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Biological feasibility and importance of a gonorrhea vaccine for global public health

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ABSTRACT

There is a growing public health interest in controlling sexually transmitted infections (STIs) through vaccination due to increasing recognition of the global disease burden of STIs and the role of STIs in women's reproductive health, adverse pregnancy outcomes, and the health and well-being of neonates. *Neisseria gonorrhoeae* has historically challenged vaccine development through the expression of phase and antigenically variable surface molecules and its capacity to cause repeated infections without inducing protective immunity. An estimated 78 million new *N. gonorrhoeae* infections occur annually and the greatest disease burden is carried by low- and middle-income countries (LMIC). Current control measures are clearly inadequate and threatened by the rapid emergence of antibiotic resistance. The gonococcus now holds the status of "super-bug" as there is currently no single reliable monotherapy for empirical treatment of gonorrhea. The problem of antibiotic resistance has elevated treatment costs and necessitated the establishment of large surveillance programs to track the spread of resistant strains. Here we review the need for a gonorrhea vaccine with respect to global disease burden and related socioeconomic and treatment costs, with an emphasis on the impact of gonorrhea on women and newborns. We also highlight the challenge of estimating the impact of a gonorrhea vaccine due to the need for more data on the burden of gonococcal pelvic inflammatory disease and related sequelae and of gonorrhea-associated adverse pregnancy outcomes and the problem of empirical diagnosis and treatment of STIs in LMIC. There is also a lack of clinical and basic science research in the area of gonococcal/chlamydia coinfection, which occurs in a high percentage of individuals with gonorrhea and should be considered when testing the efficacy of gonorrhea vaccines. Finally, we review recent research that suggests a gonorrhea vaccine is feasible and discuss challenges and research gaps in gonorrhea vaccine development.

1. Introduction

Gonorrhea is caused by the Gram-negative bacterial pathogen *Neisseria gonorrhoeae*. *N. gonorrhoeae* is highly adapted to its human host and its success as a pathogen is due to the evolution of many sophisticated mechanisms for evading host innate effectors and suppressing protective adaptive immune responses. Most gonococcal infections are uncomplicated lower urogenital tract infections of the urethra or cervix [1]. Rectal and pharyngeal infections are also common, particularly among MSM and transgender women [2,3]. Urethral infections in men are typically characterized by a purulent exudate; in contrast, up to 40% of cervical infections and most pharyngeal and rectal infections are asymptomatic [1]. Untreated urethritis in men can ascend to cause epididymitis with risk of infertility. Ascending infection is more common in females with untreated cervical infections, and can result in acute or subclinical (silent) pelvic inflammatory disease (PID). PID is a serious condition that is associated with the complications of chronic pelvic pain, infertility and ectopic pregnancy [1,4]. Maternal gonorrhea is associated with adverse pregnancy outcomes (i.e. low birth-weight, preterm delivery, premature rupture of membranes, septic abortion) [5], and babies born to infected mothers have a high risk of acute conjunctivitis that can lead to blindness [6]. Disseminated gonococcal infection can occur in both men and women and can lead to suppurative arthritis [7].

Effective control measures for gonorrhea depend upon safe-sex counseling, appropriate diagnostics, and antimicrobial therapy, the latter of which is imperiled by multidrug resistant strains.

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N. gonorrhoeae rapidly acquires antimicrobial resistance (AMR) through several mechanisms, including the acquisition of plasmids that encode β-lactamase and tetracycline resistance and point mutations in chromosomal genes that increase resistance to β-lactam, macrolide and fluoroquinolone antibiotics. The gonococcus also acquires resistance through the uptake of naked DNA from other gonococcal strains or *Neisseria* sp., which is the genetic mechanism by which resistance to the extended-spectrum cephalosporins has evolved [8]. There is no longer a single reliable class of antibiotic for empirical treatment of gonorrhea, and dual therapy with a parenteral extended-spectrum cephalosporin and oral azithromycin is the currently recommended first-line treatment [9–11]. In response to this public health alarm, large surveillance programs have been established to track the spread of resistant strains [12–14]. Decreasing susceptibility to the extended-spectrum cephalosporins and azithromycin has been documented globally [14], and the specter of untreatable gonorrhea has been raised by the isolation of ceftriaxone-resistant strains [15–17] and strains with high-level azithromycin resistance [18,19]. The reality of this threat is supported by the first reported dual treatment failure [20] and the isolation of azithromycin-resistant *N. gonorrhoeae* with reduced susceptibility to ceftriaxone in Hawaii; these isolates were also resistant to penicillin, tetracycline and ciprofloxacin [21].

2. The need for a gonorrhea vaccine

2.1. Disease burden

There is a clear need for a gonorrhea vaccine. Seventy-eight million new *N. gonorrhoeae* infections occur each year and an estimated 2300 deaths and 467,700–974,900 lost disability-adjusted life years result from gonorrhea-associated morbidity [22–24]. A disproportionate burden of disease falls on low- and middle-income countries (LMIC) and other economically and socially disadvantaged populations [10], and although culture or NAAT testing are the diagnostic standard, syndromic management is the reality of care in many LMIC, which complicates disease reporting, documentation of AMR trends, and treatment failures. Gonorrhea is also a co-factor for increased spread of human immunodeficiency virus (HIV). Significantly higher levels of HIV-1 RNA are detected in seminal plasma in HIV-seropositive men with urethritis, with the highest HIV-1 RNA levels in men with gonorrhea [25]. In addition to these findings, a prospective STI study in South Africa showed an almost 5-fold increased risk of HIV in patients when gonorrhea was present [26].

In response to the current AMR threat, research on novel anti-infectives for gonorrhea has increased and three new antimicrobials have been tested in Phase II or III clinical trials (reviewed in [10,27]). In 2016, the World Health Organization (WHO) and the Drugs for Neglected Disease initiative launched the Global Antibiotic Research and Development Partnership (GARDP). In addition to setting up multiple programs to develop new treatments for STIs, the GARDP drafted ideal and acceptable Target Product Profiles (TPPs) for treatment of gonorrhea to stimulate drug discovery and development [27]. However, even when effective therapy for gonorrhea is available, gonorrhea remains a highly prevalent disease, and new antimicrobials may be a short-term solution based on the historical propensity of the gonococcus to develop resistance. Besides providing a more effective public health tool, a gonorrhea vaccine would also drive antibiotic sparing and reduced use, which in turn would extend the lifespan of licensed antibiotics and reduce the enormous investment of finances, time and labor required for global surveillance and the frequent revision of treatment guidelines.

2.2. Impact of gonorrhea on women's health

The major morbidity and mortality associated with gonorrhea is due to ascending infections in females [1]. Upper reproductive tract infections are complicated infections that can be difficult to diagnose and require a higher level of medical management [28]. More data on the incidence of gonococcal PID in different populations are needed so that the benefit of a gonorrhea vaccine can be more accurately modeled, especially in LMIC where diagnosis is often syndromic. In many studies, *Chlamydia*-associated PID is more common than PID associated with gonorrhea, which is thought to reflect the relative prevalence of these pathogens in the communities being studied. Approximately 18–20% of untreated cervical gonococcal infections ascend to cause PID [1], and in populations where gonorrhea rates are high, gonorrhea may more often be associated with PID. In a recent retrospective study from Western Australia, the rate of PID from women who had tested positive for gonococcal infection or gonococcal/chlamydial coinfection was higher than in women who had tested positive for chlamydial infection alone or in women who tested negative for both infections [29]. These investigators also found that gonorrhea-associated PID is clinically more severe than that associated with *Chlamydia*, based on the higher hospitalization rate for women with gonorrhea or concurrent gonococcal/chlamydial infection versus chlamydial infection alone [29,30]. The rate of chlamydial infection in individuals with gonorrhea typically ranges from 20 to 50% [31–33], but can be as high as 60–70% [34,35]. The prevalence of PID due to gonorrhea plus chlamydia or another infection should be better assessed; this information is important to consider when testing candidate gonorrhea vaccines due to the high rates of coinfection.

Involuntary infertility afflicts men and women world-wide, but rates in LMIC are as high as 15–30% [36]. Infertility due to infection-mediated damage to the fallopian tubes is called tubal factor infertility (TFI). Globally, TFI is implicated as the cause of infertility in 33% of women [37]. Estimates are higher in LMIC with >85% of female infertility in Sub-Saharan Africa attributed to TFI in 1985 [38]; more recently, 69% of infertile females in a Rwandan study were diagnosed with TFI [39]. Chlamydial infections are more often linked to TFI; however, gonococcal PID remains a significant cause of TFI based on serological studies, the high percent of acute PID due to *N. gonorrhoeae*, and laboratory studies that demonstrate the toxicity of the gonococcus for the epithelium of fallopian tube tissue (reviewed in [37]). Damage to fallopian tubes can also lead to ectopic pregnancy, which is an acute emergency and a life-threatening condition. Recent data from Saudia Arabia [40] and Myanmar [41], strongly associate chlamydial infection, but not gonorrhea with increased risk of ectopic pregnancy; however, more data are needed to better estimate the contribution of gonorrhea to ectopic pregnancy rates world-wide.

2.3. Impact of gonorrhea on neonatal health

Reducing the impact of STIs on maternal health is challenged by the lack of pre-natal care and maternal screening in disadvantaged populations and the high rate of asymptomatic infection [42–44]. The rate of *N. gonorrhoeae* infection in asymptomatic pregnant women was estimated at 0.5–14% in a literature-based study on lower genital tract infections in pregnant women that emphasized LMIC [45]. Maternal gonorrhea is strongly associated with low birth-weight [46,47]. While chlamydial infection is more often identified as a factor associated with premature rupture of membranes and pre-mature delivery [5], a reported 5-fold increased risk of very pre-term birth (<32 weeks) in rural women with gonorrhea in Nepal [48] suggests better global estimates are needed. Infants born to *N. gonorrhoeae*-infected mothers have a 30–45%

increased risk for ophthalmia neonatorum (ON), which is an acute conjunctivitis that can lead to scarring and blindness if untreated. [49]. ON is more common in LMIC; for example, 231 cases of ON were reported over a 3 year period in large tertiary hospital in Malawi in 2014 [50]. Data on the relative frequency by which ON is caused by *N. gonorrhoeae*, *C. trachomatis* or simultaneous infection with both pathogens are more available than for other adverse pregnancy outcomes, and ON due to *N. gonorrhoeae* alone can be as high as 12–20% of cases [51,52]. A lack of routine maternal screening for STI [51] and inconsistent treatment of all newborns likely contribute to the higher incidence of ON in LMIC. Recently reported treatment regimens in LMIC include prophylactic tetracycline ointments or saline washes [50,51,53]. There are no data on the effectiveness of treatment, however, which may be a concern in countries where tetracycline resistance is high.

2.4. Treatment and socioeconomic costs

A systematic review of treatment costs for curable STIs in LMIC estimated a cost of 21.66 USD per case of gonococcal infection when treating with ceftriaxone and azithromycin. The cost of managing symptomatic STIs at STI clinics in LMIC was estimated to be in excess of 187 USD, while NAAT testing added another $1.4 billion USD [54]. This study also predicted that efforts to strengthen national STI surveillance through increased laboratory capacity, quality assurance, and the introduction of Point-of-Care diagnostics to monitor STI prevalence and AMR would be $100,000 per year, per LMIC. While it is difficult to determine costs directly attributable to AMR, an analysis from 2005 estimated that AMR could contribute to 3 million gonorrhea treatment failures globally per year and a conservative cost of 500 million USD per year [55]. This study pre-dates the loss of fluoroquinolones as recommended therapy for empirical treatment of gonorrhea. New estimates predict that the increased number of gonococcal infections and gonorrhea-associated HIV cases due to emerging ceftriaxone resistance over a ten-year period will cost 378.2 million USD [56].

The cost of managing PID-associated sequelae was recently estimated for several high-income countries, and in general, fertility treatment causes a financial burden for those affected [57]. Fertility treatment is usually unaffordable or unavailable in most LMIC [38]; however, infertility-associated economic losses due to a reduced future work-force are considerable. Infertility can have heavy psychological costs world-wide, and in cultures where fertility in women is highly valued, it can lead to ostracism, divorce and abuse [58]. The long-term medical and financial burden that premature delivery has on affected children, families and the health care system should also be considered as was recently reviewed in a study from Nigeria [59].

3. Current research efforts

3.1. Biological feasibility of a gonorrhea vaccine

Gonorrhea vaccine development was an active area of research forty years ago. Evidence of vaccine-induced immunity against *N. gonorrhoeae* was first observed in chimpanzees immunized with whole bacteria [60]. Similar studies in humans with a killed whole cell vaccine, however, were unsuccessful [61,62]. The demonstration that immunization with purified gonococcal pili protected human subjects from experimental urethral challenge was also promising (reviewed in [63]), however, no protection was observed in a heterologous challenge study [64] or a large field trial [65], most likely due to antigenic variability of gonococcal pilin. An unpublished clinical trial with purified gonococcal porin (PorB) was also unsuccessful (reviewed in [66]). The discovery that several *N. gonorrhoeae* surface molecules undergo antigenic variation or phase variable expression [67–71] and the lack of evidence that gonorrhea induces protective immunity in humans dampened hopes for a gonorrhea vaccine. At the time, chimpanzees were the only animal model of gonococcal genital tract infection, which limited the research tools available for studying immune responses. The development of a female mouse genital tract infection model [72,73] has since provided a robust system for systematic screening of candidate antigens [63,74–76], and examining mechanisms by which the gonococcus evades protective immune responses in an intact host [73,77–80]. The potential of reversing *N. gonorrhoeae*-mediated immunosuppression has given new direction to gonorrhea vaccine development ([81] and reviewed in [82]). Progress in antigen discovery, molecular epidemiology, mucosal immunology, and genomics has also rekindled gonorrhea vaccine research [83], as has the successful licensure of human papillomavirus (HPV) vaccines, which proved that immunization of the genital tract is possible [84].

An international workshop was sponsored by the U.S. National Institute of Allergy and Infectious Disease (NIAID) in 2016 to mobilize the revival of gonorrhea vaccine research. As reported in the meeting proceedings [83], efforts to develop a gonorrhea vaccine are in the stages of (i.) modeling the impact of vaccination against gonorrhea; (ii.) identification of clinical study sites and defining the logistics for clinical trials, of (iii.) antigen discovery; (iv.) investigation of immune correlates in humans; (v.) identification of vaccine-induced, protective responses in the mouse model, and (vi.) establishment of genome databases for data sharing and antigen sequence comparisons. Following this meeting, a large retrospective case-control study in New Zealand showed that a group B meningococcal outer membrane vesicle (OMV) vaccine (MeNZB) was associated with reduced risk of gonorrhea in adolescents and adults aged 15–30 years. Using cases of chlamydia as a control, the estimated effectiveness of the meningococcal vaccine against gonorrhea among adolescents and adults aged 15–30 years was predicted to be 31%. Protection waned with time and vaccine efficacy was lower (14%) in individuals with a concurrent chlamydial infection [85]. However, these data are the first evidence in humans in over 40 years that suggest vaccination against gonorrhea is possible.

3.2. Antigen discovery

Several conserved candidate gonorrhea vaccine antigens have been identified (extensively reviewed in [66]). Vaccine antigens that show promise in various stages of pre-clinical testing are listed in Table 1. Antigens that showed protection against experimental murine infection include a peptide mimetic of a highly bactericidal lipooligosaccharide (LOS) epitope called 2C7 [74] and gonococcal OMVs given vaginally with microencapsulated IL-12 as an adjuvant [75]. Protection was also observed in mice immunized with recombinant, refolded porin (rrPorB) using a viral delivery system, followed by rrPorB boosts [63]. The T cell bias was examined in these immunization/challenge studies, and interestingly, all antigen/adjuvants formulations or delivery routes that showed protection induced Th1 responses [63,74,75]. This finding is consistent with the demonstration that *N. gonorrhoeae*-mediated suppression of the host adaptive response can be reversed by vaginal delivery of IL-12 to infected mice, which results in higher antibody titers, clearance of infection, and a humoral memory response [81].

Candidate vaccine antigens that have been tested for the capacity to induce antibodies with anti-gonococcal activity in mice include the transferrin receptors TbpA/TbpB [86], a truncated non-glycosylated recombinant nitrite reductase (AniA) protein

Table 1
Development Status of Current Vaccine Candidates.

Candidate Name/Identifier	Preclinical	Clinical
2C7 epitope mimetic with MAP1 adjuvant (58)	Reduced duration of infection and bacterial burden in mice; induced bactericidal antibodies and Th1 responses; passive protection with anti-2C7 monoclonal antibodies	
OMV given with IL-12 (59)	Reduced duration of infection and bacterial burden in mice challenged with homologous or heterologous strains; induced Th1 responses and serum and vaginal IgG and IgA; protection dependent on INF-γ and B cells	
rrPorB-VRP (viral replication particle vector) boosted with rrPorB + Ribi-700 (54)	Reduced duration of infection in mice and a polarized Th1 response	
TbpA, TbpB (62)	Induced bactericidal antibodies and antibodies that block the capacity of *N. gonorrhoeae* to grow with human transferrin as the sole iron source	
AniA (63)	Induced bactericidal antibodies and antibodies that block AniA nitrite reductase activity	
MetQ (65)	Induced bactericidal antibodies and antibodies that block gonococcal adherence to epithelial cells	
MtrE (64)	Induced bactericidal antibodies	
MeNZB vaccine (57)		Prospective study in adolescents and adults 15–30 years old; predicts 33% efficacy against gonorrhea

[87], MtrE, the outer membrane channel of the MtrCDE active efflux pump [88], and a methionine transporter (MetQ) [89]. Other possible antigens include 168 conserved surface proteins that are expressed under different physiologically relevant conditions that were identified by a nonbiased proteomics screen [90] and several gonococcal homologs to meningococcal proteins that induce bactericidal antibodies against *N. meningitidis* (reviewed in [66]).

3.3. Infection models

Animal modeling for gonorrhea, like for most human STIs, is challenged by the strict human-specificity of the pathogen. Due to the low risk of complications, experimental urethral infection of male subjects is used to study the kinetics of infection, host responses, and the importance of virulence factors in infection [91–95]. This model, which is currently conducted at the University of North Carolina [96], has utility for studying events that occur in the early stages of male urethral infection, but may not reliably predict vaccine efficacy in women or against complicated infections. The potential of complications in women prohibits experimental infection of females.

A well-characterized female mouse model of lower genital tract infection has been used for pathogenesis and immune response studies [73,80,97–99], examination of the fitness cost of antibiotic resistance mutations [100,101], and the pre-clinical testing of vaccines, vaginal microbicides, novel immunotherapies, and new antimicrobials against gonorrhea [63,74–76,102–105]. A neutrophil influx occurs during gonococcal infection of BALB/c mice, and similar to humans, infection persists during periods of inflammation. Cyclical fluctuations in colonization and inflammation occur in response to hormonally driven changes in host factors, as was observed in women with gonorrhea (reviewed in [73]). Several host-restrictions limit the capacity of mice to fully mimic human infection. These limitations include restrictions for human transferrin and lactoferrin, soluble negative regulators of the complement cascade (factor H, C4b-binding protein), and receptors for several known gonococcal adhesins and invasins (i.e. carcinoembryonic antigen-cellular adhesion molecules (CEACAMs), the C3R integrin, CD46, and the elusive pilus receptor) (reviewed in [73]). Transgenic mice that express various host-restricted factors are now available [106–108]. Mouse models of PID are also under development and should facilitate investigation of immune responses and vaccine efficacy against upper reproductive tract infection [109].

3.4. Identification of correlates of protection

The inability of natural infection to induce long-lasting immunity hinders gonorrhea vaccine development. Repeated infections are common and can occur with the same strain or serotype, although there is evidence of serovar-specific immunity in high-risk women [110]. A reduced rate of upper reproductive tract infection was also found in high-risk women, and was associated with the presence of antibodies to gonococcal opacity proteins, and the absence of "blocking antibodies" [110–112]. Blocking antibodies are induced by the gonococcal restriction modifiable protein (Rmp), and reduce the bactericidal activity of antibodies against gonococcal PorB or LOS. Other studies also implicate the absence of blocking antibodies as a protective correlate for gonorrhea [reviewed in [66]].

The recognition that mucosal gonococcal infections induce an unremarkable and transient antibody response in humans [113] and mice [114,115] led to the identification of several *N. gonorrhoeae*-mediated mechanisms of immunosuppression using human cells or the mouse model (reviewed in [82]). One of these pathways can be reversed by treating mice with antibodies to TGF-β or IL-10 or by vaginal administration of microencapsulated IL-12, which results in increased proliferation of Th1 and Th2 cells and a humoral memory response [78,81]. Consistent with this observation is the success of candidate vaccines that induced Th1 responses in the mouse model as discussed above. Whether similar immune pathways are induced or suppressed during gonococcal infection in humans is not known and a detailed examination of immune responses in infected humans is seriously lacking.

Exposure and transmission rates suggest mechanisms of natural immunity exist. Following a single exposure to an infected man or woman, 20–35% men and 60–90% of women become infected, respectively [116]. As has been done for other diseases, gonorrhea vaccine development could benefit from natural history studies of exposed uninfected and infected individuals and the use of modern technology to more comprehensively identify host factors that may influence susceptibility to infection. These factors include serum and mucosal antibodies, complement components and regulatory factors, cellular factors, receptor polymorphisms, the microbiome,

and host factors that are specific to the luteal (high-progesterone) phase of the menstrual cycle.

3.5. Investigation of vaccine efficacy in the context of chlamydial/gonorrhea coinfection

A strong risk factor for any STI is the presence of another STI. In the case of gonorrhea, the percent of individuals with gonorrhea that have a concurrent chlamydial infection is sufficiently high to warrant treatment for *Chlamydia* in patients who test positive for gonorrhea [9,11]. The life-style of these pathogens is markedly different, with *N. gonorrhoeae* being both extracellular and intracellular [117–120] and *C. trachomatis* obligately intracellular [121]. Accordingly, the host immune responses induced by these pathogens also differ. *Chlamydia* induces vigorous humoral and cell-mediated immune responses [122,123]; *N. gonorrhoeae*, in contrast, induces a robust inflammatory response through the Th-17 pathway [124,125], but a suppressed and nonprotective adaptive response characterized by low antibody titers of short duration [98,113]. Yet, despite the high prevalence of gonococcal/chlamydial coinfection, host immune responses to coinfection have not been well-characterized and it is not known if one pathogen influences susceptibility or *in vivo* survival of the other.

The possibility that chlamydiae create a more hospitable environment for *N gonorrhoeae* is suggested by a natural history study in adolescent girls in which higher numbers of gonococci were recovered from *Chlamydia*-infected subjects compared to girls with gonorrhea alone [126]. This difference was also observed in a murine coinfection model in which mice were first infected with *Chlamydia* followed by inoculation with *N. gonorrhoeae* [127]. The basis for these observations is not known, but could be related to immunological factors. It is therefore important that candidate gonorrhea vaccines be tested in a gonorrhea/chlamydia coinfection model. This point is underscored by epidemiological data that suggest a meningococcal OMV vaccine was less effective against gonorrhea when a concurrent *Chlamydia* infection is present [85]. Improved animal models of gonococcal/chlamydial coinfection are under development that could be used for this purpose, including PID models in which mice are first exposed to *N. gonorrhoeae* or *C. trachomatis*, or simultaneously inoculated with both pathogens (Alison C. Costenoble-Caherty and A.E. Jerse, unpublished data).

4. General approaches to vaccine development for LMIC markets

In general, inexpensive vaccines that do not require a cold chain or multiple doses are preferable for LMIC. Certainly a parenterally delivered vaccine in humans would be acceptable, however, mucosal vaccines given orally or nasally might be more effective against this mostly mucosal pathogen that infects a variety of mucosal sites, including the urethra, cervix, pharynx and rectum, as well as upper reproductive tract tissues.

Target groups should also be considered; while gonorrhea is transmitted through core groups in higher income countries, transmission patterns in LMIC are not well documented. It is generally thought that the best target group would be girls and boys aged 9–13, preferably before sexual debut, similar to the HPV vaccination program. Based on vaccine modeling for *Chlamydia*, it was predicted that vaccination of 13-year olds with a vaccine with a 20-year duration of protection and either 100% efficacy or 60% efficacy could lead to a 90% reduction in population prevalence after 15 years or 20 years, respectively [128]. The effectiveness of the newly licensed meningococcal OMV-based vaccine, Bexsero (Glaxo-Smith-Kline) against gonorrhea was also modeled. Assuming a 20% efficacy in a 2-dose campaign that targets adolescents in the US, the results suggested that 83,167 infections would be prevented, 28.7 million USD would be saved in costs, and a significant decrease in HIV infections (55 per vaccinated birth cohort) would occur, as well as 40 million USD saved in income and productivity, mostly due to avoidance of HIV infection [129].

5. Conclusions

Gonorrhea research has been revived by increased attention on the need for STI vaccines by the public health community and the problem of antibiotic resistance. The initial obstacle of antigenic variation that frustrated early gonorrhea vaccine development has been overcome by the identification of several conserved antigens, and a growing availability number of sequenced genomes, which should facilitate antigen discovery. Some candidate vaccine antigens induce bactericidal antibodies or inhibit target function and three candidate vaccines showed protection in the gonorrhea mouse model. Delineation of at least one immunosuppressive pathway has led to a strategy for reversing *N. gonorrhoeae*-mediated immunosuppression of the adaptive response and restoration of a protective humoral memory response. Finally, and most recently, data suggest vaccination of humans with a group B meningococcal OMV vaccine reduces the risk of gonorrhea [85]. Valuable information as to cross-reactive antigens and the host immune responses associated with protection should follow.

Research gaps include the following. Better estimates of the burden and financial costs of gonorrhea in LMIC with respect to PID, infertility and adverse pregnancy outcomes are needed, as are data on the burden of disease due to gonococcal/chlamydial coinfection. While several antigens are under development, only a handful have been tested for efficacy in the mouse model and no candidate vaccine has been tested in humans for over 30 years. There is a serious lack of data on human immune responses to gonococcal infection. Prospective trials should be conducted to determine whether the OMV-based meningococcal vaccine Bexsero is protective against gonorrhea. Clinical studies are also needed to determine whether immunosuppressive pathways identified in the mouse model are induced in humans. Testing of novel adjuvants and delivery systems for optimizing mucosal responses against candidate antigens is also under-developed. Finally continued investigation of differences in the pathogenesis of, and host response to *N. gonorrhoeae* in the presence and absence of a concurrent *C. trachomatis* infection is needed. The influence of chlamydial coinfection on the efficacy of candidate gonorrhea vaccines is also warranted.

Conflict of interest

The authors have no financial or personal interest that could affect their objectivity.

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