Past And Current Vaccine Development Effort of Gonorrhea

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Abstract. Neisseria gonorrhea causes gonorrhoea, which is one of the sexually transmitted infections (STI) diseases that can affect the health of women, men, and neonates. Reflecting on its history of treatment, the development and distribution of a vaccine hold significant potential for mitigating the impact of this disease, especially in vulnerable populations. However, developing a novel vaccine for Neisseria gonorrhoeae has posed considerable challenges. This is primarily due to the Gonorrhea's antigenic variation, rendering it difficult for the human immune system to identify. Neisseria Gonorrhea is currently exhibiting significant antimicrobial resistance, raising concerns about the potential for it to evolve into a superbug in the future. This escalating antimicrobial resistance has led to a diminishing effectiveness of antibiotics in treating Neisseria gonorrhoeae infections. Consequently, there is an increased risk of reinfection, potentially necessitating higher antibiotic doses during treatment. This, in turn, contributes to elevated treatment costs. Thus, the development of a new vaccine against Neisseria gonorrhoeae becomes imperative. This urgency is particularly pronounced for safeguarding the health of women and newborns. In this review, I explored the progress and efficacy of both historical and contemporary vaccines designed to address Neisseria gonorrhoeae infections.

Keywords: Gonorrhea; Neisseria gonorrhea; Vaccine.

1. Introduction

Neisseria gonorrhoeae (N. gonorrhoeae) is currently the second most prevalent sexually transmitted disease worldwide [1]. The causative agent of this infection is the gram-negative diplococcus bacterium known as Neisseria gonorrhoeae. The disease is initiated when Neisseria gonorrhoeae adheres to the surface of epithelial cells using its hair-like appendages called pili, which cover the bacterial surface and promote attachment to epithelial cells, facilitating cellular invasion [1]. This bacterium is primarily transmitted through sexual contact, including vaginal, anal, and oral sex, when one person with an active gonorrhea infection passes it to their partner. Moreover, untreated gonorrhea elevates the risk of acquiring HIV infection [2]. The World Health Organization previously estimated that in 2016, approximately 87 million new cases of infection were expected among individuals aged 15 to 49 years worldwide. This disease predominantly affects low- and middle-income countries (LMICs) and specific populations, including Black or African American, American Indian, and Alaska Native communities [2]. It can be classified as both a sexually transmitted disease (STD) and a sexually transmitted infection (STI), and it can infect the mucous membranes of the genitourinary tract, rectum, eyes, and throat. Neisseria gonorrhea only infects humans, and it usually happens between the ages of 15 and 24 in young people [1, 3]. The most common infection consequence in females is cervicitis, and so this will make females show symptoms of vaginal discharge and pelvic pain. If cervicitis hasn't been detected, it will cause pelvic inflammatory disease and show symptoms of pelvic pain and infertility [1]. Neisseria gonorrhea will also impact newborns if a pregnant female gets infected with gonorrhea, and then newborns may get conjunctivitis as they pass through the birth canal, and severe cases can lead to blindness [4]. For men, N. gonorrhea will cause epididymitis, and a severe case may lead to infertility as it does for women. Overall, if N. gonorrhea is left untreated, it can spread into human blood and cause disseminated gonococcal infection (DGI), which usually shows as arthritis, tenosynovitis, and dermatitis [5]. Due to its antimicrobial resistance, Neisseria gonorrhoeae (N. gonorrhea) has shown the potential for reinfection even after patients have undergone antibiotic treatment. As a precautionary measure, scientists recommend combining two or more antibiotics simultaneously to prevent the development of antibiotic resistance in N. gonorrhea and improve treatment effectiveness [6]. Notably, in a 2018

publication, it was reported that a man hailing from England had become the inaugural instance of exhibiting resistance to both ceftriaxone and azithromycin antibiotics [9]. Therefore, the emergence of such resistance in Neisseria gonorrhoeae (N. gonorrhea) should be a grave concern, as it would pose a significant threat if the bacterium were to develop resistance to all available antibiotics, potentially leading to a global public health crisis. However, Antimicrobial resistance is not the sole major concern. One article highlights that populations residing in low- and middle-income countries (LMICs), where sexual education is often lacking, face the highest risk of contracting Neisseria gonorrhoeae (N. gonorrhea) infections [8]. This underscores the importance of comprehensive sexual education and access to preventive measures in addressing the global burden of gonorrhea. So based on these facts, it is urgent to develop an efficiency vaccine to prevent the spread of Neisseria gonorrhoeae (N. gonorrhea). According to certain published articles, there is a vaccine known as serogroup B meningitidis outer membrane vesicle (OMV) that has demonstrated partial effectiveness in preventing Neisseria gonorrhoeae (N. gonorrhea) infection [10]. However, the results show that it can only reach 31% efficiency in preventing N. gonorrhea [11].

2. The infection of Neisseria gonorrhoeae

In the beginning of the infection, Neisseria gonorrhoeae adheres to the epithelium mucosal cells through its type IV pili, which is very important for the further colonization and cell adherence to the epithelium mucosal cell surface [12]. After the N. gonorrhoeae attach to the cell surface, it will go through 'transcytosis', which the N. gonorrhoeae is being endocytosed and then successfully invade into the cells. During the attachment (first step) of N. gonorrhoeae to the cell surface, the peptidoglycan, lipooligosaccharide, and its outer membrane vesicles will be released (second step). These released products will be detected by NOD-like receptors (NLR) and Toll-like receptors (TLR) on the epithelial cell surface, leading to the activation of these receptors (third step). Once activated, both NLR and TLR facilitate the transfer of the invading bacteria and activate the signaling molecules in macrophages and dendritic cells. Subsequently, macrophages will recognize the N. gonorrhoeae bacteria and initiate phagocytosis. Moreover, N. gonorrhoeae can survive from the macrophage phagocytosis. Consequently, the macrophages undergo pyroptosis (cell death), releasing cytokines and chemokines to attract other immune cells, including neutrophils (fifth step). The released cytokines IL-1β will recruit the chemokine CXCL8 to neutrophil. Following the receipt of the signal from CXCL8, neutrophils become the primary responders to macrophages and commence their migration from the bloodstream into the infected tissue area. Subsequently, neutrophils will initially capture the bacteria using their CD14 and CR4 receptors, allowing them to adhere to the N. gonorrhoeae bacteria. After this adhesion, neutrophils can initiate the process of phagocytosis. Ultimately, neutrophils will successfully remove N. gonorrhoeae bacteria from the epithelium and generate purulent exudate at the infection site. However, the N. gonorrhoeae still can survive even during neutrophil phagocytosis, prompting neutrophils to undergo NETosis. This process involves the extrusion of various products, including DNA, histones, and any surviving bacteria. The overview of Neisseria gonorrhoeae infection is shown in **Figure 1**.

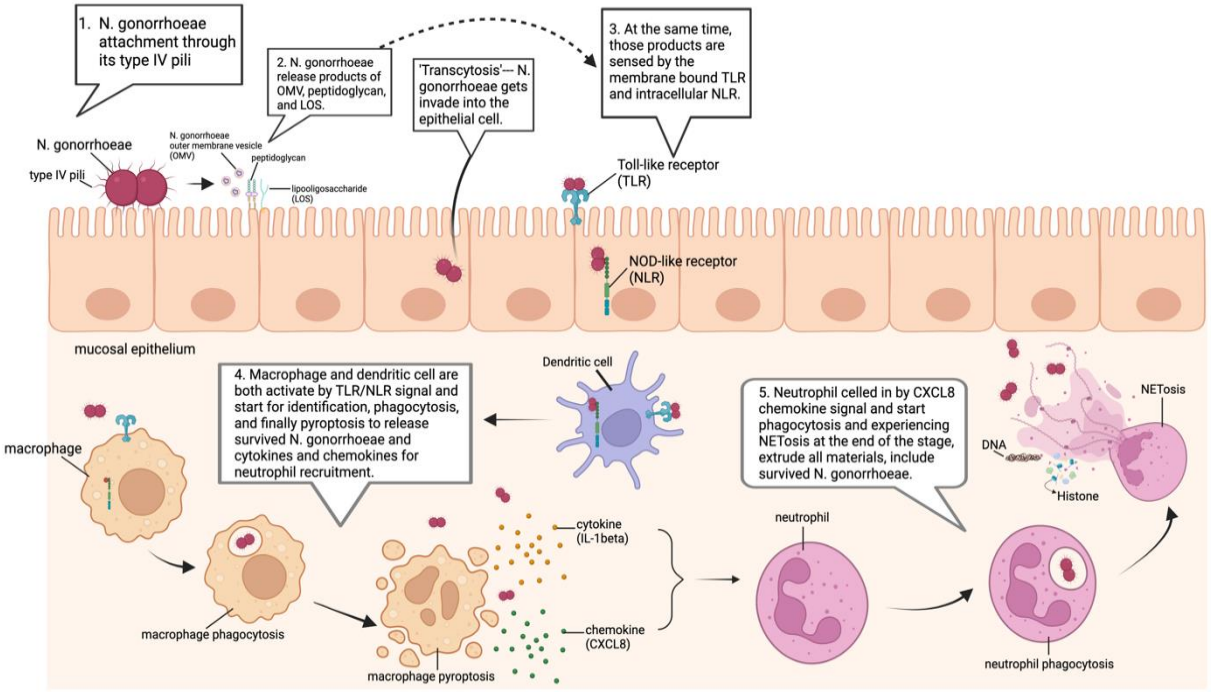


Figure 1. The overview of Neisseria gonorrhoeae infection.

3. Past vaccine development effort

The antigenic variation exhibited by N. gonorrhoeae poses a significant challenge for the human immune system in terms of identification. Reflecting on the historical challenges in developing a vaccine for N. gonorrhoeae, it's noteworthy that only two candidate vaccines have progressed to human trials up to this point [13]. One of these vaccine candidates, published in 1995, was developed to target pilin, a component of N. gonorrhoeae's type IV pilus. Pilin was initially identified as a pathogenic factor in 1972 due to its role in adhering to the surface of the bacterium [13,14]. However, utilizing pili as the basis for the vaccine poses a challenge due to its antigenic variation. When scientists administered this type of vaccine, which contained purified pili, to military patients, the outcome was that the vaccine could not effectively prevent N. gonorrhoea infection [14]. In another study, 3,123 male and 127 female volunteers were tested. Both the control group and the test group received a dosage of 100 μg on days 1 and 2 [15]. The results revealed that none of the women participating in the study became infected with N. gonorrhoea during the testing period. However, among the male volunteers, there were 108 cases of infection in the vaccine group and 102 cases in the control group after the first vaccine injection. [14]. Scientists also found out that the gonococcal outer membrane and lipopolysaccharides (LPS) are more readily recognized by the human immune system compared to pili [14]. Another candidate vaccine, published in 1974, employed heat-killed, partially lysed whole gonococcal cells to induce the production of tissue culture neutralization (TCN) antibodies [13,16]. However, the clinical outcome yielded unsatisfactory results since the vaccine's efficacy was of insufficient duration, ultimately leading to its failure in eliciting adaptive immune responses in humans. The experimental findings indicate that a total of 62 individuals volunteered to partake in the vaccine trial. Among these participants, 10 individuals belonged to the vaccine group, while 7 individuals were assigned to the placebo group. Notably, both groups experienced instances of N. gonorrhea infection one year following the administration of the injection [16,17]. Porin B

(PorB) has been identified as an additional potential antigen for the production of vaccines [13]. According to the study conducted by Zhu et al., PorB, a membrane protein derived from plasmids, has been identified as a potential component of DNA-based vaccines. These vaccines have demonstrated the ability to elicit T helper cell (Th1 and Th2) responses. [13]. Nevertheless, clinical trials have not yet been conducted [13,18]. In summary, due to the challenges posed by antibiotic resistance and the difficulties encountered in creating a specific vaccine, scientists are persistently exploring alternative vaccine components and strategies in their ongoing efforts to combat N. gonorrhoeae.

4. Efficacy and effectiveness of Current Vaccine

Due to the lack of success in prior explorations and tests, scientists are persistently endeavoring to discover and develop a novel candidate vaccination with the capacity to effectively prevent N. gonorrhea. a vaccination known as meningococcal B (MenB) has emerged as a potential tool in addressing the issue of N. gonorrhea to some extent [17]. This particular vaccine is designed for the prevention of meningitis, a condition caused by gram-negative bacteria belonging to the Neisseria family. The meningitis vaccination is comprised of two distinct types: MenB, also known as serogroup B meningococcal vaccine, which consists of the outer membrane vesicle and four recombinant proteins as its constituents [19]. Another vaccination that might be mentioned is the MenACWY vaccine, also known as the meningococcal conjugate vaccine. This particular vaccine is formulated using a capsular polysaccharide vaccine and is designed to provide protection against serogroups A, C, W, and Y. Notably, it does not contain any adjuvant [19]. The MenB vaccine is derived from the surface protein of bacteria. While these surface proteins are not exclusive to meningitis-causing bacteria, they can also be found on the surfaces of other Neisseria bacteria, including N. gonorrhea [17]. The MenB vaccine has the potential to offer partial protection against N. gonorrhea due to the close relationship between N. meningitides and N. gonorrhoea, both belonging to the gram-negative Neisseria family. These two bacteria share a high degree of similarity at the amino acid level, with a 95% identity. Consequently, the structural similarities between meningitis and gonococcal infections are noteworthy. [20]. Furthermore, it's worth noting that a vaccine called MeNZB was specifically developed and employed during the New Zealand meningococcal epidemic from 2004 to 2011. MeNZB is distinct from the MenB vaccine [23]. However, it was not intended for long-term use and was withdrawn once the disease rate declined in New Zealand. As a result, MeNZB is currently unavailable. [23]. Based on these facts, scientists have made improvements by incorporating the meningitide bacterial outer membrane vesicle (OMV) from the MeNZB vaccine as an active component in the 4CMenB vaccine, which is also known as Bexsero [21,23]. The 4CMenB vaccine is a multi-component MenB vaccine, and it contains four antigens: factor H-binding protein (fHbp), neisseria adhesin A (NadA), neisseria heparin binding antigen (NHBA), and porin A (PorA) [21]. Researchers want to incorporate MenB's outer membrane vesicle (OMV) into the 4CMenB vaccine as an additional component due to the presence of the OMV antigen in Neisseria gonorrhoeae [11]. According to a study, individuals who received the 4CMenB vaccine shown the ability to generate antibodies and exhibit recognition of gonococcal antigens. This suggests that the 4CMenB vaccine may have the potential to provide cross-protection against N. gonorrhea, hence aiding in its prevention [11]. A separate research endeavor was conducted in Southern California, focusing on young people and teenagers, with the aim of comparing the injection efficiency of 4CMenB and MenACWY. The study encompassed a total of 6,641 individuals who received the 4CMenB vaccine and 26,471 individuals who received the MenACWY vaccine. The findings indicate that individuals who received the 4CMenB vaccine saw a 46% reduction in n. gonorrhea infection compared to those who received the MenACWY vaccine [17]. While the 4CMenB vaccine demonstrates superior efficacy compared to the MenB vaccine and exhibits potential effectiveness against N. gonorrhea, its efficiency is limited to a range of 33% to 40% when administered in two doses [22]. In summarizing the available vaccinations for the prevention of N.

gonorrhea, it has been observed that these vaccines have demonstrated limited duration of efficacy or ineffectiveness in preventing the transmission of Gonorrhea. The outer membrane vesicles (OMVs) are anticipated to have a significant impact, with potential emphasis on gonococcal OMV rather than solely meningococcal OMV, in the development of the vaccine [11]. Excitingly, there is a vaccine for N. gonorrhoea prevention that has received fast track designation from the US Food and Drug Administration (FDA), as recently announced by GSK [24]. Although detailed information about this vaccine is not yet available, it has been revealed that the vaccine is currently undergoing a phase 2 trial that began in November 2022 [24]. This clinical trial has enrolled 750 participants from eight different countries, with the aim of assessing the vaccine's effectiveness in preventing N. gonorrhoea in healthy adults aged 18 to 50 who may be at risk of infection [24].

5. Summary

As one of the sexually transmitted diseases, Neisseria gonorrhea differs from other STDS for which there is a vaccine option. Its antimicrobial resistance and surface variation make Neisseria gonorrhea difficult to overcome. But as studies described above have shown, scientists have been working for decades to overcome the problem of preventing gonorrhea, and with increasing resistance to antimicrobial agents, scientists have struggled to develop a preventive vaccine. The last few years have seen glimmers of hope. New vaccine candidates are also in the pipeline, and we hope they will be available within the next few years. Once the N. gonorrhea vaccine is developed, gonorrhea will no longer be a "superbug" risk, the disease will be prevented, and people will be free of gonorrhea.

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