A year in review
2018-2019
WHO PDVAC meeting
26-28 June 2019

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Overview and objectives of this ‘Year in Review’ presentation

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

- Following this presentation by WHO, Barney Graham (PDVAC member and xx NIAID, NIH) will provide an update on the Universal Influenza Roadmap and associated activities
Broader context: Latest visual for strategic framework

Fig. 6 – The seven strategic priorities for 2021-2030.
What is the scope and objective of PDVAC?

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

- Vaccines
- Monoclonal antibodies
- Delivery technologies
<table>
<thead>
<tr>
<th>Pathogen-specific documents developed by WHO’s PDVAC</th>
<th>Purpose/description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred product characteristics (PPC)</td>
<td>Describe <strong>preferred characteristics</strong> for vaccines <strong>with emphasis on the LMIC use context</strong></td>
</tr>
<tr>
<td>Vaccine R&amp;D roadmap</td>
<td>Provides a <strong>high-level vision, near and long term goals, and strategic framework of priority activities</strong></td>
</tr>
<tr>
<td>Considerations for product development pathways</td>
<td>Considers the manufacturing, clinical development, regulatory, policy and commercialization <strong>pathways and barriers</strong></td>
</tr>
<tr>
<td>Full value of vaccines</td>
<td>Describes the <strong>full health, economic and societal value</strong> of a vaccine to a <strong>broad range of global stakeholders, including from a LMIC perspective, and aims to articulate the full direct (individual) and indirect (population) effects</strong> of a vaccine</td>
</tr>
</tbody>
</table>
Additional guidance to inform product development of pipeline vaccines for LMIC contexts

<table>
<thead>
<tr>
<th>WHO generic guidance that informs vaccine development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Preferred Product Profile for Vaccines (gPPP) (2015)</td>
</tr>
<tr>
<td>Assessing the programmatic suitability of vaccine candidates for WHO prequalification (2014)</td>
</tr>
</tbody>
</table>
## Status of WHO guidance document development for vaccines against PDVAC prioritized pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Landscape analysis*</th>
<th>PPC</th>
<th>RM</th>
<th>Pathways</th>
<th>VP underway</th>
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<tbody>
<tr>
<td>Tuberculosis</td>
<td>✓</td>
<td>✓ (P&amp;T)</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Influenza</td>
<td>✓</td>
<td>✓ (improved Vx)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>GBS</td>
<td>✓</td>
<td>✓ (P&amp;T)</td>
<td>✓ (STI RM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV</td>
<td>✓</td>
<td>✓ (P&amp;T)</td>
<td>✓ (STI RM)</td>
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<tr>
<td>GC</td>
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<td>✓ (✓)</td>
<td>✓ (STI RM)</td>
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<tr>
<td>ETEC</td>
<td>✓</td>
<td>✓ (✓)</td>
<td></td>
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<tr>
<td>Shigella</td>
<td>✓</td>
<td>✓ (✓)</td>
<td>✓ (✓)</td>
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<tr>
<td>GAS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

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

http://www.who.int/immunization/research/ppc-tpp/preferred_product_characteristics/en/
Overview of cross-cutting initiatives

- Value Attribution Framework For Vaccines Against Antimicrobial Resistance
- Total Systems Effectiveness
- Enteric burden of disease (mortality) models
- Vaccine Innovation Prioritization Strategy

Full value of vaccines
New areas of engagement for IVR and PDVAC

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

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

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

Consultation on public health need and potential use cases (combination) funded by BMGF and Wellcome Trust
Horizon scanning: what other vaccines should PDVAC and IVR be tracking going forward?

Historical criteria for engagement:

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

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

Areas of horizon scanning going forward:
Chlamydia, Norovirus, Dengue, Otitis media, Staph aureus, AMR pathogen list, ....
Vaccine development updates for specific priority pathogens
Enteric vaccines development: ETEC

Current ETEC vaccine landscape—Standalones and combinations

**Oral administration**

- ETVAX inactivated (SBH, UG, PATH)
- ACE527 live attenuated (PATH, NVSI, UGA)

**Parenteral injection**

- FTA (PATH, NMRC, IDRI)
- MEFA (ILLU, JHU, PATH)
- LT/ST conjugate toxoids (Univ. of Bergen)
- Flagelin, EtpA, EtaA, EaeH, YghJ (WASHU)

**Preclinical candidates**

- CVD GuaBA mutants expressing ETEC Ags. (UMB, PaxVax)
- ShigETEC (EveliQure)
- Ty21a expressing Shigella LPS and MEFA (Protein Potential)
- STM expressing ETEC, Campy Ags. (IVI, UGA, NMRC, WASHU, WRAIR, Tulane, PATH) (New candidate)

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

- Vaccines in or poised to begin clinical trials; STM = inactivated mutant Shigella with truncated LPS giving conserved protein Ags. greater exposure (Kim et al. 2018, Frontiers in Microbiology)
6-11-month-old infants given the **ETVAX** inactivated whole-cell ETEC vaccine

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

**Ongoing late phase development program in Africa funded by EDCTP**

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

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Licensed</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live</strong></td>
<td><strong>Phase 2</strong></td>
<td><strong>Phase 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD1208S</td>
<td>SC802</td>
<td>Oag-TT conjugate (S. sonnei)</td>
<td>Streptomycin-dep LAV (historic/various)</td>
<td>Historic LAVs no longer in use</td>
</tr>
<tr>
<td>(S. flex 2a)</td>
<td>(S. flex 2a)</td>
<td>(S. sonnei)</td>
<td>(Yugoslav Army/other)</td>
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<tr>
<td>U Maryland/PATH</td>
<td>WRAIR</td>
<td>GMM (S. sonnei)</td>
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<td>GVGH (GSK)</td>
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<tr>
<td><strong>Killed</strong></td>
<td><strong>Phase 2</strong></td>
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<td>TSWC</td>
<td>SC802</td>
<td>Oag-TT conjugate (S. sonnei)</td>
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<tr>
<td>(S. flex 2a)</td>
<td>(S. sonnei)</td>
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<tr>
<td>WRAIR/PATH</td>
<td>WRSS1</td>
<td>GMM (S. sonnei)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(S. sonnei)</td>
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<tr>
<td></td>
<td>WRSS1</td>
<td>Oag Bioconjugate (S. flex 2a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(S. sonnei)</td>
<td>Limmtech (GSK)</td>
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<tr>
<td></td>
<td>WRAIR</td>
<td>Innaplex</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>(S. flex 2a)</td>
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<td></td>
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<td>WRAIR</td>
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<td><strong>Subunit</strong></td>
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<td>Oag Bioconjugate (S. dysenteriae)</td>
<td>Oag Bioconjugate (S. flex 2a)</td>
<td>GMM (S. sonnei)</td>
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<tr>
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<td></td>
<td></td>
<td>WRAIR</td>
<td></td>
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</tr>
</tbody>
</table>

**Notes**
- NIH vaccine never licensed despite efficacy in phase 3

- BMGF funded
- Wellcome funded
- DFID funded
- EU funded

Courtesy of Calman MacLennan, BMGF
### Shigella vaccine candidate pipeline

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<tr>
<td><strong>Live</strong></td>
<td><strong>Killed</strong></td>
<td><strong>Subunit</strong></td>
<td><strong>O-Ag ELISA standardization and development of reference reagents underway (NIBSC)</strong>&lt;br&gt;<strong>WHO consultation on the potential role of CHIM in licensure; question regarding acceptability to LMIC regulators and data requirements for policy</strong>&lt;br&gt;<strong>Engagement of WHO technical standards &amp; norms to convene a regulators to discuss CHIM and immunobridging strategy to historical conjugate candidate</strong></td>
<td></td>
</tr>
<tr>
<td>CVD1208S (S. flex 2a)&lt;br&gt;U Maryland/PATH</td>
<td>SC602 (S. flex 2a)&lt;br&gt;WRAIR</td>
<td>WRSS1 (S. sonnei)&lt;br&gt;WRAIR/PATH</td>
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<tr>
<td>TSWC (S. flex 2a)&lt;br&gt;WRAIR/PATH</td>
<td>GMMA (S. sonnei)&lt;br&gt;GVGH (GSK)</td>
<td>Oag Bioconjugate (S. flex 2a)&lt;br&gt;Limmatech (GSK)</td>
<td>Oag Bioconjugate (S. dysenteriae)&lt;br&gt;Limmatech (GSK)</td>
<td>Invaplex (S. flex 2a)&lt;br&gt;WRAIR</td>
</tr>
</tbody>
</table>
Tuberculosis vaccine development

Next steps:
Move M72/AS01 forward

R&D Technical Roadmap
Public Health Value Proposition
Recent updates:

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

Summary profiles of large-scale efficacy trials

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

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

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

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**Regimen to be selected after Phase 1/2a**

- **Double Prime**
  - Ad26.Mos4.HIV
  - Ad26.Mos2.Gag-Pol
  - Ad26.Mos1.Env (clade B-like)
  - Ad26.Mos2S.Env (clade C-like)

- **Double Boost**
  - gp140 Clade C
  - Soluble trimeric gp140 Env protein with Alum

**OR**

- gp140 Clade C + Mosaic
  - Soluble trimeric gp140 Env proteins with Alum
WHO focus on downstream pathways
IVB – UNAIDS – WHO HIV collaboration

2018 HIV vaccine R&D WHO consultation outcome:
- Expression of key considerations about the down-stream pathway.
- Report submitted to Lancet HIV

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

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

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

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

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

**Health systems preparation, country ownership**
- Engage international, country, community leadership to make sure all perspectives are considered.
- Clarify the role of integrated health care delivery vs dedicated HIV programs
- Identify and enable financing mechanisms in advance
GBS vaccine development: Leading IVB activities

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

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

- Defining RSV epidemiology and its relevance for RSV preventive products

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

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

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

SEVENTY-FIRST WORLD HEALTH ASSEMBLY
Provisional agenda item 12.8

A71/25
12 April 2018

Rheumatic fever and rheumatic heart disease

Report by the Director-General

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

Superficial infection
• Pharyngitis
• Pyoderma

Invasive diseases
• Septicaemia
• Pneumonia, osteomyelitis…
• Necrotising fasciitis

Toxin mediated diseases
• Scarlet fever
• Streptococcal toxic shock syndrome

Post-streptococcal autoimmune sequelae
• Acute rheumatic fever / rheumatic heart disease
• Post-streptococcal glomerulonephritis
Updated estimates of global Strep A burden

<table>
<thead>
<tr>
<th>Disease</th>
<th>Year of Publication</th>
<th>Number of Existing Cases</th>
<th>Number of New Cases Each Year</th>
<th>Number of Deaths Each Year</th>
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</thead>
<tbody>
<tr>
<td>Rheumatic heart disease (RHD)</td>
<td>2017, 2005</td>
<td>33.4 million³, 1.88 million</td>
<td>282,000²</td>
<td>319,000⁶</td>
</tr>
<tr>
<td>History of acute rheumatic fever without carditis, requiring secondary prophylaxis²</td>
<td>2005</td>
<td>1.88 million</td>
<td>188,000⁷</td>
<td>14,000</td>
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<tr>
<td>RHD-related infective endocarditis²</td>
<td>2016</td>
<td>640,000²</td>
<td>134,000²⁰</td>
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<tr>
<td>RHD-related stroke</td>
<td>2016</td>
<td>640,000²</td>
<td>134,000²⁰</td>
<td>134,000²⁰</td>
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<tr>
<td>Acute post-streptococcal glomerulonephritis²</td>
<td>2005</td>
<td>§</td>
<td>472,000</td>
<td>9,000</td>
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<tr>
<td>Invasive group A streptococcal diseases²</td>
<td>2005</td>
<td>§</td>
<td>663,000</td>
<td>163,000</td>
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<tr>
<td>Pyoderma⁹</td>
<td>2015</td>
<td>162 million</td>
<td>616 million</td>
<td>616 million</td>
</tr>
<tr>
<td>Pharyngitis²</td>
<td>2005</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
</tbody>
</table>

All estimates rounded down.

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

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

Ω Inferred from relevant reference.

GAS vaccine R&D technical roadmap
Strategic goals

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

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

While the medical need is highest in high endemicity LMIC, the potential value of a vaccine, primarily for prevention of GAS pharyngitis, skin infections, cellulitis and invasive disease and associated antibiotic use in HIC, is also acknowledged.
February 24th 2019
AU $35m Strep A vaccine funding announced

The Hon Greg Hunt MP
Minister for Health
Member for Flinders

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

MEDIA RELEASE

24 February 2019

$35 Million for Vaccine to End Rheumatic Heart Disease

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

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

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

"Today is a game-changing step," said Minister Wyatt. "Ending RHD is a critical, tangible target to close the gap in Indigenous life expectancy."
Global Strep A vaccine consortium
- Advocacy, coordination, industry liaison, vaccine pipeline
- Contribute to implementation of the WHO Tech R&D Roadmap
- Investment case (Public Health Value Proposition)

Critical aim – a Phase 2b efficacy trial for pharyngitis!
Vaccines for sexually transmitted infections (STIs)
Outline

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

- Global roadmap to advance STI vaccine development
- Critical next steps from pre-vaccine development through vaccine introduction
Current status of the development pathway of STI vaccines

- **Trichomonas**
- **Syphilis**
- **Gonorrhea***
- **Chlamydia**
- **Herpes (HSV)**

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

**HSV** = herpes simplex virus
**Chlamydia** = *Chlamydia trachomatis*
**Gonorrhea** = *Neisseria gonorrhoeae*
**Syphilis** = *Treponema pallidum*
**Trichomonas** = *Trichomonas vaginalis*
HSV vaccines: progress and plans

Toward reducing the impact of genital HSV infection:

Genital ulcer disease
Impact on sexual & reproductive health
Neonatal herpes
HIV acquisition and transmission risk
Progress: HSV vaccine PPCs published

- For prophylactic and therapeutic vaccines
- Strategic public health goals
  - Reducing HSV disease, including neonatal herpes, other effects on SRH
  - Reducing HSV-associated HIV infection, especially in high-burden areas or populations
- Key question: how to get PPCs to key stakeholders and optimize impact

Available at: https://www.who.int/reproductivehealth/publications/HSV-Vaccine-PPCs/en/
Progress and next steps: HSV vaccine full public health value proposition

- Current activities to outline public health and financial rationale for HSV vaccines:
  - Estimating disease burden
    - HSV infections
    - Genital ulcer disease (GUD)
    - HSV-associated HIV infection
    - Neonatal herpes
    - HSV-1 outcomes: oral, CNS, ocular
  - Estimating economic burden
    - Costs of HSV care and treatment
  - Modelling vaccine impact
    - HSV vaccine impact on HSV + HIV
  - Assessing cost-effectiveness
  - Assessing other benefits
473 million prevalent HSV-2 infections

Preliminary WHO estimates for 2016, among 15-49 year-olds

HSV-2 = herpes simplex virus type 2

Source: James et al, manuscript under review
473 million prevalent HSV-2 infections

Preliminary WHO estimates for 2016, among 15-49 year-olds

HSV-2 = herpes simplex virus type 2

Also estimated between ~130-200 million HSV-1 genital infections, mostly in HICs

Source: James et al, manuscript under review
HSV genital ulcer disease (GUD)

Preliminary estimates for 2016, among 15-49 year-olds

- Estimated **180 million people** with at least one episode of HSV GUD in 2016
  - Vast majority due to HSV-2 (95%, 171 million)
  - Sensitive to assumptions: ranged from 138 to 235 million based on recurrence rates used

- Translates into ~**8 billion person-days** with symptoms

Source: Looker et al, manuscript in preparation
HSV-associated HIV infections

Preliminary estimates, PAFs applied to 2016 UNAIDS data for 15-49 year-olds

- PAFs of HIV due to HSV-2 ranged from:
  - 12-13% in Europe and Asia
  - 21% in the Americas
  - 37% in Africa
- Overall >400,000 HIV infections estimated to be related to HSV-2 infection
  - Most in Africa due to high burden of both infections
  - Provides a starting point for understanding

Source: Looker et al, manuscript under review
Summary next steps: HSV vaccine

- Assemble health and economic burden, modeling data to develop early value proposition

  - **Estimating disease burden**
    - HSV infections
    - Genital ulcer disease (GUD)
    - HSV-associated HIV infection
    - Neonatal herpes
    - HSV-1 outcomes: oral, CNS, ocular

  - **Estimating economic burden**
    - Costs of HSV care and treatment

  - **Modelling vaccine impact**
    - HSV vaccine impact on HSV + HIV

  - **Assessing cost-effectiveness**

  - **Assessing other benefits**
Gonorrhoea vaccines: new activities

Toward reducing the impact of gonorrhoea:

Common bacterial STI
Increasing AMR
Important cause of infertility
Adverse pregnancy & neonatal outcomes
87 million new cases of gonorrhoea

WHO estimates for 2016, among 15-49 year-olds

Untreated, can lead to:

- PID, infertility
- Adverse pregnancy outcomes
- Neonatal ophthalmia
- Increased HIV risk

Gonorrhoea vaccine development increasingly important due to AMR

- 66% of countries with AMR to extended-spectrum cephalosporins
- Documented treatment failures with MDR strains

Group B *Neisseria meningitidis* outer membrane vesicle (OMV) vaccines and gonorrhoea

- Large case-control study in NZ: group B meningococcal OMV vaccine MeNZB seemed to reduce gonorrhoea risk
  - After mass MeNZB campaign, vaccinated people less likely to be gonorrhoea cases than controls
  - Estimated vaccine effectiveness 31% (Petousis-Harris, Lancet, 2017)
Group B meningococcal OMV vaccines and gonorrhoea – further data

- Retrospective cohort in NZ found MeNZB associated with reduced gonorrhoea hospitalization
- Observational studies in Quebec, Norway, Cuba: similar findings
- 4CMenB (Bexsero®) accelerated clearance of *N. gonorrhoeae* in a mouse genital tract infection model
- Antibodies from people vaccinated with meningococcal OMV vaccines recognize gonococcal antigens

Sources: Paynter, Vaccines 2019; Longtin, Open Forum Infect Dis 2017; Whelan, Emerg Infect Dis, 2016; Connolly, abstract 21st IPNC 2018; Semchenko, CID 2018
Recent developments have jumpstarted interest in gonococcal vaccines

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

- Main approaches
  - **Outer membrane vesicle vaccines**
    - Meningococcal OMVs
      - 4CMenB (Bexsero®)
      - MC58ΔABR (FDA/CBER)
    - Gonococcal OMVs
  - **LOS epitope (peptide mimetic)**
  - **Purified protein subunit vaccines**
    - Antigens involved in:
      - physiology or metabolism
      - evasion of innate effectors
      - bacterial structure

Reviewed in Rice et al, Annual Rev Microbiol 2017; Matthias et al, IPNC 2018 abstract #0113; Connolly et al, IPNC 2018 abstract #0110
Progress and next steps: gonococcal vaccines

- Global stakeholder consultation meeting held Jan 2019 to lay groundwork for understanding potential public health value and developing PPCs
- Need better data! Prioritization of research activities to fill in gaps
  - Gonorrhoea-associated disease burden, esp in LMICs
  - Current and projected AMR and predicted impact on disease outcomes
- Modelling vaccine impact: multiple data and coordination needs
  - How to ascribe a value to the threat of AMR and vaccine’s potential role
  - Coordination across multiple groups: AMR, other interventions
- Ideally: direct evaluation of the ability of meningococcal B OMV vaccines to reduce gonorrhoea acquisition
Chlamydia vaccines: update

Most common bacterial STI worldwide

Important cause of infertility, EP, chronic pelvic pain

Disproportionately affects adolescents

Control programs hard to bring to scale

Scanning electron microscopy photos courtesy of Dorothy L. Patton, University of Washington
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- Vaccine based on the chlamydial MOMP (CTH522, SSI) completed Phase 1 trial
  - Safe and induced significant levels of neutralizing antibodies
  - Robust cellular response and levels of vaginal IgG and IgA
  - CTH522:CAF01 superior to CTH522:Alum
- Clinical Phase 2a study planned for 2019

Source: Frank Follmann, Statens Serum Institut
Summary next steps

- HSV vaccines: assemble health burden, economic burden, and modeling data to develop early value proposition

- Gonorrhoea vaccines: build on current activities
  - PPC development
  - Prioritization of data gaps/research for value proposition
  - Modeling coordination/meeting

- NIAID grants to 6 research centers on STI vaccines: coordination across roadmap activities and partners

- Update of STI vaccine roadmap
Vaccines for sexually transmitted infections (STIs)
Outline

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

- Global roadmap to advance STI vaccine development
- Critical next steps from pre-vaccine development through vaccine introduction
Current status of the development pathway of STI vaccines

- Trichomonas
- Syphilis
- Gonorrhoea*
- Chlamydia
- Herpes (HSV)

Discovery & exploratory stage → Preclinical stage → Phase I clinical studies → Phase II clinical studies → Phase III clinical trials → Regulatory approval & introduction

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

HSV = herpes simplex virus
Chlamydia = *Chlamydia trachomatis*
Gonorrhoea = *Neisseria gonorrhoeae*
Syphilis = *Treponema pallidum*
Trichomonas = *Trichomonas vaginalis*
HSV vaccines: progress and plans

Toward reducing the impact of genital HSV infection:

- Genital ulcer disease
- Impact on sexual & reproductive health
- Neonatal herpes
- HIV acquisition and transmission risk
Progress: HSV vaccine PPCs published

- For prophylactic and therapeutic vaccines
- Strategic public health goals
  - Reducing HSV disease, including neonatal herpes, other effects on SRH
  - Reducing HSV-associated HIV infection, especially in high-burden areas or populations
- Key question: how to get PPCs to key stakeholders and optimize impact

Available at: https://www.who.int/reproductivehealth/publications/HSV-Vaccine-PPCs/en/
Progress and next steps: HSV vaccine full public health value proposition

- Current activities to outline public health and financial rationale for HSV vaccines:
  - Estimating disease burden
    - HSV infections
    - Genital ulcer disease (GUD)
    - HSV-associated HIV infection
    - Neonatal herpes
    - HSV-1 outcomes: oral, CNS, ocular
  - Estimating economic burden
    - Costs of HSV care and treatment
  - Modelling vaccine impact
    - HSV vaccine impact on HSV + HIV
  - Assessing cost-effectiveness
  - Assessing other benefits
473 million prevalent HSV-2 infections

Preliminary WHO estimates for 2016, among 15-49 year-olds

HSV-2 = herpes simplex virus type 2

Source: James et al, manuscript under review
473 million prevalent HSV-2 infections

Preliminary WHO estimates for 2016, among 15-49 year-olds

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Source: James et al, manuscript under review

Also estimated between ~130-200 million HSV-1 genital infections, mostly in HICs
HSV genital ulcer disease (GUD)

Preliminary estimates for 2016, among 15-49 year-olds

- Estimated 180 million people with at least one episode of HSV GUD in 2016
  - Vast majority due to HSV-2 (95%, 171 million)
  - Sensitive to assumptions: ranged from 138 to 235 million based on recurrence rates used

- Translates into ~8 billion person-days with symptoms

Source: Looker et al, manuscript in preparation
HSV-associated HIV infections

Preliminary estimates, PAFs applied to 2016 UNAIDS data for 15-49 year-olds

- PAFs of HIV due to HSV-2 ranged from:
  - 12-13% in Europe and Asia
  - 21% in the Americas
  - 37% in Africa

- Overall >400,000 HIV infections estimated to be related to HSV-2 infection
  - Most in Africa due to high burden of both infections
  - Provides a starting point for understanding

Source: Looker et al, manuscript under review
Summary next steps: HSV vaccine

- Assemble health and economic burden, modeling data to develop early value proposition

- Estimating disease burden
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Normal tubal tissue, 1200x Post-PID, 1200x

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Vaccine delivery technologies: Microarray patches
MR-MAP TPP development process

Draft MR-MAP TPP developed by PATH/WHO/DTWG → MR-MAP consultation & Update → IPAC/Technet Survey to assess thermostability, wear time and disposal → MR-MAP WG formed & Updated

July 2018

Expert consultation with regulators, PQ team, BMGF, PATH, EPI at WHO → Review of comments by the WG → Consolidation and Analysis of Comments → 21 Sets of Comments Received (CSOs, PDPs, manufacturers, MAP developers)

One Month Public Consultation → Final draft → Publication (expected July 2019)
MR-MAP Working Group:

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

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

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

R. Karron
27 June 2019
# RSV Vaccine and mAb Snapshot

## Maternal

### Preclinical
- **Live-Attenuated/Chimeric**
  - Codagenics, LID/MAAC/R/M
  - LID/MAAC/R/N
  - FULL-MAAC
  - Matelica Vaccines
  - RSV

### Phase 1
- **Intrexon**
  - RVP-6
  - Pseudovirus
  - Universidad Catolica de Chile
  - RSV

### Phase 2
- **Sanofi, LID/MAAC/R/N**
  - RV/MAAC/R
  - RV/MAAC/R

### Phase 3
- **Sanofi, LID/MAAC/R/N**
  - RV/MAAC/R

## Pediatric

### Whole-Inactivated
- **Rec Ninyo Biologics**
  - PIV

### Particle-Based
- **Ag8/12**
  - PIV
  - PIV
  - University of Massachusetts
  - PIV

### Subunit
- **Instituto de Salud Carlos III**
  - PIV
  - PIV
  - PIV

### Nucleic Acid
- **CorVec**
  - RNA
  - DNA

### Recombinant Vectors
- **Breoncor**
  - Adenovirus

### Immuno-Prophylaxis
- **Arcarex**
  - Anti-F mAb
  - Anti-F mAb
  - Anti-F mAb

## Market Approved
- **Novavax**
  - PIV
  - RSV
  - Nanoparticle

## Additional Information
- **PATH**
- **http://vaccineresources.org/details.php?id=1562**

**Updated:** April 5, 2019

*Indicates Change*
# RSV vaccines for maternal immunization: PPC excerpts

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


## RSV vaccines for maternal immunization: PPC (2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred Characteristic</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogenicity</td>
<td>Established correlate/surrogate of protection based on a validated assay measuring antibody levels in the mother and/or the neonate.</td>
<td>A detailed quantitative profiling of passively transferred antibodies, and relationship to timing of vaccination in pregnancy is desirable. Longevity of vaccine-induced maternal antibodies in infants should be characterized and the relationship to duration of protection should be investigated. The fine specificity of vaccine antigen neutralizing epitopes should be characterized, as they may have a significant influence on binding and functionality of the antibody induced. The generation of clinically relevant validated neutralization assay data, ideally using high-throughput formats, is an important goal. Quantitative assays measuring the ability of vaccine-induced antibodies to compete with monoclonal neutralizing antibodies (such as palivizumab or motavizumab) are interesting, but may not be reflective of all effector functions of vaccine-induced immunity, and should not replace the need to evaluate neutralization. The role of antibody transferred through breast-feeding should be investigated. The influence of maternal HIV infection and malaria in pregnancy should be evaluated.</td>
</tr>
</tbody>
</table>
GSK’s maternal immunisation RSV candidate vaccine is being developed to provide passive protection to the newborn\(^1\)

Purified recombinant F protein engineered to preferentially maintain its pre-fusion form:\(^1\)

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

**Native structure** of prefusion protein\(^2\) used to **engineer vaccine antigen**


RSV, respiratory syncytial virus

Overview of clinical development for maternal RSV candidate vaccine


Phase 1
- Non-pregnant women
- Safety
- Immunogenicity
- Dose-ranging

Phase 2
- First study in pregnant women
- Safety
- Immunogenicity
- Dose confirmation

Phase 3
- Pregnant women
- Efficacy

All trials in pregnant women in scope of IDMC oversight

IDMC, Independent Data Monitoring Committee
Important features of Pfizer’s RSV vaccine candidate

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

INDICATIONS
- Maternal
  - Immunize pregnant women to prevent RSV-associated lower respiratory tract illness (LRTI) in infants
  - Aim to protect infants from birth to 4-6 months of age
- Older adult
  - Prevent RSV-associated moderate to severe LRTI in adults ≥ 60 years of age
  - May be administered annually concomitant with flu vaccine
Maternal phase 2 study: description and objectives

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

<table>
<thead>
<tr>
<th>Description</th>
<th>Phase 2 randomized, placebo controlled, observer-blind, dose-ranging</th>
</tr>
</thead>
</table>
| **Objectives** | **Primary**: Safety and tolerability mother and infant  
**Secondary**: Immunogenicity  
- RSV neutralizing antibody titers in cord blood and infants  
- To describe rates of RSV positive LRTI in the study population  
- Follow for 12 months |
GSK and Pfizer Maternal RSV vaccines in phase 1-2 development

• Contain stabilized versions of RSV F in the prefusion conformation
• Induce high levels of RSV neutralizing antibodies
• For both products, phase 2 trials in pregnant women scheduled to begin within the coming year
### RSV vaccines for pediatric immunization: PPC excerpts

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred Characteristic</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Active immunization of infants, for prevention of RSV disease in infants and young children.</td>
<td>Preferred endpoint case definitions have been published (10).</td>
</tr>
<tr>
<td>Target population</td>
<td>Infants, for co-administration with existing vaccines from the Expanded Program on Immunization.</td>
<td>HIV infection and mild/moderate malnutrition should not be a contra-indication to vaccination.</td>
</tr>
<tr>
<td>Schedule</td>
<td>The vaccination regimen should provide the earliest protection and longest duration of protection possible.</td>
<td>The optimal age schedule will depend on whether a maternal RSV immunization or infant RSV monoclonal antibody program is already introduced, in which case the infant vaccination schedule should aim to extend protection, as maternally-derived or monoclonal antibody levels wane. The development plan should assess interference between maternally acquired/monoclonal antibodies and infant vaccine immunogenicity and protection. The optimal age will depend on a balance between immunogenicity and whether or not interference is seen between paediatric vaccination and pre-existing circulating antibodies. Some vaccines may be less prone to interference from pre-existing antibodies than others, either because of the nature of the platform itself or based upon the route of delivery (e.g. mucosal rather than parenteral).</td>
</tr>
</tbody>
</table>
### RSV vaccines for pediatric immunization: PPC (2)

<table>
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<tr>
<th>Parameter</th>
<th>Preferred Characteristics</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine platform and adjuvant requirement</td>
<td>A well-characterized platform with existing favorable data on safety and immunogenicity in early life is preferred.</td>
<td>Adjuvant requirement should be investigated and justified if included.</td>
</tr>
<tr>
<td>Safety</td>
<td>Safety and reactogenicity at least as favorable as other WHO-recommended matrix vaccines for use in the Expanded Program on Immunization.</td>
<td>Safety profile demonstrates no or only mild, transient reactogenicity and no serious adverse events related to vaccination.</td>
</tr>
<tr>
<td></td>
<td>Safety profile demonstrates no or only mild, transient reactogenicity and no serious adverse events related to vaccination.</td>
<td>No indication of ERI in vaccinated children.</td>
</tr>
<tr>
<td></td>
<td>Safety profile demonstrates no or only mild, transient reactogenicity and no serious adverse events related to vaccination.</td>
<td>In addition to typical toxicology evaluation of investigational pandemic vaccines, presclinical investigations should include the evaluation of the risk of post-vaccination ERI.</td>
</tr>
<tr>
<td></td>
<td>Safety profile demonstrates no or only mild, transient reactogenicity and no serious adverse events related to vaccination.</td>
<td>Safety in children should first be investigated in RSV-experienced subjects, after favorable evaluation in older subjects.</td>
</tr>
<tr>
<td></td>
<td>Safety profile demonstrates no or only mild, transient reactogenicity and no serious adverse events related to vaccination.</td>
<td>An ERI has historically been associated with vaccination of children without past RSV exposure, progression to younger infants and children with no past RSV infection who are seronegative at screening should be done under intensive safety surveillance. Paediatric vaccination studies should include high-quality medical oversight, with independent, blinded continuous safety data review, allowing detection of cases of RSV disease with features of enhanced severity, and early trial termination accordingly.</td>
</tr>
<tr>
<td></td>
<td>Safety profile demonstrates no or only mild, transient reactogenicity and no serious adverse events related to vaccination.</td>
<td>A small number of severe infections only should be included initially, to allow for faster enrollment when enough evidence is accrued about the likelihood of post-vaccination ERI occurrence. This should be tailored to the available evidence about the level of risk, which may be lower for some vaccine platforms than others.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Greater than 70% vaccine efficacy against confirmed severe RSV disease over at least one year post-vaccination.</td>
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<tr>
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<td>Reduction in frequency and severity of RSV illness.</td>
<td>Proposed priority study endpoint case definitions have been published (28).</td>
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<td></td>
<td>Reduction in frequency and severity of RSV illness.</td>
<td>The dynamic of protection over time should be described, taking seasonality patterns into account. Protection over at least 2 years or successive RSV seasons, or more, would be preferred.</td>
</tr>
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<td></td>
<td>Reduction in frequency and severity of RSV illness.</td>
<td>The vaccine efficacy against other endpoints of public health interest should also be evaluated:</td>
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<td>Reduction in frequency and severity of RSV illness.</td>
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<td>• hyper-reactive airway disease and recurrent wheezing in children,</td>
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<td>• reduction of antibiotic use.</td>
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<tr>
<td></td>
<td>Reduction in frequency and severity of RSV illness.</td>
<td>The demonstration of an effect of vaccination on RSV transmission, possibly requiring booster doses, would be of great public health interest, but may be left for evaluation in specifically designed post-approval trials.</td>
</tr>
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GSK’s paediatric candidate vaccine (ChAd155-RSV) uses a chimpanzee adenovirus vector to encode RSV proteins.

**Chimpanzee-derived adenovector (ChAd155)**

- **RSV proteins:**
  - Fusion protein F
  - Nucleocapside protein N
  - Matrix protein M2.1

**ChAd155-RSV**

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

nAb, neutralising antibody; RSV, respiratory syncytial virus

Overview of clinical development for paediatric RSV candidate vaccine

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

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

<table>
<thead>
<tr>
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<th>Description</th>
<th>Schedule</th>
<th>Dosing</th>
<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>JR2001</td>
<td>Safety and Immunogenicity</td>
<td>Phase 1/2 in 12-24 Mo</td>
<td>RSV seropositive</td>
<td>2 RSV seasons</td>
</tr>
<tr>
<td>JR2002</td>
<td>Safety and Immunogenicity</td>
<td>Phase 1/2 in 12-24 Mo</td>
<td>RSV seronegative</td>
<td>2 RSV seasons</td>
</tr>
<tr>
<td>JR2003</td>
<td>Safety and Immunogenicity</td>
<td>Phase 1/2 in 6-12 Mo</td>
<td>Follow-up</td>
<td>2 RSV seasons</td>
</tr>
<tr>
<td>JR2004</td>
<td>Safety and Immunogenicity</td>
<td>Phase 1/2 in 2-6 Mo</td>
<td>Co-administration with childhood vaccines</td>
<td>Follow-up</td>
</tr>
<tr>
<td>JR3001</td>
<td>Pivotal Efficacy</td>
<td>Phase 3 in 2-6 Mo</td>
<td></td>
<td></td>
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- **ongoing**
- **planned**
**Live-attenuated RSV vaccine candidates**

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

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

- NS2: Reduced viral suppression of host interferon responses (ΔNS1, ΔNS2)
Live-attenuated RSV vaccines in phase 1B/2 trials

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

$\Delta NS2/\Delta 1313/I1314L$

6120/ΔNS2/1030S

RSV 276 ($\Delta M2-2$ candidate)

NCT03916185
Pediatric RSV vaccines in phase I-II development

• Adenovirus vectored vaccines (GSK, Janssen) currently being evaluated in RSV-seronegative infants (GSK) and toddlers (Janssen)

• Live attenuated vaccines being evaluated in RSV-naïve infants and children ages [4] 6-24 months. Head-to-head trial underway.
With thanks to colleagues at...

• GSK
• Janssen
• Pfizer
• NIH/Sanofi Pasteur
Update on WHO activities related to RSV preventive products

Daniel Feikin, MD

Initiative for Vaccine Research/Immunizations, Vaccines and Biologicals/WHO
WHO RSV work: Topics of focus in last year

- Expanding RSV surveillance using the influenza surveillance platform
  - Led by Global Influenza Program
  - 2nd phase into 22 countries

- Development of Guidelines for Quality, Efficacy and Safety of RSV Vaccines
  - Led by Technology Standards and Norms
  - Template for PQ and LMICs market authorization
WHO RSV work: Topics of focus in last year

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

Seasonality in LMICs is apparent in most places.
RSV Technical Advisory Group

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

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

R. Karron
27 June 2019
# RSV Vaccine and mAb Snapshot

## Preclinical

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</table>
MK-1654 (Merck)

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

1. Maas et al ID Week 2018. 2. Aliprantis et al, ID Week 2018
TB Vaccines:
Pipeline Overview and Status of Late-stage Candidates

Ann M. Ginsberg, MD, PhD
PDVAC
27 June 2019 / Geneva
New TB vaccines: a critical, unmet global health need

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

Deaths in 2017

Source: WHO Global TB Report 2018
Multiple Target Populations

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

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

* Under discussion with regulators
### Overview of Global Pipeline

#### Pre-Clinical
- **Cysvac2**
  - U. Sydney, TBVI
- **BCG-ΔZMP1**
  - U. Zurich, TBVI, Aeras
- **MVA-based Multiphasic Vaccine**
  - Transgene, TBVI
- **ChAdOx1.85A/PPE15**
  - U. Oxford, TBVI
- **H64+CAF01**
  - SSI, TBVI
- **CMV-6Ag**
  - Aeras, Vir Biotech, OHSU
- **ChAd3/MVA-5Ag**
  - Aeras, GSK, Transgene

#### Phase 1
- **Ad5 Ag85A**
  - McMaster, CanSino
- **ChAdOx185A/MVA85A (ID/IM/Aerosol)**
  - U. Oxford
- **AEC/BC02**
  - Anhui Zhifei Longcom

#### Phase 2a
- **RUTI**
  - Archivel Farma, S.L
- **MTBVC**
  - Biofabri, TBVI, Zaragoza

#### Phase 2b
- **DAR-901**
  - Dartmouth, GHIT
- **M72 + AS01E**
  - GSK, Aeras
- **H56: IC31**
  - SSI, Valneva, Aeras
- **BCG Revac**
- **ID93 + GLA-SE**
  - IDRI, Wellcome Trust

#### Phase 3
- **Vaccae™**
  - Anhui Zhifei Longcom
- **VPM 1002**
  - SII, Max Planck, VPM, TBVI (Phase 2/3)
- **MIP**
  - Cadila/ICMR

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

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

---

Global Clinical Pipeline of TB Vaccine Candidates

Phase 1
- Ad5 Ag85A
  McMaster, CanSino
- ChAdOx185A/MVA85A
  (ID/IM/Aerosol)
  Univ of Oxford
- AEC/BC02
  Anhui Zhifei Longcom

Phase 2a
- RUTI
  Archivel Farma, S.L
- TB/FLU-04L
  RIBSP
- MTBVAC
  Biofabri, TBVI, Zaragoza, Aeras/IAVI

Phase 2b
- DAR-901
  Dartmouth, GHIT
- VPM 1002
  SII, Max Planck, VPM, TBVI
  (Ph2b/3)
- M72/AS01E
  GSK, Aeras/IAVI
- BCG Revaccination
- H56: IC31
  SSI, Valneva, Aeras/IAVI
- ID93 + GLA-SE
  IDRI, Wellcome Trust

Phase 3
- Vaccae™
  Anhui Zhifei Longcom
- VPM 1002
  SIIPL/VPM, Gol
- MIP Cadila, Gol

Viral Vector
Protein / Adjuvant
Mycobacterial – Killed
Mycobacterial – Live attenuated

Working Group on New Vaccines
Stop TB Partnership

Revised on October 20, 2018 – personal view!
2018 – a Year of Unprecedented Progress

• New use for 98 year old current vaccine - protect high risk, uninfected populations from Mtb infection with BCG revaccination

• Proof of concept that a subunit vaccine (2 Mtb antigens plus adjuvant) can protect against TB disease

• First demonstration that a vaccine can protect Mtb-infected adults from developing TB disease

• First opportunity to discover correlates of protection and increase understanding of protective human immune responses
Phase II Prevention of Infection Trial
H4:IC31 and BCG revaccination

Clinical Trial Sites:
SATVI and DTHF/Emavundleni
Overview – First TB Vaccine POI Trial

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

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

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

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

Study Size:
N=990 (330/arm)

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

Trial: NCT02075203
POI Trial Results and Conclusions

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

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

- H4:IC31
  - First signal of any protection against TB infection or disease in humans by a subunit vaccine
  - Suggests benefit of studying other subunit vaccines
  - Not being further developed

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

Trial: NCT02075203
M72/AS01_E Phase IIb Prevention of Disease Trial

Results of the primary analysis
M72/AS01\textsubscript{E} Candidate Vaccine

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

M72/AS01\textsubscript{E} Determines specificity of the immune response\textsuperscript{1}

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

M72/AS01\textsubscript{E} Enhances the immune response to the antigen\textsuperscript{2}

- Immunostimulants (MPL and QS21) in a liposome formulation\textsuperscript{3}


2. AS01\textsubscript{E}, Adjuvant System containing 3-\textit{O}-desacyl-4’-monophosphoryl lipid A (MPL [25 \textmu}g, produced by GSK), *Quillaja saponaria* Molina, fraction 21 (QS-21 [25 \textmu}g], licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation) and liposome.
M72/AS01\textsubscript{E} Candidate Vaccine

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

Clinical safety and immunological profiles to date

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

Phase IIb Study Design

• Subjects
  o HIV negative healthy adults (18 - 50 years)
  o Negative sputum by PCR (Xpert MTB/RIF)
  o Mtb-infected: positive by QuantiFERON

• Design
  o Double-blind, randomized (1:1)
  o M72/AS01E or Placebo
  o 2 doses 1 month apart

• TB cases determination by
  o Active follow-up every 2 months either by calls, home visits or SMS
  o TB symptoms and bacteriological confirmation (3 sputum samples)
    • By PCR and/or MGIT culture

• 3 years follow up
  o Primary analysis at year 2
  o LSLV November 2018

Van Der Meeren et al., NEJM, 2018
Study Participants

Screened: 8,336
Enrolled: 3,575
Total Vaccinated: 3,573
ATP Efficacy: 3,283
Not ATP Efficacy: 290
Screening failure: 4,761
Not vaccinated: 2

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

Wikipedia, CC BY-SA 3.0

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

**Vaccine efficacy against TB for each case definition**

<table>
<thead>
<tr>
<th>Efficacy endpoints</th>
<th>TB diagnosis</th>
<th>HIV status</th>
<th>Sputum testing</th>
<th>Vaccine efficacy % (90% CI)</th>
<th>p-value</th>
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<td>Culture</td>
<td>PCR</td>
<td>Timing vs TB treatment start</td>
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<tr>
<td><strong>Case definition 1</strong></td>
<td>Pulmonary TB Clinical suspicion</td>
<td>HIV–</td>
<td>Any positive</td>
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<tr>
<td><strong>Sensitivity analysis</strong></td>
<td>Pulmonary TB Clinical suspicion</td>
<td>HIV–</td>
<td>Any 2 positive</td>
<td>Before</td>
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<td><strong>Case definition 2</strong></td>
<td>Pulmonary TB Clinical suspicion</td>
<td>HIV–</td>
<td>Any positive</td>
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<td><strong>Case definition 3</strong></td>
<td>Pulmonary TB Clinical suspicion</td>
<td>HIV–</td>
<td>Any positive</td>
<td>Up to 4 weeks after TB treatment start</td>
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<td><strong>Case definition 4</strong></td>
<td>Pulmonary TB Clinical suspicion</td>
<td>Any</td>
<td>Any positive</td>
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<td><strong>Case definition 5</strong></td>
<td>TB diagnosed and treated by clinician</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
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<tr>
<td><strong>Modified case definition 5</strong></td>
<td>TB diagnosed and treated by clinician</td>
<td>HIV–</td>
<td>Any</td>
<td>Any</td>
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Vaccine Efficacy for Case Definition 1

Kaplan-Meier (ATP cohort for efficacy)

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

http://www.idweek.org

Van Der Meeren et al., NEJM, 2018
Conclusions and Next Steps

• M72/AS01E prevented TB disease in Mtb-infected adults
  o Efficacy of 54% [CI90% 14-75%, p=0.04] - primary endpoint met
  o Secondary endpoint met (VE of 58%; p=0.05)
  o VE calculated for the other case definitions ranged from 28-70%
  o Acceptable safety profile

• More research is warranted
  o End of study analysis
  o Aeras (now IAVI) Biobank to enable correlates discovery

• Next steps for M72 development are under discussion with key stakeholders and funders
Study participants and their communities

Investigators and their teams

Mark Hatherill
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Nduba Videlis
Elana Van Brakel
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Helen Ayles
Friedrich Thienemann
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AERAS*
Dereck Tait
Maria Lempicki
Maureen Lambrick
Kristin Croucher
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Nathalie Cadieux
Kathryn Rutkowski
Cadwill Pillay
Gretta Blatner
Sharon Sutton
Ann Ginsberg
Anja Van der Westhuizen
Jennie Willson
Sebastian Gelderbloem
Tom Evans
Jacqui Shea

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IQVIA (ex-Quintiles)

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Aisha Khatoon
François Roman
Paul Gillard
Christina Caporaso
Evi De Ruymaeker
Emelia Ferreira
Florence Richard
Anne-Sophie Perreux
Tina Singh
Paola Pirrotta
Pramod Dhole
Sagar Salvi
Naresh Patil
Neela Kumar
Roland Vaudry
Philippe Moris
Gerald Voss
Marie-Ange Demoitié

Funders:
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GSK
Anne Bollaerts
Muriel Debois
Helen Jacob
Sophie Caterina
Mohamed Amakrane
Lieven Declerck
Marc Lievens
Hildegard de Lemaire
Stéphanie Ravault
Bruno Salaun
Nathalie Baudson
Thierry Pascal
Erik Jongert
Olivier Van Der Meeren
Denis Sohy
Stéphanie Delval
Ioana Cristina Ilea
William Zonta

*Aeras TB vaccine clinical program was recently transferred to IAVI
A new model with novel partnerships and networks required to achieve ‘end-to-end’ program impact

- Clinical Development
- Manufacturing/Commercialization
- Access

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

**UNMET MEDICAL NEED**

**TARGET PRODUCT PROFILE (TPP)**

**DISCOVERY, PRODUCT OPTIMIZATION, PRECLINICAL DEVELOPMENT**

**CLINICAL DEVELOPMENT REGULATORY STRATEGY**

**COUNTRY DECISIONS**

**FINANCING, PROCUREMENT**

**LAUNCH & DELIVERY, DEMAND GENERATION**

**LOW COST MANUFACTURING, PACKAGING, SUPPLY, DELIVERY**

**IDENTIFY MEDICAL NEEDS & PRODUCT REQUIREMENTS**

**RESEARCH & DEVELOPMENT**

**LICENSURE**

**ENABLING ACCESS & SUPPLY**

- **TPP**
- WHO SAGE
- WHO Prequalification Assessments
- Cost-Effectiveness
- Population Impact
- Epidemiology Access Roadmap
- Access Agreements
- Public Health Value Proposition
- Market Potential
- Demand Forecasts
- NRA requirements
- Potential Program Partners/Funders

M72/AS01 E Phase 2b development partner
IAVI gratefully acknowledges the generous support provided by the following major donors:

- USAID
- PEPFAR
- Bill & Melinda Gates Foundation
- The World Bank
- CEPI
- UK aid
- Ministry of Foreign Affairs of the Netherlands
- Ministry of Foreign Affairs of Denmark
- Ministry of Science & Technology, Government of India
- Irish Aid
- Ministry of Foreign Affairs of Japan
- The U.S. President's Emergency Plan for AIDS Relief through the U.S. Agency for International Development
- The World Bank

And many other generous individuals and partners around the world.

As of May 2018
Thank you
ANNEX

<table>
<thead>
<tr>
<th>Duration (years)</th>
<th>VE(%)</th>
<th>% decrease in cases</th>
<th>CE vaccine price (USD)</th>
<th>% decrease in cases</th>
<th>CE vaccine price (USD)</th>
<th>% decrease in cases</th>
<th>CE vaccine price (USD)</th>
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<td>53</td>
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</tbody>
</table>
New Tuberculosis Vaccines: WHO IVR activities

Johan Vekemans, MD PhD
WHO Initiative for Vaccine Research
June 2019
TUBERCULOSIS

in 2017

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

Approximately 1/3 world infected with *Mycobacterium tuberculosis*

First cause of mortality in HIV

First cause of mortality due to AMR pathogens

  estimated third of all deaths due to AMR pathogens

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

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

2035, reducing 90% of TB cases (from 2015)
WHO IVR recent activities

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

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

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

Upcoming: participation to a Technical R&D Roadmap

Full Public Value Proposition evaluation
New TB vaccine PPC

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

INDICATION

• Immunization for prevention of active pulmonary TB

TARGET POPULATION

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

OUTCOME MEASURE AND EFFICACY

• 50% or greater efficacy in preventing confirmed pulmonary TB
• Protect both subjects with and without latent *Mtb* infection
• Protective in different geographical regions and latitudes
New TB Vaccines for Use in Adolescents and Adults: Preferred Characteristics

SAFETY

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

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

  - Safety should be favourable in particular risk groups (especially individuals living with HIV/AIDS)
New TB Vaccines for Use in Neonates and Infants: Preferred Characteristics

INDICATION

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

OUTCOME MEASURE AND EFFICACY

• Superior efficacy as compared to BCG alone

SAFETY

• Improved safety as compared to current BCG
• Demonstrated safety in HIV infected babies
New TB Vaccines: Preferred Characteristics

DURATION OF PROTECTION

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

SCHEDULE

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

IMMUNOGENICITY

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

PROGRAMMATIC SUITABILITY

- Innovation related to ease of administration and thermostability

VALUE PROPOSITION

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

- The vaccine should be cost-effective and price should not be a barrier to access
Endpoints in TB Vaccine Trials:

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

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

Clinical significance? Prevention of disease not demonstrated

Risk of false negative result: a vaccine may be found not to prevent ‘immune take’ while successfully preventing progression to disease
Vaccines for improvement of TB treatment outcome

• Aim to reduce treatment failure (increase cure rates), reduce frequency of relapse, simplify and shorten treatment regimen

• Specific interest in drug-R TB

• M72 results arguing in favour of feasibility

• Opportunity to also reduce progression to TB in recently exposed contacts, in TB infection test converters

• WHO PPC document under finalization
Vaccines for improvement of TB treatment outcome: PPC

- Diagnosis and treatment initiation
  - Sputum Screen, Mtb characterization if positive
    - Intensive phase
    - Continuation phase
- Possible vaccination timepoint for cure and PoR endpoints
- Possible vaccination timepoint for PoR endpoint
  - Proportion of cure
- End of drug treatment
  - Sputum Screen, Mtb characterization if positive
- End of follow-up
  - Proportion of subjects free of recurrence after 12 months or more

Efficacy endpoints

Recommended treatment as standards of care for initial proof of concept evaluation
Phase 2b Efficacy study of GSK’s Candidate TB Vaccine M72/AS01E in Adults with Latent TB Infection

Vaccine 2-dose IM M72/AS01E (fusion protein Mtb32A, Mtb39A)
Sponsor GSK (Aeras)
Population 3,500 IGRA+ adults
Endpoint Incident, confirmed pulmonary TB
Site/s South Africa, Kenya, Zambia

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

Impact modelling estimates awaited
M72/AS01: WHO strategic vision

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

April 5th WHO consultation:

• GSK is seeking a partner/s to take license of M72 from GSK to develop, license, manufacture, be liable for, and supply M72 for the developing world (GSK will maintain proprietary control for the non-developing world)

• Limited number of doses currently available. Process improvement needed for Phase 3 material

• No established consensus on pathway forward and investments

• Willingness from many stakeholders to contribute. Need to ensure country perspectives are taken into account, countries contribute to the research agenda and resources

• Major risk of undue delays. Need for coordination and advocacy.
Preferred scenario, for discussion

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

- progression to Phase 3 trial in a population of teenagers/young adults in settings with high incidence

- accelerated licensure with narrow indication (prevention of pulmonary TB in young adults in high endemic settings)

- parallel proof-of-concept evaluation for other indications (HIV+, pediatric, contacts, PoR) and schedule optimization

- post-licensure investigations, country-led
Next steps for WHO

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

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

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

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

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

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

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

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

Holly Prudden, Birgitte Giersing, Mateusz Hasso-Agopsowicz
PD-VAC 2018 Recap and Recommendations

Recap:

• ETEC remains a priority pathogen in LMICs and PDVAC will continue to advocate for, and support, the development of a vaccine. A key component of this effort should focus on improving the understanding and credibility of BoD estimates.

• Shigella remains a priority with primary goal to develop a safe, effective and affordable vaccines to reduce morbidity and mortality.

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>U5 Diarrheal Deaths Due to Pathogens: Shigella:</td>
<td>33 400 (24900-43500)</td>
<td>28 000 (17000-71000)</td>
<td>99 680 (59550-161235)</td>
<td>Unpublished data, expected to show minor revisions in estimates associated with both pathogens.</td>
</tr>
<tr>
<td>ETEC:</td>
<td>23 100 (17000-30000)</td>
<td>42 000 (20000-76000)</td>
<td>15 960 (4400-40300)</td>
<td></td>
</tr>
</tbody>
</table>

Recommendations:

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

Formation of Expert Working Group (Summer 2018)

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

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

Observer: Laura Lamberti (BMGF)

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

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

• IHME and MCEE produce different model estimates. This is particularly pronounced with respect to Shigella and ETEC.

• There are 3 broad levels at which differences in methodology may give rise to differences in estimates:
  • Differences in **model structure**
  • Differences in **methodology for processing the data**
  • Differences in **data quality**, inclusion and exclusion criteria
A work plan, with four corresponding workstreams* was formulated by the Working Group and both IHME and MCEE to explore methodological issues that explain the differences in estimates and address data gaps, which would improve overall understanding and quality of the modelling processes:

1. **Data Processing Exercise** – a high level assessment of similarities and differences in study data.

2. **Model Comparison Exercise** – to address structural differences in models.

3. **Data Quality Exercise** – to improve understanding of the data utilised for modelling purposes.

4. **Data Gaps** – to identify and address areas of commonality where additional evidence may improve future estimates.

*Workstreams presented to IVIR-AC committee (March 2019) with endorsement of proposals and importance of this work*
1. Data Processing Exercise

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

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

Step 2: Carry out a meta-analysis of the input data used by both groups (by region) to assess where fundamental differences may occur.
Purpose: To assess the relative differences in model outputs generated by both groups, when a common dataset is applied to both models.

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

The relative difference between these estimates is explained by differences in model structure and processing *not by the data used*
3. Data Quality Exercise

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

- **Grading Criteria (NOS):**
  - Selection criteria
  - Exposure criteria
  - Comparability criteria
  - Outcome criteria
  - Additional factors

Results, to inform a WHO paper.
4. Data Gaps

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

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

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

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

- CFR Assumed equal: Shigella, Norovirus
- Rota, Salmonella
- ETEC, Campylobacter
### Work to date

#### Data Processing Exercise:
- Initial comparison of data to identify differences between MCEE and IHME for six pathogens.
- More thorough review planned and completion of meta-analysis.

#### Data Quality Exercise:
- Grading analysis proposal generated and agreed upon with Working Group. Next step to share with groups.
- IHME and MCEE studies extracted. Grading analysis to begin, early July.

#### Model Comparison Exercise:
- Initial model input data compiled and shared.
- U5 data for MCEE model generated and shared.
- Call with IHME scheduled for next steps.

#### Data Gaps Exercise:
- Criteria defined and agreed upon for systematic reviews.
- Analysis commenced 24/06.

#### Other Key Outputs:
- Short report for (Nov 2018) meeting consultation completed and shared with meeting attendees.
- Full joint publication on meeting consultation pending submission.
Next steps

- Joint consultation publication submitted (journal tbc) July 2019.
- Publication of two separate systematic reviews.
- Joint publication, outlining proposed future methodology for recommended data used in generating enteric burden of disease estimates, summarising workstreams and key findings.
Thank you
Trivalent Rotavirus P2-VP8 Subunit Vaccine and its Public Health Value Proposition

Product Development Vaccine Advisory Committee
World Health Organization

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

Bill Hausdorff, Fred Cassels

NRRV Team
ROTAVIRUS DISEASE

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

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

• Four live attenuated oral rotavirus vaccines: WHO PQ
  
  Rotarix, GSK; RotaTeq, Merck;
  Rotavac, Bharat; RotaSiil, Serum Institute.

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

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


Slide Courtesy of Carl Kirkwood
Live Oral Rotavirus Vaccines

**Discovery & Preclinical**
- Bharat Serum
- BioFarma Hilleman
- POLyvac Wuhan
- Shantha Butantan
- Lanzhou

**DCVMs include:**
- LiquiDA VIN (liquid) POLYVAC, Vietnam
- ROTAVAC 5D (liquid) Bharat Biotech, India
- ROTARIX GSK, Belgium
- Liquid BRV Wuhan, China
- ROTASIIl (liquid) Serum Institute India
- RotaTeq Merck, USA
- RV3 – BB BioFarma, Indonesia
- Lamb rotavirus Lanzhou, China
- ROTAVAC (frozen) Bharat Biotech, India
- ROTAVIN (lyo) Serum Institute, India
- ROTAVIN-M1 (frozen) POLYVAC, Vietnam

**Phase 1**
- Live Oral Rotavirus Vaccines

**Phase 2**
- Phase 3
- Market
- WHO PQ
Rationale for Considering an NRRV Vaccine

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

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

Potential benefits include:
- Lower COGs
- Higher efficacy profile
- Decreased signal intussusception
- Potential for use in combination vaccine
- Potential for alternative dosing schedules
Characteristics of the P2-VP8 Subunit Vaccine

- Developed at US NIH by Dr. Yasutaka Hoshino
- Comprised of recombinant truncated VP8 ~ 21kDa
  - Expressed in *E. coli*
  - Simple three step column chromatography process
  - Liquid formulation, adsorbed to aluminum hydroxide
- The trivalent P2-VP8 subunit vaccine is made by combining three VP8 subunit proteins expressing P[4], P[6] and P[8] serotypes, each fused to the P2 T-cell epitope of tetanus toxin
- Elicits immunoglobulin G (IgG) and immunoglobulin (IgA) binding antibodies as well as rotavirus neutralizing antibodies in pre-clinical studies; protection from disease in neonatal piglet model
- No unexpected toxicity observed in GLP toxicology studies on rabbits and guinea pigs following administration of four doses (4 X human dose) of vaccine at two week intervals
- Two dose vial without preservative, each 0.5 ml dose contains 90 ug of antigen (30 ug per serotype)
# Target Product Profile (TPP)

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

Preclinical 2010-2013

2013

- Phase I (monovalent)
  - First-in-human Dose-escalation
  - Completed OCT 2013

2015

- Phase I/II (monovalent)
  - Descending-age, Dose-escalation
  - Completed OCT 2015

2017

- Phase I/II (Trivalent P2-VP8)
  - Descending-age, Dose-escalation
  - (Adult, toddler, infant)
  - Dose-ranging in infants
  - Completed DEC 2017

2024

- Pivotal Phase III
  - 2 active arms
  - Trivalent P2-VP8 & licensed RVV

- Expanded Safety
  - EPI Interference
  - Lot-to-lot Consistency

- BLA Preparation & Submission
- PSF Preparation & Submission to WHO for PQ

- Ethics consultation for head-to-head trial
- Assay qualification
- Thimerosal stability
End to End Clinical Development Plan

2013

Phase I VAC 009
Monovalent P[8]

Phase I/II VAC 013
Monovalent P[8]

2024

Ethics consultation for head-to-head trial
Assay qualification
Thimerosal stability

Phase I (monovalent)
First-in-human Dose-escalation
Completed OCT 2013

Phase I/II (monovalent)
Descending-age, Dose-escalation
Completed OCT 2015

Phase I/II (Trivalent P2-VP8)
Descending-age, Dose-escalation
(Antd, toddler, infant)
Dose-ranging in infants
Completed DEC 2017

Pivotal Phase III
2 active arms
Trivalent P2-VP8 & licensed RVV

Expanded Safety
EPI Interference
Lot-to-lot Consistency

BLA Preparation & Submission

PSF Preparation & Submission to WHO for PQ

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

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

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

CVIA 061

A double-blind, randomized, active comparator-controlled, group-sequential, multinational trial to assess the safety and efficacy of a trivalent P2-VP8 subunit rotavirus vaccine in prevention of severe rotavirus gastroenteritis in healthy infants
CVIA 061 Key Study Characteristics (1)

- Two arm, double-blind, group-sequential, double-dummy trial (1:1)
  - TV P2-VP8 vaccine
  - Rotarix
- Multinational
  - To include 3 countries in Africa and sites in India
- Dose-level/regimen: 3 monthly doses of 90 µg of TV-P2-VP8, administered monthly with EPI vaccines at 6, 10 and 14 weeks of age
- Follow-up through 2 years of age (unless futility criteria met)
CVIA 061 Key Study Characteristics (2)

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

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

**A.** TV P2-VP8 (90µg) + Oral Placebo  
N=4100

**B.** Rotarix® + IM Placebo  
N=4100

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

**Active Gastroenteritis Surveillance (Weekly Participant Contact)**

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

UIP Non-interference  
N=800; 400/group

Oral placebo: ORS; IM placebo: Normal saline
CVIA 061 Study Outline

Stage 1 Enrollment
3,500 infants
4-6 months

Interim analysis
once accrue
≥30 cases SRVGE

Futility Criteria
Not Met

Stage 2 Enrollment
4,700 infants
6-8 months

Primary analysis
once accrue ≥99
cases SRVGE or all
reach 2 years of age

Close enrollment
Crossover
vaccination of TV
P2-VP8 infants
Study closure

Futility Criteria Met

Final analysis after all participants reach 2 years of age
TV-P2-VP8 Future Development

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

Bill Hausdorff, PhD
Lead, Public Health Value Proposition
CVIA/PATH
Washington, DC
The solution to the problem is…

…a next generation, parenterally administered rotavirus vaccine!!

But what, exactly, is the problem?
Isn’t THIS the problem?

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

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

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

Do we even need a Value Proposition?
Yet NRRV has several other potential advantages over live oral vaccines

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

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

Alternatively, do we even have to choose among these advantages?
Yes. We have to make some choices. We can’t do everything. Choices shape clinical program & recommending body/market interest

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

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

- Critical, evidence-based process to ensure our efforts align with need and capacity for intended beneficiaries
  - Communicate value using the lens of stakeholders
  - Consider alternative solutions available to beneficiaries

- Inform planning for evidence generation during vaccine development

- Guide requirements for successful vaccine introduction
  - Identify and develop information required to support policy recommendations and uptake

In current WHO lingo: “Full Public Health Value of Vaccines”
Value Proposition Develops Over Project Lifecycle and Complements Other Project Documents

- **Explore/Early Stage Value Proposition**
- **Learn/Mid-Stage Value Prop.**
- **Confirm/Late-Stage Value Proposition**

Gap analysis and plan to address

TPP Template

Integrated Product Development Plan Template

BMGF Uptake Planning Tool

BMGF Delivery Plan Template

Lifesyle Management Plan Template (under development)
PATH’s Main NRRV Activities

NRRV Value Proposition*

- Primary research – acceptability and feasibility
- Impact and CE analysis
- NRRV vaccine development
- Evaluate the full public health value of a new injectable non-replicating rotavirus vaccine

*N Supported by a 2-year grant from BMGF
For NRRV, how are we going to do it? Project overview

- Develop detailed work plan for VP
- Do Lit Review to Assess Scientific Need for Various Desired Vaccine Characteristics
- Develop potential use cases
- Update models and conduct economic analyses
- Conduct feasibility & acceptability research
- Refine use cases & assumptions in analyses to generate impact and CE estimates
- Inform demand forecasts, value estimates, introduction strategy
- Finalize VP document
How do we align with stakeholders? VP as a living document

- Develop detailed work plan for VP
- Do Lit Review to Assess Scientific Need for Various Desired Vaccine Characteristics
- Develop potential use cases
- Update models and conduct economic analyses
- Conduct feasibility & acceptability research
- Refine use cases & assumptions in analyses to generate impact and CE estimates
- Inform demand forecasts, value estimates, introduction strategy
- Finalize VP document

- Work with WHO’s TSE methodology to get additional NRRV feedback
- Sharing with “both sides” of BMGF (periodically)
- Discuss periodically with clinical development team and other stakeholders (e.g., WHO SAGE? GAVI?)
- Present & discuss results at scientific fora
Acceptability & feasibility of introducing NRRV
A Mixed-Method Study to Assess Future Demand

**Overall objective:** Ascertain country preferences for RV products including NRRV
Based on anticipated health or economic advantages, within a range of RV vaccine options
and in different country contexts

**Specific components:**

- *key informant interviews with global stakeholders*

- *scenario-based interviews with national stakeholders*
  
  Sri Lanka, Myanmar, Malawi, Kenya, Ghana, Senegal, Peru

- *semi-structured interviews with health providers administering vaccines*
Development of RV vaccine use-case scenarios

Option 1: Oral Vaccine Scenario
Efficacy, storage, cost, presentation attributes of licensed LORVs, as well as RV3-BB (neonatal dose), are provided

Option 2: NRRV Scenario
NRRV as a co-administered intramuscular vaccine requiring three doses starting at 6-8 weeks during primary EPI series.
Efficacy may be higher or similar to LORVs
Cost and storage assumptions provided
May be standalone, part of a DTP-combination, and/or co-administered with LORVs

Essentially, a series of forced choices:
Which option would you prefer if NRRV looked like this? Or like this? Or this?
One early output of the NRRV Value Proposition
(Example of an Ad hoc focused analysis)

Critical assessment of the potential value of a booster dose of NRRV
The problem: Oral RV VE in some settings reported to wane by 20% or more in 2\textsuperscript{nd} year of life (Rogawski JID 2018)

<table>
<thead>
<tr>
<th>LORV Efficacy Study</th>
<th>Waning: Percent decrease between 1\textsuperscript{st} and 2\textsuperscript{nd} year efficacies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madhi</td>
<td>36.9%</td>
</tr>
<tr>
<td>Armah &amp; Tapia</td>
<td>35.1%</td>
</tr>
<tr>
<td>Colgate</td>
<td>42.2%</td>
</tr>
<tr>
<td>Armah &amp; Sow</td>
<td>23.7%</td>
</tr>
<tr>
<td>Cunliffe &amp; Madhi</td>
<td>31.8%</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>33.9%</strong></td>
</tr>
</tbody>
</table>

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

Is this an important avenue of research to prioritize?

Value Proposition Approach: Slow down, take a critical look at the potential public health value of a Booster Dose
Results I
A significant portion of the “waning” would be “unfixable” by NRRV as it is due to age-related accumulation of naturally protected controls

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

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

This percentage of artefactual waning likely underestimated, since (unmeasured) sub-clinical RV infection in controls further contributes to natural protection (Lopman JID 2018)
A highly effective NRRV booster dose at 9 or 12 mos. is too late for major incremental impact on RV mortality

*(Model-based analysis by Burnett Vaccine 2017)*

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

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

**Other Assumptions**

- Waning can occur in abrupt step-wise fashion [highly unlikely], linearly, or logarithmically
- In best case scenario, boosting increases VE by 50%

### Results II

<table>
<thead>
<tr>
<th>Region</th>
<th>Linear waning</th>
<th>Logarithmic waning</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths occurring in ABSENCE of boost despite high oral RV coverage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>62,466</td>
<td>62,382</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>28,507</td>
<td>27,838</td>
</tr>
<tr>
<td><strong>Deaths preventable by 12 mo. booster increasing VE by 50% (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>2,658 (4.3%)</td>
<td>4,035 (6.5%)</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>2,153 (7.6%)</td>
<td>3,269 (11.7%)</td>
</tr>
</tbody>
</table>
A boost at 9 and/or 12 months is not likely to make a major impact because

1. a significant portion of “waning” appears artefactual

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

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

• The NRRV Value Proposition is already helping us to garner insights on where there is—and isn't—significant public health value for an effective next generation rotavirus vaccine

• The NRRV VP is most useful if it is
  o A critical, rather than promotional, assessment
  o Has outputs that are disseminated as they are generated to help inform strategy, clinical trial design, vaccine development rather than bunched together years later

• Tangible outputs include
  o Presentations at international meetings
  o Peer-reviewed publications
  o A summary report
### Variety of expertise utilized to develop NRRV Value Proposition

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

Plus potentially: WHO (TSE), others?
Collaborators/Funding

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

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

- Biochemical/Biophysical Characterization of Vaccine Antigens: Kansas University

- Phase I/II Clinical trials:
  - Johns Hopkins University, Baltimore MD USA
  - South African Clinical Research Centers:
    - RMPRU, Soweto / Shandukani, Johannesburg / FAMCRU, Tigerburg

- Phase III Clinical trial:
  - Africa:
    - CIDRZ, Lusaka, Zambia / Dodowa Health Research Center, Ghana / MLW, Blantyre, Malawi
  - India:
    - CHRD-SAS, New Dehli / KEM Hospital Research Centre, Pune / NICED, Kolkata

Funding Provided by Bill and Melinda Foundation
Paratyphoid vaccine development

CONFIDENTIAL

Andrew J Pollard
Typhoid vaccines

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

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

UOXF, UMB

UOXF  UMB

Nepal  Bangladesh  Malawi

20,000  >58,000  28,000

Buddha Basnyat  Shrijana Shrestha  John Clemens  Firdausi Qadri  Melita Gordon

Interim analysis
2019 BMGF/WELLCOME
SALMONELLA CONVENING: SALMONELLA PARATYPHI

London, May 1, 2019
Typhoid & paratyphoid incidence rates per 100,000, age-standardized, 2017

14.3 million (12.5 – 16.3) cases in 2017
## Paratyphoid, global estimates by year (thousands)

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

Acute hepatitis E

Paratyphoid fever

Acute hepatitis A

Dengue

Typhoid fever

Malaria

Yellow fever

Rabies

Acute hepatitis B

Dalys (thousands)
Variation

• Time
• Vaccination
• Geography
• Age
Variable incidence of S. Paratyphi A over time

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

Adapted from data by Zellwegger et al, PLoS NTDs, 2017
Shifting burden related to vaccination?

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

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

Schwartz et al, Ann Int Med 1990
Bodhidatta et al, Rev Inf Dis, 1987
Fig. 2. Estimated *Salmonella typhi* and *Salmonella paratyphi* A incidence with cumulative Vi polysaccharide immunization coverage in Guangxi province, China, 1994–2004

Dong et al, *BWHO* 2010

**Shifting burden related to vaccination?**
Summary

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

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

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

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

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

S. Paratyphi A (NVGH308)
Paratyphoid CHIM

Andrew J Pollard FMedSci
59 volunteers assessed for eligibility

19 Excluded post screening visit:
• Health concerns (n=11)
• Unavailable for visits (n=5)
• Withdrew consent (n=3)
• Prior residence in an enteric fever endemic country (n=2)
• Enrolled in another clinical trial (n=1)

40 enrolled

20 participants received 1-5x10⁹ CFU S. Paratyphi A (Group 1)

20 participants assessed for primary endpoint

Dose De-Escalation

20 participants received 0.5-1x10⁷ CFU S. Paratyphi A (Group 2)

20 participants assessed for primary endpoint
Paratyphoid attack rates
Composite diagnosis

Dobinson et al, 2017
More symptomatic with S Typhi

Dobinson et al, 2017
S Typhi vs S Paratyphi CFU

Dobinson et al, 2017
Blood Culture  Stool  Max Temp

Dobinson et al, 2017
Acknowledgements

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

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

Cal MacLennan, Duncan Steele

Confidential and proprietary data
INTRODUCTION AND OBJECTIVES

Background

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

Co-interest from

• Wellcome Innovations and Vaccines
• BMGF Enteric and Diarrheal Disease
• National Institute of Allergy and Infectious Diseases
• Initiative for Vaccine Research, WHO
Scientific Consultation on Pan-Salmonella Approaches, London. May 2019

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

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

• Disease burden
  Discussion - strength of case for vaccine need, data gaps, plan to address

• Vaccines in development
  Discussion - comparison of approaches, clinical trials considerations

• Pathway to licensure, value proposition, CHIM, assays & standards, regulatory considerations
  Discussion - pathway feasibility, data gaps, regulatory engagement
Two potential combination *Salmonella* vaccines

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

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

Jeff Stanaway, UW IHME. Pan-Salmonella Meeting, London 2019
The burden of iNTS disease, caused by *Salmonella* Typhimurium and *Salmonella* Enteritidis, is a serious public health concern in Sub-Saharan Africa.

600,000 to 3.4M cases of iNTS disease occurred globally in 2010*. >50% of cases of iNTS disease occur in Sub-Saharan Africa. Case-fatality rates commonly reported at ~15-20%

~622,000 cases estimated in 2017 (490,000 – 800,000). ~68,000 deaths in 2017**

High prevalence of iNTS disease seen in children under 3 years of age

Clinical presentation is most commonly with fever alone: diagnosis not usually possible

Diagnosis requires blood culture facilities that are uncommon in Sub-Saharan Africa

Antimicrobial drug resistance to iNTS isolates, including MDR, is common. Emergence of fluoroquinolone and ceftriaxone resistance makes treatment increasingly difficult

Effective methods for disease control as improvement to water supply and sanitation is lagging and cost prohibitive in endemic countries

---

*Ao et al, 2015; **GBD, 2017*
RESULTS: COMPARING GBD AND OTHER PUBLISHED ESTIMATES

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

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

Ao et al include deaths for which HIV is underlying cause
Kirk et al exclude such deaths
INTS INCIDENCE RATES PER 100,000, AGE-STANDARDIZED, 2017

[Map showing incidence rates around the world]
NON-TYPHOIDAL SALMONELLA INVASIVE DISEASE DALYS AND DEATHS BY AGE, WORLDWIDE, GLOBAL BURDEN OF DISEASE 2017

Disability Adjusted Life Years

Deaths

http://vizhub.healthdata.org/gbd-compare/
A ROLE FOR ANTIBODIES IN IMMUNITY TO iNTS DISEASE IN AFRICAN CHILDREN

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

**RESEARCH HIGHLIGHTS**

**IMMUNOLOGY**

**Antibiotic antibodies**


The discovery of functional antibodies against strains of *Salmonella* that do not cause typhoid raises hopes that a vaccine can be developed. In Africa, such strains kill up to 24% of infected children in communities in which appropriate antibiotics and blood-culture facilities are available.
• iNTS disease incidence appears to be falling in some settings
• Complexity due to co-dependence of iNTS disease on co-morbidities - that are potentially preventable (malaria) and treatable (HIV infection)
• Complexity due to co-dependence of iNTS disease on co-morbidities - disparity in key mechanisms of immunity with different co-morbidities (malaria, HIV infection, malnutrition)
• Crowded EPI schedule at point where the vaccine is most likely needed (infants at 6/10/14 weeks)
• Lack of commercial incentive – diseases of the most vulnerable populations
• Large financial/time commitment required before efficacy read out – phase 3 field study required, as there is no CHIM available
VARIATION IN INVASIVE NON-TYPHOIDAL SALMONELLA DISEASE INCIDENCE IN AFRICA OVER TIME
HIV AND NTS DISEASE

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

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

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

Gordon MA et al, AIDS 2002
# THE VACCINE CANDIDATES

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Developer</th>
<th>Stage of development</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:4,5/0:9-flagellin</td>
<td>O:4,5/0:9 Conjugate</td>
<td>University of Maryland</td>
<td>Preclinical</td>
<td>50,69</td>
</tr>
<tr>
<td>0:4,12-TT</td>
<td>O:4-TT Conjugate</td>
<td>NIH</td>
<td>Preclinical</td>
<td>51</td>
</tr>
<tr>
<td>Os-po</td>
<td>O:4-porin Conjugate</td>
<td>National Bacteriology Laboratory, Stockholm</td>
<td>Preclinical</td>
<td>146</td>
</tr>
<tr>
<td>O:4,5/O:9-CRM&lt;sub&gt;gly&lt;/sub&gt;</td>
<td>O:4,5/O:9 Conjugate</td>
<td>NVGH</td>
<td>Preclinical</td>
<td>145</td>
</tr>
<tr>
<td>WT05</td>
<td>Live attenuated</td>
<td>Microscience, Wokingham Berkshire</td>
<td>Phase 1</td>
<td>147</td>
</tr>
<tr>
<td>CVD 1921 and CVD 1941</td>
<td>Live attenuated</td>
<td>University of Maryland</td>
<td>Preclinical</td>
<td>148</td>
</tr>
<tr>
<td>S. Typhimurium ruv8 mutant</td>
<td>Live attenuated</td>
<td>Seoul National University</td>
<td>Preclinical</td>
<td>149</td>
</tr>
<tr>
<td>Salmonella hfg deletion mutant</td>
<td>Live attenuated</td>
<td>Indian Institute of Science Bangalore</td>
<td>Preclinical</td>
<td>150</td>
</tr>
<tr>
<td>SA186</td>
<td>Live attenuated</td>
<td>Istituto Superiore di Sanità Roma</td>
<td>Preclinical</td>
<td>151</td>
</tr>
<tr>
<td>MT13</td>
<td>Live attenuated</td>
<td>KIIT University Odisha</td>
<td>Preclinical</td>
<td>152</td>
</tr>
<tr>
<td>Various</td>
<td>Live attenuated, DNA adenine methylase mutants</td>
<td>University of California, Santa Barbara</td>
<td>Preclinical</td>
<td>153,154</td>
</tr>
<tr>
<td>Various</td>
<td>Live attenuated, regulated delayed attenuation</td>
<td>Arizona State University</td>
<td>Preclinical</td>
<td>155-157</td>
</tr>
<tr>
<td>Porins</td>
<td>S. Typhimurium porins</td>
<td>National Bacteriology Laboratory, Stockholm</td>
<td>Preclinical</td>
<td>146</td>
</tr>
<tr>
<td>OmpD</td>
<td>Outer membrane protein</td>
<td>University of Birmingham, UK</td>
<td>Preclinical</td>
<td>73</td>
</tr>
<tr>
<td>S. Typhimurium and S. Enteritidis GMMA</td>
<td>Generalized Modules for Membrane Antigens</td>
<td>NVGH</td>
<td>Preclinical</td>
<td>65,158,159</td>
</tr>
</tbody>
</table>

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

Bharat Biotech, Hyderabad, India

Bio E, Hyderabad, India
LIPOPOLYSACCHARIDE (LPS) & FLAGELLA

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

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

CVD iNTS vaccine: Core-OPS conjugate with phase 1 flagellin protein (FliC)
A VACCINE TO PREVENT INVASIVE SALMONELLA DISEASE INCLUDING NTS AND TYPHOID FEVER IN SUB-SAHARAN AFRICA

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

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

Attenuated engineered *Salmonella* mutants:

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

• Tri-valent parenteral conjugate vaccine to prevent invasive Salmonella disease in Sub-Saharan Africa with the pre-qualified Typbar TCV.
PROTECTION AGAINST FATAL INFECTION WITH MALIAN S. ENTERITIDIS (R11) OR S. TYPHIMURIUM (D65) BLOOD ISOLATES IN MICE IMMUNIZED WITH THE HOMOLOGOUS PATHOGEN MONOVALENT COPS:FLIC VACCINES

**Immunization**: D0, D14, D28 with 2.5 µg conjugate polysaccharide or PBS

**Challenge**: IP infection at D56 with $1 \times 10^6$ CFU S. Enteritidis R11 (IP LD50 = $2 \times 10^5$) or $5 \times 10^5$ CFU S. Typhimurium D65 (IP LD50 = $2 \times 10^4$); *P<0.0001 (log-rank)
PROPOSED CLINICAL DEVELOPMENT

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

GMMA

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

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

(Slide courtesy of Oliver Koeberling)
**2-COMPONENT iNTS-GMMA VACCINE**

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

**iNTS-GMMA vaccine approach**

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

(Slide courtesy of Oliver Koeberling)
SUMMARY

- A comprehensive preclinical data package for the iNTS-GMMA vaccine in place demonstrating iNTS-GMMA
  - Immunogenicity in mice and rabbits
  - Manufacturability
  - Stability
- iNTS-GMMA project is at the stage to proceed with early clinical development
WHAT IS THE PATH FORWARD FOR UPTAKE OF AN INTS VACCINE...AND GAPS

Current status

(Slide courtesy of Birgitte Giersing WHO)
CONCLUSIONS FROM SALMONELLA CONVENING: iNTS

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

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

Are candidates sufficiently immunogenic to confer protection in LMIC children?

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

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

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

WHY WE DO IT IS NOT.