Gonorrhea: key immunological considerations for vaccine development & potential cross protection with 4CMenB

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Key issues that highlight the need for a gonorrhoea vaccine

- > 82 million cases per year
- Majority of infections have no/mild symptoms
- Infection can have significant, long term health consequences
- No natural immunity after infection and reinfection is common
- May become untreatable due to antibiotic resistance
- Prevention by vaccination is essential for long term control of gonorrhoea

https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis)
90% reduction in the number of new cases of gonorrhoea by 2030

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Baseline – 2020</th>
<th>Targets - 2025</th>
<th>Targets - 2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of new cases of gonorrhoea among people 15–49 years old per year</td>
<td>82.3 million</td>
<td>65.8 million</td>
<td>8.23 million</td>
</tr>
</tbody>
</table>

Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022–2030

**Action 103:** New vaccines for sexually transmitted infections.
Activities to facilitate vaccine development

- **Preferred product characteristics (PPC)**
  - Promote development of vaccines with optimal effectiveness and suitability, particularly in LMIC
  - Maximise global impact

- **Vaccine value profile (VVP)**
  - Provide a high-level assessment of current data to inform the potential public health, economic and societal value of a vaccine

https://www.who.int/publications/i/item/9789240039827
Obstacles to gonorrhoea vaccine development

- **Antigenically variable** bacteria
  - Selection of broadly protective antigens is challenging
  - Multicomponent vaccine needed

- **Humans are only natural host**
  - Difficult to fully test vaccine candidates in animal models that lack human specific receptors and molecules

- **No / limited protective immunity** after infection
  - Limited data on immune protection to guide vaccine development
  - No correlate of protection

- Gonorrhoea is highly adapted to evade / avoid immune system
Evades / inhibits immune responses

- **Highly variable** surface structures both between strains and within strains over the course of infection

Bayliss FEMS Microbiol Rev (2009)
Evades / inhibits immune responses

- **Mimics** host structures
  - Lipooligosaccharide (LOS) sialylation
- **Recruits complement inhibitors**
  - blocks alternative and classical complement pathways

Evades / inhibits immune responses

- **Suppresses T cell proliferation** and activation of adaptive immune responses
- **Promotes survival** in macrophages and neutrophils
- Th1/Th2 responses are blunted - pro-inflammatory **Th17 responses dominate**
Modest immune responses following infection

- **Antibodies present** to gonorrhoea LOS/proteins in sera, seminal plasma, cervical secretions **following infection**
- **Pre-existing antibodies** to gonorrhoea LOS/proteins are common
  - Cross-reaction to nasal carriage of *N. meningitidis* or commensal *Neisseria*?
- **Some association** between antibodies to
  - LOS and resistance to infection in human re-challenge model
  - Opa and reduced relative risk of salpingitis in sex workers in Kenya
- **Cellular immune responses** poorly understood

> A vaccine needs to induce a non-native immune response

Lovett & Duncan, Front Immunol (2019)
Preclinical vaccine development

- Characterisation of promising gonococcal vaccine antigens

Preclinical vaccine evaluation

- In vitro efficacy based on
  - Immunogenicity and surface-binding of antibodies (ELISA titres)
  - Bactericidal or opsonophagocytic activity (SBA / OPA titres)
  - Inhibition/neutralisation of target function

Preclinical vaccine evaluation

- **In vitro efficacy based on**
  - Immunogenicity and surface-binding of antibodies (ELISA titres)
  - Bactericidal or opsonophagocytic activity (SBA / OPA titres)
  - Inhibition of target function

- **In vivo efficacy**
  - Female *mouse genital tract infection model*
    - Does not replicate infection and transmission

Clinical vaccine evaluation

• Investigation of **cross-protection** by a meningococcal vaccine

Meningococcal 4CMenB vaccine

GMMA = generalized modules for membrane antigens

Gonorrhoea GMMA

NCT05630859
Vaccine trials for gonorrhea

- **1970**: Heat-killed, partially lysed whole cells
- **1990**: Pilin
- **2020**: 4CMenB
- **2030**: Gonorrhoea GMMA

Questions:
- **Porin (PorB)**

The timeline is set from 1970 to 2030.
Evidence for MenB vaccine cross protection

- *Neisseria gonorrhoeae & Neisseria meningitidis*
  - closely related bacteria
  - share most genes/virulence factors
- Have had distinct vaccine development pathways
  - Outer membrane vesicle (OMV) vaccines to serogroup B (MenB)
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Vaccine</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational, case control, cohort</td>
<td>Cuba(^1)</td>
<td>VA-MENGOC-BC</td>
<td>30 - 50% effectiveness against gonorrhoea</td>
</tr>
<tr>
<td></td>
<td>Norway(^2)</td>
<td>MenBvac</td>
<td></td>
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<tr>
<td></td>
<td>New Zealand(^3)</td>
<td>MeNZB</td>
<td></td>
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<tr>
<td></td>
<td>Canada(^4)</td>
<td>MeNZB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>USA(^5)</td>
<td>MeNZB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Australia(^6)</td>
<td>MeNZB</td>
<td></td>
</tr>
<tr>
<td>Randomised control trial</td>
<td>France(^7)</td>
<td>4CMenB</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Pérez et al., 2009, Ochoa Azze, 2019, Reyes Diaz et al., 2021. \(^2\)Whelan et al., 2016. \(^3\)Petousis-Harris et al., 2017. \(^4\)Longtin et al., 2017. \(^5\)Abara et al., 2022. \(^6\)Wang et al., 2022. \(^7\)Molina et al. 2023 NCT04597424.
Potential mechanism of action for MenB vaccines against *N. gonorrhoeae* (Ng)

- 4CMenB NHBA and OMV antigens have **homologues in Ng**\(^1\)\(^-\)\(^3\)
- Sera from vaccinated humans **cross-reacts** with Ng\(^1\)
- 4CMenB immunized **mice**\(^4\)
  - **accelerated clearance and reduced Ng bacterial burden** in upper and lower reproductive tract
  - 4-fold increase in **serum bactericidal titers**
  - serum IgG and vaginal IgA & IgG **cross-reacts** with Ng
  - antibodies recognize Ng PilQ*, BamA, MtrE, NHBA*, PorB, and Opa (*also shown for human serum)

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<table>
<thead>
<tr>
<th>Trial number</th>
<th>Study type</th>
<th>Study name</th>
<th>Location, numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTRN126190 01478101</td>
<td>RCT efficacy Immunogenicity</td>
<td>MenGO: Does the licensed meningococcal vaccine Bexsero® provide cross- protection against gonorrhoea?</td>
<td>Australia 130</td>
</tr>
<tr>
<td>NCT04415424</td>
<td>RCT efficacy Immunogenicity</td>
<td>GoGoVax: Efficacy study of 4CMenB Bexsero® to prevent gonorrhoea infection in gay and bisexual men</td>
<td>Australia 730</td>
</tr>
<tr>
<td>NCT04350138</td>
<td>RCT efficacy</td>
<td>Safety and efficacy study of meningococcal group B vaccine rMenB+OMV NZ Bexsero to prevent gonococcal infection</td>
<td>USA, Thailand 2,200</td>
</tr>
<tr>
<td>NCT05294588</td>
<td>RCT challenge</td>
<td>Efficacy of Immunization With 4C-MenB in Preventing Experimental Urethral Infection With Neisseria Gonorrhoeae</td>
<td>USA 140</td>
</tr>
<tr>
<td>NCT04722003</td>
<td>Immunogenicity</td>
<td>Mucosal immunity against <em>Neisseria gonorrhoeae</em> after 4CMenB vaccination</td>
<td>USA 50</td>
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<tr>
<td>NCT04094883</td>
<td>Immunogenicity</td>
<td>Study to assess gonorrhoeae immune responses induced by a <em>N. meningitidis</em> vaccine 4CMenB</td>
<td>USA 15</td>
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<tr>
<td>NCT04297436</td>
<td>Immunogenicity</td>
<td>Gonococcal vaccine study in key populations in Kenya BexKPK</td>
<td>Kenya 50</td>
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<tr>
<td>NCT04398849</td>
<td>Observational prospective cohort</td>
<td>Immunisation for adolescents against serious communicable diseases B Part of it NT</td>
<td>Australia 7,100</td>
</tr>
</tbody>
</table>

Ongoing research towards establishing a correlate of protection

- Several 4CMenB clinical trials are investigating immune responses\textsuperscript{1-5}

- **Humoral** immune responses
  - **Antibody levels** - Serum and mucosal IgG, IgA, IgM specific for recombinant protein antigens or OMVs
  - **Antibody function** - Serum bactericidal activity (SBA), opsonophagocytic killing (OPK), function neutralising

- **Cellular** immune responses
  - Peripheral blood mononuclear cells (PBMC) collected
  - Antigen-specific IFN secreting T cells and memory B cells investigated

1. NCT04722003; 2. NCT04297436; 3. NCT04415424; 4. ACTRN12619001478101; 5. NCT04094883
Ongoing research towards establishing a correlate of protection

• Controlled Human Infection Model (CHIM)¹
  • Experimental urethral infection in 18-35 year old males - symptomatic urethritis seen in 80-90% of participants within 5 days
  • Participants will receive 2 doses of vaccine (4CMenB or comparator vaccine) then intraurethral challenge with Ng

¹ NCT05294588
Many obstacles to gonorrhoea vaccine development
Several promising vaccine candidates in preclinical development
2 vaccines undergoing clinical evaluation
  - hopefully show protection
  - help identify correlates of protection
Feasibility of mRNA gonorrhoea vaccine?