Scoping Review On Gonorrhea Vaccines

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Scoping Review on Gonorrhea Vaccines

Leah Li

Thesis submitted in partial fulfillment for the conferral of the degree:
Master of Public Health
Epidemiology of Microbial Diseases
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Abstract

Gonorrhea infection is caused by Neisseria gonorrhoeae and it is the second most common bacterial sexually transmitted infection (STI) around the globe [1]. Although gonorrhea infection is treatable with antibiotics, the level of antimicrobial resistance (AMR) continues to increase and has become a major public health concern [2]. As options of available treatments are reduced by the emergence of AMR, it has become urgent to develop effective vaccines against gonorrhea infection. The purpose of this scoping review is to describe existing epidemiological evidence in support of gonorrhea vaccine development, to discuss the current vaccine candidates in clinical stages, and to evaluate the theoretical impact of gonorrhea vaccines. Published papers and clinical trial records on gonorrhea vaccine immunogenicity and efficacy, vaccine effectiveness and potential impact were reviewed after selection. Outer membrane vesicles (OMVs)-based meningococcal serogroup B vaccination showed moderate (approximate 30%) cross-protection against gonorrhea infections in multiple retrospective studies, and subsequent clinical studies assessing the immunogenicity and vaccine efficacy are currently undergoing. Modeling studies suggested that the theoretical impact of gonorrhea vaccines vary by vaccine efficacy, mode of action, duration of protection, uptake percentage, and disease prevalence in the population, but a vaccine with efficacy and duration of protection equivalent to the meningococcal serogroup B vaccine can have substantial impact and public health value if delivered in optimal vaccination strategy. However, generalizability of the study results remains questionable because studies included were mostly limited to developed country settings. To investigate vaccines with higher efficacy and to better evaluate the value of potential gonorrhea vaccines, research on disease natural history and gonorrhea epidemiology in low- or middle-income countries (LMIC) in the near future.
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Introduction

Epidemiology of gonorrhea

Gonorrhea is a sexually transmitted infection (STI) caused by the bacteria *Neisseria gonorrhoeae*. It affects both men and women, and is the second most common STI in the world after chlamydia infections, with an estimated global incidence of 82.4 million new cases in 2020 [3]. World Health Organization (WHO) estimated the global prevalence of gonorrhea in 2016 to be 0.9% in women and 0.7% in men, which corresponds to a total prevalence of 30.6 million cases worldwide [3]. Global incidence per year was 20 per 1000 women and 26 per 1000 men, which translates to 86.9 million newly identified cases in 2016 [4]. These numbers are likely to be underestimation due to inadequate surveillance systems in resource-limited countries. By geographic region, both prevalence and incidence rate of gonorrhea is highest in the WHO African region, the region of the Americas, and the Western Pacific region, and lowest in the European region [3]. Geographic disparities may be caused by variability in the availability of effective prevention, screening and diagnostic programs, and treatment methods.

On individual level, sex and sexual orientation, socioeconomic status, demographics and cultural factors also affect individual’s risk of gonorrhea [2]. Men who have sex with men (MSM), migrants, younger adults (15 – 24 years of age) and sex workers are at higher risk of gonorrhea infection and are disproportionately affected by the disease [2].

In the U.S., 710,151 cases of gonorrhea were reported to the Centers for Disease Control and Prevention (CDC) in 2021, showing a 4.6% increase from 2020 [5]. The incidence rate is higher among men than women, among individuals aged 15 to 29 [6], and in Black/African American, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander [7]. In the European Union/European Economic Area (EU/EEA), the surveillance data showed a total of 117,881 reported cases and a 19.2% increase in 2019 [8]. The incidence rate was higher in northern Europe and MSM accounted for more than half of the
reported cases [8]. Compared to the U.S. and the EU/EEA, surveillance for gonorrhea is less robust in low- or middle-income countries (LMIC). For example, in South Africa, STIs are typically managed syndromically without diagnosis using laboratory testing. The prevalence of STIs was estimated either by collecting data through sentinel surveys in clinics and biological and behaviors surveys in key populations, such as in the case of syphilis, or through research projects or clinical trials, such as in the case of gonorrhea [9].

Prevention and treatment

*Neisseria gonorrhoeae* infects multiple sites in human body, including the cervix, uterus, and fallopian tubes in women, the urethra, throat, and rectum in both men and women [2]. Gonorrhea infection in men can present as dysuria or unusual urethral discharge [10]. Symptoms presented in infected women are often nonspecific, including dysuria, unusual vaginal discharge, or vaginal bleeding between periods [10]. Infections can cause pain or discharge in rectum and sore throat in throat, but rectal and pharyngeal infections usually cause no symptoms [10]. While many cases of infections are asymptomatic, untreated gonorrhea can cause serious complications such as epididymitis in men, pelvic inflammatory disease (PID), ectopic pregnancy, and infertility in women [10]. Like other STIs, gonorrhea also increases an individual’s risk of HIV infection and transmission [10].

Effective method to control transmission of gonorrhea include primary prevention, screening and testing, timely treatment and the use of surveillance system. Primary prevention methods of gonorrhea and other STIs include training and promotion of safe sexual behaviors, such as increasing condom use and decreasing casual, unprotected sexual contacts [2]. Secondary prevention includes screening for asymptomatic cases, promoting health care-seeking behavior, treating other STIs such as chlamydia to
reduce co-infections, and treating sexual partners [10]. Reducing STI-related stigma, which affects both infected individuals and healthcare providers, is another key factor for gonorrhea prevention.

Treatment of gonorrhea is mainly administered empirically based on international and national evidence-based treatment guidelines. In European countries, dual antimicrobial therapy (intramuscular ceftriaxone plus oral azithromycin) or ceftriaxone monotherapy is the currently first-line treatment regimen for uncomplicated gonococcal infections in adults and adolescents [11]. In the U.S. and the U.K., single dose ceftriaxone is recommended [12, 13]. In resource-limited countries where diagnosis capacity is insufficient, syndromic management flow charts are the current standard of care. However, syndromic management cannot detect asymptomatic infections and tend to overtreat people infected by other bacteria that lead to similar symptoms (e.g., *C. trachomatis* and *Mycoplasma genitalium*) [2].

The emergence and spread of antimicrobial-resistant *Neisseria gonorrhoeae* has posed serious challenges to the control of the disease. According to the WHO, resistance to azithromycin is rapidly increasing and decreased susceptibility to ceftriaxone and cefixime continue to emerge in many countries [3]. In the U.S., according to the Gonococcal Isolate Surveillance Project (GISP), approximately half of the gonorrhea infections were estimated to be resistant to at least one antibiotic [14]. To control the high prevalence of gonococcal infections and slow down the speed of developing resistance, it is urgent to promote known preventions strategies and to find effective vaccines and develop vaccination strategies for gonorrhea under the rapid rise of antimicrobial resistance and a lack of new antibiotics.

*Gonorrhea vaccines*

To address the global disease burden, impact on socioeconomically disadvantaged populations including women and infants, and emerging “super-bug” status of gonococci with increase in antimicrobial
Resistance levels in gonorrhea, vaccine development is critical. Despite ongoing efforts in gonorrhea vaccine development, there currently is no approved vaccine. Since the early 1900s, 4 gonorrhea vaccine candidates have advanced to the clinical trial or human challenge trial stage, yet none has shown statistically significant vaccine efficacy or protection against challenge [15]. Gonococcal vaccine development is challenging for several reasons. First, human beings do not acquire immunity from natural infection of gonorrhea. So, conventional methods, such as using inactivated or live-attenuated N. gonorrhoeae, will not be effective. This is caused by N. gonorrhoeae having a high level of surface antigen variability and multiple immune evasion mechanisms [16]. Vaccines based on antigenically variable gonococcal proteins fail to provide a broad antibody response. Secondly, N. gonorrhoeae is a human-specific pathogen, making the disease mechanism hard to study using animal models. Although there are multiple approaches for gonorrhea vaccine development and many ongoing studies, the development of gonorrhea vaccines is still predominantly in the preclinical stage and no data from human clinical trials are available to date [17]. Fortunately, observational data showed that vaccine developed against Neisseria meningitidis group B (MenB) might provide cross-protection against its closely related pathogen Neisseria gonorrhoeae.

In 2013, WHO and the NIH proposed a global roadmap for STI vaccine development, which outlined 9 priority action areas. One of the key areas to advance STI vaccine development and policy-making is to model the theoretical impact and cost-effectiveness of STI vaccines [16]. Since then, many studies using mathematical models including decision analysis models, transmission dynamic models, and individual- or population-based models have provided insights on future decision-making on gonorrhea vaccine. Modeling studies also help define preferred product characteristics (PPCs), such as desired efficacy and possible immunization strategies of STI vaccines, and it counts as another priority action area proposed by the WHO and the NIH.
This scoping review aims to describe the epidemiological data in support of gonorrhea vaccine development, to discuss the current vaccine candidates undergoing clinical trial stage, and to assess the theoretical impact of potential gonorrhea vaccines.

Methods

Search strategy

Different from systematic reviews, this scoping review aims to include diverse literature on the topic of gonorrhea vaccine and to discuss current knowledge gap and future research direction on this topic. Literature review was conducted using the PubMed and ClinicalTrials.gov databases on March 1, 2023. Search strategy on PubMed was based on concepts including “gonorrhea” or “gonococcal”, “N. Gonorrhoeae”, “vaccine”, “effectiveness”, “impact”, “implication”, or “protection”. Search strategy on ClinicalTrials.gov focused on keywords including “gonorrhea”, “gonococcal”, “N. Gonorrhoeae”, and “vaccine”.

Study selection criteria

Reviewer retained studies on PubMed that meet these criteria:

1. written in English language
2. peer-reviewed
3. published from 2013 to 2023
4. reviewer has full-text access
5. research types are epidemiological studies, including observational studies such as cohort and case-control studies, mathematical modeling studies, and random-controlled trials
6. research focusing on human subjects
Outcomes of interest are safety, efficacy, effectiveness or theoretical impacts of gonorrhea vaccines.

Studies were excluded if they focused on research methodologies or other infectious diseases, such as meningitis or HPV infections.

**Study selection**

Searching was conducted by the reviewer. Titles, abstracts, and full texts were reviewed to determine the eligibility of studies. Duplicated studies were removed after review. Research articles that failed to meet inclusion criteria were removed. In the end, 11 research articles and 8 clinical trials were retained. Reviews, comments, and journal articles were used to supplement this scoping review.

**Results**

**Characteristics of included studies**

A total of 262 studies and 12 clinical trials were found in PubMed and ClinicalTrials.gov databases, of which 62 studies were reviewed and 11 studies and 8 clinical trials were eligible (Figure 1). Four retrospective observational studies were identified, including three case-control studies [18-20] and one cohort study [21] (Table 1). Among observational studies, two were conducted in New Zealand [19, 21], one in the U.S. [18], and one in Australia [20]. Among the eight identified clinical trials, four focused on the U.S. population [22-25], one on the U.S. and the European population [26], two on the Australian population [27, 28], and one was conducted in Kenya [29]. Clinical trials included two single-arm studies [22, 29], one phase I/II study [26], three phase II studies [23-25], one phase III study [27], and one large-scale prospective cohort study [28] (Table 2). Seven of the identified research are modeling studies, including one decision-analysis modeling [30], one static modeling [31], four transmission-dynamic modeling studies [32-35], and one integrated transmission-dynamic health-economic modeling study.
Three modeling studies focused on England specifically [32, 35, 36], two focused on the U.S. population [30, 31], and one on the Australian population [34]. In terms of the targeting population, three modeling research studied MSM exclusively [32, 34, 36] and three studied the heterosexual populations exclusively [31, 33, 35].

Figure 1. Consort diagram

Proof-of-concept real-world data

Surveillance reports from the late 1980s in Norway (MenBvac, Norwegian Institute of Public Health) and Cuba (VA-MENGOC-BC, Finlay Institute) were the first data that indicated MenB outer membrane vesicle (OMV) vaccines may offer protection against *N. meningitidis* [37]. Tailored-made vaccine MeNZB (Novartis Vaccines and Diagnostics), the meningococcal B vaccine for a specific epidemic strain in New Zealand, was tested and rolled out from 2004 to 2008 in response to a serogroup B meningococcal epidemic [38]. After the vaccine roll-out, New Zealand also observed a decline in reported gonorrhea but not in other STIs during the same period [39]. Using individuals infected with chlamydia as the control group in their case-control study, Petousis-Harris and colleagues assessed the effectiveness of the MeNZB vaccine against the acquisition of gonorrhea in young adults aged 15-30 years, the same
ages as the population eligible for the mass immunization program from 2004 to 2006 in New Zealand. After adjusting for ethnicity, deprivation level (based on data from the 2013 census), geographical area, and sex, the estimated vaccine effectiveness was 31% (95% CI 21-39) [19]. The estimated vaccine effectiveness against chlamydia and gonorrhea co-infection was 14% (95% CI 1-26), lower than its effectiveness against gonorrhea only. Paynter and colleagues focused on the same cohort of New Zealanders, used a retrospective cohort study and estimated the effectiveness of the MeNZB vaccine against hospitalization caused by gonorrhea to be 24% (95% CI 1-42) after adjustment for sex, ethnicity, and deprivation [21]. The MeNZB vaccine was most effective in the subgroup who was vaccinated at an age likely to be before sexual debut (at age 13). Their research result also suggested waning effectiveness because such effectiveness was not observed in the older cohort subgroup with median age at 18 [21].

As MeNZB was withdrawn from the market, case-control studies and clinical trials have been conducted to assess the cross-protection provided by the 4CMenB (Bexsero, GlaxoSmithKline) vaccine, which is a broader spectrum four-component serogroup B vaccine that contains the same OMV antigen as the MeNZB vaccine [39]. In the U.S., since 2015, meningococcal B vaccine is recommended for 16-23-year-olds who are at increased risk for short-term protection against serogroup B meningococcal disease, based on discussion between the patient and healthcare provider [40]. A case-control study by Abara and colleagues used surveillance data from New York City and Philadelphia from 2016 to 2018 and estimated a 4CMenB vaccine effectiveness against gonorrhea of 40% (95% CI 23-53) in fully vaccinated people (2 doses) and 26% (95% CI 12-37) in partially vaccinated people (1 dose) after adjusted for sex, race/ethnicity, and jurisdiction. When assessing the vaccine effectiveness against co-infection of chlamydia and gonorrhea using infection of chlamydia as the control group, the result is statistically insignificant (adjusted prevalence ratio = 0.85, 95% CI 0.64-1.13) [18]. In South Australia, a 4CMenB
vaccination program was introduced for individuals aged 0 – 3, 15 – 16, and 17 – 20 in 2018. Using age-matched individuals infected with chlamydia as control, Wang and colleagues estimated the effectiveness of 4CMenB vaccine against gonorrhea in adolescents and young adults to be 32.7% (95%CI 8.3-50.6) after adjusted for age, sex, Aboriginal and Torres Strait Islander status, and socioeconomic status [20].

**Vaccines in clinical trials**

Following the positive result from observational studies in different countries, multiple clinical trial focusing on the 4CMenB vaccine were initiated and are currently undergoing. Two single-arm clinical studies, one in the U.S. and one in Kenya [29], tried to identify the immune response induced by the 4CMenB vaccine in the human body after complete series of vaccination (2 doses), by measuring the change in anti-*N. Gonorrhoeae* OMV-specific IgG, IgM, IgA, and proportion of CD4+ T-cells expressing markers after immunizations [22, 29].

Three phase II clinical trials studying the efficacy of the 4CMenB vaccine against gonorrhea infection are undergoing in the U.S. One trial intends to evaluate the overall and anatomical site-specific efficacy of the 4CMenB vaccine against gonorrhea and it’s expected to be completed in 2023 [23]. Another Phase II study with an estimated completion date in 2023 aims to investigate the systematic and mucosal immunogenicity of the 4CMenB vaccine after 2 doses of vaccination by measuring the rectal mucosal IgG concentrations against *N. gonorrhoeae* OMV antigens as primary outcome [24]. There is also a phase II clinical trial focused specifically on the 4CMenB vaccine’s protection against urethral infection in male adults, and it’s expected to be completed in 2028 [25].
A phase III trial conducted in Australia aims to evaluate the vaccine efficacy of 4CMenB against gonorrhea infection in the MSM population who have high incidence rates of gonorrhea and are recommended by the Australian national guideline to have regular, comprehensive sexual health screening [27]. There is another prospective cohort study trying to assess the vaccine impact and effectiveness of the 4CMenB immunization program against invasive meningococcal disease and gonorrhea in young adults in the Northern Territory of Australia [28]. Both trials are expected to be completed by 2025 [27, 28].

Besides the 4CMenB vaccine, which is approved as a serogroup B meningococcal vaccine in many countries, there is another GMMA-based investigational vaccine developed by GlaxoSmithKline undergoing phase I/II clinical trials to determine the safety and efficacy in healthy adults [26]. The study started in 2022 and its estimated completion date is in 2025 [26].

*Theoretical impact of gonorrhea vaccine*

Seven modeling studies assessed the theoretical impact of gonorrhea vaccine on disease prevalence or cost-effectiveness of vaccination programs by using mathematical models and making assumptions about the efficacy, duration of protection, and coverage level of the vaccine.

Among the seven studies, three studies modeled the effect of heterosexual transmission and stratified the population into “male” and “female”. A study conducted by Craig et al. that was published in 2015 concluded that a vaccine with moderate efficacy and duration of protection could have substantial impact on gonorrhea prevalence, if the uptake percentage of vaccine is high. Based on their model, a 40% efficacious vaccine with 20 years duration of protection could reduce disease prevalence by 80% within 20 years, if all individuals get vaccinated at 13 years of age before their sexual debut and the
percentage uptake is 100%. Craig et al. also suggested that targeting core group members who are at higher risk of gonorrhea could be more effective than implementing the vaccination program on a population-level [31].

Carey et al. developed a mathematical model and simulated vaccine impact among U.S. adolescents age 15-24 if the vaccine candidate has 30% efficacy and a 2-year duration of protection, based on the result from the case-control study by Petousis-Harris et al. in New Zealand [19]. Assuming a baseline prevalence of 1.125% in women and 0.75% in men, prevalence of gonorrhea will decrease by 8.6% or 21.9% after 10 years, if the percentage uptake is 20% or 50% respectively [33]. Vaccines with greater performance in efficacy and duration of protection could have greater impact. With a hypothetical vaccine candidate similar to 4CMenB, the theoretical vaccine impact is larger if more sexual contacts occur between individuals in the same sexual activity groups (more high-high and low-low contacts) and if the sub-population size of high sexual activity group is larger.

Recently published research by Looker et al. further explored the theoretical impact of an adolescent National Immunization Program (NIP) of gonorrhea vaccine and the effect of catch-up programs and the use of boosters. Vaccinating the 14-year-old cohort with a vaccine that has efficacy of 31%, 6 years of protection, and 85% uptake, 10% of heterosexual incident gonorrhea infection could be averted [35]. When comparing a catch-up program and a booster, under the same 40% uptake, catch-up vaccination for the 15-18-year-olds would have a larger short-term effect (54% more averted cases than no catch-up scenario over 10 years) and booster vaccination for the 19-24-year-olds would have a larger long-term effect (61% more averted cases than no booster vaccination over 70 years).
The WHO announced a global health sector strategy on STIs, targeting a 90% reduction in gonorrhea incidence by 2030 [1]. Previous research showed that targeting core group individuals will have a comparable impact on population-level gonorrhea prevalence as targeting all men and women [41], suggesting that targeting the core group could be more cost-effective because fewer vaccines need to be distributed. The MSM population has the highest incidence rate and the highest level of antimicrobial resistance in England [36]. Whittles et al. developed a model that answered the question of how protective and long-lasting a vaccine targeting the MSM population needs to be to achieve the goal proposed by the WHO, under the emergence of extensively-resistant gonorrhea. They assessed the potential impact of 3 vaccine deployment strategies: “vaccination before entry” to the sexually active stage, “vaccination on diagnosis” with gonorrhea, and “vaccination on attendance” at sexual health clinics for any reason in the MSM population. In the “best-case” scenario of their analysis, in which antimicrobial-resistant level stays stable and infections remain treatable, vaccination all MSM attending sexual health clinics from 2020 onward with a vaccine of 40% efficacy and ≥4 years of protection or a 50% efficacy with ≥2 years protection would be able to meet the WHO target. In the “worst-case” scenario in which untreatable *N. gonorrhoeae* strains emerge, vaccination of all MSM attending sexual health clinics from 2020 onward with a vaccine with ≥52% efficacy lasting ≥6 years would be necessary.

Another integrated transmission-dynamic health-economic model developed by Whittles et al. further looked into the cost-effectiveness of gonorrhea vaccination and how it is affected by vaccine efficacy and duration of protection. Building on to the previously listed vaccine deployment strategies, Whittle et al. added the fourth option “vaccination according to risk”, which vaccinates individuals who are currently infected and who test negative but report having more than five sexual partners per year when attending sexual health clinics. The monetary value of gonorrhea vaccine is calculated by summing the averted cost of testing and treatment and the monetary value of averted QALY losses, at £20,000
per QALY. Assuming using a vaccine with 31% (95% CI 21-39) efficacy and 18-month protection after primary vaccination and 36-month protection after booster, vaccinating MSM in sexual health clinics under the “vaccination according to risk” strategy, NHS pricing the vaccine at £8 per dose, and the sexual behavior patterns stay the same, it would avert 110,200 (95% CI 36,500-223,600) gonorrhea infection cases in England, save £7.9 (95% CI 0.0-20.5) million and lead to 100.3 (95% CI 21.0-215.8) gained QALYs over 10 years [36].

Hui et al. focused on MSM in Australia and built a model to identify key characteristics required for the vaccine to have optimal public health impact. The model was an anatomical-site specific mathematical model assuming 3 potential anatomical sites of infection (urethra, anorectum, and oropharynx) and 3 types of vaccine efficacy based on vaccine mode of action (efficacy in protecting individual from acquiring gonorrhea, efficacy in reducing transmission, efficacy in reducing symptoms of gonorrhea). Their research result showed that a vaccine with high protective efficacy is the primary aim for the MSM population. A gonorrhea vaccine with 100% protective efficacy could lead to a 94% reduction in disease prevalence 2 years after introduction in Australia. Also, for gonorrhea vaccines that suppress symptoms, their efficacy in preventing people from getting infected and preventing transmission would need to be larger than 25% to reduce gonorrhea prevalence. A vaccine with low protective efficacy and suppresses symptom development may not be beneficial to the population given most infections are managed under symptom-based strategies. Furthermore, the model indicated that the vaccine needs to be effective against oropharyngeal infection to substantially reduce gonorrhea prevalence in the MSM population due to asymptomatic transmission. Based on their model, a vaccine with 100% efficacy against urethral and anorectal infection, but has no efficacy against acquisition or transmissibility of oropharyngeal infection would a substantially reduced impact [34].
### Table 1. Characteristics of proof-of-concept real-world study on cross-protection of serogroup B meningococcal vaccines against gonorrhea

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Purpose</th>
<th>Study Design</th>
<th>Research Population and Sample Size</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petousis-Harris et al., 2017</td>
<td>To assess the effectiveness of the MeNZB vaccine against gonorrhea infection</td>
<td>Retrospective case-control study</td>
<td>15-30-year-olds between 2004 and 2016 in New Zealand (N=14,730)</td>
<td>31% (95% CI 21–39)</td>
</tr>
<tr>
<td>Paynter et al., 2019</td>
<td>To estimate the effectiveness of the MeNZB vaccine against gonorrhea-associated hospitalization</td>
<td>Retrospective cohort study study</td>
<td>Individuals born from 1984 to 1999 residing in New Zealand N=935,496 (cases=261)</td>
<td>24% (95% CI 1–42)</td>
</tr>
<tr>
<td>Abara et al, 2022</td>
<td>To evaluate the vaccine effectiveness of 4CMenB against gonorrhea infection</td>
<td>Case-control study</td>
<td>16-23-year-olds in the U.S. (NYC and Philidophia) N=167,706</td>
<td>complete series: 40% (95% CI 23–53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>partial vaccination: 26% (95% CI 12–37)</td>
<td>partial vaccination: 26% (95% CI 12–37)</td>
</tr>
<tr>
<td>Wang et al., 2022</td>
<td>To evaluate the effectiveness of the 4CMenB vaccine against gonorrhea 2 years after the implementation of vaccination program</td>
<td>Case-control study</td>
<td>14-25-year-olds in South Australia N=3,652</td>
<td>Complete series: 32.7% (95% CI 8.3–50.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Partial vaccination: 32.6% (95% CI 10.6–49.1)</td>
<td>Partial vaccination: 32.6% (95% CI 10.6–49.1)</td>
</tr>
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</table>

### Table 2. Ongoing clinical trials associated with gonorrhea vaccines

<table>
<thead>
<tr>
<th>Clinical Trial Identifier</th>
<th>Purpose</th>
<th>Study Design/Interventions</th>
<th>Sample Size</th>
<th>Primary Outcome</th>
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<tbody>
<tr>
<td>Immunogenicity Studies</td>
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<tr>
<td>Study ID</td>
<td>Location</td>
<td>Objective</td>
<td>Design</td>
<td>Age</td>
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<tr>
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</tr>
<tr>
<td>NCT04094883</td>
<td>USA, 2019</td>
<td>To assess gonorrhoeae immune responses induced by the 4CMenB vaccine</td>
<td>Single arm (2-dose)</td>
<td>Aged 18-25 N=11</td>
</tr>
<tr>
<td>NCT04297436</td>
<td>Kenya, 2021</td>
<td>To assess if immunization of people at risk of gonorrhea with 4CMenB will elicit humoral and T-cell cross-reactive response</td>
<td>Open-label single arm (2-dose)</td>
<td>Aged 18-25 N=50</td>
</tr>
<tr>
<td>NCT05630859</td>
<td>USA and EU, 2022</td>
<td>To assess the safety and efficacy of GSK <em>N. gonorrhoeae</em> GMMA investigational vaccine</td>
<td>Phase 1/2 Randomized, observer-blind, placebo-controlled, multi-country</td>
<td>Age 18-50 N=774</td>
</tr>
<tr>
<td>NCT04350138</td>
<td>USA, 2020</td>
<td>To assess the safety and efficacy (overall and by anatomical site) of 4CMenB vaccine in preventing gonorrhea infection</td>
<td>Phase 2 Randomized, observer-blind, placebo-controlled, multi-site (2-dose)</td>
<td>Aged 18-50 N=2200</td>
</tr>
<tr>
<td>NCT04722003</td>
<td>USA, 2021</td>
<td>To assess the systemic and mucosal immunogenicity of the 4CMenB vaccine against <em>N. gonorrhoeae</em></td>
<td>Phase 2 Double-blinded, randomized, placebo-controlled (2-dose)</td>
<td>4CMenB vaccine: N=40 Placebo vaccine: N=10</td>
</tr>
<tr>
<td>NCT05294588</td>
<td>USA, 2022</td>
<td>To test whether vaccination with 4CMenB provides</td>
<td>Phase 2</td>
<td>Male aged 18-36 N=140</td>
</tr>
</tbody>
</table>
Table 3. Characteristics of modeling studies on the theoretical impact of gonorrhea vaccines

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Purpose</th>
<th>Research Population</th>
<th>Models</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Régnier &amp; Huels, 2014</td>
<td>To assess the theoretical impact of a U.S. 4CMenB vaccination program on gonorrhea outcomes</td>
<td>Adolescents and adults in the U.S.</td>
<td>A decision-analysis model, assuming 20% efficacy</td>
<td>A vaccine of 20% efficacy could have substantial reduction in gonorrhea infections and associated cost</td>
</tr>
<tr>
<td>Craig et al., 2015</td>
<td>To understand the preferred product characteristics, target population, and expected impact of gonorrhea vaccines</td>
<td>Heterosexual population</td>
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<td>A vaccine of moderate efficacy and duration could have substantial impact on gonorrhea prevalence, if coverage is high and protection lasts over the highest risk period</td>
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<td>Whittles et al., 2020</td>
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<td>Whittles et al., 2022</td>
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Discussion

Estimated vaccine effectiveness of serogroup B meningococcal vaccine against gonorrhea

The mass immunization program with MeNZB vaccine in New Zealand (3 doses of primary series and no booster) showed a 31% (95% CI 21–39) effectiveness against gonorrhea infection and a 24% (95% CI 1–42) effectiveness against hospitalization caused by gonorrhea. Although the estimated effectiveness of MeNZB is relatively low, the vaccine was shown to be effective in both preventing disease acquisition and mitigating disease development. However, the vaccine showed lower effectiveness in the population that was co-infected with chlamydia [19], and no effect in the partially vaccinated population [19, 21]. Both studies suggested waning of the protective effect, but the proposed duration of protection varies and ranged from 2 years [19] to 4 years [21].

Previous immunogenicity studies suggested that 4CMenB might offer additional protection against gonorrhea compared to the MeNZB vaccine [42], but the population-level observational studies showed similar results. The effectiveness of the 2-dose 4CMenB vaccine was estimated to be 40% (95% CI 23–53) in the Abara et al. study and 32·7% (95% CI 8·3–50·6) in the Wang et al. study. Partial vaccination is associated with lower effectiveness in the Abara et al. study but not in the Wang et al. study. Moreover, in the Abara et al. study, the 4CMenB vaccine did not provide protection against gonorrhea and chlamydia co-infection, but the Want et al. study showed comparable effectiveness among the population infected with gonorrhea only and the population co-infected with gonorrhea and chlamydia.

Although serogroup B meningococcal vaccines showed moderate effectiveness against gonorrhea infection, how effectiveness vary by co-infection and vaccination status (fully vs partially vaccinated) is not fully understood. Individuals co-infected with other STIs may differ from individuals with gonorrhea infection only regarding the probability of acquisition and transmission of the disease, in addition to the
potential severity of disease development. However, there has been no clinical trial on gonorrhea vaccine efficacy that particularly focus on population co-infected with other STIs, such chlamydia or HIV. Due to the high prevalence of co-infection in the high-risk population [19], understanding how serogroup B meningococcal vaccines induce immune response in people with co-infection is crucial to the development of feasible vaccination program for gonorrhea.

*Theoretical impact is sensitive to parameters*

When assessing the theoretical impact of gonorrhea vaccines using transmission-dynamic modeling, uncertainty in input parameters has caused substantial variation in the result that is unrelated to vaccine efficacy, duration of protection, and vaccine uptake [33]. Uncertainty exists in key parameters on the natural history of gonorrhea, including the rate of natural clearance of disease, the proportion of asymptomatic infections, and probability of transmission per contact, and also exists in parameters describing sexual and healthcare-seeking behaviors at the population level, including the number of contacts, rate of switching sexual behavior patterns, screening rate, and symptomatic treatment rate. In many modeling studies, key parameters were collected from published research, while unknown parameters were calibrated by mathematical models using national surveillance data. If surveillance data is not stratified by anatomical site, the model would assume parameters to be equal across anatomical sites, such as in the model developed by Whittles et al. on MSM in England [32]. However, in reality, oropharyngeal gonorrhea infection is often asymptomatic in male [10], and vaccines effective against oropharyngeal infection have a substantial impact on gonorrhea transmission in the MSM population [34]. So, following the positive result from retrospective observational studies and modeling studies, clinical research was carried out to collect data on immunogenicity and vaccine efficacy in preventing gonorrhea infection, both overall and by anatomical site, including a phase II study on
urethra infection in men and another phase II study on urogenital and anorectal infection in men and women.

_Preferred product characteristics of gonorrhea vaccines_

Modeling studies showed a consistent result that vaccines with moderate efficacy and duration of protection that is comparable to the 4CMenB vaccine could have a substantial impact on the prevalence of gonorrhea in the population. Both vaccine efficacy and duration of protection can affect the estimated impact. Craig and colleagues proposed that the theoretical impact of a gonorrhea vaccine is more sensitive to the duration of protection rather than vaccine efficacy [31], while research by Carey and colleagues suggested that vaccine impact is similarly affected by vaccine efficacy and duration of protection [33]. When focusing on the MSM population, a high-risk subgroup in which the prevalence of gonorrhea is higher, Whittles and colleagues indicated that vaccine efficacy adds more to the vaccine value than the duration of protection [36]. However, their model assumed a 2-dose primary vaccination and re-vaccination after waning immunity, which suggests that the use of boosters can compensate vaccine’s short duration of protection.

Retrospective observational studies suggested that the MeNZB vaccine was effective in both preventing gonorrhea infection and reducing disease severity upon infection, but there has not been any research that reveals the exact mechanism of this immunological cross-protection. There have been discussions about the potential effect of a gonorrhea vaccine that works by suppressing symptoms but not preventing transmission, based on the assumption that treatment-seeking behavior is primarily symptom-driven and asymptomatic infection could lead to longer periods of being infectious. Results from modeling studies are inconsistent. The anatomical site-specific model built by Hui et al. proposed that such vaccine could impose negative impact and lead to an increase in gonorrhea prevalence in the
MSM population [34], by incorporating the disparities in screening and treatment rates across infections at different anatomical sites (urethra, anorectum, and oropharynx) from the surveillance data. However, the study by Craig et al. on the heterosexual model suggested the prevalence of disease will not increase if such vaccine is distributed [31]. One possible explanation for such inconsistency is the different study population they focused on and the percentage of asymptomatic infection in each population. Nonetheless, further studies need to be conducted on the natural history of gonorrhea and specifically how infectiousness is affected by the development of symptoms.

**Targeting population and vaccination strategy**

In order for the gonorrhea vaccine to have a substantial impact on disease prevalence, the vaccine uptake needs to be considerably high when considering cohort vaccination. For example, to reduce the prevalence of gonorrhea by 10% in the U.S. with a vaccine that has comparably low efficacy and short duration of protection, the vaccine uptake has to be above 50% [33]. Other modeling research suggested similarly high percentage uptake if not higher [35]. However, reaching such high coverage is challenging for a vaccine that is not required by immunization guidelines in most countries. Craig and colleagues argued that targeting the core group in the population, could be more effective: vaccinating 75% of the high-risk core group could have a similar effect as vaccinating 50% of the whole cohort [31]. Also, because the core group only consist of a small portion of the total population, less vaccines need to be distributed, making targeting the core group a potentially cost-effective strategy.

Models by Whittles and colleagues further looked into the best strategy to target the MSM population. If the goal is to reduce disease prevalence in MSM, vaccinating individuals at sexual health clinics visit is more effective than vaccinating all adolescents in schools or vaccinating individuals upon diagnosis of gonorrhea. On the other hand, when the vaccine efficacy and duration of time are moderate, offering
vaccination to individuals who are currently infected with gonorrhea and who have riskier sexual behaviors (having more than 5 sexual partners per year) is more cost-effective. However, core groups such as sex workers may be difficult to identify and reach out to in a population. Targeting core groups can be challenging in real-life implementation and could further reinforce stigmatization associated with STIs. Also, inquiring about an individual's sexual behaviors can be challenging in practice to determine an individual's risk level.

The optimal immunization strategy may vary by disease prevalence. The study by Hui et al. suggested that targeting adolescents before their sexual debut could be effective in countries where gonorrhea prevalence is high [34]. However, if the vaccine has a low duration of protection, it may have a smaller impact if administered to adolescents before sexual debut [33], which stressed the importance of identifying the appropriate vaccination target and having catch-up programs and booster vaccination.

**Future research direction**

To develop gonorrhea vaccines with better efficacy and duration of protection, it is essential to better understand the natural history of gonorrhea [16]. To make the best use of limited public health resources, it is important to identify the appropriate target population for immunization programs. Better epidemiological data on people who have high risks of gonorrhea, including female sex workers, MSM, and heterosexual adolescents and young adults, is needed [43]. For a vaccine candidate, understanding the vaccine mechanism and its effectiveness by subgroups in the population is also important for making public health decisions.

Moreover, more efforts should be used to collect epidemiological data from the resource-limited population and from LMICs. Case-control studies included in this scoping review were conducted using
immunization data in high-income countries, but they fail to identify individuals who do not present for asymptomatic screenings and who do not have access to sexual health care [18]. This population tends to have lower socioeconomic status and thus are at higher risk of STIs. Similarly, modeling studies used surveillance data in developed countries where the gonorrhea prevalence is lower. If models change their assumptions to include higher prevalence, as in LMICs, the theoretical impact and cost-effectiveness of gonorrhea vaccines and the appropriate immunization strategies proposed from modeling studies may be substantially different from suggestions made for developed countries.

Further assessment of the valuation and cost-effectiveness of gonorrhea vaccines is needed to inform better public health decision-making. In the health-economic model developed by Whittles and colleagues, the value of gonorrhea vaccines is defined as the sum of testing, treatment, and the discounted willingness-to-pay per QALY. However, the proposed willingness-to-pay per QALY for gonorrhea infection varies significantly across different health-economics studies, ranging from £20,000 to $75,000[30, 36], suggesting further validation needed for this measurement. Moreover, costs of diagnosis and treatment may have large variability across countries, and the difference in calculated monetary value may influence real-life immunization practices. Also, further research should be done to quantify the long-term impact of vaccines that address antimicrobial resistance-related mortality and morbidity [44] and to measure the economic value associated with this preventive intervention.
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