

# Neisseria gonorrhoeae

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Neisseria gonorrhoeae

pelvic inflammatory disease

anti-virulence therapeutics

antimicrobial resistance

## 1. Introduction

*Neisseria gonorrhoeae* is a Gram-negative diplococcus which causes the sexually transmitted infection (STI) gonorrhea. The World Health Organization (WHO) estimates that of the 376 million new cases per annum of treatable STIs (chlamydia, gonorrhea, syphilis and trichomoniasis), *N. gonorrhoeae* caused 87 million cases global<sup>[1]</sup>. Specifically, in the United States, gonorrhea is the second most commonly reported notifiable infection. A 2018 surveillance report by the Centers for Disease Control and Prevention determined that a total of 583,405 cases had been recorded, an 82.6% increase from the historic low observed in 2009<sup>[2]</sup>. A study on the total lifetime direct medical cost of gonorrhea infections on the US healthcare system was approximately \$81.1 to \$243.2 million<sup>[3]</sup>. However, this cost does not reflect the true economic burden of *N. gonorrhoeae* infections since it did not include costs associated with adverse pregnancy outcomes, disease prevention or productivity loss.

*N. gonorrhoeae* most commonly colonizes the genital mucosa, but can also colonize the ocular, nasopharyngeal and anal mucosa. Gonococcal infections in men are predominantly symptomatic, but pharyngeal and rectal infections in men are overwhelmingly asymptomatic. Symptomatic patients usually present with acute urethritis, displaying symptoms of dysuria and urethral discharge<sup>[4][5][6][7][8]</sup>. On the other hand, infections in women are frequently asymptomatic, with some studies indicating up to 70% asymptomatic infection rates<sup>[9]</sup>. Symptomatic infections of the genital mucosa usually manifest as cervicitis, urethritis and occasionally as pelvic inflammatory disease (PID)<sup>[10]</sup>. Asymptomatic cases are reservoirs that promote gonorrhea transmission, and undetected AMR strains from these reservoir sites may promote the spread of resistance.

Gonococcal urethritis significantly increases the risk of acquiring and transmitting HIV, thus substantially contributing to the public health burden of this infection<sup>[11][12][13][14][15]</sup>. Genital infections in pregnant women can have adverse effects on the fetus including spontaneous preterm birth, chorioamnionitis, low birth weight, premature rupture of membranes and spontaneous abortion<sup>[16][17]</sup>. Additionally, transmission to the neonate may occur during passage through the birth canal. The effects of gonococcal disease for neonates include severe eye

infections and bacteremia that can lead to ulceration of the cornea, perforation of the globe of the eyes or permanent blindness<sup>[18][19][20][21]</sup>.

To date, no successful vaccine strategies have been developed for gonorrhea in humans, as individuals can contract the disease multiple times throughout their lifetime, suggesting that there is no natural immunity and therefore correlates of protection to benchmark vaccine efficacy<sup>[22][23]</sup>. Recent studies have observed an association of reduced prevalence of gonorrhea in individuals who have received the *N. meningitidis* serogroup B vaccine Bexsero<sup>®</sup>, suggesting that there may be cross-protective immunological responses elicited from common antigens in the meningococcal outer membrane (OM) vesicle component <sup>[24][25]</sup>. Further work is required to fully analyze the immune response elicited by this vaccine, but this provides a framework for future gonococcal vaccines, and reinforces the requirement for human clinical trials to identify successful vaccine antigens<sup>[26]</sup>.

## 2. Pathogenesis Mechanisms of *N. gonorrhoeae*

Following transmission from an infected to uninfected host, the gonococcus adheres to the apical side of the epithelial cells. This is mediated through gonococcal surface structures such as type IV pili (tfp), opacity (Opa) proteins, lipooligosaccharide (LOS) and the major OM protein porin, PorB. Tfp, LOS and Opa can undergo both phase and antigenic variation during infection that minimizes recognition and elimination by the immune system<sup>[27]</sup>.

Primary attachment is initiated by tfp which bind to the host cell surface receptor CD46 and/or complement receptor 3<sup>[28][29]</sup>. In vitro studies indicate that antigenic variation of tfp influences pilus-mediated adherence to human tissue, colony morphology and DNA transformation efficiency<sup>[30][31]</sup>. To promote further intimate attachment, Opa proteins, which are phase variable<sup>[32]</sup>, adhere to the carcinoembryonic antigen-related cell adhesion molecule (CEACAM) receptors, but some variants can bind to heparan sulfate proteoglycans (HSPGs) on host cells<sup>[28][33][34][35][36]</sup>. Attachment is also mediated by gonococcal LOS, which binds specifically to the host asialoglycoprotein receptor on HepG2 cells<sup>[37]</sup>, human sperm cells <sup>[38]</sup> and epithelial cells <sup>[39]</sup>. Following adhesion, *N. gonorrhoeae* replicates to form microcolonies and biofilms<sup>[40][41]</sup>, and some bacteria can proceed to invade epithelial cells by transcytosis<sup>[42][43][44]</sup>. During infection, gonococci release fragments of bacterial LOS, peptidoglycan (PG) and OM vesicles during cell growth that activate two pattern recognition receptors, toll-like receptor (TLR) and nucleotide-binding oligomerization domain-like receptor (NOD) on epithelial cells, macrophages and dendritic cells<sup>[45][46][47][48][49][52][53][54]</sup>. *N. gonorrhoeae* also releases heptose-1,7-bisphosphate, a precursor for the incorporation of heptose into LOS, which activates TNF receptor-associated factor-interacting protein with forkhead-associated protein A (TIFA)-dependent immunity<sup>[50][51]</sup>. Activation of these TIFA, NOD and TLR signaling pathways leads to the activation of inflammatory transcription factors and release of pro-inflammatory cytokines and chemokines (e.g., IL-6, IL-8, CXCL3, CXCL10 and TNF- $\alpha$ ) <sup>[28][52][53]</sup>. In response to these signals, large amounts of polymorphonuclear leukocytes (PMNs) are recruited to the site of infection, where *N. gonorrhoeae* is recognized and phagocytosed. Since gonococci can survive and replicate within PMNs, the massive influx of PMNs forms an observable purulent exudate that facilitates transmission<sup>[54]</sup>.

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