

Intractable problems require novel solutions: it's time to get serious about developing a gonorrhoea vaccine

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Neisseria gonorrhoeae, the causative agent of the sexually transmitted infection gonorrhoea, is an ancient disease with biblical references.¹ Despite ongoing efforts towards treatment and prevention, gonorrhoea remains a major public health problem worldwide with an estimated global incidence of 106 million cases/year,² leading to direct and indirect costs that exceed \$1 billion/year in the USA alone.³ The clinical outcomes of gonococcal infection range from asymptomatic infection to severe sequelae (reviewed in refs. 4, 5). Symptomatic infection typically presents as urethritis in males and cervicitis in females; however, mucosal infections of the rectum, pharynx and eye are also reported. In addition, asymptomatic infections occur in 50–80% of infected females and 1%–40% of infected males, which, if left undiagnosed or untreated, can lead to sequelae that include urogenital tract abscesses, pelvic inflammatory disease, adverse pregnancy outcomes, infertility and neonatal complications. Infection with *N. gonorrhoeae* also increases the risk of acquiring and transmitting HIV.

Current attempts to control gonorrhoea include safe-sex education, as well as prompt diagnosis and antibiotic treatment of infected persons and their recent sex partners. While diagnostics (ie, nucleic acid amplification tests or bacterial culture) are highly sensitive and specific,⁶ education and routine screening are not sufficient to stem the spread of gonorrhoea.⁷ This is especially true in light of the fact that extensively drug-resistant strains with high-level resistance to the expanded-spectrum cephalosporins (ie, ceftriaxone and cefixime) have been isolated from around the world.¹ Cephalosporins are the last line of defence for treating gonorrhoea, and the emergence of resistance to these drugs means that more costly and invasive

treatment is now required. The current recommendations for the treatment of uncomplicated infections include the use of dual antibiotic therapy with ceftriaxone (250 mg intramuscular injection in a single dose) plus azithromycin (1 g orally in a single dose).⁶ While additional combinations of existing antibiotics are currently being evaluated, there are no new antibiotics in late development. The gonococcus has developed resistance to all classes of antibiotics used to treat it since the 1940s, including the penicillins, tetracyclines, macrolides and quinolones.¹ As such, even new classes of antibiotics may only provide a short-term solution given the record of *N. gonorrhoeae* to rapidly develop resistance.

In keeping with the adage that 'prevention is better than cure', vaccination is considered the best approach for long-term control of gonococcal infection. However, there is currently no gonococcal vaccine available or in clinical trials.⁸ The continuing emergence of antibiotic-resistant and untreatable strains has led the US Centers for Disease Control and Prevention to class *N. gonorrhoeae* as an 'immediate public-health threat that requires urgent and aggressive action',⁹ adding to the fears that *N. gonorrhoeae* may become a widespread untreatable 'superbug' in the near future.¹ While attempts at vaccine development have highlighted the difficulty of this task, with only four candidates progressing to clinical trials (all prior to 1990; reviewed in ref. 5), there is an increased imperative to revisit vaccine options. To a large extent, the complexities, and our incomplete understanding, of host–pathogen interactions have posed the key obstacles to gonococcal vaccine development. However, there have been several advancements over the past two decades that indicate a vaccine is feasible and that an increased, coordinated effort in this arena is warranted.

When considering the complexities of host–pathogen interactions, on the host side, there is a lack of knowledge of what is required to induce a protective immune response against gonorrhoea. There is no protective immunity after natural infection, and there are no known correlates of protection (ie, there is no measurable

immune response that is correlated with host protection). Therefore, vaccination is especially challenging because it must achieve what natural infection cannot. Furthermore, humans are the only known natural host for *N. gonorrhoeae* and there are no animal models that accurately mimic natural infection. This is largely due to the specificity of several gonococcal proteins for human targets (eg, receptors for colonisation, iron sources required for nutrition and complement factors to evade the immune response). The optimal system available to investigate host–pathogen interactions and evaluate the efficacy of vaccine candidates is a human challenge model based on experimental urethral infection of male volunteers.¹⁰ However, the model is costly, limited to small group sizes (approximately n=4) and cannot be used to assess late stages of infection or infection in women due to the possibility of complications. However, as our understanding of the mechanisms used by *N. gonorrhoeae* to avoid and suppress the human immune response has improved in recent years, so have the model systems used to study them. For example, primary human cell or organ culture systems (ie, samples derived directly from patient tissue) and 'humanised' mice (eg, transgenic mice expressing human receptors or human complement factors; or mice treated with human iron sources and hormones) are increasingly used to investigate specific stages of infection and to evaluate vaccine candidates (reviewed in refs. 5, 8).

On the pathogen side, the gonococcus has numerous mechanisms by which it can alter its surface antigens and evade the host immune response.^{5, 8} Until relatively recently, the majority of gonococcal vaccine studies have focused on the most abundant outer membrane structures (eg, pilin and lipopolysaccharide) that are highly variable due to antigenic variation and/or phase variation, which result in changes to the antigen's sequence and expression levels, respectively. However, several novel vaccine candidates have been identified, which are conserved between strains (or have conserved components) and that are essential for different aspects of gonococcal infection (reviewed in refs. 5, 8). In addition, the ongoing search for conserved antigens is aided by new vaccine technologies that support genome-wide investigation.¹¹ For example, comprehensive lists of proteins present in gonococcal outer membranes and outer membrane vesicles have been determined using proteomic approaches,¹² and transcriptome analysis has been used to determine genes expressed during female

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genital tract infection.¹³ The ongoing technological advances in all areas of science will undoubtedly continue to improve antigen selection, formulation and delivery options for a gonococcal vaccine. It is also important to note that mathematical modelling of various vaccine scenarios predicted that even a modestly efficacious vaccine could have a substantial impact on gonorrhoea prevalence and sequelae within a relatively short time frame.¹⁴

Given that *N. gonorrhoeae* poses a growing risk to human health worldwide, action on numerous fronts is needed. In the short to medium term, strict adherence to treatment guidelines and increased screening and surveillance for infection and antibiotic resistance is needed, as well as improved case reporting to provide accurate epidemiological data. However, for a long-term solution, increased investment in vaccine development is essential. This may require a global concerted effort and the establishment of new public-private partnerships that bring together academic, government and industry stakeholders, similar to the International AIDS Vaccine Initiative (<http://www.iavi.org>) or the Dengue Vaccine Initiative (<http://www.denguevaccines.org>). A recent NIAID-sponsored workshop 'Gonorrhoea Vaccines: The Way Forward' held in Washington DC in June 2015 may be the first step in establishing coordinated partnerships. Furthermore, an increased focus on human male volunteer studies and investigation of bacterial and patient samples from natural infections is needed in order to fully characterise host-pathogen interactions and to make substantial, rapid progress. Ideally, a vaccine consisting of a combination of the most promising antigens should enter human clinical trials as soon as possible as this may be the only way to accurately assess vaccine efficacy, given that animal models may never be able to reliably mimic infection. This is especially true if vaccine-induced protection is a result of functional blocking or neutralising rather than direct bactericidal activity (eg, if antibodies that target a gonococcal adhesin are

able to block bacterial adherence to a human-specific receptor and prevent colonisation, this protection will not be evident in a mouse that does not have this receptor). Another approach could be the use of therapeutic monoclonal antibodies targeting key vaccine candidates, which could serve as a 'stopgap' in treating antibiotic-resistant gonorrhoea and may also help identify a correlate of protection.⁵ Given the time and resources needed to develop and license a vaccine, all interested stakeholders need to come together and get serious about developing a vaccine now before gonorrhoea becomes untreatable.

Contributors All authors contributed to writing this manuscript.

Funding KLS is funded by the Australian National Health and Medical Research Council (NHMRC) (project grant 1028326 and Career Development Fellowship 1045235 to KLS). EAS is funded by project grant 1028326.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.



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To cite Semchenko EA, Seib KL. *Sex Transm Infect* 2016;**92**:561–562.

Received 9 February 2016
Accepted 17 February 2016
Published Online First 1 April 2016

Sex Transm Infect 2016;**92**:561–562.
doi:10.1136/sextrans-2015-052378

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