

# Advancing vaccine development for gonorrhoea and the Global STI Vaccine Roadmap

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**Abstract.** Efforts to develop vaccines against *Neisseria gonorrhoeae* have become increasingly important, given the rising threat of gonococcal antimicrobial resistance (AMR). Recent data suggest vaccines for gonorrhoea are biologically feasible; in particular, epidemiological evidence shows that vaccines against a closely related pathogen, serogroup B *Neisseria meningitidis* outer membrane vesicle (OMV) vaccines, may reduce gonorrhoea incidence. Vaccine candidates using several approaches are currently in preclinical development, including meningococcal and gonococcal OMV vaccines, a lipooligosaccharide epitope and purified protein subunit vaccines. The Global STI Vaccine Roadmap provides action steps to build on this technical momentum and advance gonococcal vaccine development. Better quantifying the magnitude of gonorrhoea-associated disease burden, for outcomes like infertility, and modelling the predicted role of gonococcal vaccines in addressing AMR will be essential for building a full public health value proposition, which can justify investment and help with decision making about future vaccine policy and programs. Efforts are underway to gain consensus on gonorrhoea vaccine target populations, implementation strategies and other preferred product characteristics that would make these vaccines suitable for use in low- and middle-income, as well as high-income, contexts. Addressing these epidemiological, programmatic and policy considerations in parallel to advancing research and development, including direct assessment of the ability of meningococcal B OMV vaccines to prevent gonorrhoea, can help bring about the development of viable gonococcal vaccines.

**Additional keywords:** antimicrobial resistance, gonococcal infection, *Neisseria gonorrhoeae*, sexually transmitted infections, STI vaccines.

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## Introduction

Gonorrhoea, a sexually transmissible infection (STI) caused by the bacterial pathogen *Neisseria gonorrhoeae*, is a major concern for sexual and reproductive health globally, with an estimated 87 million new cases each year.<sup>1</sup> Untreated cervical infections can lead to adverse consequences, including pelvic inflammatory disease (PID), infertility, ectopic pregnancy, adverse pregnancy outcomes like preterm delivery and neonatal conjunctivitis that can lead to blindness.<sup>2</sup> Although women and infants bear the brunt of the long-term consequences of infection, men are more likely than women

to have symptomatic genital infection and commonly experience morbidity in the form of urethral discharge syndrome.<sup>3</sup> In both men and women, inflammation due to gonorrhoea likely increases the risk of acquiring and transmitting HIV infection.<sup>4,5</sup> The burden of disease falls disproportionately on low- and middle-income countries (LMICs),<sup>1</sup> where healthcare resources for diagnosis and treatment are constrained.

Efforts to control gonorrhoea are threatened by the rapid emergence of antimicrobial resistance (AMR) of *N. gonorrhoeae* to multiple antibiotics, which is currently

monitored by 67 countries in the Gonococcal Antimicrobial Surveillance Program (GASP).<sup>6</sup> The spectre of untreatable gonorrhoea has been raised by increasing reports of *in vitro* and clinical resistance to extended-spectrum cephalosporins, the only remaining first-line monotherapy for gonorrhoea.<sup>7</sup> Laboratory testing data from GASP showed that 66% of participating countries reported some resistance to extended-spectrum cephalosporins between 2009 and 2014.<sup>7</sup> Several countries, particularly in World Health Organization (WHO) Western Pacific and South-east Asian regions, reported more than 5% of isolates with decreased susceptibility or resistance to ceftriaxone.<sup>7</sup> In addition, transmission and treatment failure with multidrug-resistant strains has now been documented.<sup>8</sup> The WHO considers *N. gonorrhoeae* a 'high priority' pathogen for addressing AMR globally.<sup>7,9</sup> Efforts are underway to identify new drugs for gonorrhoea treatment; however, *N. gonorrhoeae* has successively acquired resistance to multiple classes of antibiotics.<sup>10</sup> For these reasons, development of a gonococcal vaccine has become increasingly important and may be the only long-term, sustainable solution for global gonorrhoea control.

Historically, the feasibility of developing a vaccine against gonorrhoea has been questioned because of the antigenic variability of *N. gonorrhoeae* and its ability to cause repeated infections without inducing protective immunity.<sup>11</sup> However, recent data on vaccines against a closely related pathogen, the serogroup B *Neisseria meningitidis* outer membrane vesicle (OMV) vaccines, has reinvigorated the field. A large case-control study in New Zealand suggested that vaccination with the serogroup B meningococcal OMV vaccine MeNZB reduced gonorrhoea risk.<sup>12</sup> MeNZB was developed specifically for New Zealand through a public-private partnership in response to a meningitis B epidemic. Following a mass vaccination campaign with MeNZB, researchers found that vaccinated individuals were significantly less likely to be gonorrhoea cases than controls; the estimated vaccine effectiveness was 31%.<sup>12</sup> An ensuing retrospective cohort study in New Zealand found that MeNZB vaccination was associated with a reduced rate of gonorrhoea-associated hospitalisations.<sup>13</sup> Other observational studies have reported similar findings following the use of OMV-based meningococcal vaccines.<sup>14,15</sup> These studies provide proof of principle that gonorrhoea vaccines are biologically feasible. Concurrently, a strategic global emphasis on vaccines in fighting AMR,<sup>16</sup> and efforts to develop new STI vaccines through the Global Roadmap to Advance STI Vaccine Development,<sup>17,18</sup> have further catalysed interest in gonococcal vaccine development.

### Status of gonococcal vaccine research and development

Vaccine development for gonorrhoea is currently in the preclinical phase, with no vaccine candidates yet in human clinical trials. Over two decades of detailed molecular pathogenesis studies have identified several stably expressed conserved antigens critical for infection or physiology that may be effective gonococcal vaccine targets (Table 1). Technological advances have further accelerated antigen discovery. For example, whole-genome sequencing and proteomics technology have led to unbiased, comprehensive screens for new targets<sup>19,20</sup> and have facilitated fine-tuned antigen mapping.<sup>21</sup> Recently, immunoproteomics using sera

from people immunised with serogroup B meningococcal OMV vaccines has identified cross-reactive gonococcal antigens that may contribute to the predicted cross-protection of these vaccines.<sup>22</sup>

Based on this discovery work, several promising vaccine candidates are undergoing preclinical evaluation. The main vaccine approaches include OMV vaccines (meningococcal or gonococcal), a lipooligosaccharide (LOS) epitope vaccine and purified protein subunit vaccines (Table 1; for a review, see Rice *et al.*<sup>23</sup>). Evaluation of these vaccine candidates has been challenging, because there are no established surrogate markers or correlates of protection against *N. gonorrhoeae*. Preclinical testing is based on measuring bactericidal or opsonophagocytic activity, antibody surface binding, blocking of target function and the *in vivo* efficacy of antigens and antigen formulations in a female mouse genital tract infection model. Although laboratory mice cannot fully mimic human disease, transgenic mice have been developed to alleviate some host restrictions.<sup>23</sup> However, whether host responses in mice accurately predict vaccine efficacy in humans remains unknown.

Despite these challenges, there is reason for optimism. The licenced four-component serogroup B meningococcal vaccine (4CMenB; Bexsero, GSK, Rixensart, Belgium), which contains the MeNZB OMV antigen plus three additional recombinant antigens, and candidate OMV vaccines from another *N. meningitidis* strain significantly accelerated clearance of *N. gonorrhoeae* in a mouse genital tract infection model.<sup>24,25</sup> These data provide direct evidence as to the cross-protective potential of these vaccines, which is also supported by findings that gonococcal antigens are recognised by antibodies from humans vaccinated with meningococcal OMV vaccines.<sup>22</sup> However, product development of gonococcal OMV vaccines may be more complicated than meningococcal OMVs because of the immunosuppressive properties of *N. gonorrhoeae*, and adjuvants that reverse *N. gonorrhoeae*-mediated immunosuppression may be critical for gonococcal OMV vaccines.<sup>26</sup> Other approaches including several purified protein subunit vaccines also show promising preclinical results and are under development (Table 1).

### Next steps: following the Global STI Vaccine Roadmap

The Global STI Vaccine Roadmap highlights action steps not only to build on the technical and scientific momentum to develop gonococcal vaccines, but also to consider the programmatic and policy issues that are critical for catalysing investment in vaccine development and ensuring the collection of evidence that will support eventual uptake.<sup>17,18</sup> Key overarching roadmap activities include: (1) obtaining better epidemiological data; (2) modelling theoretical vaccine impact; (3) advancing basic science and translational data; (4) defining preferred product characteristics (PPCs) for first-generation vaccines; and (5) characterising the full public health value of vaccines to encourage investment and guide policy decisions.<sup>18</sup> Each of these is described in detail below.

#### Obtaining better epidemiological data

Underpinning every aspect of the roadmap to develop gonococcal vaccines is the need for improved epidemiological data on the

**Table 1. Overview of gonococcal vaccine research and development**

4CMenB, four-component meningococcal B vaccine (Bexsero, GSK); Acp, adhesion complex protein; AniA, nitrite reductase; BamA, outer membrane protein assembly factor; CpG, cytosine–phosphorous–guanine; IL-12, interleukin-12; LOS, lipooligosaccharide; LptD, LPS-assembly protein; MeNZB, New Zealand meningococcal B vaccine; MetQ, methionine transporter; MsrA/B, methionine sulfoxide reductase; MtrE, multi-transferrable resistance efflux pump outer membrane channel; Ng, *Neisseria gonorrhoeae*; Nm, *Neisseria meningitidis*; NspA, *Neisseria* surface protein A; OMV, outer membrane vesicle; OpcA, outer membrane protein adhesion; PorB, porin; TamA, translocation and assembly module subunit A; TbpA and TbpB, transferrin-binding protein subunit A and B, respectively; ZnuD, zinc uptake component D

Strategy or candidate	Status and results
<b>Antigen discovery strategies</b>	
Identification of conserved, stably expressed virulence factors or proteins involved in cell envelope biogenesis or cell structure	TbpA, TbpB, OpcA, ZnuD, PorB, MetQ, TamA, BamA, LptD, Acp, <sup>22</sup> AniA, <sup>46</sup> MtrE, <sup>47</sup> MsrA/B, <sup>48</sup>
Generation of genetically diverse whole-genome sequence databases	Now available and used to identify new conserved antigens or conserved regions within semivariably antigens <sup>19,21</sup>
Proteomic screens	Non-biased approach; 168 conserved surface proteins have been identified <sup>20</sup>
Immunoproteomics	Cross-reactive Ng antigens identified with serum from subjects vaccinated with 4CMenB or MeNZB <sup>22</sup>
<b>Vaccine approaches and candidates</b>	
Licensed Nm OMV vaccines (e.g. 4CMenB)	Human observational studies suggest possible cross-protection against gonorrhoea <sup>12–15</sup> 4CMenB accelerated clearance of gonococcal infection in mouse model <sup>24</sup>
Other Nm OMVs	Wild-type and genetically engineered Nm MC58 OMVs accelerated clearance of gonococcal infection in mouse model <sup>25</sup>
Ng OMVs	Vaginal immunisation of mice with Ng OMVs formulated with IL-12 in microspheres accelerated Ng clearance following vaginal challenge with homologous or heterologous Ng strains <sup>26</sup> Ng OMVs given with NspA adjuvant significantly accelerated clearance of experimental murine infection <sup>49</sup> Other studies did not show protective efficacy in the mouse model for Ng OMVs given intranasally with alum or alum plus CpG adjuvant <sup>50</sup>
2C7 LOS epitope	Accelerated clearance in a mouse model <sup>51</sup> and elicited bactericidal and opsonophagocytic antibodies <sup>52</sup>
Purified protein subunit vaccines	MtrE, BamA, LptD, TamA, MetQ, TbpA/B, AniA and MsrA/B are highly conserved and induce bactericidal antibodies <sup>22,53,54</sup> Antibodies to candidate TbpA, AniA and MsrA/B vaccines also block the use of transferrin as an iron source, <sup>55</sup> nitrite reductase activity <sup>53</sup> and methionine sulfoxide reductase activity <sup>54</sup> respectively in Ng
Novel vaccine delivery systems	Several vaccine platforms using viral vectors, <sup>56</sup> protein scaffolds <sup>57</sup> or transdermal needle patches <sup>58</sup> have been adapted for Ng antigens

burden of gonorrhoea infection, disease and AMR, especially in LMICs. Although global and regional burden of infection has been estimated,<sup>1</sup> disease outcomes like gonorrhoea-associated infertility, ectopic pregnancies and other poor pregnancy and birth outcomes are less well defined. In some settings, the potential magnitude of gonococcal disease burden, and its associated economic burden, is completely unknown. A large study in the 1980s showed that up to 85% of female infertility in Sub-Saharan Africa was related to tubal scarring from genital infection.<sup>27</sup> However, little has been studied since then to clarify the burden of tubal factor infertility in different settings and the likelihood that gonorrhoea is a contributing factor. In most resource-poor settings, patients receive STI care through syndromic management, without the use of diagnostic tests. Especially for women, syndromic diagnosis is a poor predictor of laboratory-confirmed gonococcal infection,<sup>28</sup> and this approach limits data available for infection and disease burden estimates because many infections are asymptomatic. Even when cervicitis, urethritis or PID is apparent, no aetiological diagnosis is made to distinguish gonococcal, chlamydial and other reproductive tract infections or to establish the presence of

coinfections. This highlights the critical need not only for more aetiological and prevalence studies, particularly in LMICs,<sup>29</sup> but also for affordable, feasible point-of-care diagnostics appropriate for these settings.<sup>30</sup>

The GASP surveillance network has made great progress in understanding the growing threat of gonococcal AMR globally.<sup>6</sup> However, most participating laboratories are in countries with better infrastructure and access to health care. Many countries contribute no data on gonococcal AMR, particularly those in Sub-Saharan Africa, where the burden of gonorrhoea-related disease may be highest. Because gonococcal AMR may be a key driving force in determining the need and urgency to develop gonococcal vaccines, expanded collection of gonococcal AMR data from more countries is essential, particularly in regions for which surveillance is currently challenging.

#### *Modelling the theoretical impact of vaccines against gonorrhoea*

Existing mathematical models suggest that even a partially effective gonococcal vaccine could have substantial impact

at a population level.<sup>31,32</sup> In an individual-based simulation model, high coverage with a gonococcal vaccine that has only 20% efficacy, below the level of cross-protection suggested in the New Zealand observational study of MeNZB,<sup>12</sup> led to a predicted 40% reduction in gonorrhoea prevalence after 20 years.<sup>31</sup> More modelling is needed, including assessments of potential cost-effectiveness, which may be particularly relevant in areas where gonorrhoea prevalence is low in the general population but high in key populations.<sup>32</sup> Modelling of sexually transmissible coinfections, such as chlamydia, will also be important both to consider possible decreased vaccine efficacy in the setting of coinfections<sup>12</sup> and to highlight the need for potential combined vaccine approaches. Finally, it will be essential to use models to predict how AMR will likely increase over time given current trends,<sup>33</sup> and how increases in AMR and *N. gonorrhoeae* treatment failure rates would affect infection rates, disease burden and costs. If gonorrhoea truly becomes untreatable, these types of assessments are likely to provide the most compelling rationale for the need of a vaccine.

#### *Advancing basic science and translational data*

Using animal models and cultured human cells, new insights have been gained into how *N. gonorrhoeae* immunosuppresses the adaptive response, which can occur at the level of antigen-presenting cells or suppression of T cell responses.<sup>23</sup> Continued unravelling of the complexity of *N. gonorrhoeae* immunobiology may lead to inclusion of novel adjuvant or delivery systems or genetically engineered gonococcal OMVs that lack immunosuppressive factors. Evaluation of vaccine-induced T cell responses has not been vigorously used, but could help define protective pathways in the future, for example by defining the T cell response in mice immunised with vaccines that do and do not show *in vivo* efficacy, and in humans vaccinated with meningococcal OMV vaccines.

A pressing need is human data on the immune responses to *N. gonorrhoeae* infection. Clinical studies that examine host responses predicting the likelihood of gonorrhoea infection, reinfection or ascension to the upper genital tract are needed, and can be modelled on innovative studies that have evaluated these factors for chlamydia.<sup>34</sup> A well-characterised human challenge model could be adapted for evaluating immune responses and testing the efficacy of candidate vaccines;<sup>35</sup> however, at this time these exist only for male urethral infection. There are no female models, genital tract transmission models or models of pharyngeal or rectal infection, which may be important reservoirs of *N. gonorrhoeae*.<sup>36</sup> Importantly, a critical next step is continued evaluation of the effect of currently licenced meningococcal B OMV vaccines on gonorrhoea, through either prospective observational studies as the vaccines are rolled out in new areas or through clinical trials specifically designed to examine efficacy against acquisition of gonorrhoea.

#### *Defining PPCs*

WHO PPCs describe vaccine attributes that would help maximise the public health value, particularly from an LMIC perspective, for characteristics like vaccine indications, target groups, immunisation strategies and important safety and

efficacy considerations.<sup>37,38</sup> Describing the attributes that meet LMIC needs, in addition to those that address high-income country (HIC) concerns, can help shape the development of vaccines that are suitable for global use. PPCs aim to consider, early in research and development, the most important public health needs that should be addressed by gonococcal vaccines and how the vaccines would be used and implemented if they were available.

In January 2019, the WHO convened a global stakeholder consultation to lay the groundwork for understanding the potential public health value of gonorrhoea vaccines and developing gonococcal vaccine PPCs. In discussing the global strategic public health goals for gonococcal vaccines, the experts highlighted the need to control gonorrhoea to prevent adverse sexual and reproductive health outcomes such as tubal factor infertility and to reduce the impact of gonococcal AMR, which could markedly worsen these outcomes. Broad-based vaccination of adolescents was proposed as a potential implementation strategy, especially in areas with high incidence rates of gonorrhoea.<sup>29,39</sup> This becomes increasingly feasible as human papillomavirus (HPV) vaccination programs are rolled out in more countries. However, in areas where gonorrhoea prevalence in the general population is low but can be very high in specific subpopulations,<sup>40,41</sup> a potential alternative strategy may be to target key populations. Although targeted vaccination programs have been difficult to implement in the past,<sup>42</sup> the expansion of HIV prevention programs and pre-exposure prophylaxis (PrEP) to key populations provide novel opportunities to explore new strategies for targeted vaccination.

#### *Characterising the full public health value of gonorrhoea vaccines*

Describing the full potential public health value of gonorrhoea vaccines would not only rationalise investment in vaccine development, but could also aid in future decisions around vaccine policy and implementation. Public health value propositions include estimated global and regional disease burden, economic burden, modelled vaccine impact, economic assessments (e.g. cost-effectiveness analysis) and a discussion of potential broader societal benefits and considerations. They describe likely individual- and population-based effects of a vaccine for a broad range of stakeholders.

To fully build a public health value proposition to incentivise investment and accelerate the development of gonococcal vaccines, several fundamental research gaps need to be urgently addressed. This includes improving epidemiological data on gonorrhoea disease burden, estimating the current and future health and economic effects of gonococcal AMR, modelling vaccine impact, including predicted costs averted by preventing gonorrhoea treatment failures, and gaining consensus on how gonococcal vaccines would be used through the development of PPCs. As part of the value proposition, we also need a better understanding of how to ascribe a value to AMR, how a vaccine's effect on AMR can be measured and quantified, and therefore how AMR plays into the potential value of a vaccine.<sup>16,43</sup> Gonococcal AMR is part of a larger global antibiotic resistance problem.<sup>9</sup> Use of antibiotics for one infection

can select for AMR in a variety of other pathogens. Conversely, preventing antibiotic use through effective interventions could have far-reaching benefits beyond just the pathogen in question. Studies to model this complex interaction are in development, and the WHO and collaborators are developing a value attribution framework for vaccines against antimicrobial resistance<sup>44</sup> (J. Vekemans, WHO, pers. comm.).

## Conclusion

New interventions are urgently needed to control gonorrhoea globally. Our ability to treat the estimated 87 million new *N. gonorrhoeae* infections occurring annually<sup>1</sup> is being threatened by the rapid emergence of drug-resistant strains.<sup>7</sup> After decades with little progress in gonococcal vaccine development, recent evidence supporting the biological feasibility of gonorrhoea vaccines and technological advances in antigen discovery provide new hope.<sup>12,23</sup> Given that gonococcal vaccine candidates are currently in the preclinical phase, defining the value proposition will be critical to justify investment in product development and evaluation in clinical trials.<sup>45</sup> The global disease burden related to gonorrhoea is likely high, because untreated infection can lead to a range of adverse health outcomes, and many countries lack adequate programs to test and treat for the infection. However, the magnitude of the burden, for outcomes like infertility, needs to be better quantified to build the value proposition. Tracking and understanding the possible future impact of AMR is also critical. The value proposition can be further refined with an understanding of how best to attribute health and economic value to the predicted role of gonococcal vaccines in fighting AMR, for *N. gonorrhoeae* strains and more broadly. The potential market for gonococcal vaccines is shaped by their use case (i.e. who would receive them and how they would be implemented). Efforts are underway to define PPCs for gonorrhoea vaccines by gaining consensus on target populations, implementation strategies and other attributes needed for the vaccines to be suitable for both LMIC and HIC use. Addressing these epidemiological, programmatic and policy issues in parallel to advancing gonococcal vaccine research and development, including direct assessment of the ability of meningococcal B OMV vaccines to prevent gonorrhoea, can help drive momentum and advance the roadmap to developing viable gonococcal vaccines.

## Conflicts of interest

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