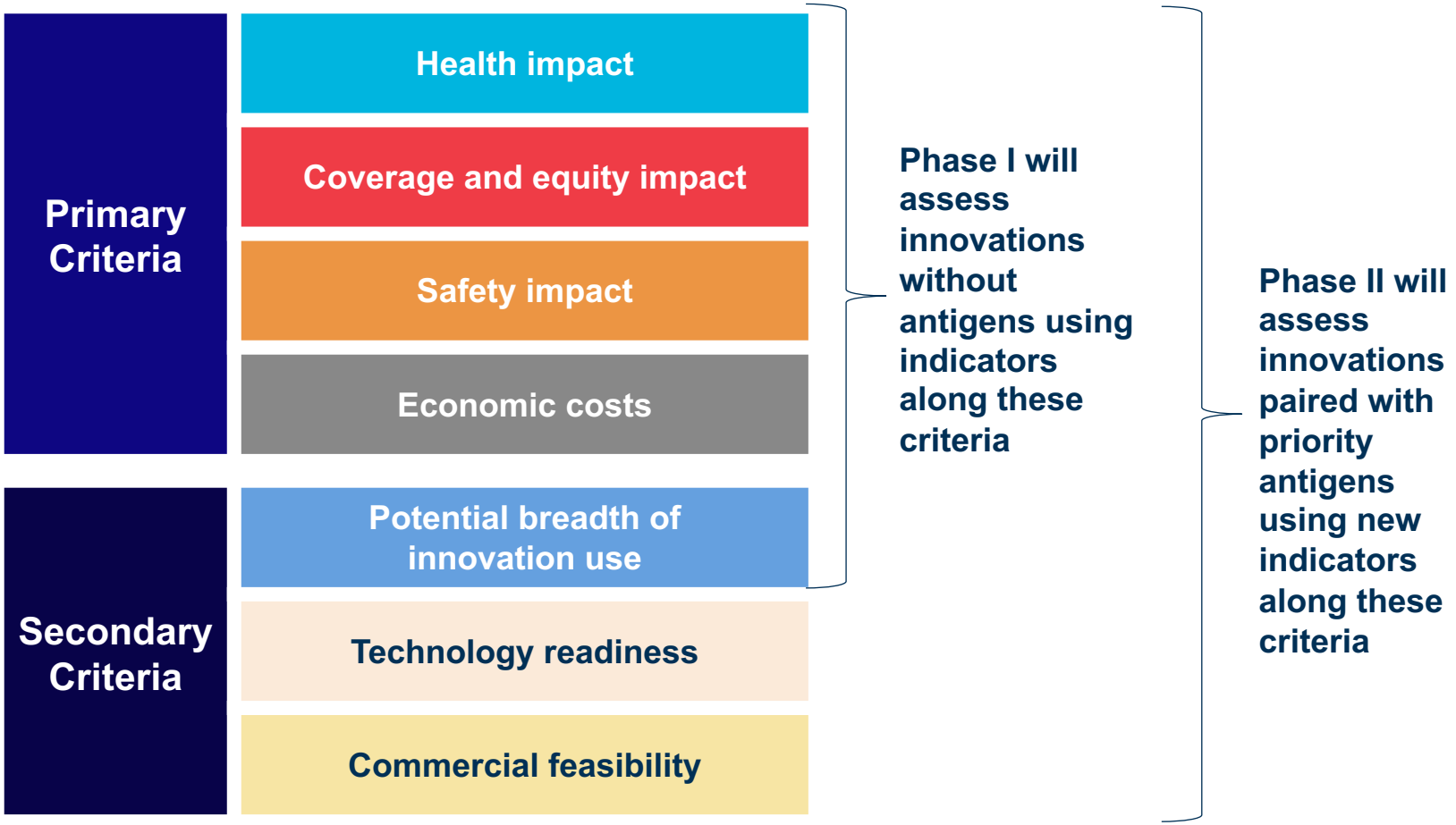
Will be used to **qualitatively score and rank candidates in terms of public health value** – against a comparator

Will be used to provide **additional context to support the prioritisation** – in an absolute manner

[1] Although coverage and equity measures are typically a subset of the health impact criteria, given the importance of improved coverage and equity as one of the ultimate objectives of VIPS, it was decided to have Coverage and Equity as a separate criterion.

VIPS evaluation framework includes different and complementary indicators for Phase I and Phase II

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY



Evaluation framework for Phase I

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

	Criteria	Indicators
Primary ranking criteria	**Health Impact**	• Ability of the innovation to withstand **heat exposure** • Ability of the innovation to withstand **freeze exposure**
	Coverage and Equity impact	• **Ease of use** • Potential to reduce **stock outs** based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities • **Acceptability** of the innovation to patients/caregivers
	Safety impact	• Likelihood of **contamination** • Likelihood of **needle-stick injury**
	Economic costs *(i.e. Delivery and Introduction and recurrent costs)*	• Total **cost of storage and transport** of commodities per dose • Total **cost of the time spent by staff** per dose • Total **cost of introduction and recurrent costs** (not otherwise accounted for)
Secondary criteria	**Potential breadth of innovation use**	• Applicability of the innovation to **one or several types of vaccines** • Ability of the innovation to facilitate **novel vaccine combination**

Some indicators were assigned more importance based on country inputs

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Primary ranking criteria	VIPS criteria	Indicator	RI facility	RI community	Campaigns
Primary ranking criteria	Health impact	Ability of the vaccine presentation to withstand **heat exposure**	+	++	++
		Ability of the vaccine presentation to withstand freeze exposure			
	Coverage & equity impact	**Ease of use**	+	+	++
		Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities			
		Acceptability of the vaccine presentation to patients/caregivers		+	+
	Safety impact	**Likelihood of contamination**			+
		Likelihood of needle stick injury			
	Economic costs *(i.e. Delivery and Introduction and recurrent costs)*	Total economic **cost of storage / transport** of commodities per dose	+		
		Total economic **cost of the time spent by staff** per dose	++	++	+
		Total economic cost of one-time / upfront purchases or investments required to introduce the vaccine presentation and of recurrent costs associated with the vaccine presentation (not otherwise accounted for)			

++ Give significantly more importance in evaluation

\+ Give more importance in evaluation

Keep weight neutral

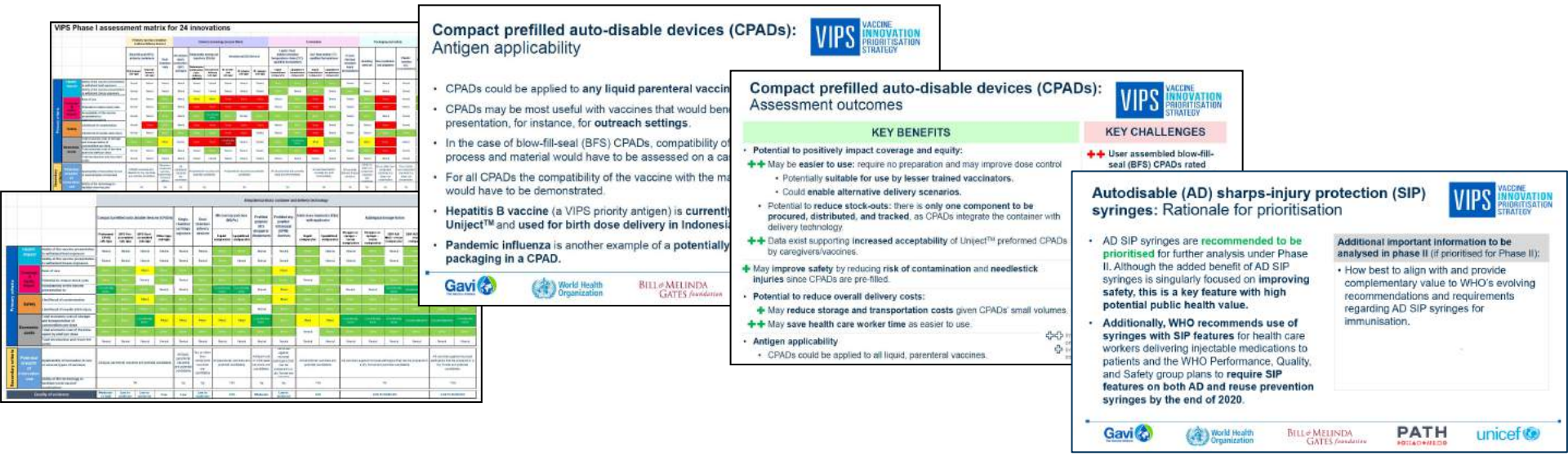
[1] The VIPS framework indicators have been assigned a level of importance (i.e. significantly more importance or more importance) based on countries' inputs and prioritised barriers to immunisation and vaccine product attributes for the 3 different use-settings. The indicators that have not been assigned an importance level by countries are kept neutral.

VIPS Phase I prioritisation process

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Prioritisation process was **qualitative** and based on **4 steps**:

1 2 3 4



Potential **public health benefits** using the primary criteria and indicator assessment and scores

Secondary criteria, especially the **breadth of antigen applicability** based on technical feasibility

Relative benefits across 'similar' innovations or innovations that address same delivery issues, e.g. reconstitution

Additional insights and expert knowledge

Process for defining the list of priority antigens

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Define a long list of vaccines / antigens

Prioritise based on predefined criteria proposed by the VIPS SC

Apply additional considerations and criteria

Preliminary list of 17 priority antigens (10 licensed Vx and 7 pipeline Vx candidates)

Get feedback on initial antigen prioritization strategy and list from IVB (vaccine focal points)

Validation of Ag prioritization strategy and list with PDVAC & IPAC

Define specific issues / problem statements per antigen that could be addressed through VIPS technology innovations

Validation and ranking of 'problem statements' for priority antigens

In Phase II, the prioritised innovations in Phase I will be further analysed with 17 antigens (10 licensed, 7 pipeline)

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

VIPS priority antigens – LICENSED antigen/ vaccine or family of vaccines
Men Vaccines
M or R containing
DT containing
Hepatitis B (birth dose)
Human papillomavirus (HPV)
Poliovirus, inactivated (IPV)
Rabies
Rotavirus
Typhoid (Salmonella typhii),
Yellow Fever (YF)

VIPS priority antigens – PIPELINE specific candidate identified for each antigen
Enterotoxigenic E coli (ETEC)
Ebola
Human immunodeficiency virus (HIV)
Influenza (pandemic)
Mycobacterium tuberculosis (next generation)
Respiratory syncitial virus (RSV)
Malaria (RTS,S & next generation)

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Selection criteria for the VIPS priority antigens

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

These 17 antigens have been selected based on several criteria, including:

- For **existing vaccines**, preferentially select those that are **WHO PQ'd, GAVI funded and UNICEF procured**
- Prioritize antigens that have an **elimination or eradication agenda**
- Pathogens likely to cause an outbreak, target atypical population, benefit from dose sparing
- Standard multi-dose vial w/ preservative not feasible
- Prioritize antigens that have **a robust pipeline or number of producers** (both for prelicensed and licensed vaccines)
- Unique delivery considerations, e.g. HepB: 40% of deliveries are outside of health facility, by community volunteers.
- For pipeline, select the most advanced, with highest probability of success

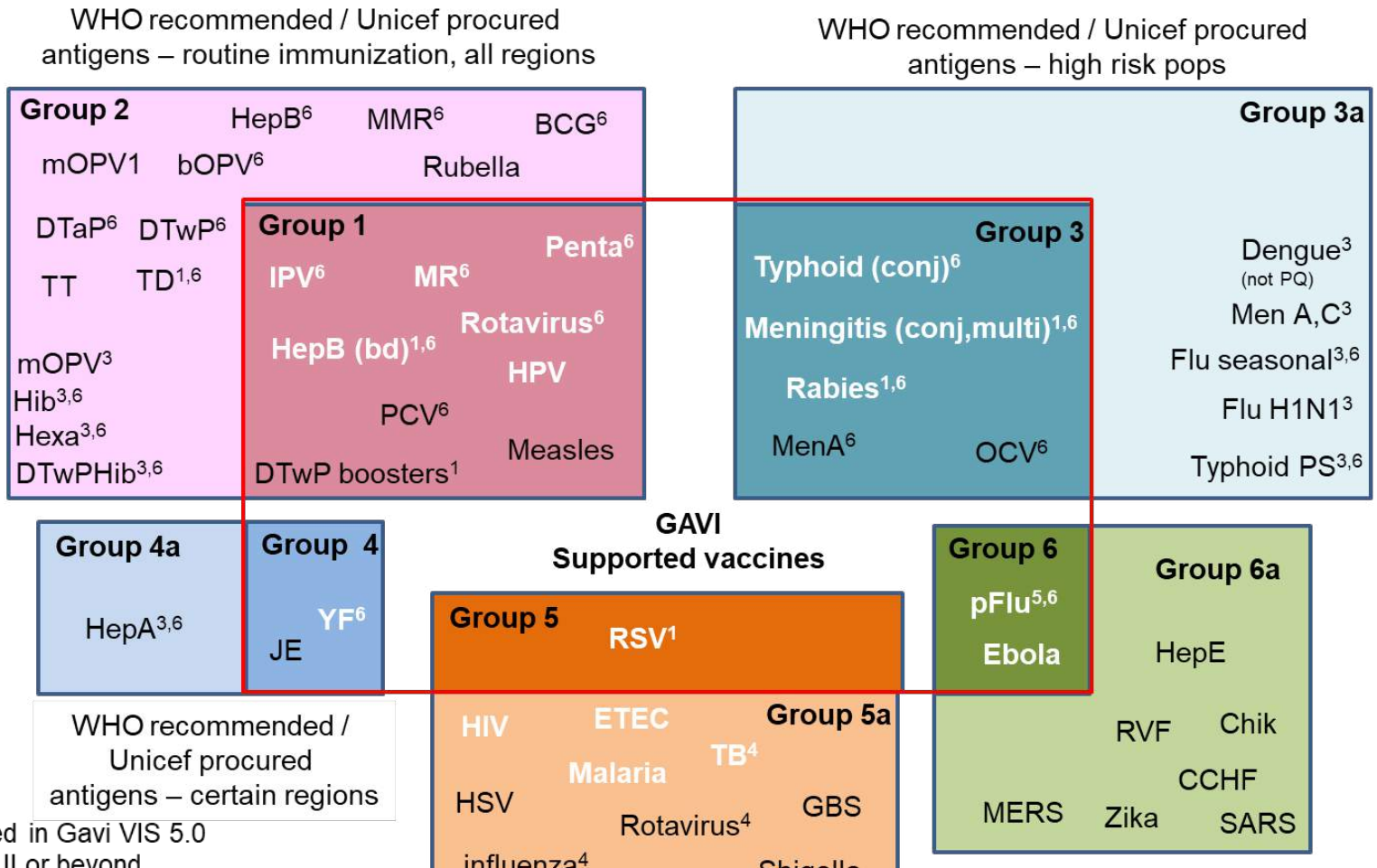
Prioritization of pipeline (unlicensed vaccine) candidates

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Antigen	Vaccine candidate	Platform	Phase	Rationale for inclusion	Reference
Malaria	RTS,S	Adjuvanted recombinant protein (ARP)	IV	Potential for inclusion of fractional dose in schedule (currently 4 doses)	NCT03806465
Ebola	rVSV-ZEBOV	viral vector	compassionate use	Requires storage at -80°C	https://www.who.int/ebola/drc-2018/faq-vaccine/en/
Human immunodeficiency virus (HIV)	P5: ALVAC/ gp120 + MF59	viral vector + ARP	IIb/III	Heterologous prime boost approach, requiring 2 different vaccines in the same regimen	NCT02968849
Influenza (pandemic)	VAL-506440	lipid nanoparticle (LNP)-formulated, modified mRNA	I	Novel vaccination platform with applicability to emergency response pathogens	NCT03076385
Mycobacterium tuberculosis	VPM1002	recombinant BCG	II/III	New generation BCG approaches in late stage clinical development still require ID administration	NCT03152903
Respiratory syncitial virus (RSV)	ResVax	ARP	III	Potential for near term licensure; use of mapping innovations that could facilitate delivery in LMICs	NCT02624947
Enterotoxigenic E coli (ETEC)	Etvax	Inactivatedwhole cell + adjuvant	IIb	Complex formulation, including multiple components	EUCTR2016-002690-35-FI

Distribution of selected antigens within the vaccine landscape

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY



KEY:

1 Included in Gavi VIS 5.0
2 Phase II or beyond
3 Not procured by UNICEF
4 Next generation
5 Gavi learning agenda
6 PAHO Revolving Fund

Evaluation framework for Phase II (1/2)

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

	Criteria	Indicators
Primary ranking criteria	**Health Impact**	• Vaccine **efficacy** • Vaccine **effectiveness** • Ability of the innovation to withstand heat exposure[1] • Ability of the innovation to withstand freeze exposure[1]
	Coverage and equity impact	• Number of fully or partially **immunised individuals** (relative to target pop) • Ease of use[2] • Presentation which helps prevent **missed opportunities due to reluctance to open MDV without preservative**
	Safety impact	• Number of vaccine product-related **adverse events** • Likelihood of contamination[2]
	Economic costs *(i.e. Commodity, Delivery and Introduction and recurrent costs)*	• Total **cost of a vaccine regimen with the innovation**, including wastage • Total **cost of delivery technology(ies)** used for the vaccine regimen, including wastage • Total **cost of safety boxes** used for the vaccine regimen, incl wastage • Total cost of storage and transport of commodities (per vaccine regimen)[1] • Total cost of the time spent by staff (per vaccine regimen)[1] • Total cost of introduction and recurrent costs (not otherwise accounted for)[1]

[1] Same indicators as for Phase I but further assessed under Phase II due to the antigen/vaccine pairing

[2] This indicator is re-assessed in Phase II only when the comparator for a specific vaccine is a MDV, requiring a new evaluation – The comparator SDV is assessed in Phase I

Evaluation framework for Phase II (2/2)

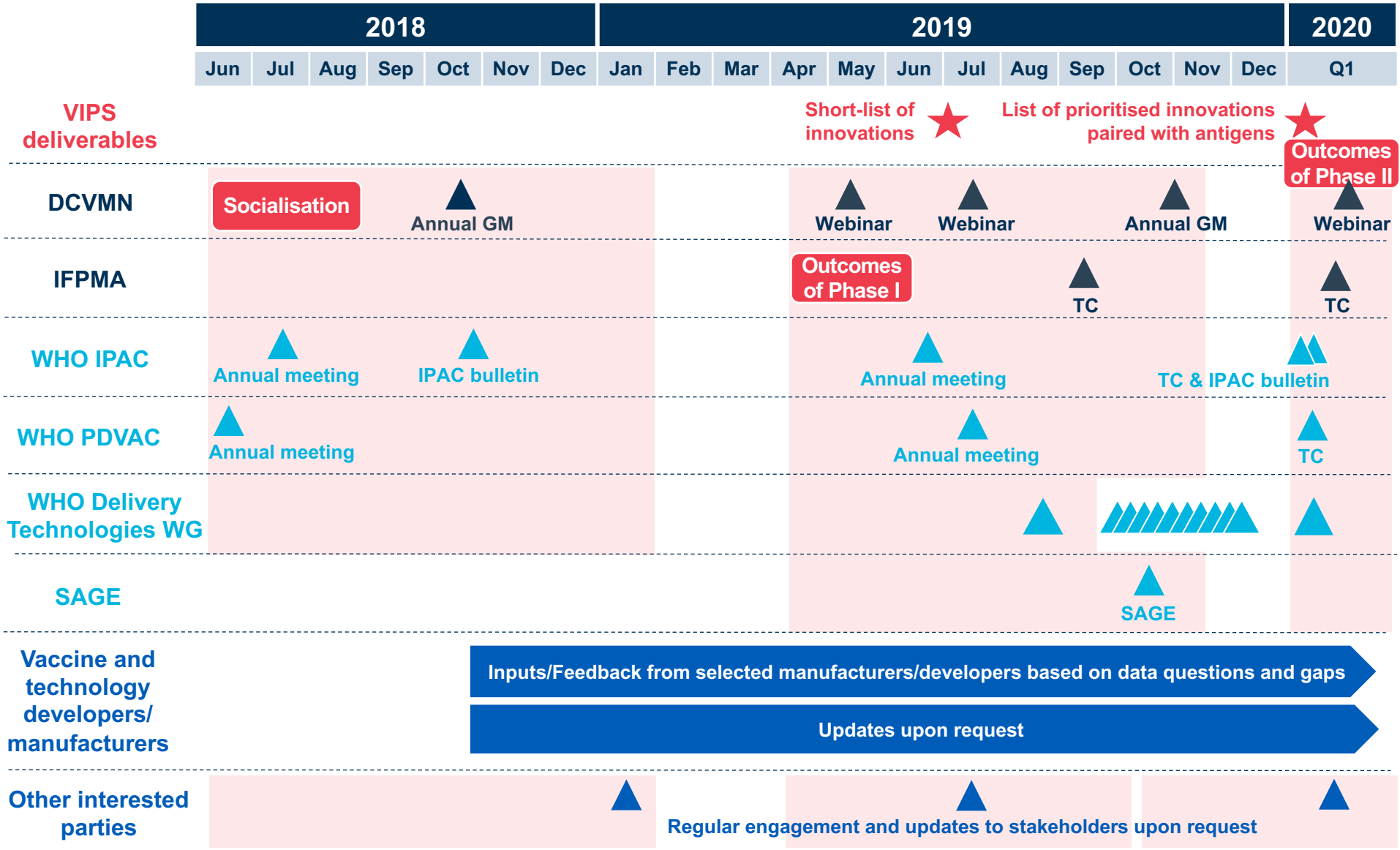
VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

	Criteria	Indicators
Secondary ranking criteria[1]	**Technology readiness**	• **Clinical development** pathway complexity • **Technology development** challenges • **Regulatory** pathway complexity • Complexity of **manufacturing** the innovation • Robustness of the innovation **pipeline**
	Commercial feasibility	• Potential breadth of **market size** • Existence of **partnerships** to support development and commercialisation • Known **barriers to global access** to the innovation • **Stakeholders' interest**

[1] These criteria will be evaluated in an absolute manner, not relative to a comparator.

In Phase II, the VIPS team will further engage with industry

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY



VIPS engagement with Delivery Technologies Working Group

- The VIPS team will engage with the DT-WG under Phase II with the objectives to:

  - Update broader set of immunization stakeholders, **including industry,** on VIPS objectives, process, and progress.

  - Provide feedback on VIPS prioritised innovations for Phase II from the perspective of technical feasibility, manufacturability, regulatory hurdles, alignment with manufacturer priorities, and incentives needed to encourage product development and uptake.

High level outcomes of Phase I prioritisation

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

VIPS Steering Committee has recommended 2 short-lists of innovations for further analysis under Phase II.

5 'upstream' innovations have been recommended for deeper analysis with antigens under Phase II

4 mostly 'downstream' innovations have been recommended for lighter analysis with antigens under Phase II (as innovations are more broadly applicable to antigens) **and/or understanding of required support for scale up.**

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High level outcomes of Phase I prioritisation

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

5 'upstream' innovations recommended for deeper analysis with antigens under Phase II

- Microarray patches (MAPs)
- Solid-dose implants (as a 'back-up' to MAPs)
- Compact prefilled auto-disable devices (CPADs)
  - Separately and then combined with heat stable/ qualified liquid formulations
- Heat stable/controlled temperature chain (CTC) qualified liquid formulations
- Dual-chamber delivery devices
  - Separately and then combined with heat stable/ CTC qualified dry formulations

4 more 'downstream' innovations recommended for lighter analysis with antigens and/or understanding of required support under Phase II

- Combined Vaccine Vial Monitor (VVM) and Threshold Indicator (TI)
- AD sharps-injury protection (SIP) syringes
- Freeze damage resistant liquid formulations
- Barcodes / Radio Frequency Identification (RFID) *(no further analysis with antigens)*

Post 2019 VIPS aspirational vision

VIPS VACCINE INNOVATION PRIORITISATION STRATEGY

Beyond prioritisation and signalling, the Alliance recognises the need to support development and/or uptake of the prioritised innovations

Beyond 2019

Depending on Gavi 5.0 mandate and resources, **the Alliance will consider how to support the prioritised innovations beyond prioritisation and signalling**

Depending on each innovation, support may be needed for:

- **Product development**
- **Regulatory pathway**
- **Field studies**
- **Policy**
- **Procurement**
- **Country uptake**
- **Etc.**

Gavi The Vaccine Alliance · World Health Organization · Bill & Melinda Gates foundation · PATH · unicef

June 28, 2019

PATH's Microarray Patch Center of Excellence

2019 Product Development for Vaccines Advisory Committee (PDVAC) Consultation

Darin Zehrung
Medical Devices and Health Technologies Global Program

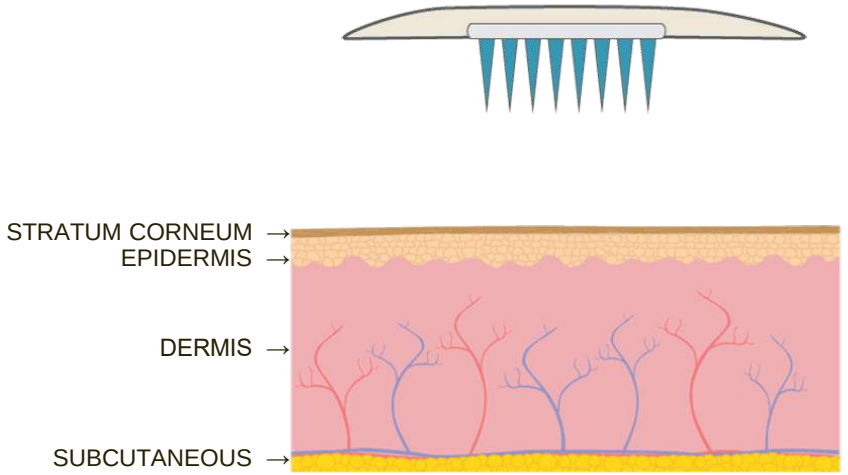
PATH

All photos: PATH unless otherwise noted

Microarray patches (MAPs)

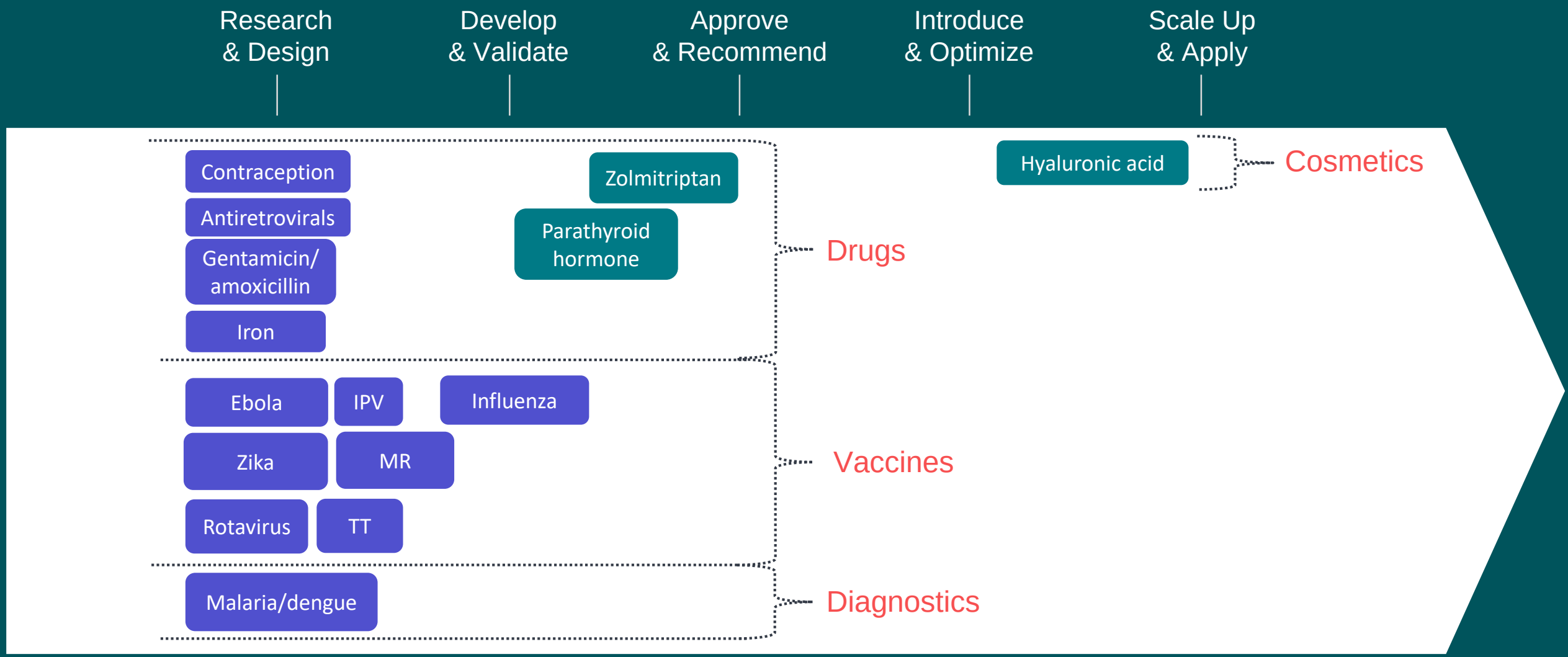
Opportunities

- Enable alternative delivery scenarios—increasing coverage
- Enhance immunogenicity of novel vaccines
- Improve adherence to drug regimens
- Reduce burden on health systems



Images: PATH/Patrick McKern

MAP development status



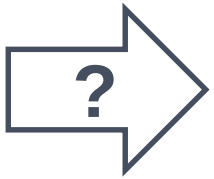
Abbreviations: LMIC, low- and middle-income country; MAP, microarray patch; MR, measles/rubella; TT, tetanus toxoid; IPV, inactivated poliovirus vaccine.

Challenges

Advancing MAPs for use in LMICs

Product-specific focus limits opportunity for platform-wide efficiencies

Siloed information



Unclear pathway to manufacturing scale-up and regulatory approval

Uncertain market potential in LMICs

Abbreviations: LMIC, low- and middle-income country; MAP, microarray patch.

PATH

PATH has established a MAP Center of Excellence

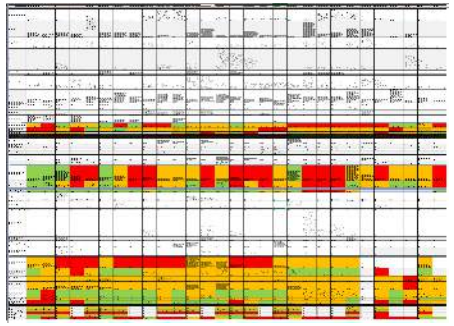
GOAL: Advance MAPs as a technology platform for high-priority needs in LMICs

Project donor:
Department for International Development

Abbreviations: LMIC, low- and middle-income country; MAP, microarray patch.

Development of short list of high-potential MAP applications

Background research



Stakeholder feedback

Key Questions	Rapid evaluation spreadsheet	Notes
Value proposition	**The case for manufacturers, regulators, and purchasers**	
Is it cheaper (cost of the current presentation)?	*Row 48 (commercial viability): Are the MAPS COGs lower? Will we say either "Higher" or "Higher"?* *Row 47 (commercial viability): Is the vCOG lower?* **All are Maybe/Maybe?**	If it's really cheap/inexpensive, probably not a good candidate for a map. Interviewees noted the price sensitivity, particularly for essential medicines.
	Suggest adding a new row with the **cost of the existing presentation** *and then create bins, with the lowest cost taken out of consideration.*	Could also look at vaccines/drugs that currently use or are candidates for pre-filled syringes.
	Row 7 (disease background): Disease control goals *Row 8 (disease background): Current donor/GH support*	Another way of looking at this is price sensitivity. What type of donor support? Would there be an institutional buyer? Also, does this relate to MAP development or chance size?
	Row 10: size of potential high income market	Could subsidize costs for LMICs, also could provide proof of concept/hint to market.
Is it simpler/easier to use for system, provider, or patient?	*Row 27 (programmatic benefits): presentation challenges, current presentation?* *Row 28 (programmatic benefits): potential for enhanced thermostability?* *Row 29: Increases cold-chain/logistics issue*	This applies to very few, would need to be clear on the VP that this would provide. Clear benefit for LMIC.
	Row 24: potential for increased efficacy	Does this include allowing for fractional dosing, reducing wastage? Also ease to use.
	Suggest adding a new row with a focus on age the vaccine or drug is given.	More than one interviewee suggested a MAP could fill a gap for the **pediatric population**. This was also a finding of the PQ MAP value proposition work.
Is it more convenient?	**Sub-questions:** *does it reduce barriers to access? Does it improve the TPP?*	
	Suggest adding a new row for vaccines: Is it **part of** *the* **routine EPI program?**	Stakeholder interviewees suggested that this would be difficult to beat existing options in terms of price. However, vaccines that are given at unusual intervals may benefit (increase access) by being made available in a

Key indicators for consideration

- Potential health impact.
- Probability of technical and regulatory success.
- Potential commercial viability.

Short list of high-potential MAP applications

Abbreviations: MAP, microarray patch.

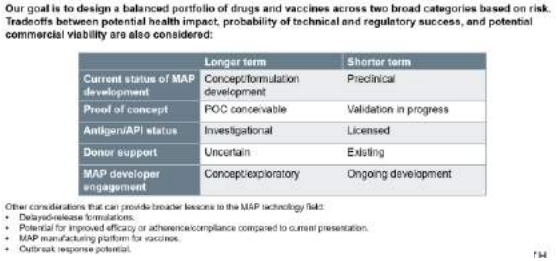
Prioritization of MAP applications for CoE portfolio

In-depth analysis of high-potential MAP applications

Literature research

SAG, DFID & expert review

Portfolio strategy analysis



Our goal is to design a balanced portfolio of drugs and vaccines across two broad categories based on risk. Tradeoffs between potential health impact, probability of technical and regulatory success, and potential commercial viability are also considered:

	Longer term	Shorter term
Current status of MAP development	Concept/formulation development	Preclinical
Proof of concept	POC conceivable	Validation in progress
Antigen/API status	Investigational	Licensed
Donor support	Uncertain	Existing
MAP developer engagement	Concept/exploratory	Ongoing development

Other considerations that can provide broader lessons to the MAP technology field:

- Delayed-release formulations.
- Potential for improved efficacy or adherence/compliance compared to current presentation.
- MAP manufacturing platform for vaccines.
- Outbreak response potential.

Abbreviations: CoE, Center of Excellence; DFID, Department for International Development; MAP, microarray patch; SAG, Scientific Advisory Group.

MAP Center of Excellence Portfolio Strategy

Advancing MAP platform

Generation of information and resources that will broadly support the MAP technology field.

Complementary support for lead products

For priority MAP products that are already the focus of **coordinated product development efforts**, PATH will **fill information gaps** to **catalyze** more rapid advancement.

- Measles-rubella vaccine
- Hormonal contraceptive

Formative support for early-stage, high-impact candidates

For **high-priority** candidates at an **early stage** of development, PATH will generate data to **determine feasibility** and **demonstrate value** to potential development partners and global health stakeholders.

- HPV vaccine
- Rabies vaccine
- HIV treatment and prevention

Abbreviations: HPV, human papillomavirus; MAP, microarray patch.

Platform-wide support

Outbreak response

- Assessment of opportunities and challenges of using MAPs for outbreak response vaccination

Regulatory Working Group

- Identify Critical Quality Attributes
- Develop test methods for pharmacopoeia standard
- Assess risks of low bioburden manufacturing

Manufacturing

- Gap assessment
- Scale-up equipment information
- Workshop

Dissemination

- MAP resources website
- Newsletter
- Publications


PATH

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Microarray Patch Center of Excellence

Welcome from the director

IN THIS ISSUE

I'm excited to share the first issue of our newsletter focused on providing news, information, milestones, and technical resources from the new PATH Microarray Patch Center of Excellence.

Together with the community of microarray patch (MAP) developers, industry, and global health stakeholders, our MAP Center of Excellence will lead efforts to establish the feasibility of MAPs as a technology platform that is still in early-stages of development for vaccines and drugs needed in low-resource settings. Our work under this four year grant aims to mobilize and coordinate a strategic effort to identify, assess, and accelerate high-priority health applications for MAP technology.

MAPs provide a revolutionary approach with the potential to transform delivery of vaccines, drugs, and diagnostics. The sticker-like patches have an array of micro-structures, which contain medication that painlessly dissolves in the skin. If advanced, MAPs could offer patients a needle-free way to take drugs and vaccines and provide health systems with a simplified way to supply, store, and administer drugs in the clinic.

The Center of Excellence will leverage PATH's experience in advancing high-impact vaccine and pharmaceutical technologies and delivery devices. For the past decade, PATH has taken a

Darin Zehnung

PATH

Product-specific support

Target product profile

Formulation & preclinical research

User needs evaluation

Human factors/usability

Regulatory strategy

Cost effectiveness analysis

Manufacturing assessment

Business case

June 28, 2019

Delivery Technologies Working Group

2019 Product Development for Vaccines Advisory Committee (PDVAC) Consultation

Darin Zehrung
Medical Devices and Health Technologies

PATH

All photos: PATH unless otherwise noted

Overview

- Scope and functions of DTWG (revised 2019)
- Structure and membership
- Accomplishments of DTWG (2015 – 2018)
- VIPS engagement

Abbreviations: DTWG, Delivery Technology Working Group; VIPS, Vaccine Innovation Prioritisation Strategy.

DTWG overview

Goals

- Provide platform to enable industry and the public sector to engage in constructive dialogue on the presentation, packaging, and delivery aspects of vaccine products.
- Optimize innovation and maximize the appropriateness of immunization products for public-sector use.

Objectives

- Inform industry about LMIC programmatic preferences and operational realities.
- Sensitize the public sector to industry constraints and economic realities of investing in product development.

Immunization Practices Advisory Committee

Abbreviations: DTWG, Delivery Technology Working Group; IPAC, Immunization Practices Advisory Committee; LMIC, low- and middle-income countries.

DTWG scope

- Primary vaccine containers: the immediate receptacle in direct contact with the vaccine as distributed for sale.
- Delivery devices and technologies: stand-alone or combination vaccine/device technologies used to administer a vaccine by a specific vaccine administration route.
- Formulation with the objective of thermostability, i.e., the combination of chemical and biological substances used to produce a final vaccine product.
- Packaging, i.e., the containers that enclose or protect vaccine products for distribution, storage, sale, and use.

Abbreviation: DTWG, Delivery Technology Working Group.

Functions of DTWG

- Raise awareness of novel vaccine delivery technologies.
- Provide expert review from multiple sectors.
- Identify bottlenecks for private-sector investment.
- Create subgroups to provide guidance around individual technology categories (e.g., target product profiles).
- Conduct stakeholder consultations on programmatic or product development aspects.
- Facilitate bilateral consultations between technology developers and the public sector.

Abbreviation: DTWG, Delivery Technology Working Group.

DTWG structure

Leadership

- Jointly led by PATH and WHO.

Membership

- Up to 15 members with diverse expertise in global public health, product development and manufacturing, vaccine policy and implementation, LMIC immunization programs, new delivery technologies, and marketing.
- Representation from IPAC, PDVAC, VIPS, IFPMA, DCVMN, MSF, JSI, UNICEF, and Gates Foundation.

Abbreviations: DSVMN, Developing Countries Vaccine Manufacturer's Network; DTWG, Delivery Technology Working Group; IFPMA, International Federation of Pharmaceutical Manufacturers & Associations; IPAC, Immunization Practices Advisory Committee; JSI, John Snow, Inc.; LMIC, low- and middle-income countries; MSF, Médecins Sans Frontières; PDVAC, Product Development for Vaccines Advisory Committee; UNICEF, United Nations Children's Fund; VIPS, Vaccine Innovation Prioritisation Strategy; WHO, World Health Organization.

PATH

DTWG accomplishments 2015 – 2018

- Development of Global Vaccine Action Plan (GVAP) Platform Delivery Technology (Indicator G4.2) report and recommendations.
- Reviewed nine vaccine technologies, MR MAP TPP, and two usability studies.
- Developer/manufacturer engagement through conferences and workshops.
- Review of Vaccine Technology Impact Assessment (VTIA) economic analysis tool, Total Systems Effectiveness (TSE) project, and Vaccine Innovation Prioritisation Strategy (VIPS).
- DTWG has been on hiatus since 2018 to focus on launching VIPS.

Abbreviations: BFS, blow-fill-seal; DTWG, Delivery Technology Working Group; MAP, microarray patch; MR, measles rubella; TPP, target product profile.

Stevanato – Frog design

Photo: Stevanato Group

BD Unijject 2.0

Photo: BD

Duoject Vaccject

Photo: Duoject

ApiJect BFS prefilled device

Vaxess MIMIX™ MAP

Photo: Vaxess

Global Good BFS ampoule

Photo: Global Good

Inovio CELLECTRA-3P applicator

Photos: Inovio

Technology progress facilitated by consultation with DTWG

- MAPs
  - TPP developed.
  - Country evaluations completed.
  - WHO MR MAP Product Development Working Group established.
  - Increased focus from MAP developers globally.

- Blow-fill-seal compact prefilled autodisable devices (CPADs)
  - Prototypes developed.
  - Country evaluations completed.
  - Cost analysis conducted.
  - TPP established.

Abbreviations: DTWG, Delivery Technology Working Group; MAP, microarray patch; MR, measles rubella; TPP, target product profile; WHO, World Health Organization.

VIPS consultations

Purpose of DTWG engagement

- Update broader set of immunization stakeholders, including industry, on VIPS objectives, process, and progress
- Provide feedback on 10 VIPS prioritized innovations from the perspective of technical feasibility, manufacturability, regulatory hurdles, alignment with manufacturer priorities, and incentives needed to encourage product development and uptake.

Abbreviations: DTWG, Delivery Technology Working Group; VIPS, Vaccine Innovation Prioritisation Strategy.

Overview of PATH's Vaccine Product Innovations grant

Donor: Bill & Melinda Gates Foundation

Intended outcomes:

1. Global consensus is reached on prioritized vaccine innovations for further investment and market shaping via the Gavi VIPS initiative.
2. Global consensus is reached on a TSE process and tools for countries to assess hypothetical products, in the context of their immunization barriers, as well as make informed vaccine product procurement decisions.
3. New vaccine product innovations are continually identified and assessed, and pathways are created to advance those innovations that are aligned with VIPS recommendations.

Duration

October 2018 to February 2022

Abbreviations: TSE, Total System Effectiveness; VIPS, Vaccine Innovation Prioritisation Strategy.

Thank you

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Microarray patch resources website:
https://www.path.org/programs/mdht/mapresources/


PATH