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The potential impact of vaccination on the prevalence of gonorrhea

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ABSTRACT

Gonorrhea, one of the most common sexually transmitted infections worldwide, can lead to serious sequelae, including infertility and increased HIV transmission. Recently, untreatable, multidrug-resistant *Neisseria gonorrhoeae* strains have been reported. In the absence of new antibiotics, and given the speed with which resistance has emerged to all previously used antibiotics, development of a vaccine would be the ideal solution to this public health emergency. Understanding the desired characteristics, target population, and expected impact of an anti-gonococcal vaccine is essential to facilitate vaccine design, assessment and implementation. The modeling presented herein aims to fill these conceptual gaps, and inform future gonococcal vaccine development. Using an individual-based, epidemiological simulation model, gonococcal prevalence was simulated in a heterosexual population of 100,000 individuals after the introduction of vaccines with varied efficacy (10–100%) and duration of protection (2.5–20 years). Model simulations predict that gonococcal prevalence could be reduced by at least 90% after 20 years, if all 13-year-olds were given a non-waning vaccine with 50% efficacy, or a vaccine with 100% efficacy that wanes after 7.5 years. A 40% reduction in prevalence is achievable with a non-waning vaccine of only 20% efficacy. We conclude that a vaccine of moderate efficacy and duration could have a substantive impact on gonococcal prevalence, and disease sequelae, if coverage is high and protection lasts over the highest risk period (*i.e.*, most sexual partner change) among young people.

1. Introduction

Neisseria gonorrhoeae, the causative agent of the sexually transmitted infection (STI) gonorrhea, is a growing global public health problem. The World Health Organization (WHO) estimates that, worldwide, there are over 106 million new cases of gonorrhea annually [1]. However, incidence is expected to continue to rise with the increasing reports of treatment failures, particularly because of increasing levels of untreatable multidrug-resistant *N. gonorrhoeae* strains [2]. The Centers for Disease Control (CDC) recently prioritized *N. gonorrhoeae* as one of three bacteria that pose an "urgent" public health threat for which immediate aggressive action is greatly needed. This is in large part because of the rapid increase in *N. gonorrhoeae* antibiotic resistance and, thus, the limited availability of effective therapeutics. Thereby, it is anticipated that there will be an increase in the health and economic burden of *N. gonorrhoeae*-related diseases [3].

The gonococcus has developed resistance to multiple classes of antibiotics that have been used for treatment over the past decades, including the penicillins, tetracyclines, macrolides, and quinolones. Although ceftriaxone and cefixime exist as the last remaining options for empirical first-line *N. gonorrhoeae* treatment, high-level resistance (with treatment failure) to these expanded-spectrum cephalosporins is now reported [2]. As a result, effective treatment has become increasingly unaffordable, or non-existent, in those communities with the highest burden of disease [4]. Although new combination antibiotic treatments are being evaluated [5], there are no alternative therapeutic options currently available, or in the pipeline, for the treatment of gonococcal disease. Given the speed at which *N. gonorrhoeae* develops resistance to newly introduced antibiotics, it is also feared that even newly developed antibiotics will only provide a short-term solution to control *N. gonorrhoeae* [6]. In light of these issues, vaccination is considered the best

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long-term approach for control of gonococcal disease. However, despite continued research over the last century, there is currently no gonococcal vaccine or vaccine candidates in advanced stages of clinical development [7]. In line with the CDC's call for action, it is essential that gonococcal vaccine development be made a priority, if we are to effectively combat this threat.

N. gonorrhoeae causes a range of clinical outcomes, including severe sequelae. In men, gonococcal infection is typically characterized by a profusely symptomatic, localized inflammatory response of the urethra (*i.e.*, urethritis). A proportion of men with gonococcal urethritis are asymptomatic (typically reported as 1–3% [8,9] but believed to be as high as 30–40% [10–12]), and complications of untreated infection can include urethral stricture, urogenital tract abscesses, prostatitis, and epididymo-orchitis [9]. The situation is more complicated and serious in women, with 50–80% of lower genital tract *N. gonorrhoeae* infections (*i.e.*, gonococcal cervicitis) remaining asymptomatic [9,10,12]. Bacterial ascension from the cervix to the fallopian tubes occurs in up to 45% of gonococci-infected women, and can result in pelvic inflammatory disease (PID: inflammation of the uterus, fallopian tubes, and/or ovaries) [13,14]. Other sequelae include adverse pregnancy outcomes (pre-term birth, spontaneous abortion, stillbirth, low infant birth weight, ectopic pregnancy, chorioamnionitis, postpartum endometriosis or sepsis, ophthalmia neonatorum), infertility, and disseminated gonococcal infection [9]. Infection with *N. gonorrhoeae* also increases HIV replication, transmission, and infection [15–17]. In terms of economic burden, gonococcal infections are estimated to account for annual medical costs exceeding $1.1 billion in the United States alone [18].

The WHO's "Global Action Plan to Control the Spread and Impact of Antimicrobial-Resistance in *N. gonorrhoeae*" [1] recommends the use of mathematical modeling to analyze the feasibility of new interventions. To this end, we aimed to investigate various aspects (*e.g.*, vaccine efficacy, duration of protection, and coverage levels) of potential gonococcal vaccines to estimate the possible impact on disease prevalence. Information obtained will help guide future vaccine development. For example, similar modeling of vaccines for *Chlamydia trachomatis* indicates that vaccine strategies should focus on women and that even partially effective vaccines can greatly reduce the incidence of chlamydia [19]. Modifying the chlamydia vaccine mathematical model to represent gonorrhea, we simulated gonococcal transmission by considering the biology of susceptible (non-infected) and infected individuals, as well as their sexual behaviors and partnership dynamics. This model tracks those parameters critical to gonococcal incidence and prevalence rates and includes: duration and dynamics of infection and infectivity, disease progression, and transmission rates. We then used this model to investigate the population-level impact of different vaccine/vaccination scenarios.

2. Materials and methods

We adapted an established, individual-based model developed for the study of *Chlamydia* vaccines [19] to explore *N. gonorrhoeae* transmission in populations, disease progression in individuals, and the potential impact of various hypothetical vaccines with specified characteristics. This model represents the sexually-active, general heterosexual population, and allows for both ongoing regular and casual (short-term) partnerships. A section of the population is considered to be a highly active "core group" and can have concurrent partnerships. We used the same behavioral parameters as those previously applied to *Chlamydia* [19] (Table S1). In addition, gonorrhea-specific parameters (Table S2) were incorporated based on reference to the literature, and by calibration, such that the mean prevalence of gonococcal infection in the absence of a vaccine was 1.6–1.7% (based on the mean prevalence seen in different regions [20]). We assumed that there is no immunity after the resolution of an infection, which is in keeping with the high rates of reinfection and the low levels of acquired immunity or immunological memory following gonorrhea [21–24].

In our model, the per-exposure probability of transmitting gonorrhea depended on the gonococcal load of the infected partner and followed the dynamics commonly seen in other bacterial and viral infections. That is, initially, a low number of gonococci rapidly reproduce until a peak level is reached, and bacterial numbers then slowly decline to a low number at which point the infection is considered resolved. The mathematical details of these in-host dynamics are described previously [19]. We adjusted the infectivity at peak gonococcal load (see Table S2; 0.5 (female to male) and 1 (male to female)) to produce the expected prevalence in the absence of a vaccine. Peak infectivity is attained only briefly in each infection; averaging over the full duration of infection, the per-exposure probability of a woman infecting a man was 0.28, and the probability for a man infecting a woman was 0.50. These probabilities are comparable to those of 0.19–0.53 [25,26] (female to male) and 0.5–0.65 [27,28] (male to female) noted in the literature.

We simulated vaccination programs in which vaccination takes place at 13 years of age, assumed to be before sexual debut. Vaccines were assumed to be prophylactic with constant efficacy for the duration stated, this being the relative chance the vaccine would prevent any given transmission event. We considered vaccines with efficacies of 10–100% and durations of 2.5–20 years; once the duration is exceeded, the individual would no longer be protected by the vaccine. In that the possibility exists that a partially effective vaccine could have the undesired side-effect of increasing the proportion of infections that are asymptomatic (and, thereby, reduce the proportion of infections that are treated), we also investigated how this would affect prevalence.

First, we simulated an unvaccinated population of 100,000 individuals for 50 years to allow the sexual partnership, and the gonococcal transmission dynamics to stabilize to equilibrium at a population level (with individuals entering and exiting the population over time). We then simulated the vaccination of cohorts of young people and how this would affect the dynamics of gonococcal transmission in the population over 20 years. Ten simulations were run for each vaccine/vaccination scenario, with the results presented as the point-wise medians of the simulations' trajectories.

As our model is individual-based, "stochastic extinction" sometimes occurs at very low prevalence levels. That is, at low prevalence levels, random fluctuations can result in the prevalence dropping to zero, whereas this would probably not happen in a more realistically sized population of millions of people. Such "stochastic extinction" was observed to happen when the prevalence level had fallen by over 90%. As such, even though some of our simulations show extinction of gonorrhea from the population, it is not possible to determine whether this would be seen in a real population. In our results we refer to such decreases in prevalence as being greater than 90%, rather than 100%.

3. Results

If a gonorrhea vaccine with 100% efficacy and 20 years duration of protection becomes available, our simulation modeling analysis predicts a more than 90% decrease in population prevalence within 15 years, provided all 13-year-olds are vaccinated (Fig. 1A). However, our simulations also indicated that even a partially efficacious vaccine would have a large effect on gonococcal prevalence in that a vaccine of just 20% efficacy could reduce gonorrhea prevalence by approximately 40% after 20 years. The predicted prevalence under this high coverage vaccination program, for vaccines ranging from 20 to 80% efficacy, is shown in Fig. 1A.

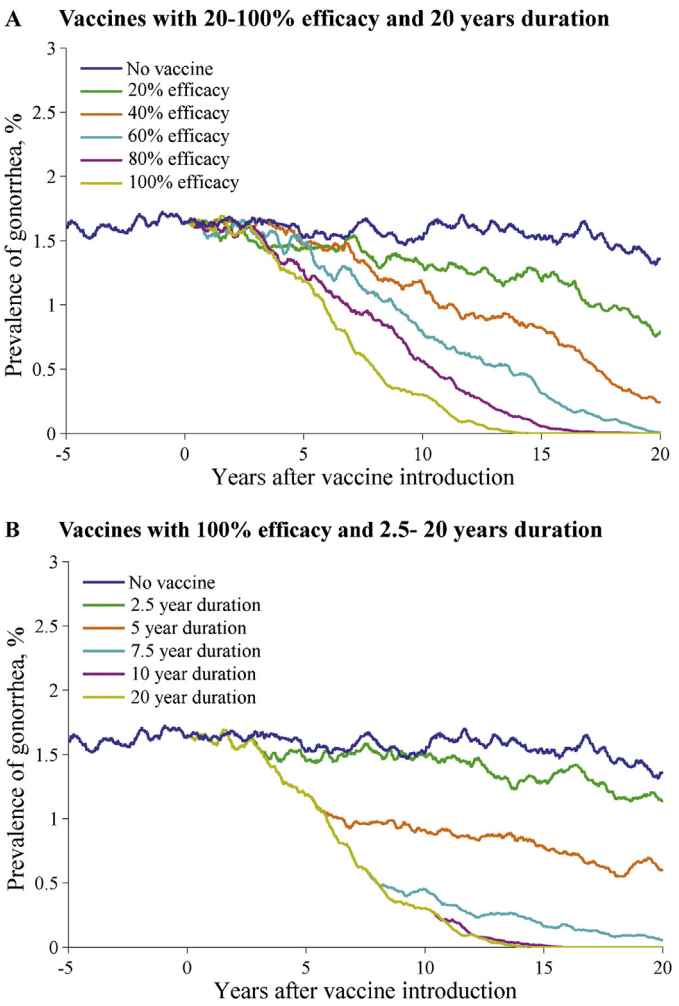

Fig. 1. The prevalence of gonorrhea in the absence of a vaccine, and with (A) vaccines of differing efficacies and 20 years duration of protection, or (B) vaccines with 100% efficacy and of differing durations of protection. Vaccine coverage is 100% of 13-year-olds.

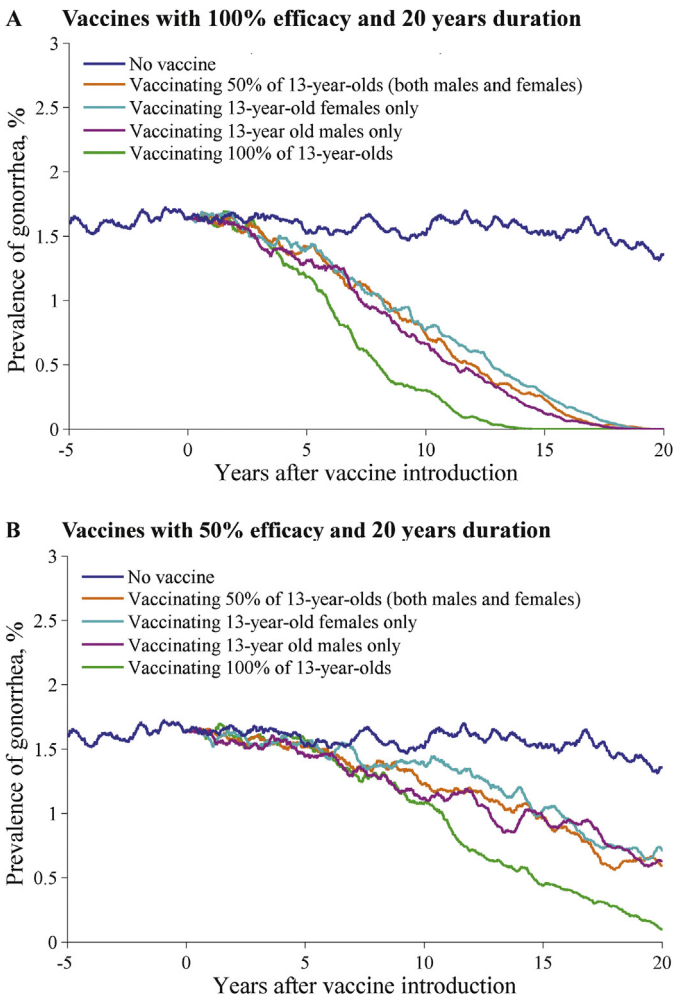

Fig. 2. The prevalence of gonorrhea in the absence of a vaccine, and with different rates and types of vaccine coverage. (A) Vaccines have 100% efficacy and 20 years duration. (B) Vaccines have 50% efficacy and 20 years duration.

A gonorrhea vaccine of short duration could also achieve a substantial impact on prevalence if it has a high protective efficacy, is implemented with high coverage, and its duration is sufficient to protect people during periods of high sexual mixing. In this regard, we predicted that a vaccine of 7.5 years duration and 100% efficacy could reduce prevalence by more than 90% in 20 years (Fig. 1B). A vaccine of 5 years duration could halve prevalence after 20 years. However, even at 100% efficacy, a vaccine with duration of only 2.5 years would be expected to have a negligible impact on disease prevalence.

In practice, vaccine coverage may not be universal. Nevertheless, our simulations suggested that the impact of a vaccine could be substantial even if a vaccination program achieved only 50% coverage of the overall population. For example, the effect of vaccinating 50% of 13-year-olds with a vaccine of 100% efficacy and 20 years duration is expected to reduce prevalence by 90% after approximately 17 years (approximately five years longer than if 100% of 13-year-olds were vaccinated) (Fig. 2A). If the vaccine efficacy were 50%, we would then expect 50% coverage of 13-year-olds to result in a reduction in prevalence of approximately 50% of pre-vaccine levels after 20 years (Fig. 2B), as opposed to approximately 90% reduction if coverage were 100%. Surprisingly, we found that the sex of those vaccinated was unimportant as long as 50% of the eligible population is vaccinated (Fig. 2A and B). However, policy makers might be interested in targeting vaccination at high-risk individuals, rather than vaccinating the general population. Therefore, we simulated vaccination of 25, 50 and 75% of incoming high-risk "core group" individuals. With a vaccine of 100% efficacy and 20 years duration, vaccinating 75% of incoming core group individuals is about as effective, at a population level, as vaccinating 50% of all 13-year-olds (Fig. S1A). With a vaccine of 50% efficacy and 20 years duration, vaccinating 75% of incoming core group individuals is marginally more effective than vaccinating 50% of all 13-year-olds (Fig. S1B).

Given the difficulty of vaccine development for *N. gonorrhoeae*, and the fact that the potential efficacy and duration that a gonorrhea vaccine will have is unknown, we sought to calculate the expected 20 year (Fig. 3A) and 10 year (Fig. 3B) prevalence rates following vaccination of all 13-year-olds with vaccines of differing combinations of efficacy and duration. The unshaded area in Fig. 3A shows where the model estimated a reduction in prevalence of more than 90%. For example, our simulations indicated that a vaccine of 20 years duration would be expected to reduce gonococcal prevalence by more than 90% in 20 years, provided it has an efficacy greater than 50%. Whereas to obtain the same (90%) reduction in disease prevalence, an efficacy of 75% was necessary for a vaccine with only 10 years duration. However, even a vaccine of 50% efficacy and 10 years duration was expected to reduce prevalence by approximately 50% after 20 years. It is also expected that an impact would be seen after 10 years post-vaccination, with prevalence reduced by more than 50%, for vaccines with efficacy greater than 70% and durations of at least 10 years (Fig. 3B).

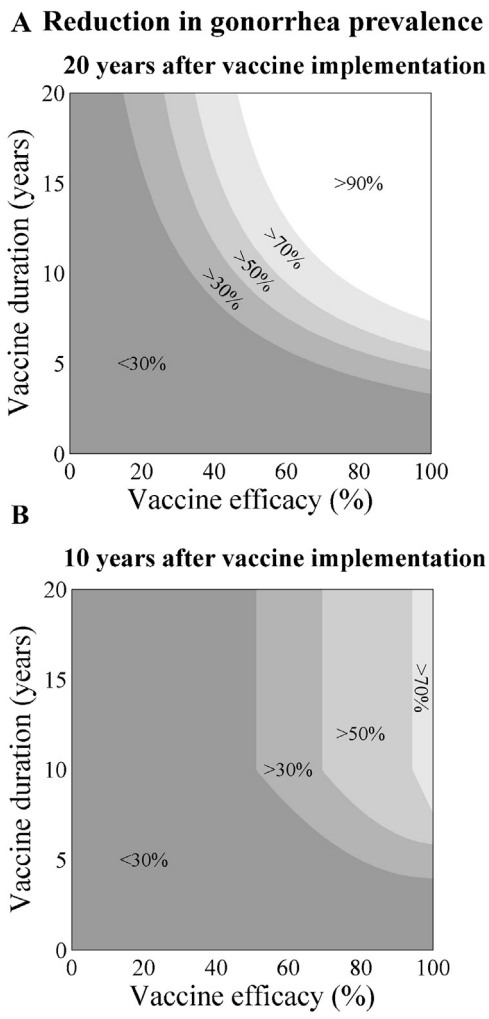

Fig. 3. The reduction in gonorrhea prevalence expected after (A) 20 years and (B) 10 years of vaccination. Simulations were run for combinations of efficacy in 10% increments and duration in 2.5 year increments, and curves were fit to obtain the smooth region boundaries. The reduction is relative to the prevalence in the no-vaccine scenario after the given number of years. In panel B, vaccines with duration of ≥10 years are indistinguishable from one another because at that point in our simulation model there has only been 10 years of vaccination.

It is conceivable that a partially protective vaccine could result in a higher proportion of asymptomatic cases, resulting in a lower proportion of cases being treated. We found that a vaccine of 50% efficacy and 20 years duration that caused all infections to be asymptomatic would have a population-level impact virtually unchanged from a similar vaccine that had no effect on symptoms (Fig. S2A). However, at lower efficacies (*e.g.*, 20%), the effect of a vaccine that caused all infections to be asymptomatic would be largely indistinguishable from the no-vaccine scenario (Fig. S2B).

4. Discussion

In light of the rising incidence of *N. gonorrhoeae* [1], the sequelae associated with infection, and the significant level of antibiotic-resistance that has emerged, there is an urgent need for the development of a gonococcal vaccine. The majority of vaccines licensed to date target microorganisms that have little or no antigenic diversity and were developed using conventional vaccinology approaches (*e.g.*, the use of inactivated or attenuated microbes), which aim to replicate the type of immunity seen after natural infection while removing the ability to cause disease [29]. However, natural infection with *N. gonorrhoeae* does not provide immunity against reinfection [21–23], and attempts to develop a gonococcal vaccine over the past century have proven unsuccessful, with very few candidates progressing into clinical development [30,31]. This is largely because of a lack of knowledge as to what constitutes a protective immune response against *N. gonorrhoeae*, the heterogeneity and variability of gonococcal strains, and the absence of robust animal models in which to study this obligate human pathogen [30,32,33]. The feasibility of gonococcal vaccine development is fueled by: (1) the recent increased need for a gonococcal vaccine because of treatment failures [2] and the consequent potential change in the cost benefit of a vaccine, (2) new vaccine technologies that enable engineering of antigens, optimization of immune responses and target delivery [34], and (3) the success of the vaccine against the STI, human papilloma virus (HPV) [35]. Given the challenges encountered to date, it is unlikely that a gonococcal vaccine will provide complete and life-long protection. Therefore, a clear understanding of the level of protection required to have a meaningful impact on *N. gonorrhoeae* prevalence at the population level is needed. Here we used computational modeling as a means to predict the impact of different vaccines and to better guide decisions related to advancing vaccine targets into, and through, clinical development.

In this study, we adapted a model previously used for *Chlamydia* [19] to simulate the transmission and prevalence of *N. gonorrhoeae* associated with implementation of different hypothetical vaccines: vaccines with different efficacies (10–100%) and durations (2.5–20 years) when administered to different groups within the population (*e.g.*, 50–100% of either males, females, or both sexes over the age of 13 years). We found that gonorrhea vaccines with modest efficacies and durations of protection could have a substantive impact on *N. gonorrhoeae* prevalence. A "perfect" vaccine with 100% efficacy and 20 years duration could reduce gonorrhea prevalence by more than 90% in less than 15 years (Fig. 1). However, "imperfect", or partially efficacious, vaccines could also be valuable from a public health perspective, with a 40% efficacious vaccine with 20 years duration reducing prevalence by approximately 80% within 20 years. A vaccine of shorter duration (7.5 years) and 100% efficacy could achieve a similar impact. In this latter scenario, vaccination would largely target, and thereby protect, the age group with the highest rate of disease (*i.e.*, 15–24 years) [36]. Importantly, we would also expect reductions in infection incidence and prevalence to result in similar reductions in the incidence of PID and other disease sequelae. This is of significant importance as the CDC has predicted that, if cephalosporin-resistant *N. gonorrhoeae* strains become widespread, there would be an estimated additional 75,000 cases of PID, 15,000 cases of epididymitis, 222 HIV infections, and over $200 million of direct medical costs in a 10-year period in the USA alone [3].

Considering concerns about increasingly widespread, untreatable *N. gonorrhoeae* in the near future, it is important to note that the impact of a gonococcal vaccine could be very fast. We predicted that a vaccine with 100% efficacy and 20 years duration would halve prevalence in just seven years (Figs. 1A and 3A), and even a vaccine with >70% efficacy and 10 years duration could halve prevalence by 10 years (Fig. 3B). Indeed, it is previously noted that gonorrhea responds very quickly to real-world interventions with impacts seen in just months [37]. The effect of a vaccine on another STI, HPV, has also been rapid; five years after its introduction in Australia in 2007 there were 93% fewer diagnoses of genital warts [35]. We found that, if vaccines with 100% or 50% efficacy and 20 years duration were restricted to just half of 13-year-olds, it would not matter whether they were females, males, or an even mix of the two sexes (Fig. 2). This is, again, consistent with experience with the HPV vaccine, which lowered genital warts by 82% in males, despite them being unvaccinated [35]. That the benefits of a gonorrhea vaccine would extend across sexes is an important finding, as human

challenge trials maybe limited to males [38], and our results suggest that this would not substantially bias estimates of the vaccine's effectiveness.

We found that targeting high-risk "core group" members was very effective; vaccinating 75% of incoming core group members achieved a comparable population-level result to that determined for vaccinating 50% of all 13-year-olds (Fig. S1). As the core group is assumed to be just 5% of the population, targeting this group would require far less vaccinations to achieve a similar outcome (as is observed in other modeling studies [39]). However, a key question for policy makers would be how easily the core group can be accessed. In regions in which there is a high concentration of gonorrhea cases among sex workers, and in which there exist good outreach programs for sex workers, we would expect targeting this population to be a particularly effective approach. However, if core group members are more difficult to identify, or to reach, then vaccinating the general population might be more efficient.

This study provides findings that can help guide vaccine development. We provide vaccine characteristic targets for efficacy and duration of protection necessary for a vaccine to have an impact. Vaccine characteristics (as indicated in our simulations) required to yield a population-level impact are in-line with currently licensed vaccines profiles that have had substantial public health impacts. For example, in terms of coverage, >70% of ~12-year-old girls have received 3 doses of the HPV vaccine in many countries, following targeted national HPV immunization programs (*e.g.*, in Australia) [40,41]. In terms of protective efficacy and duration, whereas some vaccines have estimated efficacies of >90% and provide lifelong protection after a single dose (*e.g.*, the rubella vaccine [42]), the majority of currently licensed and widely used vaccines have "less optimal" profiles in terms of their efficacy, duration, and immunization schedule. For example, BCG vaccination is estimated to provide 52% protection against tuberculosis for 10 years [43,44]; and the DTP vaccine has 80–100% efficacy with three doses being required in infancy to provide protection for 3–5 years against tetanus and with additional boosters needed throughout life [45]. It is also important to note that, like gonorrhea [22], recovery from clinical tetanus does not typically result in protection against the disease in the future, yet the tetanus toxoid-based vaccines are highly effective at preventing disease [45].

There are some limitations to our analyses. First, we have assumed an entirely heterosexual population. Men who have sex with men (MSM) have an increased prevalence of gonorrhea [46,47]. Therefore, a vaccine might be expected to have an increased impact in these communities. Alternatively, the higher number of partnerships, and consequent higher number of gonococcal challenges, seen in this population could also mean that a gonorrhea vaccine could be less effective than our simulations indicated for the heterosexual population. This is an important subject for future research. Whereas links between gonococcal load and transmissibility are suggested [48], to our knowledge, this has not been directly investigated and prospective partner studies are needed to confirm this association. However, the load versus transmission relationship has been investigated for human immunodeficiency virus and HPV [49–51] and is featured in a more simplified form in a model of trachoma (*C. trachomatis*) [52]. We assumed that a similar relationship exists for *N. gonorrhoeae*. Second, we based our model on a vaccine that provides high strain coverage, which is possible given the ongoing advances in antigen discovery and engineering and the likelihood that a gonococcal vaccine will contain a combination of antigens. A vaccine that does not provide protection against all strains of *N. gonorrhoeae* would be expected to reduce prevalence, as predicted in our results, for those strains against which it is protective, while leaving the prevalence of other strains unchanged. Finally, there are several aspects of gonococcal infection that we have not attempted to include in our model. We did not attempt to estimate the gonococcal-related PID incidence and potential cases averted due to vaccination. Our model also does not take into account the confounding issue of the female genital tract microbiome or co-infection with other STIs, both of which may increase, or decrease, the rate of transmission and/or acquisition of *N. gonorrhoeae* [53,54]. Moreover, we assumed that 66% of infected women and 36% of infected men are asymptomatic [12], but this may vary based on prevalence and screening methods used. Lastly, our model assumes a prevalence of gonorrhea that is intermediate in terms of levels reported for different WHO regions worldwide [20], and a vaccine may have a different impact in higher or lower prevalence settings. For the purposes of this study, we have chosen to take a simplification approach to these points, albeit they could be explored, and expanded upon, in future modeling studies.

In summary, our mathematical simulation indicates that even partially effective vaccines could have a significant impact on the prevalence of *N. gonorrhoeae*. These data, regarding the potential ability of a *N. gonorrhoeae* vaccine to reduce the prevalence of infections, will provide a basis for future development, implementation, and evaluation of candidate vaccines.

Conflict of interest statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.07.015

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