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

<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 broad range of global stakeholders, including from a LMIC perspective, and aims to articulate the full direct (individual) and indirect (population) effects of a vaccine</td>
</tr>
</tbody>
</table>
### WHO generic guidance that informs vaccine development

<table>
<thead>
<tr>
<th>Generic Preferred Product Profile for Vaccines (gPPP) (2015)</th>
<th>Recommendations on <strong>presentation and packaging</strong> of new vaccines for use in LMICs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessing the programmatic suitability of vaccine candidates for WHO prequalification (2014)</td>
<td><strong>Process and criteria</strong> for prospective <strong>vaccine PQ</strong> in terms of their programmatic suitability for LMICs</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>
</tr>
</thead>
<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>
</tr>
<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>✓ (✓)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HSV</td>
<td>✓</td>
<td>✓ (P&amp;T)</td>
<td>✓ (STI RM)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>GC</td>
<td>✓</td>
<td>✓ (✓)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETEC</td>
<td>✓</td>
<td>✓ (✓)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigella</td>
<td>✓</td>
<td>✓ (✓)</td>
<td></td>
<td>(✓)</td>
<td></td>
</tr>
<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)

**Clinical candidates**
- ETVAX inactivated (SBH, UG, PATH)
- ACE527 live attenuated (PATH; NVSI; UGA)

**Preclinical candidates**
- CVD GuaBA mutants expressing ETEC Ags. (UMB, PaxVax)
- ShigETEC (EveIQure)
- 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.

2 = Vaccines in or poised to begin clinical trials; STM = inactivated mutant Shigella with truncated LPS giving conserved protein Ags. greater exposure (Kim et al 2018. Frontiers. Microbiol).

Slide courtesy of Lou Bourgeois, PATHc
6-11-month-old infants given the **ETVAX** inactivated whole-cell ETEC vaccine

- **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
Shigella vaccine candidate pipeline

**Phase 1**
- **Live**
  - CVD1208S (S. flex 2a) U Maryland/PATH
- **Killed**
  - TSWC (S. flex 2a) WRAIR/PATH
  - Oag synthetic conjugate (S. flex 2a) Pasteur Institute
  - Oag Bioconjugate (S. dysenteriae) Limmatech (GSK)

**Phase 2**
- **SC602** (S. flex 2a) WRAIR
  - WRSS1 (S. sonnei) WRAIR/PATH
  - GMMA (S. sonnei) GVGH (GSK)
  - Oag Bioconjugate (S. flex 2a) Limmatech (GSK)
  - Invaplex (S. flex 2a) WRAIR

**Phase 3**
- **Licensed**
  - Streptomycin-dep LAV (historic/various) (Yugoslav Army/other)
  - Oag-TT conjugate (S. sonnei) NIH

**Notes**
- Historic LAVs no longer in use
- 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

- **Phase 1**
  - **Live**
    - CVD1208S (S. flex 2a)
      - U Maryland/PATH
  - **Killed**
    - TSWC (S. flex 2a)
      - WRAIR/PATH
    - Oag synthetic conjugate (S. flex 2a)
      - Pasteur Institute
  - **Subunit**
    - Oag Bioconjugate (S. dysenteriae)
      - Limmatech (GSK)

- **Phase 2**
  - SC602 (S. flex 2a)
    - WRAIR
  - WRSS1 (S. sonnei)
    - WRAIR/PATH
  - GMMA (S. sonnei)
    - GVGH (GSK)
  - Oag Bioconjugate (S. flex 2a)
    - Limmatech (GSK)
  - Innaplex (S. flex 2a)
    - WRAIR

- **Phase 3**
  - Licensed
    - Streptomycin-dep LAV (historic/various)
      - (Yugoslav Army/other)

- **Notes**
  - Historic LAVs no longer in use

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

Next steps:
Move M72/AS01 forward

R&D Technical Roadmap
Public Health Value Proposition
Malaria vaccine development

Consultation on malaria vaccines and biologicals R&D
MALVAC meeting
July 15-17\textsuperscript{th}, Geneva, Switzerland

Recent updates:

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

Summary profiles of large-scale efficacy trials

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

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

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

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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)
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
### TABLE 40.1 Summary of Estimated Global Burden of GAS Diseases

<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>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic heart disease (RHD)</td>
<td>2017, 2005</td>
<td>33.4 million⁹</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>188,000⁹</td>
<td></td>
</tr>
<tr>
<td>RHD-related infective endocarditis²¹</td>
<td>2016</td>
<td>640,000²</td>
<td>500,000 – 600,000 deaths each year</td>
<td></td>
</tr>
<tr>
<td>RHD-related stroke</td>
<td>2016</td>
<td>640,000²</td>
<td>134,000²⁰</td>
<td></td>
</tr>
<tr>
<td>Acute post-streptococcal glomerulonephritis²</td>
<td>2005</td>
<td>§</td>
<td>472,000</td>
<td>9,000</td>
</tr>
<tr>
<td>Invasive group A streptococcal diseases²</td>
<td>2005</td>
<td>§</td>
<td>663,000</td>
<td>163,000</td>
</tr>
<tr>
<td>Pyoderma⁹</td>
<td>2015</td>
<td>162 million</td>
<td>616 million</td>
<td></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.*
$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!
PHARYNGITIS

Vaccine
OR
Placebo

NO PHARYNGITIS
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

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

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

[Diagram showing the relationship between HSV-2 and HIV]
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

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**
- 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 gonorrhea 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®)
      - MC58∆ABR (FDA/CBER)
      - Gonococcal OMVs
  - **Purified protein subunit vaccines**
    - Antigens involved in:
      - physiology or metabolism
      - evasion of innate effectors
      - bacterial structure

- LOS epitope (peptide mimetic)

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

Normal tubal tissue, 1200x Post-PID, 1200x

Scanning electron microscopy photos courtesy of Dorothy L. Patton, University of Washington
Chlamydial vaccine candidate now under clinical evaluation

- 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)
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Current status of the development pathway of STI vaccines

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

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

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- 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

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
  - 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

World Health Organization
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 gonorrhea 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
  - **Purified protein subunit vaccines**
    - Antigens involved in:
      - physiology or metabolism
      - evasion of innate effectors
      - bacterial structure
  - **LOS epitope (peptide mimetic)**

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

Normal tubal tissue, 1200x Post-PID, 1200x

Scanning electron microscopy photos courtesy of Dorothy L. Patton, University of Washington
Chlamydial vaccine candidate now under clinical evaluation

- 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

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

1. Draft MR-MAP TPP developed by PATH/WHO/DTWG
2. MR-MAP consultation & Update
3. IPAC/Technet Survey to assess thermostability, wear time and disposal
4. 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
- IPAC Consultation June 2019
- 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