Could vaccination against *Neisseria gonorrhoeae* be on the horizon?

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“The scientific stage is therefore set for significant advances in comprehending immunity to *N. gonorrhoeae* and making an effective vaccine against gonorrhea a reality.”

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Despite public health control measures, gonorrhea remains an all too common disease, and is the second most frequent reportable infectious disease in the USA at a reported incidence of >350,000 cases per annum [1], although the real incidence is thought to exceed 800,000 cases per annum. Worldwide incidence is now estimated at approximately 78 million new cases per annum [2], and the burden is greatest in sub-Saharan Africa and Southeast Asia where diagnostic and treatment facilities are underdeveloped. Women bear the greater morbidity rate since untreated gonorrhea can lead to upper tract infection and pelvic inflammatory disease presenting with tubal scarring, infertility and risk for ectopic pregnancy which can be life-threatening. Insidiously, genital gonococcal infection can be clinically inapparent ('asymptomatic') in up to 50% of cases in women, and it is increasingly recognized that a significant proportion of infected men can also be asymptomatic. As a result, individuals may not be provoked to seek treatment, and can be unwitting sources of infection for others, thereby vitiating public health efforts to control the disease. Gonorrhea also increases the risk of acquisition and transmission of HIV up to fivefold in both the sexes [3]. Since no vaccine is available [4], both control and treatment depend upon antibiotics. However, *Neisseria gonorrhoeae* has steadily developed resistance to each class of antibiotic deployed against it, including fluoroquinolones and most recently even extended-spectrum cephalosporins, raising serious concerns that gonorrhea could become untreatable [5]. The US Centers for Disease Control and Prevention listed antibiotic-resistant *N. gonorrhoeae* as one of the top three pathogens presenting “an immediate public health threat that requires urgent and aggressive action” [6]. A recent report from the WHO lists *N. gonorrhoeae* as a high priority for new antibiotic development [7]; despite this, there appear to be no new drug candidates available in the foreseeable future. Even if a new antibiotic were to be developed, the track record of *N. gonorrhoeae* in rapidly acquiring resistance suggests that it might not remain effective for very long. These considerations all reinforce the need for a preventive vaccine against gonorrhea, especially but not exclusively in resource-poor settings where healthcare facilities for diagnosis and treatment are lacking. A technical consultation held at the WHO in April 2013, on vaccines against sexually transmitted infections, called for renewed efforts to develop a vaccine against gonorrhea [8]. Encouragingly, modelling studies have suggested that even an imperfect vaccine could yield substantial benefits [9].

Several previous attempts have been made to develop vaccines against gonorrhea, three in modern times although only two went to clinical trials [4,10]. The first whole-cell vaccine proved ineffective, as did a later and substantially larger effort to create a vaccine based on gonococcal pili, while a third based on porin protein was abandoned. These disappointments discouraged further efforts and engendered pessimism that vaccination against gonorrhea might not be feasible. Compounding this situation is the well-known observation that gonorrhea can be acquired repeatedly with no apparent development of protective immunity from previous infection. The reasons for this are poorly understood, but it is generally thought that extensive antigenic variation involving most of the major surface components of *N. gonorrhoeae* (including porin, lipooligosaccharide, Opa and pilus proteins), coupled with multiple mechanisms for resisting complement, enable *N. gonorrhoeae* to evade whatever adaptive immune response the host develops against it [10]. It has been proposed that the ratio of antibodies to porin-plus-lipooligosaccharide:antibodies

to Rmp (an immunogenic protein against which antibodies have a counter-effective blocking activity) affords protection [10]. However, in the absence of a recognized and reproducible state of immunity in humans, the determinants of immune protection have not been defined.

Several new developments, however, now combine to bring hope that an effective vaccine against *N. gonorrhoeae* is indeed on the horizon. The first of these, is the recent findings that *N. gonorrhoeae* proactively manipulates the host immune response for its own benefit, by selectively eliciting innate host defenses that it can survive while concomitantly suppressing adaptive immune responses that would eliminate it [11]. Several mechanisms have been described that contribute to this ability, including inactivation of T-helper cells [12], modulation of dendritic cells or macrophages [13,14] and upregulation of IL-10, TGF- β and type 1 regulatory T cells [15]. These findings reveal new understandings of immunity to *N. gonorrhoeae* and suggest that novel approaches to reverse gonococcus-induced immunosuppression might be fruitful; moreover they inform new strategies for vaccine development. Second, animal models have been developed for preclinical evaluation of vaccine candidates; it is noteworthy in this context that all previous attempts to create gonococcal vaccines lacked any such *in vivo* models in which to test candidates. The estradiol-treated female mouse model [16] has now been applied to this effort [17], and further refinements of the model using transgenic mice that express various human factors involved in gonococcal pathogenesis afford scope for more detailed analysis of the mechanisms whereby immune protection can be attained [10]. Third, efforts are now underway to apply proteomics technology to the discovery of novel, conserved surface antigens shared by different strains of *N. gonorrhoeae* [18]. Already some initial candidate antigens have been identified, although these have not yet been evaluated in animal models of protection. Nevertheless, these findings raise the exciting prospect that protective immunity might not necessarily depend on previously known, highly variable major antigens, whose diverse epitopes and variable expression appear to be used by *N. gonorrhoeae* in effect to confuse the immune system. Finally, it has been reported that subjects in New Zealand, who had been immunized against *Neisseria meningitidis* using the MeNZB vaccine (which is no longer available), were less likely to be diagnosed with gonorrhea over the ensuing 10 years than unimmunized subjects [19]. While the degree of protection was modest (~31%), this finding represents the first report of protective immunity against gonorrhea in humans. Further investigation of the antibodies developed in immunized subjects and their specificity for gonococcal antigens can be expected to yield valuable insights. Interestingly, the antigen components of the MeNZB vaccine (the outer membrane vesicles of a group B strain of *N. meningitidis*) are used in the new group B meningococcal vaccine, Bexsero[®], now licensed by GlaxoSmithKline (Rixensart, Belgium). Thus it will be important to confirm and extend the New Zealand findings in a wider geographical context.

Results obtained from immunization of mice indicate that both antibodies (IgG and/or IgA) and IFN- γ are required for immunity to *N. gonorrhoeae* [17], but the mechanism of protection is uncertain, and it cannot be assumed that findings from mice will necessarily apply to humans. Unfortunately, no other animal model is available for this exclusively human infection, as nonhuman primates (with the possible exception of chimpanzees) cannot be infected with *N. gonorrhoeae*. Nevertheless, it should be possible to evaluate immune responses to vaccination in nonhuman primates in order to determine whether similar responses are elicited in a species that is more closely related to humans. Furthermore, it is possible that responses and mechanisms of immune defense may be different in males and females, but in the absence of an animal model of male infection this has not been examined. Hitherto, attention has been focused on complement-mediated bacteriolysis or opsonophagocytosis as mechanisms of defense, as these can be readily demonstrated *in vitro*, and because it is known that immunity to *N. meningitidis* depends on complement. Neutrophils are abundant in the purulent exudate typical of symptomatic gonorrhea, but it is now clear that *N. gonorrhoeae* can at least partially survive phagocytosis by neutrophils [20]. However, it cannot be assumed that these mechanisms, which may be relevant in female upper tract infection or in disseminated gonococcal infection (a rare complication in both sexes), are applicable in uncomplicated gonococcal cervicitis or urethritis. Other mechanisms of defense can be envisaged at mucosal surfaces, including inhibition of adherence and invasion of the epithelium, and inhibition of metabolic functions. The goal of vaccination should also be considered: whether the objective is to prevent the serious effects of upper tract infection in females (tubal scarring, hence infertility and increased risk of ectopic pregnancy, and pelvic inflammatory disease) which are difficult to quantify clinically and may have multiple etiological causes, or to prevent cervical gonococcal infection in the first place. Vaccination of men must also be considered, not only to prevent infection and disease, but because they serve as the essential vectors of infection in women and are therefore important for epidemiological control of the disease.

The scientific stage is therefore set for significant advances in comprehending immunity to *N. gonorrhoeae* and making an effective vaccine against gonorrhea a reality. Much work remains to be done, and it will take time to accomplish, but the results should yield fascinating insights into an extremely well adapted human pathogen. The limitations are whether there is the socio-political will to achieve this and make the necessary funding available.

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