Gonorrhoea vaccines: a step in the right direction

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The sexually transmitted infection gonorrhoea is a global public health problem for which no vaccine is available. More than 106 million new cases of gonorrhoea are estimated to occur yearly worldwide.¹ Furthermore, incidence is rising,² and is expected to continue to rise because of the prevalence of multidrug-resistant strains of *Neisseria gonorrhoeae*.³ As a result, the US Centers for Disease Control and Prevention and WHO have prioritised *N gonorrhoeae* as an urgent public health threat for which immediate action is needed.^{4,5}

Gonococcal infection can result in a range of clinical outcomes and caused 444 900 years lived with disability in 2015.² Asymptomatic infection occurs in 50–80% of infected women, and 1–40% of infected men, which, if left untreated, can lead to severe consequences such as pelvic inflammatory disease, poor pregnancy outcomes, infertility, and neonatal complications. Furthermore, infection with *N gonorrhoeae* increases the risk of acquiring and transmitting HIV.^{6,7}

After decades of research, only four gonococcal vaccine candidates have progressed to clinical trials (all before 1990), and none of these vaccines provided any protection against gonorrhoea.⁷ These failures were largely due to the variable nature of *N gonorrhoeae* antigens, and lack of knowledge about what is required to induce a protective immune response. No protective immunity occurs after natural gonococcal infection, so there is no basis to establish correlates of protection.⁷ The efficacy of gonococcal vaccines will probably need to be tested directly in human beings without the benefit of pre clinical studies in animal models that mimic human transmission and pathology. These barriers have resulted in poor investment in gonococcal vaccine development in the past 25 years. However, recent findings, including new research by Helen Petousis-Harris and colleagues in *The Lancet*, are a step in the right direction, and will hopefully reinvigorate interest and investment in the field.

Petousis-Harris and colleagues show that the *Neisseria meningitidis* serogroup B vaccine MeNZB was associated with decreased rates of gonorrhoea.⁸ *N gonorrhoeae* and *N meningitidis* are closely related bacterial pathogens, which, despite causing distinct diseases, are genetically and antigenically very similar. MeNZB is an outer membrane vesicle vaccine that was delivered to more than 1 million New Zealanders (81% of the New Zealand population aged younger than 20 years) between 2004 and 2008 in response to a serogroup B meningococcal epidemic.⁹ In Petousis-Harris and colleagues' retrospective case-control study of data from 15–30-year-old patients from sexual health clinics in this setting, individuals who had been vaccinated were significantly less likely to have gonorrhoea, especially in the years during and immediately after use of the vaccine, than were those who were not vaccinated. The estimated vaccine effectiveness of MeNZB against gonorrhoea was 31% (95% CI 21–39),⁸ the first instance of a vaccine being associated with any protection against gonorrhoea.

MeNZB is no longer available, but the licensed broad-spectrum four-component serogroup B (4CMenB) vaccine Bexsero contains the same outer membrane vesicle antigen as MeNZB, in addition to three recombinant proteins (NHBA, fHbp, and NadA).¹⁰ Petousis-Harris and colleagues postulate that administration of Bexsero to adolescents could also result in a decline in gonorrhoea as a result of cross-protection.⁸ However, this vaccine is not included in routine vaccine schedules outside the UK.

Further evidence is needed to support the hypothesis that the *N meningitidis* outer membrane vesicle vaccine provides cross-protection against *N gonorrhoeae*. Nonetheless, the reduced gonococcal rates after MeNZB vaccination support the feasibility of a vaccine to protect against gonorrhoea. An effectiveness of 31% against gonococcal infection does not suggest a strong a-priori case for application of this vaccine to address the public health challenge posed by *N*

gonorrhoeae. However, mathematical modelling¹¹ has shown that even a vaccine of moderate efficacy and duration could have a substantial effect on the transmission and prevalence of gonorrhoea, if coverage in the population is high and protection lasts during the highest risk period (ie, the period in which people have the most sexual partners).¹¹ A key role of vaccination would be to reduce the pool of asymptomatic carriers, which would decrease transmission and the severe sequelae associated with gonococcal infection.

Further investigation of the antigens and mechanisms responsible for the MeNZB-mediated protection against gonococcal infection will provide unique information to guide future vaccine development. In light of the high burden of disease and the threat of gonorrhoea becoming untreatable because of antibiotic resistance, there is an increased imperative to revisit vaccine options and reinvigorate research in this field.

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