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# Vaccines against gonorrhea: Current status and future challenges

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ABSTRACT

Gonorrhea occurs at high incidence throughout the world and significantly impacts reproductive health and the spread of human immunodeficiency virus. Current control measures are inadequate and seriously threatened by the rapid emergence of antibiotic resistance. Progress on gonorrhea vaccines has been slow; however, recent advances justify significant effort in this area. Conserved vaccine antigens have been identified that elicit bactericidal antibodies and, or play key roles in pathogenesis that could be targeted by a vaccine-induced response. A murine genital tract infection model is available for systematic testing of antigens, immunization routes and adjuvants, and transgenic mice exist to relieve some host restrictions. Furthermore, mechanisms by which *Neisseria gonorrhoeae* avoids inducing a protective adaptive response are being elucidated using human cells and the mouse model. Induction of a Th1 response in mice clears infection and induces a memory response, which suggests Th1-inducing adjuvants may be key in vaccine-induced protection. Continued research in this area should include human testing and clinical studies to confirm or negate findings from experimental systems and to define protective host factors.


## 1. Introduction

### 1.1. Epidemiology

Gonorrhea is a sexually transmitted bacterial infection caused by the Gram-negative diplococcus *Neisseria gonorrhoeae* (Gc). Gonorrhea is one of the most common infectious diseases worldwide, with significant immediate and long-term morbidity and mortality. In sexually active adolescents and adults Gc causes clinically inapparent mucosal infections (most common in women), symptomatic urethritis and cervicitis, upper urogenital tract infections, and pelvic inflammatory disease. Extra-genital rectal and pharyngeal infections occur frequently and coinfections with other sexually transmitted pathogens are common. Systemic or disseminated gonococcal infections (DGI) are infrequent (0.5–3%), occur mainly in women, and include a characteristic gonococcal arthritis-dermatitis syndrome, suppurative arthritis, and rarely endocarditis, meningitis or other localized infections. Neonates exposed during birth may develop ophthalmia neonatorum, skin infections, or, rarely, disseminated disease.

Complications from Gc infections are frequent, debilitating, and disproportionately affect women. Untreated cervical infections commonly progress to the upper reproductive tract, which contributes to pelvic inflammatory disease (PID), infertility, life-threatening ectopic pregnancy, and chronic pain. Infertility rates following PID are high, at >10% following a single episode and >50% following three or more episodes [1]. In men 10–30% of untreated urethritis cases may progress to epididymitis, a common cause of male infertility in some regions [2]. During pregnancy, Gc causes chorioamnionitis complicated by septic abortion in up to 13% of women, preterm delivery in 23% of women, and premature rupture of membranes in 29% of women [3]. Neonatal conjunctival infections are destructive, leading to corneal scarring and blindness. Gonorrhea also dramatically increases the acquisition and transmission of human immunodeficiency virus (HIV) [4].

An estimated 106 million Gc infections occur annually, worldwide [5]. Diagnostic capabilities and surveillance systems vary between nations, and thus, infection is greatly underreported and prevalence is often highest among economically or socially disadvantaged populations. Microbiologic culture is diagnostic, but syndromic management alone is standard for many regions of the world. Rapid DNA-based tests have improved sensitivity, especially for asymptomatic disease, but are not available in all countries. In all situations, treatment is empiric at the initial point of care to eliminate further transmission.

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**Table 1**
Potential gonorrhea vaccine antigens.

| Antigen | Function | Expression | Variability | Immunogenicity | Reference |
|---|---|---|---|---|---|
| PilC | Pilus-associated adhesion | Phase variable | Variable and conserved regions | | [89,90] |
| PilQ | Outer membrane channel for pilus extrusion | Stable | Conserved at C-terminus | fPilQ406-770 mouse immunization: surface-binding and bactericidal antibodies | [91] |
| Opa | Adherence, invasion | Phase variable | Variable | Bactericidal antibodies, meningococcal Opa proteins protective in mice | [92,93,94] |
| AniA | Nitrite reductase, biofilm formation | Induced by nitrite and low oxygen tension | Conserved, variable glycosylation | Antiserum to truncated non-glycosylated recombinant protein blocks AniA function | [69] |
| TdfJ | Iron-induced zinc transporter | Regulated | Conserved | Antiserum to the meningococcal homologue ZnuD is bactericidal | [95,96] |
| PorB | Porin, major OMP, nutrient acquisition, antibiotic and serum resistance, invasion | Stable, essential | Variable | Cyclic loop peptides induce cross-reactive bactericidal antibodies | Garvin et al., 2010 IPNC Abstract #P235 |
| Lst | α-2,3-Sialyltransferase; increases serum resistance | Constitutive | Conserved | Antibodies reduce sialylation | [97] |
| TbpB, TbpA | Transferrin receptor | Induced in iron-limiting conditions | TbpA, conserved; TbpB variable | Antibodies are bactericidal and block Tf-dependent growth Tf required for infection of male volunteers by strains lacking Lf receptor | [50,60] |
| 2C7 epitope | Monoclonal antibody to lipooligosaccharide (LOS) | Phase variable; expressed by most Gc strains | Common epitope in variable LOS | Antibodies to peptide mimic are bactericidal and opsonic; protection in mouse model | [65,66] (Gulati et al., 2012 IPNC, Abstract #0118 |
| OmpA | Adherence, invasion | Transcriptional regulation | | Bactericidal antibodies | [98] |
| OpcA | Adherence, invasion | Stable | Conserved | Bactericidal antibodies | [99] |

Antimicrobial resistance patterns guide treatment recommendations, the goal of which is to effectively treat ≥95% of infections at first presentation. Antibiotic resistance is widespread and has developed rapidly with each successive treatment regimen. Alarmingly, with the advent of resistance to extended-spectrum cephalosporins, we have now reached the point where untreatable disease can be anticipated in the near future [6]. Although rapid effective treatment of gonorrhea decreases long-term sequelae and can eliminate the effect on HIV transmission [7], expansion of multi-drug resistant Gc is a global threat to public health and amplifies the urgent need for novel prevention methods.

### 1.2. Modeling vaccine impact

Development of an effective gonorrhea vaccine is likely to have significant benefits given the impact of gonorrhea on human health. Ebrahim et al. estimated 1326 disability-adjusted life years (DALYs) are attributable to 321,300 Gc infections. Applied to WHO global estimates of new Gc infections, this translates to 440,000 DALYs per year [8,9]. The benefits of effective treatment to women also have been estimated: treatment of 100 women with gonorrhea, of which 25% are pregnant, would prevent 25 cases of PID, one ectopic pregnancy, 6 cases of infertility, and 7 cases of neonatal ophthalmia. Additionally, treatment of 100 high-frequency transmitters of Gc could prevent 425 new HIV infections over 10 years [10]. This projection is supported by experience in Mwanza, Tanzania where HIV infection was several times greater among individuals with gonorrhea [11]. Given the increases in duration of infection, transmission rates, and complications that can be anticipated with rising antibiotic resistance, there is an urgent need for expanded efforts to develop preventive vaccines.

Modeling studies are needed to assess the impact of various vaccination strategies. While an ideal vaccine would eliminate Gc from all mucosal surfaces, as observed with *Haemophilus influenzae* B conjugate vaccines [12], this vaccine outcome may not be achievable for Gc. Estimates of the impact of gonorrhea vaccines that decrease extension of disease, decrease transmissibility, or eliminate only complicated disease are needed and may support multiple early approaches. In one model, focused treatment of core groups results in collapse of disease transmission. However, when antibiotic resistance is added to the model, there is rebound and increased dissemination of disease [13]. Similar studies should investigate whether vaccination of only women, core groups, or all individuals who present with a sexually transmitted infection (STI) would be adequate, or whether broader vaccination strategies are needed.

## 2. Pathogenesis

Gc is a human-specific pathogen with no animal or environmental reservoir. Initial adherence to epithelial cells is mediated by type 4 colonization pili, which are multifunctional appendages that also mediate genetic exchange, twitching motility, bacterial aggregation, and cell signaling [14]. Gc also has an intracellular niche; invasion of urethral cells occurs through the binding of the lacto-*N*-neotetraose (LNT) species of lipooligosaccharide (LOS) to the asialoglycoprotein receptor. Gc also invade epithelial cells of the female genital tract, and the best characterized pathways are uptake through complement receptor 3 (CR3) on cervical cells due to binding of a complex formed by LOS, porin (PorB) and host C3b molecules [15], and interactions between Gc opacity (Opa) proteins and human carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) on cervical or endometrial cells [16]. PorB1a-mediated invasion of epithelial cells occurs through the scavenger receptor SREC [17] and may explain in part the strong association between PorB1a strains and DGI.

Gc is also well adapted to evade host innate defenses. Gc circumvents iron sequestration on host mucosal surfaces by expressing receptors for hemoglobin, human transferrin (Tf) and human lactoferrin [18]. The MtrC–MtrD–MtrE active efflux pump system protects Gc by actively expeling hydrophobic antimicrobial substances (e.g. fatty acids, bile salts, progesterone, antimicrobial peptides). Similarly, the FarA–FarB–MtrE pump likely protects Gc from long fecal lipids found in rectal mucosae [19]. Gc has several mechanisms for evading complement-mediated defenses. Sialylation of the lacto-neotetraose species of LOS increases resistance to the bactericidal activity of human serum and significantly reduces opsonophagocytosis by polymorphonuclear leukocytes

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