Group B streptococcus vaccine R&D

Update on WHO IVB activities

PDVAC

June 2019
Why pursue a maternal GBS vaccine?

- 21.7 million pregnant women colonized with GBS
- Increased risk of maternal death but unable to quantify
- At least 33,000 Maternal invasive GBS disease
- Increased risk of neurodevelopmental disability but unable to quantify
- At least 57,000 stillbirths
- Increased risk of neurodevelopmental disability but unable to quantify
- 90,000 infant deaths (mostly neonatal)
- 10,000 with neurodevelopmental disability after meningitis, unable to quantify after sepsis
- At least 320,000 Infants with GBS Sepsis and Meningitis
- Including at least 7,000 also with neonatal encephalopathy
- Up to 3.5 million Preterm births attributable to GBS

PLUS UNQUANTIFIED CASES, DEATH AND DISABILITY FOR UNMEASURED GBS DISEASE AND UNMEASURED BURDEN IN NON-INVASIVE GBS DISEASE

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
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

**MINERVAX** 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)

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

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.

<table>
<thead>
<tr>
<th>Projected VE (LL 95% CI of 25%)</th>
<th>Expected disease rate in placebo recipients (cases per 1000 livebirths)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>80%</td>
<td>30,000</td>
</tr>
<tr>
<td>60%</td>
<td>90,000</td>
</tr>
</tbody>
</table>

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.
• 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
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
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

1. **Prevention and Epidemic Control**
   - Through development and enhanced access to affordable vaccines, effective prophylactic measures and targeted control interventions

2. **Diagnosis and Treatment**
   - Achieving access to appropriate diagnostic tests at all levels of care, to enhance surveillance and ensure patients can be promptly treated through effective antibiotics and adjunctive care

3. **Disease Surveillance**
   - Encompassing all main causes of bacterial meningitis and their sequelae to guide meningitis control policies and accurately monitor progress toward goals

4. **Support and Care for people & their families after meningitis**
   - So that the heavy burden of meningitis sequelae is recognized and alleviated in every community around the world

5. **Advocacy and Engagement**
   - To raise public and political awareness of meningitis as a health priority and improve health-seeking behavior and access to control measures

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

Summary of updated WHO minimum recommended VPD surveillance standards

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
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

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 pregnancy)
• 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)
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.

## Category

<table>
<thead>
<tr>
<th>1) Burden (disease)</th>
<th>2) Cost of investment</th>
<th>3) Impact of investment (economic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>Total cost</td>
<td>Incremental Cost-Effectiveness Ratio (ICER)</td>
</tr>
<tr>
<td>Cases</td>
<td>Direct cost of treatment</td>
<td>Direct cost savings</td>
</tr>
<tr>
<td>Long-term sequelae/Disability</td>
<td>Indirect cost of treatment</td>
<td>Total revenues from vaccine sales</td>
</tr>
<tr>
<td>Cases- Outbreaks</td>
<td></td>
<td>Benefit-Cost Ratio (BCR) estimates</td>
</tr>
<tr>
<td>Deaths- Outbreaks</td>
<td></td>
<td>Indirect cost savings</td>
</tr>
<tr>
<td>Number of outbreaks</td>
<td></td>
<td>Return on Investment (ROI) estimates</td>
</tr>
<tr>
<td>DALY</td>
<td></td>
<td>Procurement cost per death or case averted</td>
</tr>
</tbody>
</table>

## Components

- Deaths
- Cases
- Long-term sequelae/Disability
- Cases- Outbreaks
- Deaths- Outbreaks
- Number of outbreaks
- DALY
- Total cost
- Direct cost of treatment
- Indirect cost of treatment
- Vaccine price
- Quantity demanded
- Total procurement cost
- Total delivery cost
- Country introduction scenario (adoption forecast)
- Clinical trials (Phase 1 - 3)
- Discovery
- Total development cost
- Cost of capital
- Manufacturing
- Post-marketing activities
- Process development
- Marketing
- Regulatory
- Deaths averted (loss saved)
- Cases averted
- DALY averted
- Number vaccinated per year
- Long term sequelae or disability averted

## Frequency

- **Deaths**: 26
- **Total cost**: 15
- **Direct cost of treatment**: 13
- **Indirect cost of treatment**: 12
- **Vaccine price**: 17
- **Total procurement cost**: 11
- **Total delivery cost**: 10
- **Country introduction scenario (adoption forecast)**: 5
- **Clinical trials (Phase 1 - 3)**: 4
- **Discovery**: 4
- **Total development cost**: 4
- **Cost of capital**: 3
- **Manufacturing**: 3
- **Post-marketing activities**: 3
- **Process development**: 3
- **Marketing**: 2
- **Regulatory**: 2
- **Deaths averted (loss saved)**: 17
- **Cases averted**: 12
- **DALY averted**: 7
- **Number vaccinated per year**: 7
- **Long term sequelae or disability averted**: 5

## Impact of Investment (broad)

- Equity (health)
- Herd immunity
- Synergy with other health interventions
- Macroeconomic impact
- Financial protection
- Public sector budget impact
- Educational and cognitive outcomes
- Equity (private expenditure)
- Antimicrobial resistance
- Disease control cost averted
- HIV-related costs
- Health system capacity
- Vaccine financing landscape
- Alignment with global health goals
- Presence of other interventions
- Production capacity
- Vaccine attributability (PPA, TPP elements)
- Vaccine supply
- Institutional role & constraints
- Epidemiologic & environmental constraints
- Market landscape
- Probability of success
- Risk & risk mitigation strategies
- Current R&D landscape
- Alignment with target audience goals
- Future epidemic potential
- Sociocultural elements (beyond gender)
- Gender gap
- Scientific challenges
- Regulatory process
- Climate change

## Other considerations for implementation

- 0
- 5
- 10
- 15
- 20
What outcomes of GBS should be included?

- Maternal, perinatal and child outcomes including cases, deaths and disability
- Major focus in the past
- NOW

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.


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**
Infants with GBS from cohort re-enrolment / registries / records

Matched controls

Capturing long-term outcomes

- Physical, neurological, cognitive, educational, psychological, economic outcomes including QALY/DALY weights (current and retrospective).
- Covariates including household socioeconomic status/wealth.

Birth

- Measure costs of acute care

Late childhood / adolescence
Capturing long-term health and economic outcomes

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

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

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

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.

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

**Audience: research funders**
- Key requirements:
  - Value of information
  - Cost-effectiveness
  - Broader return on investment
  - Economic surplus

**Audience: manufacturers**
- Key requirements:
  - Market shaping
  - Appropriate price range
  - Financial return on investment

**Audience: donors and countries**
- Key requirements:
  - Cost-effectiveness and budget impact within basic benefits package
  - Equity (extended CEA)

**Translation gap**
- Bench research
- Clinical studies

**Marketing gap**
- Clinical studies
- Licensure and market access

**Implementation gap**
- Licensed vaccine
- Population programme
<table>
<thead>
<tr>
<th>Workstream 1</th>
<th>Workstream 2</th>
<th>Workstream 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of GBS disease and medical need for a vaccine</td>
<td>Economic evaluations of maternal GBS vaccination</td>
<td>Operationalisation of GBS vaccine implementation</td>
</tr>
<tr>
<td>- Systematic review of GBS serotype distributions</td>
<td>- Systematic review of acute costs of neonatal sepsis and meningitis</td>
<td>- Expert group agreed on research questions on operationalization of GBS vaccination in countries</td>
</tr>
<tr>
<td>- Protocol for cohort re-enrolment / electronic database review</td>
<td>- Review of costs of maternal vaccine delivery</td>
<td>- Maternal immunization data repository (situation analysis and identification of factors affecting of GBS vaccination during pregnancy)</td>
</tr>
</tbody>
</table>
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?
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 role as a facilitator

CEPI's role as a funder
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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Lassa and MERS</th>
<th>Lassa and MERS</th>
<th>Lassa</th>
<th>Nipah</th>
<th>Lassa</th>
<th>MERS</th>
<th>Lassa, MERS, and Nipah</th>
<th>Nipah</th>
<th>Chik</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology</td>
<td>Measles vector</td>
<td>DNA</td>
<td>rVSVΔG</td>
<td>rVSVNC4ΔG</td>
<td>Protein sub-unit</td>
<td>MVA</td>
<td>ChAdOx</td>
<td>Measles vector</td>
<td>Measles vector</td>
</tr>
<tr>
<td>Investment (up to)</td>
<td>$37.5 M</td>
<td>$56.0M</td>
<td>$54.9 M</td>
<td>$25.0 M</td>
<td>$36.0 M</td>
<td>$36.0 M</td>
<td>$19.0M</td>
<td>$30 M</td>
<td>$21 M</td>
</tr>
</tbody>
</table>

### Rapid response Platforms

<table>
<thead>
<tr>
<th>Disease</th>
<th>Rabies, flu &amp; Marburg</th>
<th>RSV, flu &amp; MERS</th>
<th>Rabies, Yellow Fever &amp; Lassa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology</td>
<td>Self-amplifying RNA</td>
<td>Molecular clamp</td>
<td>RNA</td>
</tr>
<tr>
<td>Investment (up to)</td>
<td>$8.4M</td>
<td>$10.6M</td>
<td>$34M</td>
</tr>
</tbody>
</table>

As of 28th June 2019

Note: This is publicly announced funding. Some of these have options for further investment.
CEPI priority pathogen portfolio

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

Ebola
- Investments in clinical trials to support licensure

As of 28th June 2019
## Lassa portfolio – Vaccine profiles

<table>
<thead>
<tr>
<th>Technology</th>
<th>Themis</th>
<th>Inovio</th>
<th>IAVI</th>
<th>Emergent Biosolutions</th>
<th>Oxford Janssen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles virus Live rep</td>
<td>DNA + Electroporation</td>
<td>rVSVΔG Live replicating</td>
<td>rVSVNC₄ΔG Live replicating</td>
<td>Chimp Adeno Rep incomp</td>
<td></td>
</tr>
<tr>
<td>Lassa transgene Josiah strain</td>
<td>GPC + NP</td>
<td>GPC</td>
<td>GPC</td>
<td>GPC</td>
<td>GPC</td>
</tr>
<tr>
<td>Project status</td>
<td>Preclinical</td>
<td>Phase I¹</td>
<td>Preclinical Historically protection observed in NHP²</td>
<td>Preclinical</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

¹NCT 03805984  
²Geisbert et al PLOS Medicine 2005
### MERS-CoV portfolio - Vaccine profiles

<table>
<thead>
<tr>
<th>Technology</th>
<th>Oxford/Janssen</th>
<th>IDT</th>
<th>Themis</th>
<th>Inovio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chimp Adeno Rep incompetent</td>
<td>MVA Rep incompetent</td>
<td>Measles virus Live replicating</td>
<td>DNA + Electroporation</td>
</tr>
<tr>
<td>MERS transgene</td>
<td>Spike</td>
<td>Spike</td>
<td>Spike</td>
<td>Spike</td>
</tr>
<tr>
<td>Project status</td>
<td>Phase I study ongoing¹ (different cell line)</td>
<td>Phase I study ongoing² (different cell line)</td>
<td>Preclinical</td>
<td>Phase I data with IM injection³. Phase I/II ID ongoing in Korea⁴</td>
</tr>
</tbody>
</table>

¹NCT03399578  ²NCT03615911  ³NCT02670187  ⁴NCT03721718
# Nipah Portfolio: Vaccine Profiles

<table>
<thead>
<tr>
<th></th>
<th>University of Tokyo</th>
<th>Profectus Biosciences</th>
<th>University of Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology</td>
<td>Measles virus</td>
<td>Recombinant subunit Alum</td>
<td>Chimp adeno Repl. incompetent</td>
</tr>
<tr>
<td>Nipah transgene</td>
<td>Glycoprotein</td>
<td>Hendra Glycoprotein</td>
<td>Glycoprotein</td>
</tr>
<tr>
<td>Project status</td>
<td>Pre-clinical protection data in Syrian hamster and AGMs ¹</td>
<td>Pre-clinical PoC and tox. study performed²</td>
<td>Pre-clinical protection in Syrian hamster³</td>
</tr>
</tbody>
</table>

¹Yoneda et al PLoS one, 2013  
²Bossart et al Sci Transl Med, 2012  
³Van 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
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
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

As of 28th June 2019
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
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
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

- 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 equipment status in low- and lower-middle-income countries in 2014 (n = 57).

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 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
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
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

• Update PDVAC on the progress of VIPS
• Share initial high-level outcomes of the first prioritisation phase
VIPS: Vision and goal

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
VIPS is a close Alliance-wide collaboration effort
VIPS also relies on a Steering Committee: an independent and expert advisory body

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.
VIPS includes two analytical and prioritisation phases

**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.
Overall prioritisation ‘aim’ and VIPS deliverables

We are here

Phase I: The initial prioritisation of innovations

Purpose is to prioritise ~10 innovations

Analysis of 24 innovations

Further analysis of the 10 prioritised innovations paired with antigens in scope of VIPS

Phase II: The final prioritisation of innovations paired with antigens

Purpose is to prioritise ~3-4 innovations

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.
Under Phase I, 24 innovations have been assessed

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

<table>
<thead>
<tr>
<th>Innovation Category</th>
<th>Innovation type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery technology (not pre-filled)</td>
<td>AD sharps-injury protection (SIP) syringes</td>
</tr>
<tr>
<td></td>
<td>Disposable syringe jet injectors (DSJI) – 2 subtypes</td>
</tr>
<tr>
<td></td>
<td>ID syringes – 3 subtypes</td>
</tr>
<tr>
<td>Formulation</td>
<td>Heat stable/controlled temperature chain (CTC) qualified liquid formulations</td>
</tr>
<tr>
<td></td>
<td>Heat stable/ CTC qualified dry formulations</td>
</tr>
<tr>
<td></td>
<td>Freeze damage resistant liquid formulations</td>
</tr>
<tr>
<td>Packaging and safety</td>
<td>Bundling devices</td>
</tr>
<tr>
<td></td>
<td>Reconstitution vial adapters</td>
</tr>
<tr>
<td></td>
<td>Plastic needles (for reconstitution)</td>
</tr>
<tr>
<td>Labelling</td>
<td>Freeze indicator on primary vaccine container</td>
</tr>
<tr>
<td></td>
<td>Combined Vaccine vial Monitor (VVM) and Threshold Indicator (TI)</td>
</tr>
<tr>
<td></td>
<td>Barcodes</td>
</tr>
<tr>
<td></td>
<td>Radio Frequency Identification (RFID)</td>
</tr>
</tbody>
</table>
VIPS evaluation framework includes primary and secondary criteria – both will support the prioritisation exercise.

**Primary Criteria**
- Health impact
- Coverage and equity impact
- Safety impact
- Economic costs

**Secondary Criteria**
- Potential breadth of innovation use
- Technology readiness
- Commercial feasibility

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.

**Primary Criteria**
- Health impact
- Coverage and equity impact
- Safety impact
- Economic costs

**Secondary Criteria**
- Potential breadth of innovation use
- Technology readiness
- Commercial feasibility

Phase I will assess innovations without antigens using indicators along these criteria.

Phase II will assess innovations paired with priority antigens using new indicators along these criteria.
### Evaluation framework for Phase I

#### Criteria

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

#### Secondary criteria

| Secondary criteria | Potential breadth of innovation use | |
|--------------------|------------------------------------| |
| **Secondary criteria** | **Potential breadth of innovation use** | |
| **Criteria**       | **Potential breadth of innovation use** | |
| **Indicators**     | **Potential breadth of innovation use** | |
| - Applicability of the innovation to **one or several types of vaccines** | • Applicability of the innovation to **one or several types of vaccines** | • Applicability of the innovation to **one or several types of vaccines** |
| - Ability of the innovation to facilitate **novel vaccine combination** | • Ability of the innovation to facilitate **novel vaccine combination** | • Ability of the innovation to facilitate**novel vaccine combination** |
Some indicators were assigned more importance based on country inputs

<table>
<thead>
<tr>
<th>VIPS criteria</th>
<th>Indicator</th>
<th>RI facility</th>
<th>RI community Campaigns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health impact</td>
<td>Ability of the vaccine presentation to withstand heat exposure</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Ability of the vaccine presentation to withstand freeze exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ease of use</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Coverage &amp; equity impact</td>
<td>Potential to reduce stock outs based on the number of separate components necessary to deliver the vaccine or improved ability to track vaccine commodities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety impact</td>
<td>Acceptability of the vaccine presentation to patients/caregivers</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Likelihood of contamination</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Likelihood of needle stick injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economic costs (i.e. Delivery and Introduction and recurrent costs)</td>
<td>Total economic cost of storage / transport of commodities per dose</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total economic cost of the time spent by staff per dose</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>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)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Primary ranking criteria**

Give significantly more importance in evaluation

Give more importance in evaluation

Keep weight neutral

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

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

1. **Potential public health benefits** using the primary criteria and indicator assessment and scores
2. **Secondary criteria, especially the breadth of antigen applicability** based on technical feasibility
3. **Relative benefits across ‘similar’ innovations or innovations that address same delivery issues, e.g. reconstitution
4. **Additional insights and expert knowledge**
Process for defining the list of priority antigens

1. Define a long list of vaccines / antigens
2. Prioritise based on predefined criteria proposed by the VIPS SC
3. Apply additional considerations and criteria
4. Validation of Ag prioritization strategy and list with PDVAC & IPAC
5. Preliminary list of 17 priority antigens (10 licensed Vx and 7 pipeline Vx candidates)

- Validation and ranking of ‘problem statements’ for priority antigens
- Define specific issues / problem statements per antigen that could be addressed through VIPS technology innovations
- Get feedback on initial antigen prioritization strategy and list from IVB (vaccine focal points)
In Phase II, the prioritised innovations in Phase I will be further analysed with 17 antigens (10 licensed, 7 pipeline)

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

<table>
<thead>
<tr>
<th>VIPS priority antigens – <strong>PIPELINE</strong> specific candidate identified for each antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterotoxigenic E coli (ETEC)</td>
</tr>
<tr>
<td>Ebola</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)</td>
</tr>
<tr>
<td>Influenza (pandemic)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis (next generation)</td>
</tr>
<tr>
<td>Respiratory syncitial virus (RSV)</td>
</tr>
<tr>
<td>Malaria (RTS,S &amp; next generation)</td>
</tr>
</tbody>
</table>
Selection criteria for the VIPS priority antigens

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

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Vaccine candidate</th>
<th>Platform</th>
<th>Phase</th>
<th>Rationale for inclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>RTS,S</td>
<td>Adjuvanted recombinant protein (ARP)</td>
<td>IV</td>
<td>Potential for inclusion of fractional dose in schedule (currently 4 doses)</td>
<td>NCT03806465</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)</td>
<td>P5: ALVAC/ gp120 + MF59</td>
<td>viral vector + ARP</td>
<td>IIb/III</td>
<td>Heterologous prime boost approach, requiring 2 different vaccines in the same regimen</td>
<td>NCT02968849</td>
</tr>
<tr>
<td>Influenza (pandemic)</td>
<td>VAL-506440</td>
<td>lipid nanoparticle (LNP)-formulated, modified mRNA</td>
<td>I</td>
<td>Novel vaccination platform with applicability to emergency response pathogens</td>
<td>NCT03076385</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>VPM1002</td>
<td>recombinant BCG</td>
<td>II/III</td>
<td>New generation BCG approaches in late stage clinical development still require ID administration</td>
<td>NCT03152903</td>
</tr>
<tr>
<td>Respiratory syncitial virus (RSV)</td>
<td>ResVax</td>
<td>ARP</td>
<td>III</td>
<td>Potential for near term licensure; use of mapping innovations that could facilitate delivery in LMICs</td>
<td>NCT02624947</td>
</tr>
<tr>
<td>Enterotoxigenic E coli (ETEC)</td>
<td>Etvax</td>
<td>Inactivated whole cell + adjuvant</td>
<td>IIb</td>
<td>Complex formulation, including multiple components</td>
<td>EUCTR2016-002690-35-FI</td>
</tr>
</tbody>
</table>
Distribution of selected antigens within the vaccine landscape

WHO recommended / Unicef procured antigens – routine immunization, all regions

- HepB<sup>6</sup>
- MMR<sup>6</sup>
- BCG<sup>6</sup>
- Rubella
- DTaP<sup>6</sup>
- DTwP<sup>6</sup>
- TT
- TD<sup>1,6</sup>
- mOPV<sup>3</sup>
- Hib<sup>3,6</sup>
- Hexa<sup>3,6</sup>
- DTwPHib<sup>3,6</sup>

WHO recommended / Unicef procured antigens – high risk pops

- Dengue<sup>3</sup>
- (not PQ)
- Men A,C<sup>3</sup>
- Flu seasonal<sup>3,6</sup>
- Flu H1N1<sup>1,6</sup>
- Typhoid PS<sup>3,6</sup>

Group 1

- IPV<sup>6</sup>
- MR<sup>6</sup>
- Rotavirus<sup>6</sup>
- HPV
- PCV<sup>6</sup>
- Measles
- DTwP boosters<sup>1</sup>

Group 2

- mOPV<sup>1</sup>
- bOPV<sup>6</sup>
- Rubella

Group 3

- Typhoid (conj)<sup>6</sup>
- Meningitis (conj,multi)<sup>1,6</sup>
- Rabies<sup>1,6</sup>
- MenA<sup>6</sup>
- OCV<sup>6</sup>

Group 3a

- Dengue<sup>3</sup>
- (not PQ)
- Men A,C<sup>3</sup>
- Flu seasonal<sup>3,6</sup>
- Flu H1N1<sup>1,6</sup>
- Typhoid PS<sup>3,6</sup>

Group 4a

- HepA<sup>3,6</sup>
- YF<sup>6</sup>

Group 4

- JE

GAVI Supported vaccines

- RSV<sup>1</sup>

Group 5

- HIV
- ETEC
- Malaria
- TB<sup>4</sup>
- HSV
- Rotavirus<sup>4</sup>
- GBS
- influenza<sup>4</sup>
- Shigella

Group 5a

- HIV
- ETEC
- Malaria
- TB<sup>4</sup>
- HSV
- Rotavirus<sup>4</sup>
- GBS
- influenza<sup>4</sup>
- Shigella

Group 6

- pFlu<sup>5,6</sup>
- Ebola

Group 6a

- HepE
- RVF
- Chik
- CCHF
- MERS
- Zika
- SARS

PIPELINE Epidemic response Pathogens (phase I and beyond)

PIPECINE Priority antigens based on BoD, unmet public health need (phase II and beyond)

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)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Indicators</th>
</tr>
</thead>
</table>
| **Health Impact** | • Vaccine **efficacy**  
• Vaccine **effectiveness**  
• Ability of the innovation to withstand heat exposure \(^1\)  
• Ability of the innovation to withstand freeze exposure \(^2\) |
| **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)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology readiness</strong></td>
<td>• Clinical development pathway complexity</td>
</tr>
<tr>
<td></td>
<td>• Technology development challenges</td>
</tr>
<tr>
<td></td>
<td>• Regulatory pathway complexity</td>
</tr>
<tr>
<td></td>
<td>• Complexity of manufacturing the innovation</td>
</tr>
<tr>
<td></td>
<td>• Robustness of the innovation pipeline</td>
</tr>
<tr>
<td><strong>Commercial feasibility</strong></td>
<td>• Potential breadth of market size</td>
</tr>
<tr>
<td></td>
<td>• Existence of partnerships to support development and commercialisation</td>
</tr>
<tr>
<td></td>
<td>• Known barriers to global access to the innovation</td>
</tr>
<tr>
<td></td>
<td>• Stakeholders’ interest</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>VIPS deliverables</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCVMN</td>
<td>Socialisation</td>
<td>Annual GM</td>
<td>Webinar</td>
</tr>
<tr>
<td>IFPMA</td>
<td>Annual meeting</td>
<td>IPAC bulletin</td>
<td>Annual meeting</td>
</tr>
<tr>
<td>WHO IPAC</td>
<td>Annual meeting</td>
<td>Annual meeting</td>
<td>Annual meeting</td>
</tr>
<tr>
<td>WHO PDVAC</td>
<td>Annual meeting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO Delivery Technologies WG</td>
<td>Annual meeting</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SAGE**

Vaccine and technology developers/manufacturers

- Inputs/Feedback from selected manufacturers/developers based on data questions and gaps
- Updates upon request

Other interested parties

- Regular engagement and updates to stakeholders upon request
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 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.
High level outcomes of Phase I prioritisation

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

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.
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
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
MAP development status

Research & Design
- Contraception
- Antiretrovirals
- Gentamicin/amoxicillin
- Iron

Develop & Validate
- Zolmitriptan
- Parathyroid hormone

Approve & Recommend
- Hyaluronic acid

Introduce & Optimize
- Drugs
- Vaccines
- Diagnostics
- Hyaluronic acid

Scale Up & Apply
- Cosmetics

Relevant to LMICs
- Iron

Focused on high-income countries
- 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

- Siloed information
- Product-specific focus limits opportunity for platform-wide efficiencies
- 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 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.
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

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

Dissemination

• MAP resources website
• Newsletter
• Publications

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
Product-specific support

- Target product profile
- Formulation & preclinical research
- User needs evaluation
- Human factors/usability
- Regulatory strategy
- Cost effectiveness analysis
- Manufacturing assessment
- Business case
Delivery Technologies Working Group

2019 Product Development for Vaccines Advisory Committee (PDVAC) Consultation

Darin Zehrung
Medical Devices and Health Technologies

All photos: PATH unless otherwise noted
Overview

- Scope and functions of DTWG (revised 2019)
- Structure and membership
- 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.

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.
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.
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.
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.
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

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

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