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Abbreviations

AMR..... antimicrobial resistance

CHIM ..... controlled human infection model

GASP ..... Gonococcal Antimicrobial Surveillance Programme

HICs..... high-income countries

HIV..... human immunodeficiency virus

HPV ..... human papillomavirus

Ig..... immunoglobulin

LMICs ..... low- and middle-income countries

LOS ..... lipooligosaccharide

MenB..... *Neisseria meningitidis* serogroup B

MSM ..... men who have sex with men

NAAT ..... nucleic acid amplification test

OMP ..... outer membrane protein

OMV ..... outer membrane vesicle

PID..... pelvic inflammatory disease

PPCs..... preferred product characteristics

PrEP ..... pre-exposure prophylaxis (for HIV)

SAGE..... WHO Strategic Advisory Group of Experts on Immunization

SRH..... sexual and reproductive health

STI..... sexually transmitted infection

WHO ..... World Health Organization

Executive summary

The development of a vaccine for *Neisseria gonorrhoeae* is an important goal for improving sexual and reproductive health (SRH) worldwide. Gonorrhoea is a common sexually transmitted infection (STI); an estimated 82 million new gonococcal infections occurred worldwide in 2020 *(1)*. Gonococcal infection has substantial morbidity through a wide range of adverse SRH consequences, including pelvic inflammatory disease (PID), infertility, adverse pregnancy outcomes, elevated risk for HIV acquisition and transmission, and neonatal conjunctivitis. Increasing *N. gonorrhoeae* antimicrobial resistance (AMR) has raised the possibility of untreatable gonococcal infections, which would heighten the threat to SRH globally *(2)*.

The World Health Organization (WHO) Global Health Sector Strategy on STIs has set 2030 targets for reducing incidence of *N. gonorrhoeae* infection by 90% *(3)*. Recognizing that this reduction may not be achievable with current interventions, and given increasing AMR, the Strategy has emphasized the need to develop effective gonococcal vaccines. No currently licensed gonococcal vaccines exist. However, interest in gonococcal vaccine development has been reinvigorated not only by the marked increases in gonococcal AMR, but also by mounting scientific data suggesting gonococcal vaccines are biologically feasible, particularly observational studies suggesting that outer membrane vesicle (OMV)-based *Neisseria meningitidis* serogroup B (MenB) vaccines may provide cross-protection against *N. gonorrhoeae (4, 5)*.

WHO preferred product characteristics (PPCs) documents provide guidance on WHO's preferences for new vaccines in priority disease areas, including from the perspective of low- and middle-income countries (LMICs). Articulation of product attributes that meet the needs of LMICs, while also addressing concerns of high-income countries (HICs), can advance development of vaccines that are suitable for global use. As a first step in defining gonococcal vaccine PPCs, a WHO-convened group of experts identified two overarching public health goals, of equal priority, for gonococcal vaccines:

- to prevent adverse SRH outcomes related to gonococcal infection, and
- to reduce the impact of gonococcal AMR.

This document describes PPCs for gonococcal vaccines. To meet global public health goals, the preferred vaccine indication is prevention of gonococcal infection, given large numbers of asymptomatic infections that can lead to SRH complications and AMR. Preferred target populations may vary by setting, but include young people (defined as ages 10–24 years) and/or specific populations at higher risk for gonococcal infection, such as men who have sex with men (MSM), sex workers and other vulnerable populations based on country specificities. The choice of broad-based vaccination of young people and/or targeted vaccination of populations at higher risk will depend on such factors as gonococcal epidemiology, vaccine efficacy and cost effectiveness, duration of vaccine protection, and programmatic considerations. These factors can also help refine specific target ages for vaccination among all young people and higher-risk populations with the greatest need for vaccination, in different settings.

Although vaccines specifically formulated to optimize efficacy against gonococcal infection and related outcomes are preferred, this document also examines considerations for the potential use of MenB vaccines to prevent gonococcal infection, if these vaccines are found to provide some cross-protection against gonococcal infection in clinical trials. As these vaccines are already in use for MenB disease prevention, they could be available for gonococcal infection sooner than gonococcus-specific vaccines.

1. Purpose of WHO preferred product characteristics

The mission of the World Health Organization's (WHO's) Vaccine Product and Delivery Research Unit is to accelerate the development and optimal use of safe and effective vaccines and related technologies that could have global public health impact. Priority areas include both facilitating advancement of vaccine candidates towards licensure and generating evidence to inform policy recommendations and vaccine introduction while candidate vaccines are in development. Identifying and articulating vaccine preferences that meet global health needs, early in product development, is fundamental to this mission.

WHO vaccine preferred product characteristics (PPCs) describe such preferred parameters as vaccine indications and target populations, considerations for safety and efficacy evaluation, and delivery strategies *(6)*. WHO PPCs are intended to encourage product innovation and facilitate vaccine development, particularly for use in low- and middle-income countries (LMICs), which often have the largest unmet public health need. Because vaccine manufacturers often develop vaccines for initial use in high-income countries (HICs), first-generation vaccines may not be suitable for use in LMICs, and broader vaccine introduction and impact can be substantially delayed. WHO PPCs emphasize LMIC perspectives, in addition to those for HICs, to encourage development of vaccines for global use.

PPCs are pathogen-specific rather than product-specific, and they are intended to provide early guidance on vaccine development strategies and inform the subsequent development of target product profiles. At the earliest stages of vaccine development (as with this document), the PPC guidance is intended to be broad, to encourage innovation and stimulate further dialogue regarding the desired product attributes that will optimally address the public health need and facilitate real-world use. The PPCs will be updated with more specific guidance when clinical trial data become available, or in the event of changes in the identified need or changes in the research and development landscape.

The primary target audience for WHO PPCs is any entity intending to develop a vaccine for LMIC use and planning to seek WHO policy recommendations and prequalification for their products *(7)*. However, it is important to note that while PPCs define aspirational goals for vaccine attributes, they do not supersede the evidence-based assessment by WHO's Strategic Advisory Group of Experts on Immunization (SAGE) or other existing WHO guidance on vaccine development *(8, 9)*.

Immunization nurses in Ghana.

2. Gonococcal vaccines – a strategic priority

Gonorrhoea, the sexually transmitted infection (STI) caused by *Neisseria gonorrhoeae,* a bacterium known as the gonococcus, has been a persistent public health problem for centuries. Although it is a curable infection, recent increases in gonococcal antimicrobial resistance (AMR) seriously threaten to further compromise gonorrhoea prevention and control *(2)*. Gonococcal infection is widespread throughout the world, with an estimated 82 million new infections each year *(1)*. However, gonococcal infection and its related disease outcomes disproportionately affect people living in LMICs. Untreated, or inadequately treated, gonorrhoea can lead to such adverse sexual and reproductive health (SRH) outcomes as infertility, adverse pregnancy outcomes, increased risk of HIV acquisition and transmission, and ongoing transmission of *N. gonorrhoeae* to sexual partners and neonates. Thus, the rising risk of untreatable gonococcal infection poses a global health threat.

Given these concerns, the WHO Global Health Sector Strategy on STIs has identified gonorrhoea as one of three prioritized STIs requiring immediate action for control, and it has set targets for reducing gonococcal infection incidence by 90% by 2030 *(3)*. However, sustainable control of gonococcal infections might not be achievable with current interventions, particularly given the evolving AMR situation. Thus, the Strategy also emphasizes the need for innovations for gonorrhoea control, including effective gonococcal vaccines. Observational studies, demonstrating that outer membrane vesicle (OMV)-based *Neisseria meningitidis* serogroup B (MenB) vaccines appear to provide some protection against gonococcal infection, support the notion that development of gonococcal vaccines is biologically feasible *(4)*.

Several global vaccine-related initiatives reinforce the importance of gonococcal vaccine development as a public health priority. The WHO Global Roadmap to Advance STI Vaccine Development and WHO's Product Development for Vaccines Advisory Committee (PDVAC) have highlighted the need for gonococcal vaccines for global use *(10–12)*. In addition, a greater global emphasis has been placed on the role of vaccines in the fight against AMR more generally, and *N. gonorrhoeae* vaccine development features prominently in these efforts *(13, 14)*.

2.1. Strategic public health goals for gonococcal vaccines

In 2019, WHO convened a global, multidisciplinary consultation comprised of basic scientists, microbiologists, clinicians, epidemiologists, vaccinologists, and public health programme and policy experts, from LMICs and HICs, to discuss the need, goals and potential value of gonococcal vaccines and key considerations for developing gonococcal vaccine PPCs *(15)*.

Gonococcal vaccines could have a range of potential benefits, at both the individual and population level, including prevention of infection, symptomatic gonococcal disease and other SRH complications, such as infertility, adverse pregnancy outcomes, and increased HIV acquisition and transmission risk. It could also potentially lead to a reduction in community-wide transmission of *N. gonorrhoeae*, including AMR strains. Considering these potential benefits in the context of the global public health need, the experts defined two overarching, strategic public health goals, of equal priority, for gonococcal vaccines for global use:

- to prevent adverse SRH outcomes related to gonococcal infection, and
- to reduce the impact of gonococcal AMR.

A complete list of adverse SRH outcomes related to gonococcal infection is shown in Box 1. Determining specific outcomes that are the highest priority prevention goal for gonococcal vaccines, such as infertility, can be refined with improved data on the global burden of each outcome, the potential impact of AMR and cost-effectiveness modelling. The full rationale for the strategic goals in the setting of detailed discussions on gonococcal infection, SRH outcomes and AMR can be found in the meeting report from the WHO consultation *(15)*.

3. Background on gonococcal infection and disease

N. gonorrhoeae is an obligate human pathogen that is primarily transmitted through genital, oral and anal sexual contact, infecting mucosal surfaces at these sites *(16)*. Transmission is highly efficient, and a substantial proportion of people become infected after a single exposure *(17)*. *N. gonorrhoeae* can also be transmitted to neonates from infected mothers during childbirth, typically infecting the conjunctival mucosa. Infection at all sites can be asymptomatic or cause acute symptom syndromes, and both asymptomatic and symptomatic acute infections can lead to additional SRH complications, which result directly from the infection itself or from the inflammatory response to infection (Box 1).

Box 1. Potential adverse SRH outcomes of gonococcal infection

- Symptomatic gonorrhoea at site of initial infection
  - Urethritis (primarily males)
  - Cervicitis
  - Pharyngitis
  - Proctitis
  - Conjunctivitis
- Symptomatic upper genital tract disease
  - Pelvic inflammatory disease (PID)
  - Tubo-ovarian abscess
  - Epididymo-orchitis
- Disease resulting from genital tract scarring
  - Infertility (primarily females)
  - Ectopic pregnancy, including risk of death due to tubal rupture
  - Chronic pelvic pain (females)
  - Urethral stricture (males)
- Adverse pregnancy outcomes
  - Miscarriage
  - Chorioamnionitis
  - Premature rupture of membranes
  - Premature birth
  - Low birth weight
- Neonatal conjunctivitis and related vision loss
- Increased risk of HIV acquisition and transmission
- Disseminated gonococcal infection
  - Gonococcemia
  - Gonococcal arthritis and tenosynovitis
  - Gonococcal endocarditis
  - Gonococcal meningitis
- Psychosocial consequences, including stigma and effects on sexual relationships

Pregnant women in Colombia awaiting medical consultation. © David Spitz

3.1. Asymptomatic infection and acute symptom syndromes

Asymptomatic and unrecognized gonococcal infections comprise a large proportion of all infections. In women, the vast majority of gonococcal cervical infections have no or only mild symptoms, such as vaginal discharge, that may be mistaken for other reproductive tract conditions *(18)*. Coinfections, particularly with *Chlamydia trachomatis*, frequently occur *(19)*.

It is generally accepted that acute lower genital tract infection is more often symptomatic in men than in women, typically manifesting as urethritis with purulent discharge or dysuria within five days of infection. However, some studies have suggested that the majority of incident gonococcal infections are asymptomatic in men as well as women *(20)*. Clinic-based studies demonstrate higher proportions of men with symptomatic gonococcal urethritis and suggest that recognition of symptoms may vary by country *(21, 22)*. Modelled estimates in an African setting suggest 45% of male gonococcal infections and 14% of female infections become symptomatic *(21)*. Extra-genital infections of the oropharynx and rectum are asymptomatic in most people, but can cause symptomatic pharyngitis and proctitis, respectively.

3.2. Upper genital tract complications

The most common severe complication of acute gonococcal infection is upper genital tract infection among women. Both asymptomatic and symptomatic cervical infections can ascend to the upper genital tract. Data regarding the precise proportion of *N. gonorrhoeae* cervical infections that ascend are limited. However, it is estimated that 15% or more of untreated infections ascend to cause clinically apparent pelvic inflammatory disease (PID), an infection of the uterus, fallopian tubes and/or ovaries that causes an acute lower abdominal pain syndrome *(23)*. Severity varies: upper tract gonococcal infections can be subclinical or unrecognized *(24)*, or they can occasionally result in tubo-ovarian abscesses or life-threatening peritonitis.

Whether from clinically diagnosed or subclinical PID, inflammation of the upper genital tract can damage and scar the fallopian tubes and other organs, which can eventually lead to such SRH complications as infertility, ectopic pregnancy and chronic pelvic pain *(24, 25)*. Up to 15–20% of women with an episode of documented gonococcal PID develop infertility *(25–27)*. The risk of upper tract scarring complications is directly proportional to the delay in treatment of PID *(28)*. In LMICs where adequate treatment of gonococcal PID may be delayed or unavailable, a higher proportion of infections might result in adverse SRH outcomes *(29)*.

Ascending infection is much less common among men, especially as infections are more likely to be symptomatic and promptly treated, but possible upper tract complications include epididymo-orchitis and, rarely, urethral stricture or male infertility *(18)*.

3.3. Adverse pregnancy outcomes and mother-to-child transmission

Gonorrhoea among pregnant women has been associated with increased risk for adverse pregnancy outcomes, including spontaneous abortion, intrauterine growth restriction, premature rupture of membranes, preterm birth, low infant birthweight, chorioamnionitis and postpartum endometrial infection *(30–32)*. However, the precise risks for each outcome have not been well defined, especially in LMICs *(30)*. Perinatal transmission of *N. gonorrhoeae* can result in neonatal conjunctivitis, which was a frequent cause of blindness before the institution of topical ocular antibiotic prophylaxis for neonates globally *(33, 34)*.

3.4. Increased HIV acquisition and transmission risk

Epidemiologic and biologic data indicate a link between the inflammatory STIs, such as gonorrhoea, with a two- to three-fold increased risk for HIV infection *(35, 36)*. Although gonococcal infection may be a marker of unprotected sex, which also increases HIV acquisition risk, it is thought that the inflammatory response to infection damages the genital or rectal epithelium and increases the availability of HIV target cells, such as $CD4^+$ T cells, making the genital or rectal mucosa more prone to HIV infection *(37, 38)*. Gonococcal infection may also contribute to HIV infection indirectly through its effect on fertility, as women with secondary infertility who desire pregnancy may be at greater HIV risk because of more frequent unprotected sex *(39)*. In addition, when people living with HIV also have an acute gonococcal infection, genital HIV RNA load increases, which may increase HIV transmissibility *(38, 40, 41)*.

3.5. Other complications of gonococcal infection

Gonococcal infection is associated with a range of other adverse SRH outcomes, not least of which is the related psychosocial consequences, including stigma and effects on sexual relationships. These consequences may be related to gonococcal infection itself or associated disease

outcomes. For example, infertility can have substantial social costs, particularly in LMIC settings where fertility is highly valued *(42)*. Uncommon complications include disseminated gonococcal infection, which can manifest as gonococcal bacteraemia, tenosynovitis, septic arthritis, and occasionally gonococcal endocarditis or meningitis *(18, 43)*.

4. Epidemiology of gonococcal infection and disease

4.1. Global infection estimates

Gonococcal infections are found throughout the world, with an estimated global incidence of 82 million (CI: 48–130 million) new infections among 15 to 49-year-olds during 2020 *(1)*. This reflects global incidence rates of 19/1000 women and 23/1000 men in that age group *(1)*. However, striking variations in prevalence and incidence can exist between regions and countries. For example, general-population estimates of gonococcal infection prevalence among women have ranged from <0.1% during 2010–2012 in England *(44)*, to 6.6% in South Africa *(45)*, to >14% in antenatal clinics in Papua New Guinea *(46)*. Level of economic development is a clear predictor of country-level burden of gonococcal infection. Global estimates demonstrate that most gonococcal infections occur in LMICs, with the greatest prevalence and incidence rates in low-income countries *(1)*.

4.2. Gonococcal infection by age and population group

Gonococcal epidemiology can also vary within countries. Throughout the world, the highest incidence of gonococcal infection typically occurs in the 15 to 24-year-old age group (older adolescents and young adults) compared with older ages, with peak incidence in young adults (20–24 years) *(19, 47)*. Gonococcal infections may continue to be acquired in older age groups, particularly in populations at higher risk for gonococcal infection *(47, 48)*.

Populations at higher risk for gonococcal infection include four of the five key populations that are defined by WHO for focused HIV prevention activities: men who have sex with men (MSM), people in prisons, sex workers and transgender people. People living with HIV (PLHIV) are also at higher risk *(49)*. Key populations are groups who, due to specific higher-risk behaviours and social-economic vulnerabilities, are at higher risk for gonococcal infection in most settings. Groups at higher risk for gonococcal infection also include vulnerable populations; they are defined by WHO as groups of people who are particularly vulnerable to infection in certain situations or contexts that may vary between and within countries *(49, 50)*. Some examples of vulnerable populations with respect to gonococcal infection include ethnic minorities or Indigenous populations with historical barriers to healthcare access, migrants, or young people (especially adolescent girls and young women) living in communities with known high rates of gonococcal infection or HIV *(51)*.

Gonococcal infection prevalence and incidence can be several-fold higher for key and vulnerable populations, both in HICs with relatively low general population prevalence and in LMICs with more generalized epidemics *(17, 19, 52)*. In a global meta-analysis of studies among people using pre-exposure prophylaxis (PrEP) to prevent HIV infection, gonorrhoea incidence was approximately 37/100 person-years *(53)*. Differences in gonococcal infection epidemiology between men and women in many countries appear to be primarily due to higher rates of infection among MSM *(47, 48)*.

4.3. Gonococcal infection trends

Global estimates of gonococcal infection prevalence and incidence in 2020, based on published prevalence surveys, were not significantly different from estimates in 2016 *(1)*. However, over the past decade, surveillance data from HICs that had previously had relatively good control of gonorrhoea have shown steady increases in case reports, beyond what is likely attributable to increased testing and use of sensitive nucleic acid amplification tests (NAATs). For example, in the United States, gonorrhoea case reports increased 83% in 10 years through 2018 *(47)*; in Australia, an 80% increase in 5 years through 2017 *(54)*; and, in England, a 26% increase from 2017–2018 *(52)*. These increases were greatest among MSM and among adolescents and young adults more generally. Several health jurisdictions have noted an association between factors such as the expansion of PrEP programmes to prevent HIV, increased use of geospatial applications to find sex partners; and HIV serosorting behaviours with increases in gonorrhoea incidence *(17)*.

4.4. Burden of disease related to gonococcal infection

Given what is known about the proportion of untreated gonococcal cervical infections that cause upper genital tract disease such as infertility (Section 3.2), the global burden of adverse SRH outcomes due to gonococcal infection, especially in LMICs, could be substantial. However, gonococcal-associated disease outcomes have not been quantified with precision. During the 1980s, a large study reported that approximately 85% of female infertility in sub-Saharan Africa was due to tubal scarring resulting from infection *(55)*. However, few studies have been conducted since then to quantify the burden of infertility in different settings and the likelihood that gonorrhoea was a contributing factor. Quantifying this burden is difficult because adverse SRH outcomes have multiple infectious causes. In addition, outcomes such as infertility and ectopic pregnancy may only be recognized years after infection. Several trials are underway to assess adverse pregnancy outcomes that may be prevented by screening and treating for STIs, including gonococcal infection *(30)*.

5. Antimicrobial resistance

N. gonorrhoeae AMR is a major public health concern globally *(2, 56, 57)*. Since antibiotics were first used to treat *N. gonorrhoeae*, the organism has evolved or acquired resistance to multiple classes of antibiotics through nearly all known molecular, biochemical, metabolic and physiological AMR mechanisms, including the ability to rapidly and efficiently exchange partial or whole genes (*transformation*) with many nonpathogenic, commensal *Neisseria* species *(59)*. *N. gonorrhoeae* is a WHO high-priority pathogen for research and development because of increasing AMR to extended spectrum cephalosporins, which is the only remaining first-line monotherapy for gonorrhoea *(2, 56, 60)*.

WHO's Gonococcal Antimicrobial Surveillance Programme (GASP) laboratory network included 73 participating countries as of 2018. During 2017–2018, decreased susceptibility or resistance to ceftriaxone was reported by 21 (31%) of 68 reporting countries and to cefixime by 24 (47%) of 51 reporting countries *(2)*. In addition, six countries, primarily in the WHO Western Pacific Region, reported ≥5% of isolates with either decreased susceptibility or resistance to ceftriaxone, and nine countries, mainly in Europe, reported ≥5% of isolates with either decreased susceptibility or resistance to cefixime *(2)*. Most countries reporting to GASP are HICs; data are lacking in many settings, particularly in LMICs.

Verified clinical treatment failures with extended spectrum cephalosporins have occurred sporadically in several countries since the early 2000s, initially just with cephalosporin monotherapy and, more recently, with currently recommended dual therapy with ceftriaxone plus azithromycin *(2, 61, 62)*. Most of these treatment failures have been for pharyngeal infection, potentially related to reduced bioavailability of antibiotics in the oropharynx relative to anogenital sites, among other factors *(2)*. However, dual therapy treatment failure has now been documented for urethral infection with a *N. gonorrhoeae* isolate, with confirmed combined high-level azithromycin resistance and ceftriaxone resistance *(61)*.

Bacterial colonies to be selected for AMR testing.

6. Existing interventions for gonorrhoea management and control

Given the variability in gonococcal epidemiology between countries, which is related to the equally great variability in access to healthcare, several approaches to gonococcal infection prevention, management and control exist.

6.1. Primary prevention

Primary prevention of gonococcal infection currently consists of comprehensive sex education and condom promotion, which are essential but have had limited sustained success on their own, given difficulties in maintaining safer sex behaviour over time. In particular, condom use among MSM and other populations at higher risk has decreased in the context of expanding biomedical options for HIV prevention *(63)*.

6.2. Diagnosis of gonococcal infection

In much of the world, particularly LMICs, gonorrhoea management involves a syndromic approach, using a constellation of symptoms to guide treatment without the use of diagnostic tests. With respect to identifying gonococcal infections, the syndromic approach works better for men who are more likely than women to have symptoms. In women, the vaginal discharge syndrome is poorly predictive of gonococcal cervical infection *(64, 65)*. Gonococcal urethritis in men can also be diagnosed using Gram stain microscopy, which can be done at the point-of-care but is not available in all settings. Gram stain microscopy is not sufficiently sensitive for diagnosing cervical infections in women and extragenital infections in both sexes.

Accurate *N. gonorrhoeae* NAATs exist for etiologic diagnosis of symptomatic gonococcal infection and screening for asymptomatic infection. Laboratory-based NAATs are expensive, do not yield rapid results, and often require infrastructure and technical staff capacity that are inaccessible in many low-resource settings *(65)*. Work is underway to expand availability of accurate diagnostics for gonococcal infection that are affordable and can feasibly be performed at or near the point-of-care *(66)*. *N. gonorrhoeae* culture is not as sensitive as NAATs and is more complicated to obtain, but is currently essential for comprehensive gonococcal AMR testing. Efforts are also underway to develop rapid phenotypic approaches and genetic point-of-care tests for gonococcal AMR *(67)*.

6.3. Treatment of gonococcal infection

Existing WHO guidelines recommend dual therapy, with an extended spectrum cephalosporin plus azithromycin as a single dose to treat uncomplicated gonococcal infection *(34)*. The regimen currently has high cure rates but is being threatened by steadily progressive gonococcal AMR (Section 5). At least two new antibiotics for gonorrhoea are in clinical trials, but it is unclear when a candidate will become widely available for global use *(68)*. Given the propensity of *N. gonorrhoeae* to develop or acquire resistance to multiple classes of antibiotics, AMR will likely continue to be a concern for current and future antibiotics. Efforts are ongoing to ensure appropriate antimicrobial stewardship, improved diagnosis to guide antibiotic use, and further combination therapy approaches *(2)*. Additional interventions, such as microbicides and mouthwashes, are also being studied *(69)*.

6.4. Gonorrhoea control programmes

Gonorrhoea control programmes have revolved around primary prevention through condom promotion, finding and treating people with gonococcal infections, and finding and treating sex partners of those infected. The extent to which each of those components is conducted in different settings, however, is widely variable, based primarily on healthcare resources, infrastructure and political commitment. In most LMICs, dependence on syndromic management has left most gonococcal infections, which are asymptomatic, undiagnosed. In these settings, screening for gonococcal infection using NAATs is only recommended for populations at particularly high risk for gonococcal infection, but this is only sporadically implemented, due to cost and feasibility concerns *(49)*.

Several countries with greater resources have built effective public health programmes for gonorrhoea that not only test and treat people with symptomatic infection, but also screen broader populations for gonococcal infection and attempt to contact and treat the sex partners of infected people. Many of these programmes have been associated with decreased incidence of gonococcal infection and, in all probability, of diseases such as PID and infertility as well *(70–72)*. However, these settings have observed recent increases in the incidence of gonococcal infection, in particular among MSM *(47, 48, 52, 54)*.

7. Public health value considerations for gonococcal vaccines

Given the challenges with existing interventions and the increasing threat of AMR, gonococcal vaccines are, in all likelihood, the best option for the future sustainable control of gonococcal infection. AMR, in particular, increases the value of vaccines relative to other approaches of controlling gonococcal infection. Historically, vaccines have been used for many decades against a wide range of pathogens without generating clinically significant AMR, unlike antibiotics *(73, 74)*. In addition, vaccines can potentially reduce AMR by directly preventing gonococcal infections, including resistant infections, by interrupting transmission and by reducing antibiotic use and thus selective pressure *(75)*.

The potential value of gonococcal vaccines in meeting global public health and societal needs was discussed at the 2019 WHO-convened meeting of experts; related considerations, country perspectives and research needs are found in the meeting report *(15)*. The greatest potential value of gonococcal vaccines lies in the ability to prevent the most morbid gonococcal-related SRH outcomes, such as infertility and pregnancy complications. However, more precisely defining that value will depend on obtaining better data on the burden of these outcomes in diverse settings, including in LMICs. In addition, the value will depend on to what extent gonococcal AMR is likely to increase, over what period, and how that might translate into treatment failures, lengthier and more costly treatment regimens, and increases in infection and disease outcomes.

Given the global need for gonococcal vaccines in both HICs and LMICs, these vaccines should not only be cost-effective but also affordable, so that price is not a barrier to access, including for LMICs.

7.1. Modelling of gonococcal vaccine impact

Mathematical modelling can be used to predict current and future trends in *N. gonorrhoeae* infection, disease and AMR; the potential impact of gonococcal vaccines; and the vaccine characteristics that could affect impact *(76–80)*. Existing modelling studies suggest that gonococcal vaccines might not require high efficacy to have substantive population effects *(76, 79, 80)*. Even with gonococcal vaccine efficacy of only 20–30%, similar to what was observed in studies of OMV-based MenB vaccines and gonorrhoea in New Zealand *(4, 81)*, vaccination could result in substantial decreases in gonococcal infections if vaccine coverage is high and if protection lasts over the highest-risk period for acquiring infection *(76, 79, 80)*. A model looking at the predicted impact of gonococcal vaccination on AMR suggested that vaccines with low efficacy can delay but not prevent AMR, but vaccines with efficacy of 70% or more (with uptake of 40% among MSM with high levels of sexual activity) can prevent the spread of gonococcal AMR and potentially eliminate gonorrhoea *(82)*.

The models also allow investigation of the predicted impact of vaccinating different populations. In one model in an HIC setting, assuming all adolescents aged 13 years in a population received either a nonwaning gonococcal vaccine with 50% efficacy, or a 100% efficacious vaccine, waning after 7.5 years, gonococcal infection prevalence was predicted to be reduced by 90% after 20 years *(76)*. In some settings, gonococcal transmission within a higher-risk group may maintain gonococcal transmission in the whole community. In these settings, targeted vaccination could result in more efficient reductions in gonococcal infection prevalence, even with lower vaccine efficacy and duration of protection, provided a large proportion of the target group can be reached. A model evaluating gonococcal vaccination of all MSM attending sexual health clinics in England predicted that gonococcal incidence could be reduced by 90% over 10 years, either by using a vaccine with approximately 50% protection, lasting 6 years, or one with 70% protection, lasting 3 years *(80)*. Similar modelling studies have not been conducted for LMIC settings.

Young adult in Sierra Leone. ©WHO /Stéphane Saporito

8. Gonococcal vaccine development

The feasibility of developing gonococcal vaccines has been questioned in the past because of the antigenic variability of *N. gonorrhoeae* and its ability to cause repeated infections without inducing protective immunity *(5, 83, 84)*. However, new insights into the immunopathogenesis of gonococcal infection, and emerging data on MenB vaccines and potential cross-protection against *N. gonorrhoeae,* have led to an array of promising approaches to vaccine development.

8.1. Feasibility of gonococcal vaccine development

8.1.1. Gonococcal immunobiology

N. gonorrhoeae has evolved complex strategies to modulate and evade host innate and adaptive immune responses *(5, 83)*. As a result, protective immunity to natural infection does not appear to develop, and repeat infections are common *(5, 84–86)*. No immunologic correlates of protection are known. In addition to extensive variation in the expression and specificity of many gonococcal surface antigens, poor development of a protective immune response after gonococcal infection is likely related to induction of a strong, pro-inflammatory Th17 cellular response to infection, which suppresses Th1 and Th2 cell-mediated adaptive immune responses *(5, 87)*. Development of immunity may also be impeded by development of antibodies to the surface reduction modifiable protein (Rmp, also known as outer membrane protein III), which physically block the attachment of antibodies to other surface antigens *(88)*. Thus, gonococcal vaccines will need to induce protective immune responses that are superior to the responses generated during natural infection.

These challenges related to the immunobiology of gonococcal infection thwarted early vaccine development efforts *(5)*. However, recent advances in whole-genome sequencing, proteomics, immunoproteomics and molecular pathogenesis research, similar to the methods used to develop OMV-based MenB vaccines, have resulted in identification of several new, stably expressed and highly conserved antigens that may be effective gonococcal vaccine targets *(5, 83)*.

8.1.2. Serogroup B meningococcal vaccines and gonorrhoea

Optimism about the biologic feasibility of developing gonococcal vaccines has increased because of mounting evidence suggesting OMV-based MenB vaccines may provide cross-protection against gonococcal infections. Given poor immunogenicity of the MenB polysaccharide capsule and its potential cross-reaction with human antigens, MenB vaccines have been OMV- and/or protein-based, rather than the polysaccharide-protein conjugate vaccines that prevent diseases due to other meningococcal serogroups *(89)*. Where these OMV-based MenB vaccines have been used on a large scale, temporally related decreases in gonococcal infection incidence have been observed *(4, 90–92)*. For example, in Cuba, STI surveillance data showed a marked reduction in gonorrhoea incidence, in contrast to other STIs, following mass vaccination of 3-month-olds to 19-year-olds with a locally developed OMV-MenB vaccine *(91)*. This phenomenon was also observed in New Zealand after a mass vaccination campaign with an OMV-based MenB vaccine in response to a MenB outbreak *(4)*. These ecological data were followed up in New Zealand with a case-control study, in which MenB vaccination and gonorrhoea outcome data were linked for analysis. MeNZB, the New Zealand OMV-based MenB vaccine, had an estimated 31% (95% CI: 21–39%) vaccine effectiveness against gonococcal infection among 15 to 30-year-olds attending sexual health clinics *(4)*. A national cohort study of gonorrhoea hospitalizations was also conducted among 1.1 million people eligible for MeNZB vaccination. Adjusted vaccine effectiveness against gonococcal-associated hospitalization was estimated to be 24% (95% CI: 1–42%) for the entire cohort and 47% (95% CI: 18–66%) in those vaccinated during adolescence *(81)*.

OMVs are spherical buds of the outer membrane expressing surface antigens and filled with periplasmic and cytoplasmic proteins produced by *Neisseria* species *(92, 93)*. Several antigens present in OMV-based MenB vaccines are conserved across *N. meningitidis* and *N. gonorrhoeae (92–94)*. In a study evaluating sera from people vaccinated with 4CMenB, a licensed MenB vaccine that includes the MeNZB OMV plus three additional antigens, high levels of antibodies induced by vaccination were found to recognize gonococcal antigens *(94)*. 4CMenB also accelerated clearance of *N. gonorrhoeae* in a mouse genital tract infection model *(95)*. Although relevant antibody responses may be short-lived *(4)*, the observational and basic science findings, taken together, provide encouragement that gonococcal vaccines are biologically feasible.

8.2. Gonococcal vaccine development approaches

As of August 2020, the product pipeline for new vaccines against *N. gonorrhoeae* was in the discovery and preclinical stages of development, focusing on the identification of vaccine targets and immune correlates of protection and evaluation in animal models, with gonococcal vaccine candidates not yet being evaluated in human clinical trials *(5, 96)*. However, randomized controlled clinical trials of licensed OMV-containing MenB vaccines to prevent gonococcal infections have either started, or are planned to start, in Australia, Thailand and the United States *(97, 98)*.

Recent reviews have summarized the most promising antigenic targets, immunologic approaches, and current research and development efforts for gonococcal vaccines *(5, 83, 84, 96)*. The main vaccine approaches include meningococcal OMV vaccines, gonococcal OMV vaccines, a lipooligosaccharide (LOS) epitope and purified protein subunit vaccines *(83, 96)*. Additional strategies involve formalin-inactivated whole-cell *N. gonorrhoeae*, virus-like particles, DNA and mRNAs *(99)*. Vaccine candidates based on these approaches are undergoing evaluation using a variety of different antigen-delivery systems and adjuvants. Novel vaccine delivery systems in development include viral vectors, protein scaffolds, liposome preparations, nanoparticles or nanodiscs, and microarray patches *(5, 96, 99)*.

A meningococcal OMV approach could involve use of existing OMV MenB vaccines, which are currently or soon to be evaluated in clinical trials for efficacy against gonococcal infection *(97, 98)*, or use of new meningococcal OMV vaccines that have been specifically designed to expand or optimize protection against gonorrhoea. Because of the immunosuppressive properties of *N. gonorrhoeae*, adjuvants or other strategies that avoid or reverse gonococcal-mediated immunosuppression may be critical for gonococcal OMV-based vaccines *(100)*. Given their preclinical status, vaccine candidates designed specifically to optimize efficacy against gonococcal infection, whether OMVs, LOS, purified protein subunits or other approaches, may take a decade or more to become available for use. Thus, expanding the indication of an already licensed MenB vaccine could be an expedited or interim measure for gonococcal control, even if vaccine efficacy is less than optimal. Clinical and immunologic findings from trials of OMV-based MenB vaccines will also provide insights to aid development of more gonococcal-specific vaccines.

Single-pathogen vaccine development is typically more straightforward than development of combination vaccines; however, different combinations of meningococcal-gonococcal vaccines incorporating common antigens or fusion proteins with sequences from both *N. meningitidis* and *N. gonorrhoeae* may be possible. A combined vaccine against gonococcal infection and other STIs would be a long-term goal, particularly chlamydial infection, given similar modes of transmission, sites of infection, acute disease syndromes and adverse SRH outcomes. This would still require evaluation and licensure for each pathogen.

8.3. Clinical development considerations

8.3.1. Preclinical evaluation and models of infection

Evaluation of gonococcal vaccine candidates is challenging, as no established surrogate markers or correlates of protection exist. Preclinical testing is based on measuring bactericidal or opsonophagocytic activity, surface-binding antibodies, inhibition of target function, and/or in vivo efficacy of candidate antigen formulations in a female mouse genital tract infection model *(5, 83, 96)*. Transgenic mice have been developed to alleviate some host restrictions, but mice do not fully mimic human infection or disease *(5, 83)*. A controlled human infection model (CHIM) with *N. gonorrhoeae* exists, consisting of experimental urethral infection among male volunteers *(101)*. The window of study is 1–6 days before infection needs to be treated, and the model is not widely available. Nonetheless, it can be used to assess infection rates upon exposure, measure antibodies, cytokines and cell subsets upon infection, and can provide a relatively rapid, less expensive way to conduct preliminary efficacy evaluations of vaccine candidates in humans *(101)*.

In addition, because currently licensed OMV-containing MenB vaccines might show some cross-protection against gonococcal infection, studies of antibody titres and cellular responses following immunization with these vaccines may provide insight into immune responses providing protection against gonococcal infection. Currently, post-licensure clinical studies of licensed MenB vaccines to determine humoral and cellular immune responses to gonococcal surface antigens are underway in Australia, the United States and Kenya *(97, 98)*.

8.3.2. Clinical trial and endpoint considerations

Vaccine indications reflect the main prevention outcomes to be evaluated in vaccine clinical trials, which in turn provide the basis for regulatory review, market authorization and commercial promotion. Possible indications for gonococcal vaccines include prevention of gonococcal infection (both asymptomatic and symptomatic) and/or specific gonococcal-associated disease outcomes, such as symptomatic urethritis, cervicitis or PID. It is presumed that vaccines preventing gonococcal infection will ultimately prevent the adverse SRH consequences and AMR associated with those infections.

Disease indications may be preferred by regulators over infection indications, although not always, and might be easier to market. However, for several reasons, a primary disease indication may be less desirable for gonococcal vaccines. First, many gonococcal infections are asymptomatic but can still lead to adverse outcomes, particularly in women. With selection of a primary disease indication, a vaccine might show reductions in disease endpoints in a trial but leave residual asymptomatic infections that could still lead to adverse SRH outcomes or propagate AMR. Second, gonococcal infection can be easily and accurately measured in clinical trials with NAATs, but adverse disease outcomes, such as upper genital tract disease in women, are more difficult to measure precisely and confidently ascribe an etiology *(23*, *102)*. Reliable biomarkers of gonococcal PID have not yet been identified. PID can be multifactorial and involve coinfections, particularly with chlamydia and organisms associated with bacterial vaginosis. Gonococcal PID also occurs less frequently than infection; therefore trials with this endpoint would be larger and more costly than trials with an infection endpoint. Finally, some important adverse outcomes may take years to develop following infection, such as infertility, or are best evaluated at a population level, such as AMR.

Given the lack of currently known immune correlates of protection, a large clinical end-point trial will, in all likelihood, be required for gonococcal vaccines. For an infection indication, efficacy trials of gonococcal vaccines would use reduction in gonococcal infections as measured by NAATs as the primary clinical endpoint. Site of infection will be an important consideration, particularly for MSM, among whom rectal and pharyngeal infections may be more common than urethral infections in some settings *(103)*. Infections at the pharyngeal site are also those most implicated in clinical treatment failures *(2)*, highlighting the potential importance of inducing immunity at nonurogenital sites. Ongoing and planned trials of MenB vaccines may provide insights into use of individual versus combined site-specific infection endpoints *(98)*. Collecting additional data about disease outcomes in clinical trials, such as symptomatic gonococcal urethritis, may offer additional indications beyond infection prevention.

Evaluating acquisition of AMR *N. gonorrhoeae* strains and collecting data on antibiotic use in clinical trials will provide valuable information, although the full benefit of vaccines in reducing the impact of AMR will likely need to be measured at the population level in post-licensure studies. Documenting the reduction in such adverse SRH outcomes as infertility and HIV acquisition and transmission in pre-licensure clinical trials is probably not feasible, due to the large number of people that would need to be enrolled and followed for many years. Post-licensure impact studies would most likely be needed to demonstrate the impact of vaccines preventing gonococcal infection in achieving the overarching, long-term public health goals.

At the LGBT Centre in Mongolia. © WHO

9. Considerations for vaccine implementation

How gonococcal vaccinations should be implemented to optimally meet public health goals will be determined by a complex interplay of factors, including the target populations receiving the vaccine, the vaccine characteristics, and various health systems and programmatic considerations.

9.1. Target populations

The main epidemiologic patterns affecting choice of target populations are differences in gonococcal incidence by geographical location, age and risk group (Section 4). In all settings, gonococcal infections are more common in older adolescents and young adults (15–24 years) than in other age groups, but the overall burden of infection in those ages in the general population varies by geographical location. LMICs with less health infrastructure tend to have a greater burden in general populations, but wide variability can exist among countries, reflecting differences in sexual behavior patterns and sexual networks, among other factors. In HICs, in particular, gonococcal transmission is associated with key and vulnerable populations, such as MSM, and higher incidence can extend into older ages.

Because gonococcal infections among all people can contribute to and be affected by AMR, all can have disease consequences, and for general equity reasons, gender-neutral vaccination is desirable. However, the most direct serious gonococcal disease outcomes are among women. In general populations, vaccinating females only could provide direct benefits to them and indirect benefits to others through herd immunity, as has been observed with HPV vaccination of adolescent girls *(104)*. Therefore, although gender-neutral gonococcal vaccination is preferred, additional information about vaccine efficacy in males and females, and the relative cost-effectiveness of different vaccination strategies, could help refine preferences related to gender-neutral versus gender-specific vaccination *(105)*.

Pregnant women may fall into the age category of young people targeted for vaccination; however, maternal immunization has not been identified as a particular need for gonococcal vaccines, given no clear increased susceptibility to gonococcal infection in this group, widely available and affordable ocular prophylaxis for infants to prevent neonatal conjunctivitis, and lack of clarity on the burden of other adverse pregnancy outcomes related to gonococcal infection. Ongoing randomized controlled trials of gonococcal screening and treatment during pregnancy to prevent adverse birth outcomes could clarify whether this group should receive special consideration *(30)*.

9.2. Vaccine characteristics

Ideally, gonococcal vaccines would be delivered in a way that covers all those at risk of acquiring infection before the risk starts, with optimal protection throughout the period of substantial risk. However, pragmatic decisions about when, how and whom to vaccinate will depend on vaccine characteristics. Vaccine efficacy in preventing infection, disease or transmission helps determine population impact and cost effectiveness according to different target groups or delivery strategies.

Choice of target group and delivery strategy will also be affected by vaccine efficacy in those with previous exposure to infection and by the proportion of each group previously exposed. On one hand, effectively immunizing people who have had prior gonococcal infection may be more difficult than immunizing people naïve to infection, due to development of antibodies to Rmp (OMPIII) during natural infection that blocks access of other antibodies to important epitopes *(88)*. This phenomenon would increase the importance of vaccinating prior to sexual debut, but would not be as important for protein subunit vaccines or for OMV-based vaccines in which the *rmp* gene has been deleted *(88)*. On the other hand, it is also possible that prior gonococcal infection might prime the adaptive immune system, resulting in a booster effect with vaccination.

In addition to efficacy, vaccine characteristics affect the programmatic (for example, dose regimen) and biological (for example, durability of protective immunity) feasibility of achieving and sustaining immune protection, respectively. Duration of vaccine protection is a key consideration for determining the appropriate age at vaccination. Evidence regarding OMV-based MenB vaccines suggests possible cross-protection might be short-lived *(4)*. Clearly, the longer the duration of protection, the greater flexibility to vaccinate at earlier ages to achieve benefits through incorporation into other vaccination programmes, such as the HPV vaccine *(105)*. The full duration of immune protection will in all likelihood not be known before initial licensure of a gonococcal vaccine. Efforts to determine correlates of protection and collect other data that may provide insight into the dynamics of the immune

response will be useful in predicting the durability of protection. First-generation vaccines might have shorter durations of protection, which could be improved upon over time.

9.3. Programmatic considerations

Vaccination delivery strategies are tightly linked to the intended target populations and are influenced by an array of health systems and programmatic factors, such as existing vaccination infrastructure. For example, adding gonococcal vaccines to an adolescent vaccination platform, where HPV vaccine is already being delivered, not only makes reaching this target population more feasible, but also more cost-effective due to shared delivery costs. In the past, targeted vaccination programmes focusing on key or vulnerable populations have been difficult to implement *(106)*. However, expansion of PrEP and other HIV prevention programmes for specific populations might provide more efficient platforms for targeted gonococcal vaccination. Furthermore, if gonococcal vaccines have adequate efficacy among those with prior infection, or even a booster effect, administering the vaccine to people diagnosed with gonococcal infection and their partners, and potentially others seeking care for STIs, would be a tailored way of finding those at highest risk.

Considerations related to the epidemiology of infection in different settings, the choice of target populations, vaccine efficacy and duration of protection, and programmatic issues will combine to determine the most impactful and cost-effective strategies to implement gonococcal vaccines. In countries with higher prevalence of gonococcal infections among young sexually active general populations, broad-based vaccination of adolescents before sexual debut would be ideal. The duration of vaccine protection will need to be sufficiently long, such as 10–15 years or more, to cover the period of highest gonococcal risk if it will be infeasible to administer booster doses. More narrowly focused strategies to reach specific populations may be prioritized in countries with low prevalence of gonococcal infection within the general population but with high prevalence in key or vulnerable populations, or if the duration of vaccine protection is likely to be short, such as 2–3 years.

Acceptability of gonococcal vaccines to potential vaccine recipients (and their parents in the case of adolescents) will be a critical component of any gonococcal vaccine delivery strategy. Many countries achieve excellent coverage rates for most vaccines, and vaccines are highly acceptable, while other countries are increasingly affected by vaccine hesitancy. Demonstration of safety and efficacy is essential to counter vaccine hesitancy, but other factors are also important, particularly for STI vaccines, which may be perceived as stigmatizing *(15)*. HPV infection is an STI, but HPV vaccines are not typically viewed as STI vaccines but rather as vaccines to prevent cervical cancer. Gonococcal vaccines may be more clearly associated with an STI. Communication and marketing strategies regarding gonococcal vaccines should be considered in advance, with input from communities affected by gonorrhoea.

Finally, a critical factor in global access and uptake of vaccines relates to their costs. In addition to direct vaccine costs and immunization delivery costs, which may be influenced by the route of vaccine administration, the vaccination regimen and the delivery platform should be amenable to affordable supply so as to increase accessibility of the vaccine, including in LMICs.

Adolescents in India participating in a sexuality education session. © International Women's Health Coalition

10. Preferred product characteristics for gonococcal vaccines

The strategic public health goals for gonococcal vaccines for global use (section 2.2) form the basis of the WHO PPCs for gonococcal vaccines, with an emphasis on the potential benefits of these vaccines in meeting the needs and perspectives of both LMICs and HICs. Table 1 outlines the preferred characteristics and notes related to "ideal" gonococcal vaccines, namely, those specifically formulated to optimize efficacy against gonococcal infection and related adverse SRH outcomes, and includes additional notes for MenB vaccines with potential cross-protection against gonococcal infection.

Table 1. Preferred product characteristics for gonococcal vaccines

Parameter	Preferred characteristic	Notes for gonococcal vaccines	Additional notes for MenB vaccines with potential cross-protection[1]
Vaccine type	Gonococcus-specific vaccine.	Vaccines specifically formulated to optimize efficacy against gonococcal infection and related adverse SRH outcomes[2] are preferred. Although several potential candidate gonococcal antigens exist, as of 2020 no vaccines designed *de novo* for gonococcal infection were in clinical trials. As a result, the product development pathway for gonococcus-specific vaccines is still long, possibly 10–12 years. Gonococcal vaccines must be suitable for use globally because substantial numbers of gonococcal infections occur in all countries, regardless of their stage of economic development.	In observational studies, OMV-based MenB vaccines appeared to provide cross-protection against *N. gonorrhoeae* with an estimated vaccine effectiveness of 20–30% in preventing gonococcal infection and related hospitalizations. A MenB vaccine with an indication to prevent gonococcal infection and/or disease may be available well before a licensed gonococcus-specific vaccine, and therefore may provide an earlier intervention for gonococcal prevention and control. In addition to evaluating existing licensed OMV-based MenB vaccines in ongoing trials, other options include developing new meningococcal vaccines that provide greater cross-protection against gonococcal infection and disease.

1 Many of the notes in the "gonococcal vaccine" column also apply to a MenB vaccine with an added indication to prevent gonococcal infection. This column is intended to supplement the notes with additional considerations, or how the preferred characteristics might be thought about differently if a licensed MenB vaccine shows some efficacy against gonococcal infection and/or disease.

2 Adverse SRH outcomes related to gonococcal infection include acute gonococcal disease (e.g. urethritis, cervicitis, proctitis, pharyngitis, conjunctivitis) AND complications of initial infection affecting SRH (e.g. pelvic inflammatory disease, infertility, ectopic pregnancy, chronic pelvic pain, epididymo-orchitis) AND associated adverse clinical outcomes of pregnancy (e.g. chorioamnionitis, premature rupture of membranes, preterm birth, neonatal conjunctivitis) AND gonococcal-related HIV acquisition and transmission AND rarer complications (e.g. disseminated gonococcal infection, urethral stricture).

Parameter	Preferred characteristic	Notes for gonococcal vaccines	Additional notes for MenB vaccines with potential cross-protection[1]
Vaccine indication	Prevention of gonococcal infection.	The ultimate, long-term goals of gonococcal vaccines are to prevent adverse SRH outcomes and reduce the impact of gonococcal AMR. These goals will best be accomplished by the indication of preventing gonococcal infection, for the following reasons: • Most gonococcal infections are asymptomatic but can still lead to adverse SRH outcomes, particularly in women; and • A vaccine may show efficacy in a trial with a disease endpoint but leave residual asymptomatic infections that could still lead to adverse SRH outcomes or propagate AMR. Existing molecular diagnostic assays can easily and accurately measure gonococcal infection as an outcome variable in Phase III clinical trials, including at different sites of infection. Many gonococcal disease outcomes, such as upper-genital tract infections and complications in women, are more difficult to measure. Collecting data on measurable disease outcomes in clinical trials, such as symptomatic gonococcal urethritis in men, may offer additional vaccine indications beyond infection. Vaccine impact on most adverse SRH outcomes and AMR would likely be difficult to demonstrate in pre-licensure clinical testing. Consideration should be given to collecting supporting evidence for a positive impact on these outcomes during pre-licensure studies and designing post-licensure studies to evaluate them.	Planned clinical trials to determine the specific efficacy of OMV-based MenB vaccines to prevent gonococcal infection can provide insight on clinical endpoints for measuring gonococcal infection and other short-term disease outcomes; for example, the relative incidence of different outcomes according to anatomical site (urogenital, oropharyngeal and/or rectal). If already licensed OMV-based MenB vaccines show some efficacy against gonococcal infection, measuring their impact on adverse SRH outcomes and AMR could be done sooner and in parallel with developing more optimized gonococcal vaccines.

1 Many of the notes in the "gonococcal vaccine" column also apply to a MenB vaccine with an added indication to prevent gonococcal infection. This column is intended to supplement the notes with additional considerations, or how the preferred characteristics might be thought about differently if a licensed MenB vaccine shows some efficacy against gonococcal infection and/or disease.

Parameter	Preferred characteristic	Notes for gonococcal vaccines	Additional notes for MenB vaccines with potential cross-protection[1]
Target populations	Young people AND/OR Specific populations at higher risk for gonococcal infection.	WHO defines young people as those between the ages of 10 and 24 years, including adolescents (10–19 years) and young adults (20–24 years). Specific populations at higher risk for gonococcal infection are defined here in two categories: key and vulnerable populations. • Key populations for gonococcal infection are disproportionately affected in most contexts and include men who have sex with men (MSM), sex workers, transgender people and people living with HIV (PLHIV). • Vulnerable populations are at higher risk for gonococcal infection in certain situations or contexts that may vary between and within countries. Some examples include: incarcerated people; ethnic minorities or Indigenous populations with historical barriers to healthcare access; and migrants or young people living in communities with known high rates of gonococcal infection or HIV, especially young women, who have the greatest risk of adverse SRH consequences from gonococcal infection. The choice of broad-based vaccination of young people and/or targeted vaccination of specific populations at higher risk for gonococcal infection in different settings will depend on factors such as: • gonococcal epidemiology • vaccine efficacy in those with prior infection • duration of vaccine protection • cost-effectiveness analyses • programmatic considerations (see "Vaccine delivery strategy" below). These factors can also help refine the precise age range to be targeted among young people. Universal vaccination of young people before first sexual exposure to gonococcal infection, and aligned with existing vaccine delivery infrastructure, would be ideal, but would require durable vaccine protection and favourable cost-effectiveness analyses. It is currently unknown whether prior gonococcal infection will affect gonococcal vaccine efficacy, which may influence vaccine effectiveness among higher-risk populations. Gender-neutral vaccination is desirable, because gonococcal infections can lead to disease consequences in all people, infections in all people contribute to, and are affected by, AMR, and for general equity reasons.	The incidence of invasive MenB disease has substantial variability by geographic location and over time. The highest incidence is among infants, but disease occurs at all ages. Outbreaks can affect multiple age groups. In HICs that use MenB vaccines, infant vaccination is emphasized; however, a few countries recommend MenB vaccines for young people living in areas where close contact is frequent (for example, people entering university or the military) or for special populations. These populations may overlap with potential target populations for gonococcal vaccines. Many LMICs with a high prevalence of gonococcal infection in the general population either do not appear to have significant MenB disease incidence or do not utilize MenB vaccine widely because the cost is prohibitive. Better data are needed to understand the epidemiological overlap and populations at risk for both pathogens, as well as to understand the factors contributing to MenB vaccine use in different settings. If the preferred target populations in a setting comprise only a small proportion of the population, expanding an existing licensed vaccine may be more favourable economically than developing a *de novo* vaccine for that group.

1 Many of the notes in the "gonococcal vaccine" column also apply to a MenB vaccine with an added indication to prevent gonococcal infection. This column is intended to supplement the notes with additional considerations, or how the preferred characteristics might be thought about differently if a licensed MenB vaccine shows some efficacy against gonococcal infection and/or disease.

Parameter	Preferred characteristic	Notes for gonococcal vaccines	Additional notes for MenB vaccines with potential cross-protection[1]
Vaccine efficacy	50 to 70% efficacy or greater.	Existing mathematical models suggest that a vaccine with 50% efficacy or greater could have a marked effect in reducing gonococcal infection prevalence at a population level, particularly if vaccine coverage is high and protection lasts through periods of highest gonococcal infection risk. Preferred vaccine efficacy levels will be refined with updated vaccine impact models, input from key stakeholders, and further information about likely vaccine characteristics from ongoing research. If MenB vaccines are found to provide cross-protection and are being used for prevention of gonococcal infection, gonococcus-specific vaccines should have significantly superior efficacy.	Observational studies suggest the effectiveness of an OMV-based MenB vaccine against gonococcal infections may be 20–30%, which models predict could still have a substantial effect in reducing prevalence of gonococcal infection in the population. A lower efficacy could be acceptable for broadening use of MenB vaccines to prevent gonococcal infection compared with use of a standalone gonococcal vaccine, given an existing indication for MenB disease prevention, particularly in countries with a history of MenB endemic disease and/or outbreaks.
Duration of protection	The long-term goal is at least 10–15 years' duration for vaccinating young adolescents without a booster. However, shorter durations of protection (e.g. 3–5 years) could still provide benefits for older age groups and specific populations at higher risk.	Ideally, vaccine-induced protection from gonococcal infection should last throughout the timeframe of highest risk of infection. Therefore, the optimal duration of protection depends on target age. In most settings, peak incidence appears to be in young adults (20–24 years). For young adolescents (10–14 years), duration of protection might need to be 10–15 years or more to cover the period of peak incidence, or a booster dose may be needed. However, for older adolescents or young adults, shorter durations of protection could cover the period of highest risk. Periods of high risk may be observed over shorter time frames, such as during the use of PrEP for HIV prevention. Therefore, for some populations at higher risk, a duration of protection of only 3–5 years may still have substantial benefits. Duration of vaccine protection will likely not be known at the time of initial licensure. Although the aspirational, long-term goal for duration of protection is at least 10–15 years, first-generation vaccines may have shorter durations of protection: for example, 3–5 years. Modelling of vaccine impact and cost-effectiveness can guide use of initial vaccines with potentially limited duration of protection in different epidemiologic settings. Research to determine correlates of protection will be valuable for predicting and assessing duration of protection, as will post-licensure effectiveness data.	The duration of protection of existing MenB vaccines against MenB disease is unknown, but most likely around 36 months following three doses in infancy. Similarly short-lived protection has been suggested in observational studies of MenB vaccines to prevent gonococcal infection. Therefore, one or more booster doses may be required to cover the period of highest risk for gonococcal infection.

1 Many of the notes in the "gonococcal vaccine" column also apply to a MenB vaccine with an added indication to prevent gonococcal infection. This column is intended to supplement the notes with additional considerations, or how the preferred characteristics might be thought about differently if a licensed MenB vaccine shows some efficacy against gonococcal infection and/or disease.

Parameter	Preferred characteristic	Notes for gonococcal vaccines	Additional notes for MenB vaccines with potential cross-protection[1]
Vaccine delivery strategy	Young people: alignment with existing vaccine delivery infrastructure. Populations at higher risk: integration with HIV prevention programmes and other SRH services.	The most appropriate vaccine delivery strategies in different settings will be determined by target populations, vaccine characteristics, and related health systems and programmatic factors. Universal vaccination of young people may be more straightforward programmatically than delivering vaccine in a targeted fashion to higher-risk populations, who may be harder to identify and reach. Gonococcal vaccination in early adolescence would allow use of existing adolescent vaccine delivery infrastructure. However, the effectiveness of this approach would depend on duration of vaccine protection. In settings where gonococcal infection incidence is low in the general population but concentrated within specific populations at higher risk, a more focused vaccination programme might more efficiently interrupt community-wide transmission, depending on how easily these populations can be reached. Demand sizing and evaluation of care-seeking patterns of specific target populations will be informative. Although targeted vaccination programmes have been difficult to implement in the past, the expansion of HIV prevention programmes and other SRH services, such as increasing use of PrEP and outreach programmes for key populations, might offer novel opportunities to deliver more focused gonococcal vaccination. Communication, community outreach and marketing strategies regarding gonococcal vaccines should be considered in advance. Unlike HPV vaccines, which are widely seen as cancer-prevention vaccines, gonococcal vaccines will likely be more clearly associated with a sexually transmitted infection, which may affect acceptability, particularly to parents of adolescents.	In settings where target populations for MenB vaccine already include young people, such as those entering university or military recruits, vaccinating with an OMV-based MenB vaccine to also prevent gonococcal infection would be relatively straightforward. Adoption and uptake of existing MenB vaccines remain relatively low globally. Expanding the indication of an existing MenB vaccine to include gonococcal infection prevention could make this vaccine more cost-effective and may affect the decision to introduce MenB vaccines in more countries and in new target populations. Meningitis may be perceived as less stigmatizing than gonococcal infection. Initial promotion of the use of MenB vaccines with some potential to prevent gonococcal infection among adolescents may increase acceptability of a specific gonococcal vaccine later.

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Parameter	Preferred characteristic	Notes for gonococcal vaccines	Additional notes for MenB vaccines with potential cross-protection[1]
Route of vaccine administration	Oral or parenteral delivery.	Local mucosal immunity likely plays an important role in protection against gonococcal infection. An oral mucosal route is preferred for ease of administration in LMIC settings. Mucosal delivery via other routes, such as intra-nasal, might induce appropriate immune responses but will be more difficult to deploy, particularly in resource-constrained settings. Parenteral routes of administration include intramuscular and subcutaneous injections and intradermal routes, which can be needle-free, such as via a transdermal or microarray patch. Needle-free methods are preferred for ease of administration. Vaccine presentation and stability characteristics that facilitate storage and deployment in LMIC settings should also be considered.	Observational studies of OMV-based MenB vaccines suggest that protective mucosal immunity against gonococcal infection can result from a parenteral vaccine.
Adjuvant	Preference for no adjuvant unless required for immunogenicity.	Adjuvant could be included if proven enhancement of vaccine immunogenicity and efficacy is demonstrated in primary target populations. Adjuvant formulations with previously demonstrated safety profiles in the target population are likely to be well tolerated.	Existing licensed OMV-based MenB vaccines are adjuvanted with aluminium hydroxide.
Schedule	Ideally, up to two doses for primary immunization.	Depending on the vaccine platform and formulation, two to three doses may be required for strong and durable immunity. Research should determine the requirements for alternative primary dosing or booster doses. This might be post-licensure, as for HPV vaccines. If more than one dose is needed, aligning the dosing schedule with existing delivery platforms, such as the vaccine delivery schedule for HPV or meningococcal vaccination, is preferable.	The typical vaccination schedule for available OMV-based MenB vaccines is a two-dose primary series, followed by a booster dose at 1 year of age for infants and a two-dose primary series for older ages, including adolescents and young adults. Because the period of highest risk for gonococcal infection is typically longer than the risk period for meningococcal infection, a booster dose will likely be needed if this vaccine is also intended to prevent gonococcal infection over longer periods.

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Parameter	Preferred characteristic	Notes for gonococcal vaccines	Additional notes for MenB vaccines with potential cross-protection[1]
Safety	A safety and reactogenicity profile at least as favourable as other WHO-recommended routine vaccines.	A favourable safety profile will need to be demonstrated in adults before progressing to vaccination of young adolescents, as was done for HPV vaccine.	The safety profile of licensed MenB vaccines has been established.
Concomitant use	Demonstration of favourable safety and immunologic noninterference upon coadministration with other vaccines recommended for use.	Lack of clinically important interference in immunogenicity for gonococcal vaccines and for coadministered vaccines, as well as the safety of coadministration, should be documented in post-licensure studies. Evidence should be collected on the ability to coadminister gonococcal vaccines with other vaccines given in similar target populations: for example, HPV; tetanus, diphtheria and acellular pertussis (Tdap); and meningitis vaccines in adolescents and young adults.	If OMV-based MenB vaccines are found to show cross-protection against gonococcal infection, evidence should be collected to evaluate for clinically important interference with this effect when MenB vaccines are coadministered with other vaccines.
Value assessment and affordability	The vaccine should be cost-effective and price should not be a barrier to access, including in LMICs. Dosage, regimen and cost of goods should be amenable to affordable supply.	Obtaining more comprehensive data on the burden of adverse health outcomes related to gonococcal infection, including in LMICs, will allow more precise quantification of the full potential value of gonococcal vaccines. The value of gonococcal vaccines is heavily influenced by increasing gonococcal AMR and its predicted effect on clinical treatment failures, the costs of treatment, and increases in gonococcal infection and disease outcomes.	The cost-effectiveness of existing MenB vaccines would become more favourable if they are found to prevent gonococcal infection in addition to MenB disease.
Prequalification and programmatic suitability	The vaccine should be pre-qualified according to the WHO process outlined (107).	WHO-defined criteria for programmatic suitability of vaccines should be met *(108, 109)*.	

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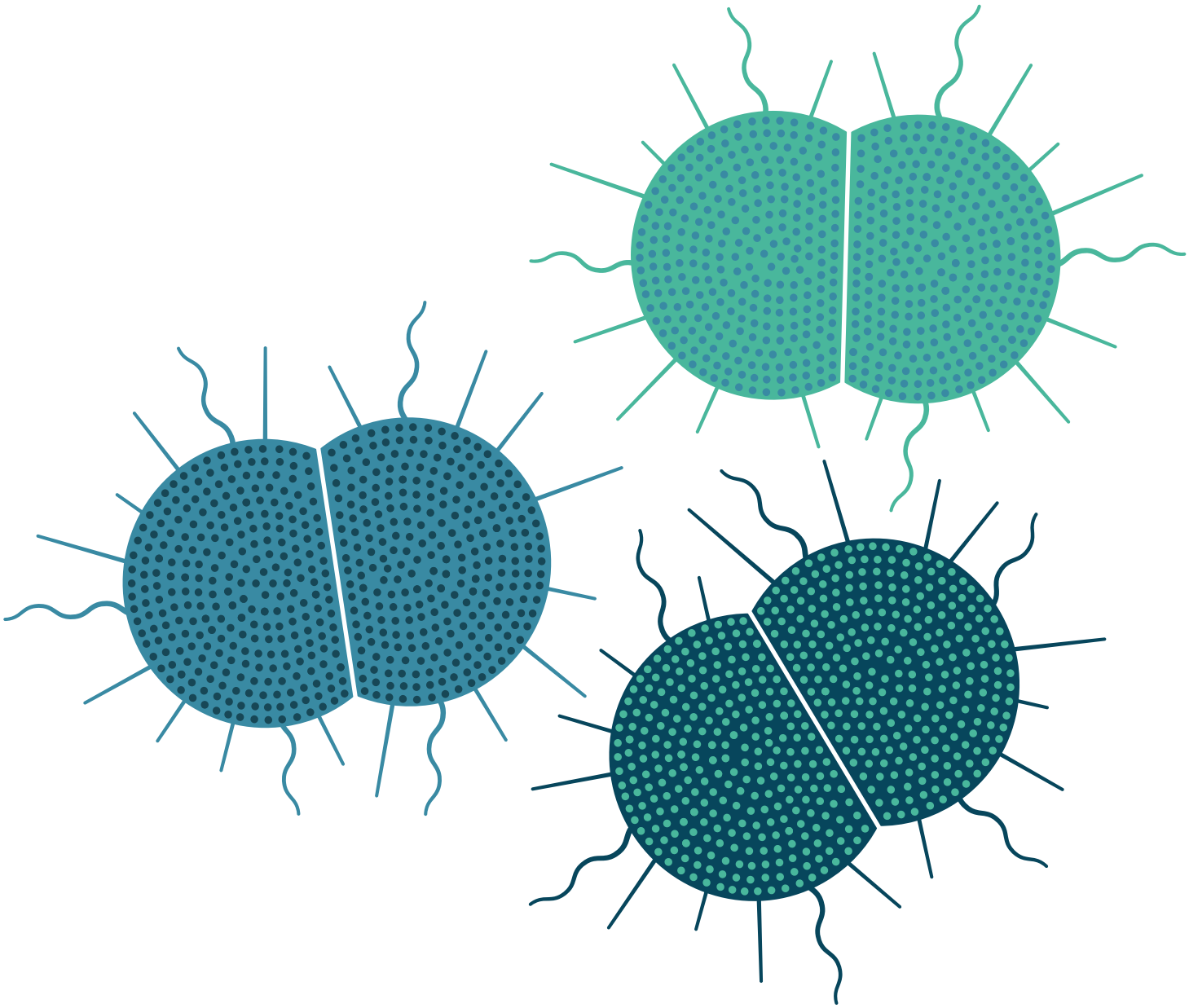

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