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Planning for a Gonococcal Vaccine: A Narrative Review of Vaccine Development and Public Health Implications

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Abstract

Declining gonococcal susceptibility to ceftriaxone and azithromycin has raised the possibility of untreatable gonorrhea in the future and reignited interest in gonococcal vaccine development. Despite decades of research, previous gonococcal vaccine candidates have been ineffective. A growing body of data suggests that meningococcal group B outer-membrane vaccines may be cross-protective against *Neisseria gonorrhoeae*. Clinical trials of a licensed vaccine against *Neisseria meningitidis* serogroup B containing an outer-membrane vaccine component are underway to determine its efficacy against *N. gonorrhoeae*. Other experimental gonococcal vaccine candidates are in the preclinical phases. Population impact of future gonococcal vaccines with different levels of efficacy and duration of protection in various populations is being evaluated using modeling studies. Despite recent progress, gaps in gonococcal vaccine research remain. Research is needed to evaluate vaccine efficacy in preventing gonococcal infections acquired via various anatomic routes and among patients coinfected with other sexually transmitted infections. Studies that model the impact of a future vaccine on high-burden populations such as men who have sex with men and estimate both vaccine cost-effectiveness and the incremental cost-effectiveness ratio of vaccination to antimicrobial resistance and treatment costs are warranted. This narrative review examines the current state of gonococcal vaccine research, the possible impact of a gonococcal vaccine on gonorrhea rates based on modeling studies, gaps in the gonococcal vaccine literature, and public health implications of a future gonococcal vaccine on reducing the gonorrhea burden in the United States.

Gonorrhea is the second most commonly reported nationally notifiable disease in the United States and of major public health concern.[1] It is a sexually transmitted bacterial infection caused by the gram-negative diplococcus *Neisseria gonorrhoeae*. After reaching a historic nadir in 2009, gonorrhea case rates steadily increased by 82.6%, from 98.1 cases per

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100,000 population in 2009 to 179.1 cases per 100,000 population (a total of 583,405 reported cases) in 2018.[1] Effective antimicrobial treatment is essential for gonorrhea prevention and control.[2] The Centers for Disease Control and Prevention (CDC) currently recommends 250 mg of intramuscular ceftriaxone and 1 g of oral azithromycin for the treatment of uncomplicated gonorrhea.[3] However, declining ceftriaxone and azithromycin susceptibility has heightened concern about the possibility of untreatable gonorrhea.[4] New approaches to prevent gonorrhea and counter the threat of antibiotic-resistant *N. gonorrhoeae* are needed.

Development of a gonococcal vaccine might be such an approach.[2] There is currently no licensed gonococcal vaccine; efforts to develop one have been unsuccessful. However, recent data suggest that serogroup B meningococcal vaccines containing *Neisseria meningitidis*–derived outer-membrane vesicles (MenB OMV) may be modestly protective against gonorrhea.[5]

These findings have reinvigorated gonococcal vaccine research efforts and provided experimental evidence to inform vaccine development. We review past challenges and new opportunities for developing gonococcal vaccines and explore the potential impact of a gonococcal vaccine in reducing disease burden. We also discuss potential populations for such a vaccine, potential barriers to vaccine uptake and strategies to overcome these barriers, and propose methods to monitor the population-level impact of vaccination.

GONOCOCCAL FACTORS, IMMUNE EVASION, AND CHALLENGES TO VACCINE DEVELOPMENT

N. gonorrhoeae has a remarkable ability to evade the immune system through antigenic and phase variation, molecular mimicry, and immune suppression.[6–8] Antigenic and phase variation of surface-exposed outer-member components type IV pili, Opa proteins, and lipooligosaccharides enable the gonococcus to avoid immune cell recognition.[6–8] *N. gonorrhoeae* can disguise itself as a host cell (molecular mimicry) to avoid immune detection; the carbohydrate component of neisserial lipooligosaccharides mimics glycosphingolipid component.[9,10] Avoidance of immune detection allows for repeated infections in previously infected people. *N. gonorrhoeae* suppresses complement immune responses through binding to complement-regulating proteins human factor H binding protein (FHbp) and complement factor 4b-binding protein (C4bp).[6–8] Binding to these proteins downregulates the complement system cascade, increases neisserial serum resistance, and inhibits serum bactericidal killing.[8,11] Neisserial porins can induce programmed cell death in human antigen-presenting cells, inhibit dendritic cell–induced T-cell proliferation, and suppress the T_H1- and T_H2-driven adaptive immune responses.[6,7,11] Gonococcal immune evasion poses substantial challenges to vaccine development.

GONOCOCCAL VACCINE CANDIDATES AND CLINICAL TRIALS

Use of MenB OMV Vaccines for Protection Against *N. gonorrhoeae*

MenB OMV vaccines have been used since the 1980s to control regional meningococcal disease outbreaks of *N. meningitidis* serogroup B (NmB) caused by predominant clonal

strains. Mass vaccination campaigns have been implemented in several countries in response to local NmB outbreaks[12–15] and were followed by declines in gonorrhea rates. For example, a decrease in gonococcal rates was observed in Cuba and Norway after OMV MenB mass vaccination campaigns in both countries,[16,17] suggesting a cross-protection of MenB OMV vaccine against *N. gonorrhoeae*.

More recently, gonorrhea incidence declined in New Zealand after a mass vaccination campaign during which more than 1 million persons aged 6 months to 20 years were vaccinated with MeNZB, a MenB OMV vaccine derived from the local outbreak strain.[5] Importantly, a large case-control study conducted among persons aged 15 to 30 years attending sexual health clinics in New Zealand to test the cross-protection hypothesis demonstrated that people vaccinated with MeNZB were less likely to have gonorrhea (i.e., to be cases) than to have chlamydia (i.e., to be controls); vaccine effectiveness was estimated to be 31%.[5]

Because MenB OMV vaccines are directed against porin A, a protein with high antigenic variability, vaccines derived from local outbreak strains have limited cross-reactivity against other circulating genetically diverse NmB strains. However, 2 recombinant MenB vaccines with broad protection are currently licensed and available worldwide for protection against NmB disease. One of these vaccines, MenB-4C (Bexsero; GSK), is a 4-component vaccine that includes an OMV derived from the New Zealand strain from which the MeNZB vaccine was developed plus 3 recombinant antigenic proteins (neisserial adhesin A [NadA], neisserial heparin-binding antigen [NHBA], and FHbp).[18] Although no epidemiologic study has evaluated the effectiveness of MenB-4C against gonorrhea, mass vaccination during an NmB outbreak in Quebec was temporally correlated with declines in gonorrhea.[19]

Experimental findings support the possibility of MenB-4C vaccine cross-protection against *N. gonorrhoeae*.[20,21] Genomic studies have shown high genetic similarity and cross-reactivity between MenB-4C antigens, including most OMV proteins and NHBA, and *N. gonorrhoeae*.[20–22] A comparison of a large number of gonococcal isolates collected in the United States to NmB reference strains identified more than 1000 proteins common to both, some of which were predicted to be recognized by vaccine-induced antibodies using in silico methods.[22] However, waning immunity to NmB strains after receipt of the MenB-4C primary series has been demonstrated,[23] and the duration of any antigonococcal cross-protection from MenB-4C is unknown. Although MenB-4C vaccination does not protect against NmB colonization in humans, MenB-4C immunization reduced vaginal gonococcal colonization load and accelerated bacterial clearance in mice.[21]

Other experimental vaccine candidates that contain gonococcal OMV[24,25] or recombinant surface-expressed antigenic proteins[26,27] successfully accelerated the clearance of lower genital tract infection in mice or elicited antigonococcal antibodies. Research to identify conserved antigens essential for gonococcal infection or physiology may support vaccine candidate development.[28,29]

In the United States, the pathway to licensure for new vaccines includes clinical trials to demonstrate vaccine safety and efficacy against disease end points. Investigators designing

clinical trials for a gonococcal vaccine will need to consider enrolling participants that represent populations that would most benefit from the vaccine. Ideal populations are those with elevated gonorrhea rates, such as sexually active gay, bisexual, and other men who have sex with men (hereafter referred to as MSM); young adults residing in geographic regions with high gonorrhea rates; and sexually active adolescents.[1] Engaging these populations will allow for the investigation of efficacy and safety among populations that will most benefit and increase statistical power. Admittedly, enrolling populations such as sexually active adolescents may prove very challenging because parental consent for the trial would require disclosure of adolescent sexual activity. The National Institute of Allergy and Infectious Diseases is currently funding a trial that is investigating the protective efficacy of MenB-4C against *N. gonorrhoeae* among men and women aged 18 to 50 years.[30]

MODELING THE POTENTIAL IMPACT OF VACCINATION ON GONORRHEA

In addition to vaccine efficacy for individuals, an important consideration is the population-level impact. Several mathematical modeling studies have estimated the potential impact on gonorrhea incidence, prevalence, and gonorrhea-attributable medical costs.[31s–33s] Heijne et al. used a deterministic compartmental model to estimate the impact of vaccination on gonorrhea prevalence among sexually active Dutch MSM. Assuming a 30% vaccine efficacy (similar to the efficacy in the New Zealand study) and a 2-year duration of protection,[5] the model predicted that 20% and 80% vaccination coverage would reduce gonorrhea prevalence among MSM by 70% and 97%, respectively, for 4 decades.[33s] Whittles et al.[34s] used a stochastic transmission dynamic model to estimate the impact of a vaccine on gonococcal incidence among MSM in England during the period 2018–2030, assuming vaccination started in 2020 Assuming a 40% vaccine efficacy and a 4-year duration of protection or a 50% efficacy and a 2-year duration, vaccinating all MSM attending sexual health clinics would reduce annual gonococcal incidence by 90% among MSM within 10 years.

Craig et al.[31s] used an individual-based epidemiologic simulation model to estimate the impact of vaccination on gonorrhea prevalence in a sexually active heterosexual population. The model accounted for ongoing regular and casual sexual partnerships and assumed that vaccination occurred at 13 years of age and before sexual debut.[31s] The model predicted that a vaccine of 40% efficacy, with a 100% vaccination coverage, and a 20-year duration of protection would decrease gonorrhea prevalence by 75% after 20 years.[31s] A vaccine with a 5-year duration of protection but a 100% efficacy and coverage would decrease gonorrhea prevalence by 50% after 20 years.[31s]

Régnier et al.[32s] modeled the potential impact of MenB-4C vaccination on gonorrhea case counts per birth cohort and gonorrhea-attributable direct and indirect costs, assuming that vaccination occurred at 15 years of age (before sexual debut). The model predicted that vaccination would prevent 83,167 gonorrhea cases per vaccinated birth cohort and reduce annual gonorrhea-attributable direct costs by $28 million and indirect costs by $40 million, assuming a 20% vaccine efficacy, a 70.5% coverage, and a 10-year duration of protection.[32s] The estimated annual direct cost of gonorrhea in the United States is approximately $162 million ($81.1–$243.2 million) in 2010 dollars.[35s] Although several models likely

overestimated the assumed duration of MenB-4C protection against gonorrhea (given that MenB antibody levels wane 2 years after vaccination with a 2-dose primary series)[36s] and the impact estimates vary, the models suggest that a durable gonococcal vaccine of even modest efficacy and robust vaccine coverage can have a substantial public health impact on gonorrhea prevalence and gonorrhea-attributable costs.

Additional modeling studies that evaluate gonococcal vaccine impact with varying durations of protection, cost-effectiveness of gonococcal vaccination, and the incremental cost-effectiveness ratio of gonococcal vaccination compared with treatment costs and antimicrobial resistance would inform future gonococcal vaccine policy and program recommendations.

RECOMMENDATIONS FOR FUTURE LICENSED GONOCOCCAL VACCINES

The Advisory Committee on Immunization Practices (ACIP) is a federal advisory committee comprising medical and public health experts who develop recommendations on vaccine use in the civilian US population.[37s] The ACIP uses an evidence-based approach that includes the evaluation of vaccine characteristics as well as the distribution of burden of disease in different populations to inform recommendations.[38s] Developing recommendations that maximize the uptake of effective gonococcal vaccines is uniquely challenging given the age and other characteristics of persons at highest risk for acquiring sexually transmitted infections (STIs). Furthermore, novaccine has ever been recommended to prevent 2 different diseases.

Universal Vaccination of Adolescents

Adolescents would likely benefit from a gonococcal vaccine, especially if given before sexual debut. Like the universal human papillomavirus (HPV) vaccine recommendation, a universal gonorrhea vaccination approach in this group may support increased vaccine coverage and acceptability, optimize its protective effect, and improve cost-effectiveness.[39s] Rates of reported gonorrhea cases among adolescents 15 to 19 years of age in the United States are consistently among the highest of all age groups.[1] Rates among 15- to 19-year-olds increased by 33%, from 2014 (325.0 cases per 100,000 population) to 2017 (432.4 cases per 100,000 population).[40s,41s] The mean age of sexual debut in the United States is 17 years, and the probability of initiating sexual activity successively increases with each year of adolescence.[42s] Among high school students surveyed in 2017, 40% had ever had sex and 30% had sex in the previous 3 months; of those who had sex in the past 3 months, 46% did not use a condom at last sexual intercourse.[43s]

Similar to the rationale behind preadolescent and adolescent HPV vaccination and because the rates of reported gonorrhea cases are greatest among young adults (20–29 years),[1] an effective vaccine that is administered during adolescence with a duration of protection (continuous or that requires booster doses) that spans late adolescence and young adulthood can protect against gonorrhea as adolescents become sexually active young adults. However, uptake may be a challenge. HPV vaccination coverage among adolescents aged 13 to 17 years is suboptimal at 72%.[44s] A universal HPV vaccine recommendation is probably easier to justify than a universal gonococcal vaccine recommendation because HPV is ubiquitous,

whereas gonorrhea is more prevalent within certain populations. Furthermore, as described hereinafter, substantial barriers to the vaccination of adolescents (as observed with HPV vaccination) are anticipated.

Targeted Vaccination of Populations

Sexually active MSM in the United States have disproportionately high gonorrhea rates.[1] During the period 2010–2018, the rate of reported gonorrhea cases among MSM increased by 375.5%, from 1368.6 cases per 100,000 MSM in 2010 to 6508.0 cases per 100,000 MSM in 2018.[1] In comparison, case rates among women and men who have sex only with women increased far less sharply (95.2% and 69.3%, respectively) than among MSM, and rates were substantially lower among these populations than rates among MSM.[1] The high gonorrhea rates among MSM and disproportionately high prevalence of gonococcal antimicrobial resistance among MSM[45]s support the consideration of MSM as a priority population for future gonococcal vaccination.

Sexually active young adults (20–29 years) should also be considered a priority population. Young adults have consistently had the highest gonorrhea rates in the United States over the past decade, eclipsing rates of 15- to 19-year-olds.,[146s] Young adults are more likely to be sexually active and report casual sex or condomless sex with multiple partners compared with persons in other age groups.[47s,48s]

Other populations that may be prioritized for gonococcal vaccination include persons who report a previous STI or behaviors such as multiple sexual partners, exchange sex, anonymous or casual sex, and condomless sex with multiple partners.[49s] Prioritizing the vaccination of sexually active populations would require a vaccine that demonstrates efficacy when administered after sexual debut.

MENB-4C VACCINATION

Several challenges will need to be overcome if vaccination with MenB-4C is Food and Drug Administration approved for the prevention of gonorrhea. The ACIP currently recommends vaccinating persons aged 16 to 23 years with a 2-dose series of either of 2 licensed vaccines (MenB-4C or MenB-FHbp) for protection against NmB disease.[50s] Partly because of the low burden of NmB disease in the United States, the ACIP recommends MenB vaccination based on shared clinical decision making rather than routine vaccination of all adolescents. Recommendations from the ACIP for a vaccine against epidemiologically different diseases will need to grapple with the potentially complex interplay and possible conflicts of vaccine recommendations for the different indications. If MenB-4C becomes licensed for gonorrhea, considerations may need to be given for preferential recommendations for MenB-4C over MenB-FHbp because no cross-protection against *N. gonorrhoeae* is expected from antigens contained in the MenB-FHbp vaccine. The recommended age for vaccination and need for potential booster doses may need to be reconsidered, especially if the vaccine demonstrates waning immunity against gonorrhea.

BARRIERS TO VACCINE UPTAKE

Barriers to the uptake of a routinely recommended adolescent gonococcal vaccine are expected.[51s] Parental attitudes that do not acknowledge that adolescents are sexually active underestimate adolescents' risk of gonococcal acquisition or promote the false perception that STI vaccines condone or disinhibit sexual behavior among adolescents can hamper vaccine uptake.[52s,53s] Moral, cultural, and religious factors that stigmatize adolescent sexual behavior and STIs may drive resistance to vaccinating adolescents in the United States.[52s,53s] Minor consent laws in the United States, which vary by states, may limit adolescents' ability to provide consent for vaccination without the permission of a parent or guardian and may be another barrier to adolescent vaccine uptake. Vaccination coverage for HPV, another STI, lags behind that of other vaccines recommended at the same age[44s]; messaging efforts for HPV vaccination have accordingly shifted to cancer prevention (a messaging opportunity not available for promotion of a gonococcal vaccine). A requirement for a multidose priming series or a periodic booster dose poses an additional challenge to vaccine uptake. For example, routine vaccination with MenACWY is recommended at age 11 to 12 years with a booster dose at age 16 tears for the prevention of meningococcal disease caused by vaccine-related serogroups. In 2019, although the coverage of one dose of MenACWY was 89%, only 54% of adolescents received a booster dose.[44s]

Other potential barriers to vaccine uptake include low self-perception of gonococcal risk and limited awareness about vaccine availability, benefits, and safety. Vaccine cost may pose challenges to vaccination of adolescents and adults who are uninsured or underinsured, especially if the ACIP does not recommend the vaccine. Lack of provider awareness about a vaccine and the appropriateness of a vaccine for individual patients are also potential barriers to vaccine uptake.[54s] Providers who do not routinely conduct sexual histories are unlikely to identify MSM or sexually active young adults with other sexual orientations for whom gonococcal vaccines may be recommended.

STRATEGIES TO PROMOTE VACCINE UPTAKE

Lessons learned from the HPV vaccine may prove useful to support the uptake of a gonococcal vaccine. A social marketing campaign was associated with increased HPV vaccination[55s]; a marketing campaign that informs (in a destigmatizing manner) the public and health care providers about gonorrhea prevention, the rationale for adolescent vaccination, and the efficacy and safety of the vaccine may address vaccine misconceptions, increase awareness, and promote uptake.[55s] However, social marketing campaigns and messaging for HPV vaccination have leaned heavily on cancer prevention, an approach that does not easily translate to the promotion of a gonococcal vaccine.

Immunization recommendations from the ACIP, the CDC, or professional associations influence provider recommendations[56s] and may increase vaccination rates.[57s] A routine vaccine recommendation statement from the ACIP may increase the likelihood that health care providers would recommend the vaccine to target populations.[56s] The CDC's STD Quality Clinical Services report recommends routine sexual history and risk assessment during clinical encounters.[58s] Systematic implementation of routine sexual history taking

may identify persons at elevated risk for gonorrhea, identify vaccination opportunities, and increase vaccine uptake.

Vaccination recommendations for adolescents that support coadministration of a gonococcal vaccine with currently recommended adolescent vaccines (including Tdap, MenACWY, and HPV) may facilitate uptake among adolescents.[59s] However, HPV and 2-dose MenACWY vaccination coverage remains suboptimal. Ensuring gonococcal vaccine availability at pharmacies and sexually transmitted disease (STD) and HIV preexposure prophylaxis clinics may increase uptake.[53s,54s] Electronic medical record reminders may support the identification of patients for whom the vaccine is recommended and vaccine uptake.[60s]

MONITORING AND EVALUATING UPTAKE AND PUBLIC HEALTH IMPACT OF A FUTURE GONOCOCCAL VACCINE

Vaccination Coverage

Monitoring vaccination uptake will support the identification of populations with suboptimal coverage and inform policies to increase vaccine access and availability. Vaccination coverage can be evaluated and monitored by determining the prevalence of full (the recommended regimen) and partial (less than the recommended regimen) vaccination receipt. Nationally representative surveys such as the National Health and Nutrition Examination Survey, National Health Interview Survey, Behavioral Risk Factor Surveillance System, and the National Survey of Family Growth include data on self-reported receipt (full or partial) of some vaccines (e.g., HPV, hepatitis A vaccine, and influenza vaccine). Questions about gonococcal vaccination potentially could be added to these surveys to evaluate and monitor coverage. Survey platforms that focus on sexual health and/or populations of interest (such as adolescents or MSM) might support the collection of data about self-reported gonococcal vaccination. Provider-verified data on vaccination among adolescents are collected by the National Immunization Survey—Teen, an annual nationally representative survey of adolescents aged 13 to 17 years.[61s] Enhanced surveillance, administrative claims data, electronic health records, and state-based vaccine registries may also serve as data sources to evaluate vaccination coverage nationally, by state, or in various populations.

Despite the anticipated utility of these data sources, there are well-known limitations to self-reported vaccination data and administrative claims databases. Strengthening systems to accurately capture receipt of gonococcal vaccines will be important. Linking state vaccine registries to health care providers' offices, health centers, STD and preexposure prophylaxis clinics, local pharmacies, and other locations where vaccines are administered and ensuring routine data reporting may improve data quality.

Public Health Impact of a Future Gonococcal Vaccine

An effective vaccine is expected to reduce the number of gonococcal infections in the population over time, especially as vaccination coverage increases. The population-level impact of a gonococcal vaccine may be evaluated by comparing gonorrhea case rates in the specific populations in the prevaccination and postvaccination periods. A decline in rates

from the prevaccination period to the postvaccination period might suggest a population-level impact. Because risk factors for gonorrhea and chlamydia are similar and rates of both can be influenced by changes in screening and testing practices, comparison of trends of reported gonorrhea cases—from prevaccination to the postvaccination periods in the target populations—with trends of reported chlamydia case rates may be informative. For example, an impact of vaccination may be suggested by stable chlamydia rates and a corresponding slowing of the trajectory of increased rates, a plateau, or a decline in gonorrhea rates.

Surveillance case report data provide gonorrhea rates at the national, state, and county levels, but data on the gender of sex partner are incomplete. The CDC-funded STD Surveillance Network, an enhanced sentinel surveillance platform, has proven useful for estimating gonorrhea rates among MSM attending STD clinics[62s] and may allow for the monitoring of gonorrhea rates among MSM in participating jurisdictions.

Mathematical models predict that population-level declines in gonorrhea may be observed decades after vaccine introduction. Short-term vaccine impact might be challenging to discern. One possible approach is monitoring for declines in the number of cases that represent repeated infections among individuals. Creative approaches to measure short-term impacts are needed.

CONCLUSIONS

The growing gonorrhea burden and emerging threat of antimicrobial-resistant *N. gonorrhoeae* have lent urgency to the search for a gonococcal vaccine. Recent findings that demonstrate the potential cross-protection of MenB OMV vaccines against *N. gonorrhoeae* have reinvigorated efforts to develop a gonococcal vaccine. Increased research funding[28,29] and advances in gonococcal vaccinology[7] have improved the prospects for an effective gonococcal vaccine. Although a commercially available vaccine is years from realization, the public health community can plan how to best implement vaccine administration, monitor vaccine uptake and impact, and address potential barriers to uptake.

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