Vaccine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The potential impact of vaccination on the prevalence of gonorrhea

Andrew P. Craig[a], Richard T. Gray[a], Jennifer L. Edwards[b], Michael A. Apicella[c], Michael P. Jennings[d,1], David P. Wilson[a,1], Kate L. Seib[d,*,1]

[a] The Kirby Institute, UNSW Australia, Sydney 2052, NSW, Australia
[b] Center for Microbial Pathogenesis, The Research Institute at Nationwide Children's Hospital, and The Ohio State University Department of Pediatrics, Columbus, OH, USA
[c] Department of Microbiology, University of Iowa, Iowa City, IA, USA
[d] Institute for Glycomics, Griffith University, Southport, QLD, Australia

ARTICLE INFO

Article history:
Received 30 March 2015
Received in revised form 2 July 2015
Accepted 7 July 2015
Available online xxx

Keywords:
Neisseria gonorrhoeae
Gonorrhea
Vaccine
Antimicrobial resistance
Epidemiological simulation model

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

* Corresponding author. Tel.: +61 755527453; fax: +61 7 5552 8098.
E-mail address: k.seib@griffith.edu.au (K.L. Seib).
[1] These authors contributed equally to the study.

http://dx.doi.org/10.1016/j.vaccine.2015.07.015

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.

Please cite this article in press as: Craig AP, et al. The potential impact of vaccination on the prevalence of gonorrhea. Vaccine (2015), http://dx.doi.org/10.1016/j.vaccine.2015.07.015