Neisseria gonorrhoeae vaccine development: hope on the horizon?

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\textbf{Purpose of review}

\textit{Neisseria gonorrhoeae} is one of the most common causes of sexually transmitted infections, with an estimated more than 100 million cases of gonorrhea each year worldwide. \textit{N. gonorrhoeae} has gained recent increasing attention because of the alarming rise in incidence and the widespread emergence of multidrug-resistant gonococcal strains. Vaccine development is one area of renewed interest. Herein, we review the recent advances in this area.

\textbf{Recent findings}

Vaccine development for \textit{N. gonorrhoeae} has been problematic, but recent progress in the field has provided new hope that a gonococcal vaccine may be feasible. Several new vaccine antigens have been characterized in various models of infection. Furthermore, the first potential vaccine-induced protection against gonorrhea in humans has been reported, with decreased rates of gonorrhea described among individuals vaccinated with the \textit{Neisseria meningitidis} serogroup B vaccine, MeNZB.

\textbf{Summary}

As antibiotic resistance continues to increase, vaccine development for \textit{N. gonorrhoeae} becomes more urgent. The MeNZB vaccine is shown to have efficacy, albeit relatively low, against \textit{N. gonorrhoeae}. This finding has the potential to reinvigorate research in the field of gonococcal vaccine development and will guide future studies of the antigens and mechanism(s) required for protection against gonococcal infection.

\textbf{Keywords}

antibiotic resistance, gonorrhea, sexually transmitted infection, vaccine development

\section*{INTRODUCTION}

\textit{Neisseria gonorrhoeae} is an obligate human pathogen that causes the sexually transmitted infection, gonorrhea. Untreated, or undiagnosed, \textit{N. gonorrhoeae} infection can lead to serious sequelae [1,2\textsuperscript{*}]. Thus, with an estimated incidence of more than 106 million cases per year, \textit{N. gonorrhoeae} is of considerable global health concern [WHO, 2012]. Despite decades of research, there is still no gonococcal vaccine. This is largely because of the exceedingly variable nature of \textit{N. gonorrhoeae} antigens, the lack of knowledge of what would constitute protective immunity, and the absence of robust animal models that accurately mimic human-specific aspects of disease processes [reviewed in 2]. The rapid, global emergence of multidrug-resistant gonococcal strains has raised concern that untreatable \textit{N. gonorrhoeae} may soon become widespread [3\textsuperscript{*}]. As a result, interest in vaccine development has increased [reviewed in 2\textsuperscript{*},4,5,6\textsuperscript{*}]]. To this end, efforts toward the development and implementation of new international collaborations, as well as a global STI vaccine roadmap, are ongoing [3\textsuperscript{**,7,8,9**},10\textsuperscript{**,11**}].

\section*{The global impact of gonorrhea}

Gonorrhea is one of the oldest diseases known to humans. Gonococcal disease typically presents as a mucosal infection of the genital tract, rectum, pharynx, or eye; although disseminated infections can also occur [1]. In recent years, the number of cases of gonorrhea has risen significantly. For example, gonorrhea prevalence has increased 63\% in Australia over the past 5 years [12] and 18.5\% in the USA between 2015 and 2016 [13]. However, asymptomatic infections are common; they occur in up to 80\% of infected females and 40\% of infected males; and hinder determination of the true prevalence of \textit{N. gonorrhoeae}. Moreover, untreated (predominately

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\textbf{Curr Opin Infect Dis} 2018, 31:000–000

DOI:10.1097/QCO.0000000000000450

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KEY POINTS

- Vaccine development for Neisseria gonorrhoeae has been challenging because of the variable nature of N. gonorrhoeae, the lack of knowledge of what type of immune response is needed for protective immunity, and the absence of robust animal models that accurately mimic disease caused by this obligate human pathogen.

- Several potential N. gonorrhoeae antigens are identified and continue to be characterized using in vitro and in vivo models of infection.

- A retrospective case-control study indicated that the outer membrane vesicle (OMV) serogroup B meningococcal vaccine, MeNZB, was associated with reduced rates of gonorrhea following a mass vaccination campaign in New Zealand.

- Additional studies are needed to fully identify and characterize the antigens, and type of immune response, required for vaccine-induced protection against gonorrhea.

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asymptomatic) infections can lead to sequelae that include: urogenital tract abscesses, pelvic inflammatory disease, adverse pregnancy outcomes, neonatal complications, and infertility; which significantly impact quality of life as well as sexual, reproductive, and newborn health. Infection with N. gonorrhoeae also increases the risk of acquiring and transmitting HIV [reviewed in 1, 2].

The control of N. gonorrhoeae is largely based on antibiotic treatment. Although once easily treatable, treatment of gonorrhea is now severely compromised because of the rapid and continued emergence of antibiotic resistance, an over-reliance on empiric treatment (i.e. treatment of patients based on symptoms rather than a definitive diagnosis), the shift from culture-based diagnostics (required for susceptibility testing) to nucleic acid amplification testing, as well as a lack of active surveillance to identify treatment failures in many regions [3**]. N. gonorrhoeae has developed resistance to all classes of antibiotics used to treat it over the past seven decades [14], which presently has left ceftriaxone as the sole last line of defense for gonorrhea treatment. However, strains with high-level resistance to the expanded-spectrum cephalosporins (i.e. ceftriaxone and cefixime) recently have been isolated from around the world [14]. This means that more costly and invasive gonorrhea treatment (typically, ceftriaxone intramuscular injection and oral azithromycin dual therapy [3**]) is now required. Such treatments are less suitable for low-income and middle-income countries, which suffer the highest burden of disease. Future potential therapies could include the use of different combinations of existing antibiotics, which are currently being evaluated. Additionally, three new drugs are in clinical development: solithromycin (phase III trial recently completed), zoliflodacin (phase II trial completed), and gepotidacin (phase II trial completed) [3**,9**,10**]. In an effort to end ‘sexually transmitted infection epidemics as major public health concerns’, the WHO recently released a draft global health strategy with a global target goal of 90% reduction in N. gonorrhoeae incidence by 2030 [15**]. Given the ability of the gonococcus to develop antibiotic resistance, a gonococcal vaccine will be key to the long-term control of gonorrhea [3**,7,8,9**,10**,11**].

Where are we on the road to gonococcal vaccine development?

Historically, gonococcal vaccine development has proven particularly difficult. Only four candidate (whole cell, partially autolyzed, pilus-based, or protein l-based) vaccines have progressed to clinical trials, and none provided protection [reviewed in 2]. However, a recent retrospective case-control study found that reduced rates of gonorrhea occurred among sexual health clinic patients (ages 15–30 years) following their vaccination with the outer membrane vesicle (OMV) vaccine, MeNZB, to Neisseria meningitidis serogroup B [16**]. The greatest protection against gonorrhea was observed in the years during, and the year immediately following, MeNZB vaccination. Although the efficacy of MeNZB against N. gonorrhoeae was relatively low (estimated to be 31%) [16**], mathematical modeling suggests that this level of protection could reduce gonorrhea prevalence by almost half within 15 years in settings with an existing prevalence of 1.6–1.7% [17].

OMVs are a complex mix of outer membrane components that are naturally released from Gram-negative bacteria, such as N. meningitidis and N. gonorrhoeae [18]. OMV vaccines have been used in several meningococcal outbreak situations. Although the antigenically variable protein, PorA, is immunodominant, functional antibodies are raised against several other OMV components [19]. N. meningitidis and N. gonorrhoeae are closely related species that share numerous antigens. Further investigation of the antigens and mechanism(s) responsible for the MeNZB-mediated protection is needed, but it is plausible to hypothesize that meningococcal OMV vaccines may also induce functional antibodies against gonococcal strains [16**,20–22]. The MeNZB vaccine is no longer available. However, the serogroup B vaccine,
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4CMenB (Bexsero), contains the same OMV component as that present in MenNZB in addition to three recombinant proteins NHBA, fHbp, and NadA [23], and may also provide protection against gonorrhea [16**,20].

The research and development pipeline for gonorrhea vaccines is presently limited, with all activity in the early, preclinical stages of development [8]. However, multiple *N. gonorrhoeae* antigens exist that show promise as vaccine candidates, based on their antigenic conservation, widespread distribution among strains, and immunogenicity/ability to induce functional antibodies [reviewed in [2*,11*]]. These antigens include: the nitrite reductase, AniA [24,25]; phospholipase D (PLD) [26]; transferrin-binding proteins, TbpAB [27]; MtrE of the Mtr efflux pump complex [28]; the outer membrane porin, PorB [29,30]; the methionine uptake receptor, MetQ [31]; the conserved 2C7 epitope of LOS [32,33]; and several outer membrane proteins recently identified by proteomic techniques [34*,35*]. Several of these antigens are shown by ex-vivo analysis of human specimens to be upregulated during natural infection [36], which alleviates some of the potential risk to biotech companies that might be associated with their development as vaccine candidates. Also of note is that a recent outbreak of urethritis was caused by an acapsular *N. meningitidis* strain that had acquired the gonococcal denitrification, norB-aniA, genes [37,38]. Loss of capsule production, together with the acquisition of norB and aniA from *N. gonorrhoeae*, is hypothesized to have allowed *N. meningitidis* to efficiently colonize the urethral mucosa and to survive under the microaerobic conditions of the urogenital tract [37,38]. Thus, incorporation of AniA; or any of the noted, or alternative, gonococcal antigens; into gonococcal-derived or meningococcal-derived OMVs could hold promise as potential *N. gonorrhoeae* vaccines. In this regard, Liu et al. [39*] show that intravaginal inoculation of interleukin-12 microencapsulated within gonococcal OMVs can confer protection to mice against *N. gonorrhoeae* infection. Even a vaccine of moderate efficacy and duration could have a substantial impact on gonococcal transmission and prevalence, if coverage is high and protection lasts over the highest risk period (i.e., most sexual partner change) [17].

**Models of infection and vaccine evaluation**

*N. gonorrhoeae* has numerous mechanisms that allow it to avoid and actively suppress innate and adaptive immune responses and natural infection with *N. gonorrhoeae* does not induce protective immunity [reviewed in 2]. Furthermore, *N. gonorrhoeae* is an obligate human pathogen, with humans serving as the only natural reservoir for infection. Thus, *N. gonorrhoeae* is highly human adapted and has developed various, distinct, mechanisms to infect different sites within its sole human host. Many of these pathogenic mechanisms are human-restricted; such as, differential expression of receptors for colonization (e.g. CR3 [40]; various CEACAMs [41,42]), iron-transport proteins (e.g. transferrin and lactoferrin [43]), and components of the immune system (e.g., C4BP and factor H (fH) [44]). Collectively, these features have posed a substantial challenge to vaccine development. A full understanding of gonococcal pathogenesis is needed to identify novel approaches to generate a protective, nonnative immune response that may encompass both functional blocking of human-specific disease processes and conventional immune killing. The development of model systems to study host-pathogen interactions, as well as to test vaccine candidates and potential vaccines, is also essential.

Various models have been used to investigate gonococcal infection, colonization, and disease pathology [2*]. Models used to date include: a human challenge model that involves experimental urethral infection of male volunteers (infection of females is ethically prohibited), several (human) cell and organ culture systems, chimpanzees, female mice treated with 17β-estradiol and antibiotics, subcutaneous chambers implanted in Guinea pigs and rabbits, as well as chicken embryos/eggs. Each of these models offers advantages, but none are without their limitations. Human and nonhuman primate models offer the best opportunity for the successful development of candidate vaccines and their translation into clinical use; however, ethical considerations, limited availability, and high costs have hindered wide-spread use of human, nonhuman primate, and human-derived (e.g. organ and tissue culture) models. The female mouse model has gained increased popularity, in part, because of the abundance of reagents currently available to allow scientific analyses in mice. However, this model does not recapitulate infection of the human female reproductive tract or the immunological responses generated by infected women. Although not in current use, Guinea pigs and rabbits are reported to be comparatively better than mice in terms of measuring the immunogenicity of gonococcal antigens [45]. These models could be re-evaluated for their potential utility in aiding vaccine development. A prospective pig model for gonorrhea is presently also under investigation [46]. The pig has been used as a model animal to study human diseases, including the STI chlamydia, based on its similarities with humans in terms of anatomy,
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genetics, immunology, and physiology, as well as the growing immunological toolbox available to conduct research in pigs [46]. Through the combined use of both human and nonhuman in vivo, ex vivo, and in vitro models, it may be possible to overcome many of the obstacles associated with N. gonorrhoeae vaccine development.

CONCLUSION

There is an ever-increasing urgency to develop a gonococcal vaccine because of the increasing incidence of infection and increasing multidrug-resistance among N. gonorrhoeae strains. Although the development of a gonococcal vaccine has been unsuccessful to date, there are several reasons to hope that success may be on the horizon. Numerous, promising, vaccine candidates exist that have undergone preclinical investigations. The reduced rate of gonorrhea seen following the use of a meningococcal OMV vaccine in New Zealand has provided the first indication that vaccination against gonorrhea is feasible. This observation may help existing gonococcal vaccine candidates to progress into clinical development. In addition, further investigation of the antigens, and the type of immune response, responsible for the OMV vaccine-mediated protection against gonorrhea will guide future vaccine development.

Acknowledgements

J.L.E. and M.P.J. are supported by the National Institutes of Health [grant R01AI134848].

Financial support and sponsorship

M.P.J. is supported by the Australian National Health and Medical Research Council (NHMRC) [Principal Research Fellowship 1138466 and Program Grant 1071659]. K.L.S. is supported by the NHMRC [Project Grant 1028326 and Career Development Fellowship].

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as follows:

+ of special interest

+ of outstanding interest


This article comprehensively reviews gonococcal pathogenesis, immunology, and vaccine development


This is one of several recent articles that provides suggestions and a roadmap to try to combat antibiotic resistant gonorrhea.


This article provides a comprehensive review of gonococcal antibiotic resistance, models of infection, and vaccine development.


This is one of several recent articles that provides suggestions and a roadmap to try to combat antibiotic resistant gonorrhea.


This is one of several recent articles that provides suggestions and a roadmap to try to combat antibiotic resistant gonorrhea.


This papers summarises the NIAID workshop that aimed to bring scientists together to share knowledge and reagents, in the hope of accelerating the process of gonococcal vaccine candidates to clinical studies.


This is one of several recent articles that provides suggestions and a roadmap to try to combat antibiotic resistant gonorrhea.


This study shows, for the first time, a vaccine associated reduction in gonorrhea.


This paper uses a proteomic approach to identify potential antigens, and their putative function, for gonococcal vaccine development.