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MINI REVIEW

Emerging threat of antimicrobial resistance in *Neisseria gonorrhoeae:* pathogenesis, treatment challenges, and potential for vaccine development

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Abstract

The continuous rise of antimicrobial resistance (AMR) is a serious concern as it endangers the effectiveness of healthcare interventions that rely on antibiotics in the long run. The increasing resistance of *Neisseria gonorrhoeae*, the bacteria responsible for causing gonorrhea, to commonly used antimicrobial drugs, is a major concern. This has now become a critical global health crisis. In the coming years, there is a risk of a hidden epidemic caused by the emergence of gonococcal AMR. This will worsen the global situation. Infections caused by *N. gonorrhoeae* were once considered easily treatable. However, over time, they have become increasingly resistant to commonly used therapeutic medications, such as penicillin, ciprofloxacin, and azithromycin. As a result, this pathogen is developing into a true "superbug," which means that ceftriaxone is now the only available option for initial empirical treatment. Effective management strategies are urgently needed to prevent severe consequences, such as infertility and pelvic inflammatory disease, which can result from delayed intervention. This review provides a thorough analysis of the escalating problem of *N. gonorrhoeae*, including its pathogenesis, current treatment options, the emergence of drug-resistant mechanisms, and the potential for vaccine development. We aim to provide valuable insights for healthcare practitioners, policymakers, and researchers in their efforts to combat *N. gonorrhoeae* antibiotic resistance by elucidating the multifaceted aspects of this global challenge.

Keywords *Neisseria gonorrhoeae* · Antimicrobial resistant · Vaccine

Introduction

Throughout human history, *Neisseria gonorrhoeae*, a Gram-negative bacterium, has been a major pathogen responsible for the widespread transmission of gonorrhea, resulting in both symptomatic and asymptomatic sexually transmitted infections. This condition poses a considerable risk to individuals of all genders, often leading to urethritis and cervicitis, with males more likely to exhibit noticeable symptoms. Gonorrhea is transmitted via sexual contact involving the penis, vagina, mouth, or anus of a partner who is infected.

Infections involving Men who have Sex with Men (MSM) are higher than in other populations. One contributing factor that supports this favoring presence of gonorrhea-infected sites among MSM is their comparatively lower rate of partner notification in comparison to individuals engaged in heterosexual relationships. This practice gives rise to a situation wherein males afflicted with pharyngeal or rectal gonorrhea frequently remain untreated, despite potentially transmitting the infection to the urethra of a sexual partner (Fairley et al. 2017). Found, in a study done by Serra-Pladevall (2017), out of 107 patients of MSM, these populations are most likely to get infected with two strains: G2992 and G2400. The sites that are most commonly infected include the pharynx, urethra, and rectum (Barbee et al. 2014). However, the rectum is frequently affected by the infection of gonococci and earlier findings suggest gonococci can attach to the sperm, implying that the infection spreads quickly in men (Anderson et al. 2016).

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One of the most intriguing and enigmatic aspects of this bacterium is its natural competence, a prevalent phenomenon that continues to mystify researchers. This unique ability enables the bacterium to consistently reinfect the same host, leading to persistent infections. The gonococcus has developed multiple strategies to evade the innate and adaptive immune systems of its host. Antigenic and phase variation of outer membrane structures, blocking antibodies, molecular mimicry, and the prevention or activation of apoptosis (Higashi et al. 2007) are methods by which the gonococcus evades the host immune system. *N. gonorrhoeae* exhibits the capacity to regulate the process of macrophage apoptosis, as it triggers apoptosis in THP-1 cells while impeding induced apoptosis in U937 cells and primary human macrophages (Chateau and Steven Seifert 2016*).* Additionally, strategies of invasion include the mechanism of bacteriolysis mediated by complements and potentially involves the synthesis of IgA1 protease (Lu et al. 2009; Ram et al. 2001).

The sophisticated molecular mechanisms utilized by *N. gonorrhoeae* to initiate infection vividly demonstrate a striking degree of gender specificity (Edwards and Apicella 2004a). The interaction between gonococci and the epithelial cells of the urethra serves as a prime example of this phenomenon. This is in interplay with the release of cytokines, which develops the influx of neutrophils and inflammatory response (Edwards and Apicella 2004b). These cytokines are tiny proteins essential for regulating the growth and functions of various immune system cells and blood cells and act as signals prompting the immune system to perform its vital tasks when released (Zhang and An 2007). Analogously, inflammation is caused by gonococcal infections of the upper female genital system. One generally held opinion is that female genital infections are typically asymptomatic with 50% of infection, while male infections are often symptomatic having 80% of the infection rate (Edwards and Apicella 2004c; Walker and Sweet 2011; Russell 2021).

The comprehension of immunity or the detection of immune cells to *N. gonorrhoeae* poses a challenge due to the absence of definitive evidence regarding the establishment of disease immunity. Symptomatic gonococci infections are primarily triggered by a rise in polymorphonuclear leukocytes (PMNs) (Chateau and Steven Seifert 2016). In this particular phase, it was observed that the behavior of infection prompts the release of pro-inflammatory cytokines and chemokines, specifically IL-6, IL-8, IL-1B, IL-17, interferon-gamma, and the transcription factor NF-κB, which regulates the expression of cytokines (Seifert and HS 2017). The absence of the pro-inflammatory cytokines IL-1, IL-6, and IL-8 as well as insufficient IgA1 induction and slightly reduced IgG levels in the cervical mucous of infected women suggests that there is no severe inflammatory response during infection (Zughaier et al. 2020). Where in an experimental setting, men that are infected with *N. gonorrhoeae* produce higher levels of inflammatory cytokines; IL-1β, IL-6, IL-8, and tumor necrosis factor-α (TNF-α) that can be detected in their urine (Russell 2021). IL-1β, interleukin-6 IL-6, and IL-8 have been widely recognized for their significant involvement in both acute and chronic inflammatory processes, which subsequently contribute to the development of pathological clot formation (Bester and Pretorius 2016).

For sexually transmitted infections to be successfully transmitted, the pathogenic bacteria must efficiently disseminate to a new host. As for *N. gonorrhoeae,* the transmission modes rely heavily on the host's interaction and the sexual networks (Seifert and HS 2017). Therefore, this pathogen is highly adapted to the human body and cannot survive outside of its host. *N. gonorrhoeae* exhibits interference with the adaptive immune response, resulting in typically weak antibody responses to uncomplicated infection (Russell 2021). IL-10, TGF-β, and IL-35 are cytokines that are important possessing the anti-inflammatory properties to safeguard the host against tissue damage that is likely to occur during the acute phases of immunological responses. Having these regulatory mechanisms, these cytokines can be manipulated by pathogens to evade and suppress immunity.

IL-10 is a regulatory cytokine that is synthesized by many immune cells, such as activated T cells, monocytes/macrophages, B cells, dendritic cells, and mast cells (Sabat et al. 2010; Iyer and Cheng 2012). TGF-β acts as a suppressor of tumor growth by facilitating its inhibitory effects on cell proliferation across a wide range of cell types (Chaudhury and Howe 2009). In *N. gonorrhoeae*, TGF-β blocked prompts it from stifling specific anti-gonococcal response and lets Type 1 T helper (Th1) and Type 1 T helper (Th2) cells emerge which helps the immune system make immune memory and protect itself (Liu et al. 2014). *N. gonorrhoeae* inhibits the Th1/Th2-mediated adaptive immune response by utilizing TGF-β-dependent mechanisms (Liu et al. 2012). A recent discovery has revealed that the ability of *N. gonorrhoeae* to inhibit the host's adaptive immune responses can be counteracted by neutralizing the regulatory cytokines, TGF-β and IL-10. This finding has subsequently led to the identification of another discovery, which suggests that the localized application of IL-12, a cytokine that opposes the effects of IL-10 and TGF-β, can have a beneficial effect (Liu et al. 2014).

After transmission, *N. gonorrhoeae* invades the mucosa of various exposed anatomical sites, including the urogenital tract, rectum, pharynx, and conjunctivae, and this pathogen has a high probability of transmission. The estimated likelihood of transmission from a penis to a vagina is approximately 50% per sexual encounter, while the probability of transmission from a vagina to a penis is approximately 20% per act (Hooper et al. 1978; Holmes et al. 1970). Prolonged

and untreated cervical gonorrhea can result in significant reproductive health complications, including but not limited to pelvic inflammatory disease (PID), chronic pelvic pain, ectopic pregnancies, and tubal factor infertility (Unemo and Shafer 2014). Gonococcal infections contracted during pregnancy have been linked to several adverse outcomes, including chorioamnionitis, premature rupture of membranes (PROM), preterm birth, low birth weight, and spontaneous abortions (Donders et al. 1993; Heumann et al. 2017; Maxwell and Watson 1992; Liu et al. 2013).

The most alarming concern is the emergence and rapid spread of antibiotic resistance among *N. gonorrhoeae* strains, raising serious challenges in managing and treating infections caused by this bacterium. *N. gonorrhoeae* has continually demonstrated an amazing capacity to develop resistance to all antimicrobials offered for therapy, since sulfonamides were initially used to treat gonorrhea in the 1930s. The effectiveness of traditional treatment options, such as penicillin, ciprofloxacin, and azithromycin antibiotics, is gradually diminishing against this strong opponent.

Sulfanilamide initially healed 80–90% of associated cases (Slyke et al. 1941; Cokkinis and Mcelligott 1938; Kampmeier 1983). From 1943 to 1944, penicillin was introduced and shown effective against gonococcal urethritis which then swiftly replaced sulfonamides, and the penicillin doses of as little as 45 mg were sufficient to achieve a 99% success rate in curing infections.(Mahoney et al. 1943; Jaffe et al. 1976). The therapeutic efficacy of this "wonder drug" for gonococcal urethritis was identified, and penicillin spawned a new era for the treatment of gonorrhea and other infectious diseases. However, due to higher MICs in circulating gonococcal strains, the comparatively low dosages of penicillin required for a cure had to be increased, resulting in treatment failures (Willcox 1970).

Penicillin's usefulness was thought to have peaked by the early to mid-1980s. This worry was realized with the identification of a strain in Durham, North Carolina that generated penicillin-resistant gonorrhea due to solely chromosomal changes (Faruki et al. 1985). Over the next 2 decades, there was a progressive increase in the fraction of gonococcal strains with increasing penicillin resistance as well as ciprofloxacin and azithromycin (Derbie et al. 2020; Unemo et al. 2021; Ortiz et al. 2021). Following that, gonorrhoeae were treated with alternative antibiotics: tetracycline until the occurrence of resistant *N. gonorrhoeae* strains carrying the ribosomal protective protein TetM, which caused the discontinuance of tetracycline as a therapeutic option (Rice et al. 2017a). Gonorrhea is seen to develop resistance, including against the first-line treatment in many countries, the extended-spectrum cephalosporins (ESCs) (Ćmara et al. 2012).

Gonococcal strains resistant to ESCs appear to have evolved in Japan and subsequently spread globally over the previous 2 decades (Tanaka et al. 2002; Akasaka et al. 2001). Failures to treat with ceftriaxone have been documented in Japan, numerous European countries, Canada, and South America (Deguchi et al. 2003; Yokoi et al. 2007; Ison et al. 2011; Unemo et al. 2012). This resistance trend is global, rendering the current antibiotic treatments ineffective against the bacteria. As a consequence, the World Health Organization (WHO) decided in 2016 to withdraw its recommendation for the use of penicillin, sulphonamides, tetracyclines, and quinolones in treating gonorrhea (World Health Organization (WHO) 2016). Figure 1 illustrates the antibiotic timeline.

Some strains have developed resistance to multiple antibiotics and the strain of gonorrhea that exhibits extensive drug resistance and high-level resistance to the presently recommended treatment for gonorrhea is commonly referred to as gonorrhea superbugs or super gonorrhea. Since then, this "Super Bug" is seen to consistently demonstrate an exceptional capacity to develop resistance to all antimicrobials given as treatments for the past 70–80 years (Unemo et al. 2016). The remarks of the decline of the susceptibility of the bacteria to the last line of the antibiotic regime make *N. gonorrhoeae* classified as a multidrug-resistant pathogen (MDR) and extensively drug-resistant (XDR). The term XDR is classified for pathogens that are non-susceptibility to at least one agent in all antimicrobial categories except for two or fewer.

The current global impact of *N. gonorrhoeae* infections, coupled with the escalating threat of antibiotic resistance, necessitates urgent and effective interventions and treatment options. The burden on healthcare systems is substantial, with considerable costs involved in diagnosing, treating

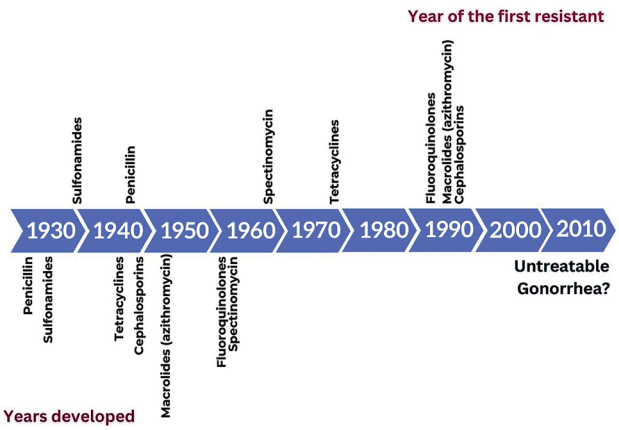

Fig. 1 Illustration of antibiotic development and first resistance identified for *N. gonorrhoeae*. This figure depicts the timeline of antibiotic development and the emergence of the first resistance in *N. gonorrhoeae*, the bacterium responsible for gonorrhea. The *x*-axis represents the years, while the *y*-axis represents the progression of antibiotic development and resistance

gonorrhea, and managing its complications. Its impact on morbidity and economic cost is substantial and widespread. These factors underscore the pressing need for comprehensive and coordinated approaches to address the challenge of antibiotic resistance in *N. gonorrhoeae* on a global scale.

Understanding the development, emergence, and spread of AMR in *N. gonorrhoeae*, as well as its molecular and phenotypic mechanisms, paves the way for the prediction of resistance to clinically applied antibiotics, the development of novel antibiotics, and vaccine development to address the issues with resistance and the development of genetic testing. This review seeks to provide a complete overview of the global viewpoint on combating *N. gonorrhoeae* antibiotic resistance, with an emphasis on recent advances, difficulties, and prospective mitigation methods for this public health risk.

Antibiotic resistance in *N. gonorrhoeae*

Mechanism of antibiotic resistance

One major contributor that leads to an increase in the resistance profile of *N. gonorrhoeae* is syndromic management. The syndromic management of sexually transmitted infections (STIs) involves the treatment of symptoms associated with the STIs rather than etiological diagnosis. Syndromic management focuses on specific pathogens that is obligated associated with the symptoms that include prescribing antibiotics. The significant limitation of syndromic care is its failure to address individuals with asymptomatic infections, therefore diminishing its potential impact on the overall burden of *N. gonorrhoeae* infections. There exists a constrained scope for extensive surveillance, and information about persons experiencing treatment failure is not systematically recorded (White et al. 2008; Garrett et al. 2017).

In a study found, it was shown that approximately 33% of the *N. gonorrhoeae* strains that were identified exhibited MDR that revealed significant levels of resistance to ciprofloxacin and tetracycline. These antibiotics are administered in the syndromic management treating STI (Kularatne et al. 2018). The utilization of Azithromycin in the syndromic management of urethral discharge in South Africa commenced in 2015, and within a short period, there was a rapid development of azithromycin resistance among MSM which is a matter of significant concern (Kularatne et al. 2018; Health Department of Republic of South Africa 2015). These findings suggest the potential of syndromic management due to prolonged consumption of antibiotics contributing to the rise of the resistance profile of *N. gonorrhoeae*.

Rectal gonorrhea is known as the substantial prevalence of STI which is seeing a rise in antibiotic resistance. Although gonorrhoeae is more common among MSM, there is also a growing concern regarding the occurrence of rectal gonorrhea in women. The prevalence rates of rectal *N. gonorrhoeae* vary across different populations. In women, estimates range from 0.6 to 35.8%. Among males who have sex with women, the prevalence ranges from 0.0 to 5.7%. Among MSM, the prevalence ranges from 0.2 to 24.0% (Chan et al. 2016). Recent research has revealed that a significant fraction of urogenital infections in women is accompanied by a simultaneous rectal infection, which suggests the potential for self-infection between these two locations (Lau et al. 2019). In another study, it is highlighted that missed diagnosis transmission or suboptimal treatment of rectal infections could lead to ongoing leading to other sexual partners and could cause reinfection (Llata et al. 2018).

Due to prolonged gonorrhea infection or recurrent infection, gonococci become resistant to antibiotics due to random mutation and the acquisition of genes (or gene segments). This bacterium consists of a mechanism that allows the high frequency of gene conversion that allows genetic information to move across organisms. The gene transfer frequency is due to the bacterium being polyploidy (Tobiason and Seifert 2006). The horizontal gene transfer (HGT) also includes spreading the resistance genes within bacteria which results in the acquisition of antibiotic resistance (Burmeister 2015). This process allows the resistance genes to be transferred by the mobile genetic elements known as plasmids (Binnicker et al. 2011). The increased prevalence of mosaic penA alleles leading to lower susceptibility or resistance to ESCs is almost certainly attributable to horizontal gene transfer (Unemo et al. 2012; Ohnishi et al. 2011, 2010).

The concomitant rectal infections also contribute to the emergence of the MDR of *N. gonorrhoeae* due to selection pressure where the bacteria develop resistance upon regular consumption of antibiotics in the treatment of rectal infections caused by *N. gonorrhoeae* (Kolář et al. 2001). The selection pressure inflicted the evolution of several resistant mechanisms of the gonococci. The gonococci obtain plasmids that encode β-lactamase, an enzyme that will degrade penicillin through the process of conjugation (Bueno 2017; Ahrens et al. 2007). In a finding by Suay-García (Suay-García and Pérez-Gracia 2017), the significant determinants of resistance are the bacterial pathogen's ability to reduce the antimicrobial agents' binding affinity. Another two antibiotics mechanism that is identified is the mutation resistance on the repressor gene (*mtrR)* or also known as the region of the promoter. The promoter suppresses the gonococcal transcription at the *mtrCDE* operon. Another mechanism is the novel MrT-independent promoter, which increases the transcription of *mrtCDE* (Rice et al. 2017b). According to research by Golparian (Golparian et al. 2014), the sequel to overexpression of *mrtCDE* activates the efflux pump resulting in mutations that cause the ability to resist macrolide antibiotics.

Unemo (Chaudhury and Howe 2009) summarized that one of the resistance determinant mechanisms against azithromycin is the MacAB efflux pump. The efflux pump exhibits the ability to facilitate the transportation of molecules with diverse structures, encompassing antibiotics, from within the bacterial cell. This serves to decrease the intracellular concentration of antibiotics, thereby enabling the pathogen to endure higher levels of antibiotic exposure (Blair et al. 2014).

The cause of overexpression of both the MacAB and *mef*-encoded efflux pumps will cause an increase in the minimum inhibitory concentration (MICs) of the antimicrobial and reduce the susceptibility. The *mef* gene is responsible for encoding a protein that is localized to the cell membrane and functions as an efflux pump. This protein is involved in the resistance mechanism against macrolide antibiotics, but it does not confer resistance to lincosamides or streptogramin B antibiotics (Shortridge et al. 1996; Sutcliffe et al. 1996). The *mef(A)* gene derived from an *N. gonorrhoeae* isolate obtained in 1975 was subjected to sequencing analysis and found to exhibit a complete identity of 100% amino acid when compared to the *mef(A)* gene originating from a *Streptococcus pneumoniae* isolate collected in the 1990s (Cousin et al. 2003). The *mef*-encoded efflux pump in *N. gonorrhoeae* drives macrolides out of the bacterial cell and increases the MICs of macrolides.

Other mechanisms contribute to the resistant determinants for azithromycin. Specifically, the C2611T and A2059G SNPs in the 23S rRNA gene reduce the affinity of the 50S ribosomal subunit for azithromycin. Similarly, the resistance determinants against Ceftriaxone are *mtrR* mutations or *mtr locus*. Significantly, this bacteria pathogen can restrict the antibiotic concentration upon entering the bacteria (Suay-García and Pérez-Gracia 2017). This information is, therefore, crucial to be targeted as a potential drug target.

There are four primary genes (*penA, penB, mtrR,* and *ponA*) that have been linked to resistance to cephalosporins (Lin et al. 2021; Unemo et al. 2019a). PBP2 encoded by *penA* is the primary target of penicillin (and other -lactam antibiotics) and is responsible for peptidoglycan cross-linking at the septum during cell division (Dougherty 1986). The *mtrR* genes are also found as the resistance determinant for ceftriaxone. A transcriptional repressor, mtrR, is encoded by the *mtr* gene locus, which in turn encodes the MtrC–MtrD–MtrE efflux pump.

MtrR protein exhibits a distinct ability to identify and attach itself to bile salts that are present in locations outside of the reproductive organs where gonococci infections occur (Beggs et al. 2019). This interaction of the transcriptional-regulatory protein subsequently leads to the activation of the mtrCDE efflux transporter genes, which were previously suppressed. This activation is primarily essential for the gonococci to exhibit resistance against specific hydrophobic antibiotics, detergents, dyes, and antimicrobials derived from the host (Folster et al. 2009). Expression of the mtrCDE efflux pump exhibited by gonococci was seen augmented through cis- or trans-acting alterations, which ultimately result in the overexpression of the mtrCDE efflux pump operon (Shafer et al. 2016).

MtrR was also found to be able to regulate other genes throughout the gonococcal genome (Folster et al. 2009). An example is the repression of rpoH which is one critical alternative heat shock sigma (sigma 32) factor that is essential for the gonococcal oxidative stress response and is directly mediated by MtrR; DNase. The DNase protection assays revealed direct MtrR binding to the rpoH operator (Folster et al. 2009). In a study found, it was identified that one rpoH-dependent gene, NGO0367, is significant in the invasion process to the epithelial cells, since the capacity of gonococci lacking rpoH to enter epithelial cells was diminished (Du and Arvidson 2006) (Tables 1, 2).

Mutations at 83 distinct amino acid positions in *penA*, which encodes the penicillin-binding protein 2, have been linked to lower susceptibility to cephalosporins. The outer membrane porin *penB* (or porB1b) is encoded by an allele of the gene *porB*; mutations at the G120 and A121 region of the protein reduce its permeability to antibiotics. Table 3 provides a detailed summary of the resistant determinants of *N. gonorrhoeae* against the antibiotics and Fig. 4 describes the mechanism of resistant of *N. gonorrhoeae.*

Current initiatives of the surveillance programs

The current treatment regimens of antibiotics for treating gonococcal infections today include third-generation cephalosporins (ceftriaxone), azithromycin, and fluoroquinolones (World Health Organization (WHO) 2016). As first-line empirical therapies for uncomplicated anogenital and pharyngeal gonorrhea, cefixime (1 g intravenously), and spectinomycin (2 g intramuscularly) have been recommended (of Sexually Transmitted Infection JS 2011). Ceftriaxone (injectable) and cefixime are the cephalosporins most widely suggested for the treatment of gonorrhea around the world (oral). However, the number of treatment options for gonorrhea has decreased due to the significant rise in antimicrobial resistance in recent years. With limited effective treatment options remaining, the WHO warns that gonorrhea could soon become untreatable if new antibiotics are not developed. In a recent report released by WHO, there were 82 million brand-new cases of gonorrhea in 2020 of which most cases were highly observed in the African Region and Western Pacific Region (World Health Organization (WHO) 2022a).

To manage this, a global network of laboratories called the WHO Gonococcal Antimicrobial Surveillance Programme (GASP) is managed by focal sites and regional

coordinating centers, and the regional GASP focal points include the African Region, Americas Region, Eastern Mediterranean Region, European Region, and South-East Asia and the Western Pacific Regions (World Health Organization (WHO) 2023a). Since 1992, the WHO-GASP has tracked N. gonorrhoeae AMR, and as of 2016, the Global Antimicrobial Resistance and Use Surveillance System (GLASS) was integrated to monitor the emergence of N. *gonorrhoeae* resistance where it is a priority pathogen and WHO-GASP collected data on reported cases of decreased susceptibility or resistance (DS/R) to antimicrobial agents.

A benchmark of ≥ 5% resistance of *N. gonorrhoeae* isolates has been established by WHO to cease the use of an antibiotic as the primary empirical treatment for gonorrhea (World Health Organization (WHO) 2023b). In 2018, 66 countries reported susceptibility data for *N. gonorrhoeae* isolates (World Health Organization (WHO) 2023b). The data indicate a resistance level of ≥ 90%, which is considered arbitrary, demonstrating a remarkably high level of ciprofloxacin resistance, particularly in the regions of South East Asia, Eastern Mediterranean, Western Pacific, Americas, and Africa.

In most regions around the world, ciprofloxacin is no longer considered an effective first-line treatment for *gonorrhea* with ≥ 5% resistance Table1. Furthermore, the report indicates an increasing trend in resistance to other antibiotics, including azithromycin, cefixime, ceftriaxone particularly ciprofloxacin (Figs. 2, 3). The findings emphasize the immediate requirement for alternative treatment choices and the importance of comprehensive surveillance programs like the Enhanced Gonococcal AMR Surveillance Programme (EGASP) in monitoring resistance patterns and guiding appropriate treatment strategies. Based on the data, from WHO-GASP and GLASS in 2017–2018, there were alarmingly high levels of ciprofloxacin resistance, a rise in azithromycin resistance, and ongoing dissemination of reduced susceptibility and resistance to cefixime and ceftriaxone Table 2. Additionally, there has been an increase in the number of countries reporting every year, as well as those reporting isolates with decreased susceptibility or resistance to examined antimicrobials. The total number of examined isolates has also seen an increase since 2015–2016 (Unemo et al. 2019b).

In line with the previous findings, the most recent report of GLASS—2022 also highlights the concerning escalation of antibiotic resistance to ciprofloxacin (World Health Organization (WHO) 2022b). The findings indicate a concerning prevalence of antibiotic resistance in gonorrhea, with ciprofloxacin resistance rates surpassing 60% globally. This conclusion is based on the analysis of ≥ 10 confirmed

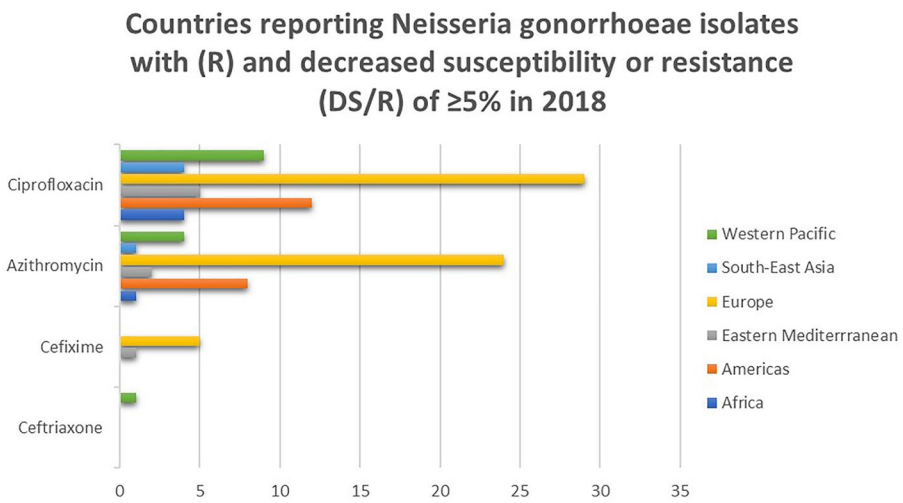

Fig. 2 An illustration depicting the number of countries reporting DS/R of *N. gonorrhoeae* isolates to WHOGASP in 2018 and indicating a higher prevalence in the regions of Europe, Western Pacific, and the Americas have been presented

Table 1 No. of countries and total reported resistance of *N.Gonorrheae* with DS/R of ≥ 5% isolates to WHO-GASP in 2018

	Africa	Americas	Eastern Mediterranean	Europe	South-East Asia	Western Pacific	Total
No countries reporting ≥ 5% DS/R							
Ceftriaxone						1	1
Cefixime			1	5			6
Azithromycin	1	8	2	24	1	4	40
Ciprofloxacin	4	12	5	29	4	9	63

Table 2 Representation of data of the number of countries across the WHO regions reporting *N. gonorrhoeae* isolates to WHO-GASP which shows an increment from the year 2015–16 to 2017–18

Year	2015–16		2017–18	
	(%)	Reported cases/total participating country	(%)	Reported cases/total participating country
Ceftriaxone	24	15/63	31	21/68
Cefixime	43	18/42	47	24/51
Azithromycin	80	45/56	84	51/61
Ciprofloxacin	100	63/63	100	73/73

cases of gonorrhea, which underwent antimicrobial susceptibility testing. It is also reported that the bacteriology confirmed infections of identified ciprofloxacin resistance were above the 75th percentile in 2020. In comparison to the WHO-GASP report 2018, the *N. gonorrhoeae* isolates are observed to increasingly develop resistance against ciprofloxacin.

The US Centers for Diseases Control (CDC) and Prevention provided treatment guidelines for the infections in December 2020, by revising the dosage for a single intramuscular (IM) dose of ceftriaxone for less severe urogenital gonorrhea from 250 to 500 mg (Barbee and St Cyr 2022). This revision aims to reduce the rate of gonococcal infection as it is to speed up the rate of recovery of the patients. While the European guidelines advise a dual antimicrobial therapy with 1 g ceftriaxone (IM) and a single 2 g azithromycin dose, or ceftriaxone 1 g (IM) alone in situations where the absence of ceftriaxone resistance is identified based on in vitro antimicrobial susceptibility testing (Cyr et al. 2020). The guidelines emphasize the importance of prescribing a doxycycline regimen when Chlamydia trachomatis infection has not been ruled out. However, in the face of growing antimicrobial resistance, promoting antimicrobial stewardship becomes paramount to ensure the responsible use of antibiotics.

Latest updates and challenges in the fight against antibiotic resistance in *N. gonorrhoeae*

The emergence of AMR has become a crucial issue in the field of global public health due to the increasing occurrence of human pathogens that are resistant to treatment including *N. gonorrhoeae* (Murray et al. 2022; Prestinaci et al. 2015). The principal factor behind this emergence is the extensive or overusing and improper usage of antibiotics (Zeshan et al. 2021; Ventola 2015). In 1945, Sir Alexander Fleming issued a grave warning regarding the emergence of a potential crisis. He predicted that the public's insatiable demand for drugs would lead to their overuse, resulting in the evolution of stronger bacterial defenses. This, he warned, would usher in an era that has come to be known as the "antibiotic apocalypse." (Bartlett et al. 2013; Spellberg and Gilbert 2014). Antibiotics have been observed to eliminate drug-sensitive competitors, thereby allowing the resistant bacteria to thrive and multiply through the process of natural selection (Read and Woods 2014).

The gut microbiome is a complex assemblage of diverse microbial species and viruses that inhabit the human gastrointestinal tract. The administration of antibiotics for bacterial infections poses a potential threat to the gut microbiome. If specific gut microbiota is disproportionately affected, the administration of antibiotics may result in an alteration of the composition of our microbiota, which is commonly known as dysbiosis (European Molecular Biology Laboratory 2021). According to a study found, the alterations in the gut microbiota's composition caused by antibiotics lead to changes in the production of mucin, cytokines, and antimicrobial peptides (AMP), ultimately resulting in a weakened intestinal epithelial cell (IEC) barrier (Duan et al. 2022).

Moreover, the administration of broad-spectrum antibiotics is seen to disrupt the abundance of 30% of the bacteria in the gut community which leads to rapid and significant drops in taxonomic richness, diversity, and evenness (Dethlefsen and Relman 2011; Dethlefsen et al. 2008). The dysbiosis that arises due to antibiotics is associated with an increased likelihood of antibiotic resistance. As per the study conducted by Palleja et al., it has been observed that the gut microbiome exhibits a response to antibiotics through the acquisition and transfer of antibiotic-resistance genes (Palleja et al. 2018). The study observed that, upon administration of antibiotics, there is a surge in Enterobacteria and other pathogenic taxa; *Enterococcus faecalis and Fusobacterium nucleatum* accompanied by declination in Bifidobacterium species (Palleja et al. 2018). A longitudinal study was conducted by sequencing the gut microbiomes pre- and post-antibiotic treatment. The study found that antibiotics induce a modification in the genetic material of specific species, frequently resulting in partial and widespread alterations of existing genetic variations; single-nucleotide variant (SNV) throughout the genome (Roodgar et al. 2021).

The gut of most healthy adults is characterized by the presence of a "core microbiota," primarily composed of microbes from the *Bacteroidetes* and *Firmicutes* families (Singh et al. 2019). In a systematic study, the resistance to β-lactams from the genus *Bacteroides* is associated with the genes *cfxA, cfiA*, and *cepA*, whereas resistance to tetracyclines is associated with the gene *tetQ* (Sóki et al. 2020).

In another study, the most comprehensive analysis of the intestinal resistome thus far is where the gut resistome is constituted by the group of genes or other genetic

Table 3 Resistant genes identified in *Neisseria gonorrhoeae*

Antibiotic class	Antibiotics	Year developed/ discovery	First resistant	Target inhibition	Resistant genes	References
Sulfonamides		1935	The 1940s	Prevents production of folic acid by blocking the enzyme dihydropteroate synthase (DHPS) in bacteria	SNPs or a mosaic folP Mutations in folP (encoding the sulfonamide target DHPS) reduce target affinity	Unemo and Shafer (2014)
Penicillin	Penicillin G and ampicillin	1928	1946	The binding of the beta-lactam ring to transpeptidase enzymes inhibits the production of peptidoglycan cross-links	Mutations in penA alleles (encoding the main lethal target PBP2) Mutations in mtrR, in the promoter (mainly a single-nucleotide [A] deletion in the 13-bp inverted repeat sequence) or coding sequence (commonly a G45D substitution), resulting in overexpression of and increased efflux from the MtrCDE efflux pump porB1b SNPs, e.g., encoding G120K and G120D/A121D mutations in loop 3 of PorB1b, reduce influx (penB resistance determinants) An SNP in *pilQ* (encoding the pore-forming secretin *PilQ* of the type IV pili), i.e., E666K, reduces influx An SNP in ponA (encoding the second penicillin target, PBP1) "Factor X," an unknown, nontransformable determinant, increases penicillin MICs three-to-sixfold Penicillinase (TEM-1 or TEM-135)-encoding plasmids,	Unemo and Shafer (2014)
Tetracycline	Tetracycline and doxycycline	1945	1980s	aminoacyl-tRNA binding to the mRNA–ribosome complex influences protein synthesis by binding the 30S ribosomal subunit	An SNP in rpsJ (encoding ribosomal protein S10), i.e., V57M, reduces the affinity of tetracycline for the 30S ribosomal target mtrR mutations penB mutations A SNP in *pilQ* TetM-encoding plasmids	Unemo and Shafer (2014; Morse et al. (1986)

Table 3 (continued)

Antibiotic class	Antibiotics	Year developed/ discovery	First resistant	Target inhibition	Resistant genes	References
Spectinomycin		Early 1960s	1967	Inhibits the 30S ribosomal subunit to block protein translation	A 16S rRNA SNP decreases drug binding to its ribosome target Mutations in rpsE (encoding the 30S ribosomal protein S5) disrupt the affinity of spectinomycin to the ribosomal target	Unemo and Shafer (2014)
Quinolones	Ciprofloxacin and ofloxacin	1960s	1990	DNA gyrase and topoisomerase IV	gyrA SNPs, e.g., S91F, D95N, and D95G, in the QRDR, reduce quinolone binding to DNA gyrase parC SNPs, e.g., D86N, S88P, and E91K, in the QRDR, reduce quinolone binding to topoisomerase IV An overexpressed NorM efflux the pump also slightly enhances quinolone MICs	Unemo and Shafer (2014), Unemo et al. (2019a)
Macrolides	Erythromycin and azithromycin	1952	The 1990s (azithromycin)	Interacting with 23S rRNA binds to the 50S ribosomal subunit and inhibits the peptide exit channel, preventing the ribosome from releasing full polypeptides and preventing protein synthesis	23S rRNA SNPs mtrR mutations *erm* genes (*ermB*, *ermC*, and *ermF*), encoding rRNA methylases that methylate nucleotides in the 23S rRNA target, block the binding of macrolides MacAB efflux pump; its overexpression increases the MICs of macrolides The *mef*-encoded efflux pump increases macrolide minimal inhibitory concentrations (MICs) by exporting macrolides out of the bacterial cell	Unemo and Shafer (2014), Douthwaite and Champney (2001)

Table 3 (continued)

Antibiotic class	Antibiotics	Year developed/ discovery	First resistant	Target inhibition	Resistant genes	References
Cephalosporins	Ceftibuten, cefpodoxime, cefixime, cefotaxime, and ceftriaxone	1948	1990s	β-Lactam ring to transpeptidases	A311V, I312M, V316T, V316P, T483S, A501P, A501V, N512Y, and G545S penA SNPs, i.e., A501V and A501T, in nonmosaic alleles, can also enhance cephalosporin MICs Some additional SNPs (G542S, P551S, and P551L) were significantly linked to higher cephalosporin MICs mtrR mutations penB mutations "Factor X," an unknown, nontransformable determinant	Unemo and Shafer (2014)

material that makes bacteria resistant to antibiotics. The study observed that the prevalence of antibiotic resistance genes (ARGs) is greatest for antibiotics that have been in circulation for a longer duration and those sanctioned for animal usage, including tetracycline, bacitracin, and the cephalosporins (Forslund et al. 2013). This leads to collateral damage where the term is utilized in the context of antibiotic therapy to denote the negative ecological consequences, such as the emergence of drug-resistant organisms and the inadvertent acquisition of colonization or infection with multidrug-resistant organisms (Paterson 2004). Recent studies conducted in vivo have demonstrated that β-lactams and macrolides have a significant impact on the gut microbiota, which in turn affects the overall health of the host and these two antibiotics are used to treat *N. gonorrhoeae* (Ruiz et al. 2017; Cox et al. 2014; Cho et al. 2012*)*.

The recent outbreak of the COVID-19 pandemic has posed a significant threat and concern to public health due to an increase in AMR. In the nascent phases of the COVID-19 pandemic, the dispensation of antibiotics to patients was widespread across several nations. Although COVID-19 is a viral illness and antibiotics are not effective against it, under circumstances in which the patient had pneumonia, which is a secondary bacterial infection, antibiotics are necessary (Townsend et al. 2020). Due to this, the pandemic has exerted significant stress on an already burdened public health system, and in a report, the inclination of gonorrhea surged up to 10% compared to 2019 during the first year of the pandemic (CDC xxxx). Although more research has not been done to determine the reason for the increase, the overuse of the drug azithromycin during the pandemic may be to blame for the "Super Gonorrhoeae" cases that are soaring (Bogdanić et al. 2022).

The emergence of COVID-19 has become a significant event in human history, altering global attitudes toward infectious diseases and shifting attention toward investment in life sciences research and development. The unbridled emergence of pathogenic drug resistance in *N. gonorrhoeae* is regarded as a significant worldwide menace, thereby mandating persistent research endeavors for novel therapeutic interventions and immunizations to manage the ailment.

According to Suay-Garcia et al., the approaches to finding new treatment are divided into three; new combinations of antibiotics that are existing, designing of new antibiotics, and alternative therapies that can decline the development of bacterial resistance (Suay-García and Pérez-Gracia 2018). Some antibiotic combinations, commonly referred to as "dual therapy," reuse new combinations of current medications. According to the most recent CDC treatment recommendations, dual therapy is advised as the recommended treatment plan as part of the antimicrobial stewardship program (Cyr et al. 2020). The use of various antibiotics with various modes of action is one of the rationales for

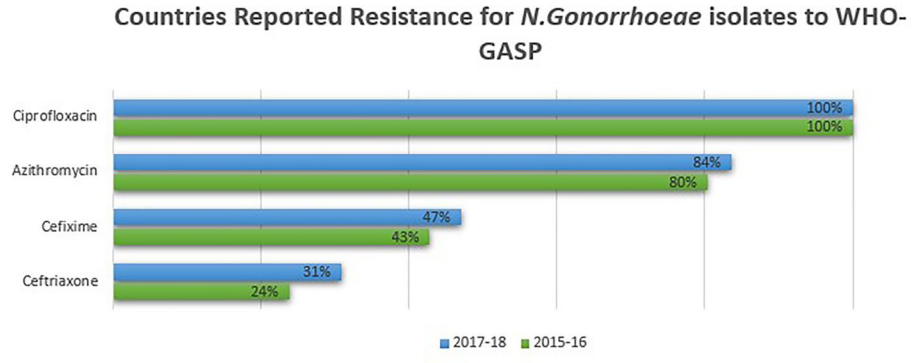

Fig. 3 Illustration of percentage (%) of *N. gonnorhoeae* isolates with decreasing susceptibility or resistance to antibiotics for 2016–2015 and 2017–2018, highlighting the significant frequency of resistance against Ciprofloxacin and increased resistance against all antibiotics from 2015–2016 to 2017–2018

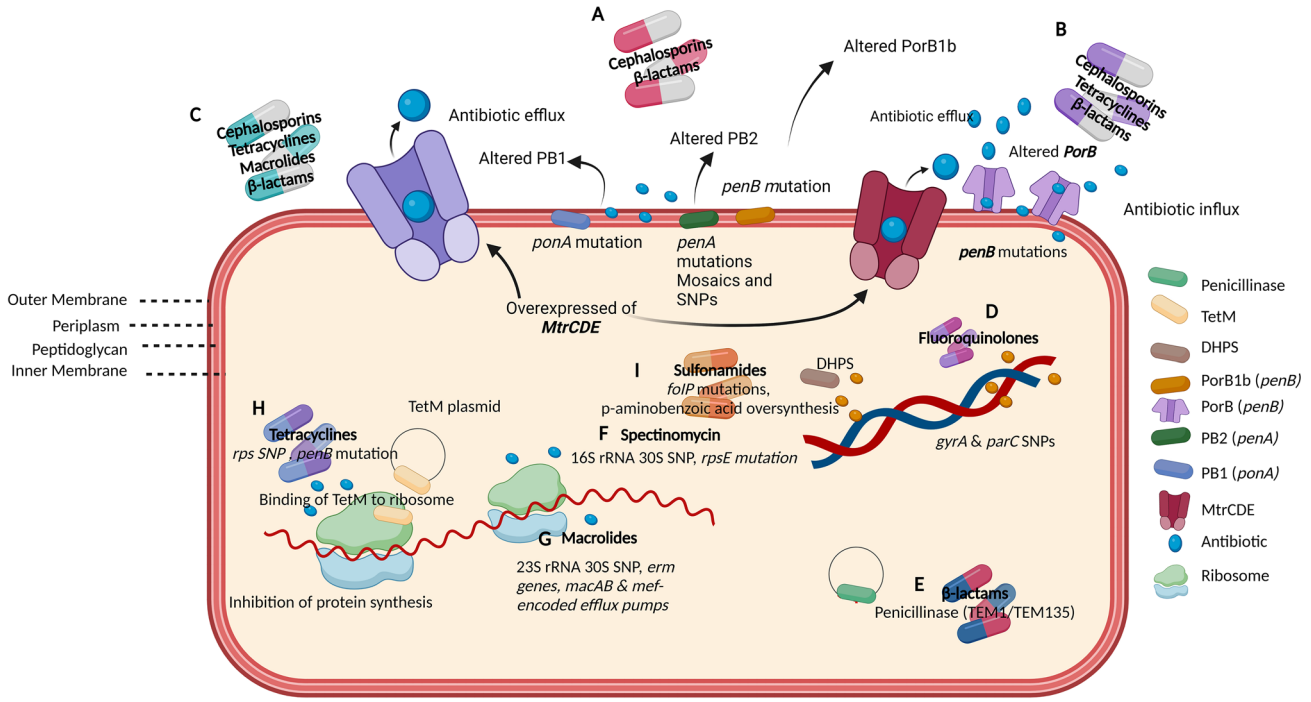

Fig. 4 Illustration of the mechanisms of antibiotic resistance in isolates of *N. gonorrhoeae* and the corresponding antimicrobial agents that experience a loss of efficacy. **A** Alterations in the penicillin-binding proteins (PB1, PB2, & PorB1b). PBP1—by single-nucleotide polymorphism (SNP)s in *ponA*, PB2—by alteration of *penA* and PorB1b-encoded by *penB*. **B** Mutations in the *penB* gene, which encodes a significant protein; porB located in the outer membrane. **C** Overexpression caused by mutations in *MtrR* encoding MtrR repressor protein surges antimicrobials efflux. **D** Mutations in DNA gyrase (*gyrA*) and topoisomerase (*parC*) resulted in a reduction in the binding affinity of these enzymes. **E** Plasmid-borne penicillinase is capable of hydrolyzing the ß-lactam ring. **F** The binding to the ribosomal target is inhibited by the *rpsE* mutation and the 16 rRNA genes' single-nucleotide polymorphism (SNPs) encoding the ribosomal protein S5 (RPS5). **G** Binding of rRNA is compromised by the presence of methylases in the 23S subunit, causing augmentation of efflux upon overexpression of MtrCDE efflux pup and/or *mef*- and *macAB*-encoded efflux pumps. **H** The single-nucleotide polymorphism (SNP) within the gene that encodes the ribosomal protein rpsJ, as well as within the gene that encodes the plasmid-borne TetM protein, results in a diminished binding affinity between the aforementioned proteins and the ribosome. **I** Resistance is conferred by over synthesis of p-aminobenzoic acid and mutations in DHPS-encoding *folP*. Image is created by BioRender and modified from (Dillon et al. 2015). Image is created using BioRender modified from antibiotic resistance in *Neisseria gonorrhoeae*: Will Infections be Untreatable in the Future? Culture 35:1–8 (Dillon et al. 2015)

gonococcal combination therapy to perhaps slow the spread of antibiotic resistance (Unemo and Workowski 2018). Of course, this treatment plan is complemented by continual monitoring to continuously assess the effectiveness and treatment failures.

In 2016, the dual therapy recommended by WHO in treating gonococcal infections is azithromycin and ceftriaxone (World Health Organization (WHO) 2016). The induction or selection of azithromycin resistance in gonococci through the implementation of dual gonorrhea therapy appears to

be limited due to the rarity of ceftriaxone resistance, especially in isolates of gonococci that are resistant to azithromycin (Unemo and Workowski 2018). In keeping with this, research using sitafloxacin, a broad-spectrum fluoroquinolone of a more recent generation that is largely used to treat respiratory infections was done (Jönsson et al. 2018). The study concluded that sitafloxacin has a rapid bactericidal effect with an MIC range of 0.001–1 mg/L, making it an excellent candidate for dual antimicrobial therapy for gonorrhea in cases of cephalosporin resistance or allergy.

Another study by Singh et al. evaluates the efficacy of 21 dual therapy combinations against 95 *N. gonorrhoeae* strains out of which five were identified as novel combinations: gentamicin + ertapenem, moxifloxacin + ertapenem, spectinomycin + ertapenem, azithromycin + moxifloxacin, and cefixime + gentamicin (Singh et al. 2018a). Gentamicin, on the other hand, is already recommended in conjunction with azithromycin in several guidelines as a secondary treatment option when primary options fail. A study concluded that gentamicin in combination with ertapenem or cefixime showed maximum efficacy and synergism against 75 gonococcal strains, making it a potential new antimicrobial dual therapy (Singh et al. 2018b). Table 4 provides a summary of drugs repurposed.

Currently, there exist multiple prospective agents in development for *N. gonorrhoeae*. Three newly discovered antibiotics have progressed to Phase III clinical trials; zoliflodacin (spiroypyrimidinetrione topoisomerase inhibitor) (Huband et al. 2015; Unemo et al. 2015), solithromycin (inhibitor of protein synthesis), and gepotidacin (inhibitor of DNA gyrase and topoisomerase IV) (Table 5). The compound zoliflodacin has been undergoing Phase III clinical trials for the treatment of multidrug-resistant *N. gonorrhoeae* since 2019. It was developed by Entasis Therapeutics in collaboration with the Global Antibiotic Research Development Programme (Bradford et al. 2020).

Zoliflodacin is a newly discovered antibiotic belonging to the spiropyrimidinetrione class. It functions by selectively targeting the GyrB subunit of DNA gyrase, which is an obligatory mechanism for DNA replication. This antibiotic stabilizes the cleaved covalent complex of DNA gyrase with double-strand broken DNA, thereby preventing the relegation process that forms circular DNA (Huband et al. 2015; Basarab et al. 2015; O'Donnell et al. 2019). Zoliflodacin has successfully undergone two Phase 1 clinical trials. The initial clinical trial was conducted to assess the safety, tolerability, and pharmacokinetics of moxifloxacin under both fed and fasted conditions. The subsequent trial was designed to investigate the ADME properties of the drug, including its absorption, distribution, metabolism, and excretion (Jacobsson et al. 2021).

Following another study of phase II clinical trials of zoliflodacin (https://classic.clinicaltrials.gov/ct2/show/NCT02257918), it was found that dosages of 2 g and 3 g resulted

Table 4 List of drugs that are repurposed as new treatment strategies for gonococci

Drug repurposing	Type of class/drug	Mode of mechanism	References
Sitafloxacin (dual therapy)	Fluoroquinolone	Inhibitor of DNA gyrase and topoisomerase IV	Jönsson et al. (2018), Soge et al. (2016)
Aztreonam	β-lactams; monobactams		Barbee and Golden (2020), Heel and RC (1986)
Delafloxacin	Fluoroquinolone	Inhibitor of DNA gyrase and topoisomerase IV	Terreni et al. (2021)
Auranofin (dual therapy)	Antirheumatic	Endocervical cells that have been infected exhibit a decrease in the secretion of the pro-inflammatory cytokine IL-8	Elkashif and Seleem (2020)
Carbamazepine and methyldopa	Anti-epileptic and anti-hypertensive	Inhibit the I-domain of the complement receptor 3 of gonococci	Poole et al. (2020)

Table 5 New agents (antibiotics) undergoing Phase III clinical trials for the treatment of *Neisseria gonorrhoeae*

Antibiotics	Class	Mode of mechanism	References
Zoliflodacin	Spiropyrimidinetriones	Target the GyrB subunit present in DNA gyrase, which is responsible for the cleavage of double-stranded DNA. Stabilizing the cleaved covalent complex of DNA gyrase with double-strand broken DNA	Huband et al. (2015), O'Donnell et al. (2019)
Solithromycin	Macrolide	Inhibit prokaryotic ribosomal	
Gepotidacin	Triazaacenaphthylene	Inhibits the DNA gyrase and topoisomerase IV of the bacteria	Farrell et al. (2017)

in treatment success rates of 98% and 100% for urogenital gonorrhea, respectively (O'Donnell et al. 2019). For rectal gonorrhea, the success rate was 100%, while for pharyngeal gonorrhea, the success rates were 67% and 78% for doses of 2 g and 3 g, respectively (O'Donnell et al. 2019). Zoliflodacin is presently undergoing a global phase 3 clinical trial in collaboration with the Global Antibiotic Research Development Programme (GARDP) (Bradford et al. 2020). At the time of this writing, one clinical trial for zoliflodacin is active but not recruiting: (https://classic.clinicaltrials.gov/ct2/show/NCT03959527).

In recent years, there has been extensive exploration of Solithromycin, a fourth-generation macrolide with broad-spectrum capabilities that target prokaryotic ribosomal sites. In a clinical trial, a total of 246 clinical isolates and reference strains of *N. gonorrhoeae* were analyzed, which comprised two extensively drug-resistant strains (H041 and F89) and other isolates with clinical cephalosporin resistance and multidrug resistance (Golparian et al. 2012). The efficacy of solithromycin was found to be predominantly superior to that of other antimicrobial agents (n = 10) that have been either currently or previously recommended for the treatment of gonorrhea (Golparian et al. 2012). At the time of writing, most clinical trials for solithromycin are completed. One phase II clinical trial observes the efficacy of Solithromycin against drug-resistant *N. gonorrhoeae*, including intracellular organisms, which have been demonstrated to be bactericidal (Vries and Schim-van der Loeff 2019). Correspondingly, a phase 3 clinical trial was conducted on 262 patients to evaluate the non-inferiority of oral solithromycin monotherapy compared to intramuscular ceftriaxone in combination with oral azithromycin for the treatment of uncomplicated gonorrhea (Fernandes and Craft 2019).

Gepotidacin also known as GSK2140944 belongs to the triazaacenaphthylene class of antibiotics and exerts its antibacterial effect by inhibiting bacterial DNA gyrase and topoisomerase IV. Its mechanism of action differs from that of previous antibiotics, such as quinolones (Soge et al. 2016). The in vitro investigations demonstrated the potent efficacy of gepotidacin against all strains of *N. gonorrhoeae*, including those that are multidrug-resistant, as evidenced by the minimum inhibitory concentrations (MICs) (Farrell et al. 2017; Jacobsson et al. 2018). In the Phase II clinical trial, a single dose of gepotidacin was evaluated for the treatment of uncomplicated urogenital gonorrhea. The trial included doses of either 1500 or 3000 mg. The results showed a 96% cure rate in urogenital, pharyngeal, and rectal sites, with 66 out of 69 participants being cured (Taylor et al. 2018). Presently, one phase III clinical trial is recruiting (clinicaltrials.gov/ NCT04010539) to examine the efficacy as well as the safety of Gepotidacin in comparison to the combination of Ceftriaxone and Azithromycin for the treatment of uncomplicated urogenital gonorrhea.

Scientists are developing new therapies to combat the increasing resistance of *N. gonorrhoeae*. These therapies encompass non-antibiotic alternatives. These options focus on preventing the reoccurrence of infections rather than providing treatment for the illness. In addition, unconventional therapies, such as non-small-molecule antibiotics, are utilized to manage the infection. The other treatments include the usage of closo-dodecaborate dianion fused with oxazoles a 3D heterocycle that has exhibited strong, selective antimicrobial activity against *N. gonorrhoeae* (Sun et al. 2018).

The studies identified that several diboraheterocycles exhibited a notably potent antimicrobial effect against *N. gonorrhoeae* based on the MIC. In another study, the intracellular transportation of molecules has been assessed using cell-penetrating peptides (CPPs), for their bactericidal properties. The findings resulted in the inhibition of gonococcal invasion of ME-180 cells. Additionally, it led to a reduction in the expression of TNF-α, which was induced in THP-1 cells by gonococci (John et al. 2019). One study observed the potential of 5-mercapto-2-nitrobenzoic acid-coated silver nanoclusters (MNBA-AgNCs) to kill the *N. gonorrhoeae* strains observed by in vitro bactericidal assay. Bacterial eradication was observed at concentrations of 0.019 and 0.467 µM of MNBA-AgNCs within 1 h, resulting in 50% and 100% mortality rates, respectively (Lucío et al. 2020). This was also compared against the concentration of ceftriaxone at 11.7 µM which was found to be insufficient to achieve complete eradication of the bacterial population, even following a 3-h incubation period (Lucío et al. 2020).

A novel non-pharmacological intervention was conducted to assess the efficacy of antimicrobial blue light (aBL) with a wavelength of 405 nm (Wang et al. 2019). The wavelength of 405 nm has been identified as the most favorable wavelength for effectively targeting porphyrins, and as for *N. gonorrhoeae,* the predominant porphyrin species observed was identified as coproporphyrin, a remarkably proficient generator of singlet oxygen $^1O_2$ (Rimington 1960; Tanielian et al. 2001).

The study observed the potentials of aBL which exhibited a higher tendency to deactivate *N. gonorrhoeae*, even those strains that were resistant to antibiotics, as compared to human vaginal epithelial cells when tested in vitro (Wang et al. 2019). No aBL-induced genotoxicity to the vaginal epithelial cells was observed and this suggested the potential of aBL as a treatment for this disease. Intriguingly, even after undergoing 15 consecutive rounds of subtherapeutic aBL inactivation, there was no emergence of aBL resistance. Notwithstanding, the utilization of this prospective therapeutic approach toward *N. gonorrhoeae* is presently in its nascent phase which requires further evaluation of clinical trials.

Table 6 Alternative treatments for use in the treatment of *N .gonorrhoeae* including non-traditional treatments of antibiotics

Name/ Treatment	Functions	References
Closo-dodecaborate dianion fused with oxazoles	Demonstrated potent and specific antimicrobial properties	Sun et al. (2018)
IL-12	Induction of immune response	Liu et al. (2018)
Lactobacillus crispatus	Exhibit biosurfactant properties and an acidic environment	Foschi et al. (2017)
Monocaprin Myristoleic acid	Disruption of the cell membrane	Churchward et al. (2017), Darling and McDonald (2010)
Bacteriophage therapy	Lysis	Connor et al. (2016), Sikora et al. (2017)
Cell-penetrating peptides (CPPs)	Bactericidal activity. Resulting in cytotoxic *N. Gonorrhoeae* (95–100%)	John et al. (2019)
MNBA-AgNCs (silver nanoclusters)	Exhibit in vitro activities	Lucío et al. (2020)
Antimicrobial blue light (aBL)	Found to selectively deactivate over human vaginal epithelial cells using aBL-activatable photosensitizing porphyrins	Wang et al. (2019)

Table 6 presents a summary of non-conventional treatments and alternative therapies for antibiotics.

The prevalence of AMR in diverse strains of *N. gonorrhoeae* has persistently hindered the effective management and regulation of gonorrhea. With the continued presence of AMR determinants in gonococci, and the lack of access to diagnostic assays that offer AMR outcomes during treatment, medical practitioners must rely on empirical treatment for gonorrhea. The WHO global health sector strategy on sexually transmitted infections 2016–2021 was endorsed by the United Nations (UN) World Health Assembly in 2016. A significant objective is to achieve a 90% decrease in the prevalence of gonorrhea on a global scale (WHO (World Health Organization) 2016). The WHO initiated a worldwide strategy in 2012 to manage the dissemination and consequences of antimicrobial resistance in gonococcal infections that highlighted key main objectives (WHO (World Health Organization) 2012). Some of the key priorities highlighted is: *research into new molecular methods for monitoring and detecting AMR and development of new treatment option* and *research into, and identification of, alternate effective treatment regimen(s) and vaccine(s) for gonococcal infection* (WHO (World Health Organization) 2012).

WHO emphasizes the importance of molecular methods to detect the prevalence of AMR. Molecular techniques are frequently employed in conjunction with phenotypic approaches but are poised to supplant them in numerous laboratories owing to their superior rapidity and precision in identifying the fundamental genetic basis for antimicrobial resistance (AMR) (Anjum et al. 2017). The aforementioned methodologies encompass PCR, DNA microarray, whole-genome sequencing and metagenomics, and matrix-assisted laser desorption–ionization-time of flight mass spectrometry (Anjum et al. 2017). As currently, the gonococcal vaccine is not available, the most effective means of maintaining public health control over gonorrhea will persist in the form of readily accessible, reasonably priced, and timely antimicrobial treatment, coupled with prevention strategies, diagnostics for both index cases and traced sexual contacts, and surveillance.

Molecular methods play a significant role in early detection to identify antibiotic resistance, and in the decisions of *N. gonorrhoeae* treatments, this can be guided by antibiotic susceptibility at the molecular level, which allows resistance-directed therapy. The proper management of gonorrhea cases is crucial in mitigating the unwarranted or inaccurate use of antimicrobial agents and the emergence of antimicrobials. The FDA has approved several molecular methods for diagnosing *N. gonorrhoeae* infection, including nucleic acid hybridization, signal amplification, polymerase chain reaction, strand displacement amplification, and transcription-mediated amplification, even though it was discovered that the transcription-mediated method has a higher sensitivity than molecular-based methods (Munson and Firmani 2009). One example is the reinstatement of ciprofloxacin as a treatment for *N. gonorrhoeae* as a result of molecular testing (Hemarajata et al. 2016; Siedner et al. 2007). In another study, the potentials of six codons that can be used to detect decreased susceptibility to cefixime with a sensitivity of 99.5% were evaluated (Deng et al. 2019). While an assay is presently under development, these alleles have shown accurately anticipated susceptibility to cefixime in 115 out of 121 (95.9%) strains of *N. gonorrhoeae* that exhibit decreased susceptibility (Deng and Klausner 2020).

The execution of the molecular assay has shown great potential to accurately detect gonococcal infections that necessitate additional antibiotic susceptibility testing or a heightened dosage of ceftriaxone for effective treatment. Adequate molecular tests for detecting gonococcal AMR determinants are crucial to predict AMR, especially when

gonococcal culture is not available. These tests are necessary to complement culture-based AMR surveillance or to provide periodic surveys of AMR (Unemo et al. 2021). Found, the efficacy of treating *Neisseria gonorrhoeae* strains with reduced susceptibility in China has been demonstrated through the administration of higher doses of ceftriaxone (≥ 1000 mg) (Han et al. 2020). However, current methods for detecting antimicrobial resistance at a molecular level may not be entirely reliable being the only provided information on the minimum inhibitory concentrations of specific antimicrobials. For many antimicrobials, especially the extended-spectrum cephalosporins that are constantly evolving in terms of resistance, and most antimicrobial resistance determinants, except for ciprofloxacin, the accuracy in predicting antimicrobial resistance is often low (Unemo et al. 2014).

Gonococcal infections have a significant impact on reproductive, maternal, and newborn health. The economic burden of these complications is significant for both patients and the healthcare system. Consequently, this development has prompted the WHO to intensify its efforts in devising more robust measures, such as the implementation of the Global Action Plan aimed at curbing the proliferation and ramifications of antimicrobial resistance in *N. gonorrhoeae*. In the latest update, WHO outlines two distinct methodologies that can be employed to address the issue at hand, namely the broad management of drug resistance and the management of gonorrhea (World Health Organization (WHO) 2022c).

WHO has established GASP—a globally distributed network of laboratories managed by designated focal points and regional coordinating centers to monitor the spread of the disease and GLASS. These are the global collaborative efforts to have a standard operating procedure for AMR surveillance. GLASS operates comprehensively at all tiers of the WHO, including the central headquarters, regional offices, and country-level offices. The WHO AMR Surveillance and Quality Assessment Collaborating Centres Network (WHO AMR Surveillance CC Network) provides support to GLASS (World Health Organization (WHO) 2019).

WHO presently is fortifying the surveillance of AMR in gonorrhea via the implementation of the EGASP (WHO 2021). The primary objectives of EGASP are to track antimicrobial susceptibility trends in *N. gonorrhoeae* through standardized protocols and quality-assured lab testing, and to epidemiologically characterize men with gonorrhea at sentinel sites, particularly those with *N. gonorrhoeae* resistant to the recommended antimicrobial agent.

While the Global Health Sector Strategy on HIV, Hepatitis, and STIs (2022–2030) has established specific objectives aimed at diminishing the incidence of gonorrhea among individuals aged 15–49 years (World Health Organization (WHO) 2022d). The plan's framework was established in the year 2022, with a designated timeline of 8 years set as the goal. The aim is to decrease the annual number of new cases from 82.3 million in 2020 to 8.23 million in 2030, resulting in a 90% reduction in the yearly incidence by 2030. These initiatives involve multidisciplinary collaboration.

Future challenges and strategies for addressing antibiotic resistance in *N. gonorrhoeae*

Gonorrhoea continues to pose a significant challenge due to the acquisition of genetically determined resistance to all antimicrobials and the potential emergence of a therapy-resistant form of gonococcal infection. The management of gonorrhea requires effective and accessible antimicrobial treatments, and to this end, numerous efforts have been made, including the development of new antibiotics, such as zoliflodacin, gepotidacin, or solithromycin. (Bradford et al. 2020; Farrell et al. 2017; Aitolo et al. 2021).

Based on the completed clinical trials findings, zoliflodacin displays a robust in vitro efficacy to hinder the development of *N. gonorrhoeae* (Foerster et al. 2019) which also signifies the efficacy against “geographically, temporally, and genetically diverse" strains, including ceftriaxone-resistant strains (Jacobsson et al. 2019). The solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhea (SOLITAIRE-U) study (Chen et al. 2019a) failed to demonstrate non-inferiority with a 4.0% lower difference in eradication rate (80% vs 84%). Some limitations identified were the usage of a single dose of solithromycin that is insufficient and some other properties, such as pharmacokinetic or pharmacodynamic properties, should be assessed (Vries and Schim-van der Loeff 2019). While, for gepotidacin, a phase III study evaluated the potential of reducing the resistance and restricting the plasma concentrations of substances that could pose a safety risk when used with a higher gepotidacin MIC against the *N. gonorrhoeae* isolates (Scangarella-Oman et al. 2023).

The study was a continued study from phase II that indicated increased exposures were necessary to achieve efficacy and inhibit the development of resistance but were constrained by the small sample size and the absence of a comparator (Scangarella-Oman et al. 2023). The microbiologically evaluable samples were solely obtained from participants in the United States. These studies of clinical trials are subject to significant limitations, primarily due to the restricted sample size and concentration employed.

Nevertheless, the widespread implementation of this bacteria ought to be contingent upon a thorough investigation into the correlation between the genetic makeup and the degree of phenotypic resilience. The probability of the pathogens evolving resistance to novel antibiotic treatments is significant. Consequently, it is imperative to explore alternative options, such as the development of new probiotics or live supplements that can leverage

the beneficial microbes to combat the pathogen. This has been explored in a study that evaluates the anti-gonococcal activity of 14 vaginal Lactobacillus strains, which are classified under different species, including *L. crispatus, L. gasseri, and L. vaginalis*. The study evaluates the reduction of the gonococcal viability, and interestingly, a 100% reduction of viability is observed for *L. crispatus BC1, BC4–BC8, and L. gasseri BC13* with a < 4 pH value of supernatant after 7 min (Foschi et al. 2017). Though it should not be sought as the panacea for treating gonorrhea, it can be useful in compromising the urogenital systems as there is a strong correlation between dysbiosis of the vaginal microbial flora and a heightened occurrence of urinary tract infections, such as gonorrhea (Shaskolskiy et al. 2022). It is pertinent to note that lactobacilli possess significant importance in light of their ability to retain their health-promoting attributes within the vaginal environment in vivo. This characteristic presents a viable alternative to antibiotic treatment, which may result in unfavorable side effects.

The emergence of antimicrobial resistance in *N. gonorrhoeae* underscores the pressing need for the development of a vaccine. According to mathematical modeling, the administration of a vaccine for 7.5 years of protection and efficacy rate at 100% with long-term immunity and 50% efficacy during early adolescence can potentially reduce gonococcal infections by up to 90% after 20 years (Craiga et al. 2015). However, the efforts on vaccine development were seen as successful, and to date, there is no effective vaccine against *N. gonorrhoeae*. The vaccine development faces significant obstacles as the association between the innate human immune system remains enigmatic; however, substantial progress has been made in recent years to resolve these obstacles, and increased vaccine research should be a top priority (Jerse and Deal 2013).

Mathematical modeling reveals that gonococcal infections can be decreased by up to 90% after 20 years if immunization is delivered in early adolescence, even with a vaccine with a protection duration of 7.5 years and 100% efficacy or a vaccine with persistent protection and 50% efficacy (Craig et al. 2015). However, previous vaccine attempts have been unsuccessful at best. The antibody response from a crude-killed whole-cell vaccine used in the 1970s was successful, but the vaccine failed to elicit an adaptive immune response in clinical studies. Since then, with no available effective vaccine, the public health society solely depends on controlling the emergence through prevention, awareness of sexual contact, antibiotic regime, and surveillance program (Suay-García and Pérez-Gracia 2017). The findings of this investigation propose that a certain degree of acquired immunity is developed through natural infection in instances of gonococcal urethritis or pharyngitis. This is supported by the observation that previously colonized chimpanzees necessitated a considerably greater bacterial dose to attain reinfection (Maurakis and Cornelissen 2022).

Newer serogroup B vaccine 4CMenB, also known as Bexsero, comprises the same outer membrane vesicle (OMV) components as MeNZB, in addition to three recombinant proteins, one of which is Neisserial heparin-binding antigen (NHBA), a target identified to be critical for gonococcal colonization and survival (Semchenko et al. 2020). OMVs have garnered significant interest as potential vaccine antigens for sexually transmitted infection (STI) pathogens (Chbib et al. 2021). The exterior of these entities is adorned with phospholipids, diverse outer-membrane proteins, and lipopolysaccharide/lipooligosaccharide (Kulp and Kuehn 2010). A phase III clinical trial with the identifier (clinicaltrials.gov//NCT04415424) has been designed to assess the effectiveness of Bexsero in preventing gonorrhea infection among men who identify as gay or bisexual. Being one limitation that further research will be necessary to assess the effects of gonococcal vaccines on the female population.

Recent times reported two vaccines administered in human trials and four clinical studies. According to Rice (Rice et al. 2017b), the first vaccine trial was a whole-cell vaccine developed from a single gonococci strain. The first human trial was given to the Aboriginal population in northern Canada. The second one was a single-antigen pilus tested on a larger scale. The vaccines were given to US-military places in Korea that are highly risked. However, both trials resulted in the sparsity of antigenic determinants. Another two vaccines that undergo clinical studies, the PorA vaccine, and the partial autolyzed vaccine, also do not seem successful in affecting the infection rate.

In one study by Petousis-Harris (Petousis-Harris et al. 2017), inoculated patients with outer membrane visible meningococcal group B vaccine (MeNZB) resulted in fewer rates of gonococci of about 24% of effectiveness. However then, the efficacy of the vaccine dropped to 9% within 5 years (Kenyon 2019). The vaccine has been shown to offer some protection against gonorrhea in several studies (Whelan et al. 2016; Azze 2019). A decrease in the incidence of gonorrhea was observed in analyses conducted in Cuba and Norway following the implementation of MenB vaccine programs (Humbert and Christodoulides 2018).

Efforts to produce a whole-cell-based vaccination for *N. gonorrhoeae* have also been revived. Gala et al. created a transdermal whole-cell-based inactivated gonococcal microparticle vaccine formulation recently (Gala et al. 2018). The proposed advantages over previous vaccines and other whole-cell preparations are the use of formalin-fixed whole gonococci, which protects all immunogenic epitopes from degradation, the use of microparticles, which mimic the shape of *N. gonorrhoeae* cocci, thereby activating the immune system without suppressing it, and transdermal administration using microneedles, which allows slow,

sustained release of antigens to enhance their uptake (Gala et al. 2018). So far, the vaccine has only been tested in mice models in vitro and in vivo, where a substantial rise in antigen-specific IgG titers was found.

The role of lipooligosaccharide (LOS) in the pathogenic lifestyle of *N. gonorrhoeae* is significant, and the potential for a vaccine based on 2C7 to provide broad cross-reactivity against various strains of the bacterium is a noteworthy advancement in the pursuit of gonococcal prevention (Gulati et al. 2019a). The study conducted has found that the administration of this mimitope in conjunction with a TH1-stimulating adjuvant led to the production of bactericidal IgG, a decrease in gonococcal colonization, and an acceleration of bacterial clearance in mice that were experimentally infected (Gulati et al. 2019a).

However, there are some challenges in vaccine development, of which the surface of the gonococcal determinants is often anti-genetically variable, and the epitopes are modified by the phase or antigenic variation (Rotman and Seifert 2014). The gonococcal microorganism is seen to be capable of changing the determinants surface. This makes the strategies of evasion of the pathogen to the host more adaptive. Moreover, during the vaccine's effectiveness assessment, those vaccinated were likely to seek care. The efficacy of vaccines might not work due to other external factors and interventions. The recent explanation of these novel targets is shown in Table 7**.**

Antimicrobial stewardship (AMS) is a healthcare system-wide strategy that aims to encourage and regulate the careful use of antimicrobials to maintain their efficacy. The implementation of Antimicrobial Stewardship (AMS) involves a series of well-coordinated strategies aimed at achieving three primary objectives. First, it seeks to enhance patient care and outcomes by ensuring optimal therapy. Second, it aims to minimize collateral damage by reducing the use of antimicrobials, which ultimately leads to less resistance. Finally, it seeks to reduce the cost of antibiotics (Dik et al. 2016; Davies et al. 2013).

The AMS programs have a primary objective of collaborating with healthcare practitioners to prescribe the **5D** of antimicrobial therapy. This includes administering the appropriate **D**rug, administering the correct **D**ose, selecting the appropriate **D**rug route, determining a suitable **D**uration, and timely **D**e-escalation to pathogen-directed therapy (Doron and Davidson 2011). An illustration of the implementation of antibiotic stewardship in China ranks as the second largest consumer of antibiotics globally (Boeckel et al. 2014). Being the most populous nation globally holds a significant responsibility in regulating the appropriate utilization of antibiotics and preventing their misuse (Lin et al. 2016). Following that, a set of policies or guidelines were introduced by the Chinese Ministry of Health, which is now known as the National Health Commission, to enhance antimicrobial stewardship. These guidelines include "Guidelines on the Clinical Application of Antimicrobials" in 2004, "Guidelines on Prescription Management" in 2006, and "The Prescription Management and Evaluation Standards in Clinical Practise" in 2010 (Chen et al. 2016).

However, the community continues to experience pervasive antimicrobial pressure as a result of the administration of antimicrobials for the treatment of infectious diseases such as gonorrhea (Chen et al. 2019b). One of the greatest challenges is the common practice of overprescription of antibiotics by physicians and self-medication with antibiotics (Fang 2014). Despite the continuous challenges, ideally, the implementation of antimicrobial stewardship (AMS) strategies would reduce the selection pressure of antibiotics by optimizing their usage and minimizing overuse or overconsumption of antibiotics to minimize adverse events (Doron and Davidson 2011). This pressure arises when antibiotics only target antibiotic-sensitive pathogens, leading to an increase in the prevalence of antibiotic-resistant bacterial pathogens (Yosef et al. 2016). The phenomenon of selection pressure can be attributed to the utilization of disinfectants in hospital environments, which impose selective pressure on pathogens, thereby facilitating the development of resistance against these agents.

The mechanisms of interspecies competition may hold a potential solution for the eradication of pathogens belonging to fulfill its nutritional needs, and *N. gonorrhoeae* is required to engage in interactions, and potentially engage in competition, with indigenous microbiota to access the available nutrients (Spurbeck and Arvidson 2010). Certain commensal microorganisms have the potential to provide protection against the pathogen by employing nutrient or adherence receptor competition, as well as the secretion of inhibitory agents (Jerse et al. 2014). However, there are limited studies which have been conducted on the competitive interactions among Neisseria species in vitro.

Utilizing cutting-edge techniques in genomics, proteomics, metabolomics, and bioinformatics may facilitate the elucidation of mechanisms of interactions in *N. gonorrhoeae* in modern research, as seen through many successful findings utilizing these methodologies (Omeershffudin Umairah Natasya Mohd Kumar Suresh 2023, 2022; Umairah and Suresh 2019). The field of drug discovery and development has been significantly propelled by genomics, particularly with the aid of innovative and advanced sequencing methods. These techniques have enabled comparative evaluations of healthy and diseased tissues, transcription and expression profiling, side-effect analysis, pharmacogenomics, and biomarker identification (Russell et al. 2013).

These available genomic data can be further explored and integrated with other in silico approaches, such as subtractive genomics. The approach appears to be efficient in terms of both research timeline and cost-effectiveness. An

Table 7 Targets in developing a vaccine against *Neisseria gonorrhoeae*

References	Target	Objective	Findings/Result
Zhu et al. (2019)	Six gonococcal proteins expressed in human mucosal infections	To evaluate the bactericidal antibody production against *N. gonorrhoeae* in mice	Antibodies and bactericidal activity in serum were found to be cross-reactive against many *N. gonorrhoeae* strains, based on the characterization of the immunological responses
Sikora et al. (2020)	L-methionine-binding lipoprotein (MetQ)	To determine MetQ's conservation and role in *Neisseria gonorrhoeae* pathogenesis, as well as its capacity to elicit protective immunological responses	The immunological response triggered by rMetQ-CpG is protective and helps get eradicate bacteria in the murine lower genital tract
Gulati et al. (2019a), Gulati et al. (2019b)	Lipooligosaccharide-derived epitope 2C7	To evaluate the effectiveness of TMCP2, when administered at 0, 3, and 6 weeks to BALB/c mice at either 50, 100, or 200 µg/dose in combination with glucopyranosyl lipid A-stable oil-in-water nanoemulsion	The 2C7 vaccine meets the requirements for an effective gonococcal vaccine candidate, including a high level of antigenic representation and the ability to elicit extensively cross-reactive IgG bactericidal antibodies
Wang et al. (2018)	MtrE protein and its surface-expressed loop "Loop 2"	Identification of a highly conserved protein found and determined its potential utility as a vaccine antigen	*MtrE* as highly conserved surface-expressed antigens and Loop 2 show promise for use in the development of a vaccine against *N. gonorrhoeae*
Almonacid-Mendoza et al. (2018)	Component of the adhesin complex in *Neisseria gonorrhoeae* (Ng-ACP)	To investigate whether or not antiserum produced in rabbits against rNg-ACP might block the inhibitory effect of Ng-ACP on human lysozyme activity in vitro	50 gonococcal strains were found to express the *N. gonorrhoeae* adhesin complex protein (Ng-ACP), and recombinant proteins generated antibodies in mice that killed the bacteria in vitro
Humbert and Christodoulides (2018)	Macrophage infectivity-enhancing truncated N. meningitidis protein (rT-Nm-MIIP) is a recombinant protein	To study with the hypothesis that antisera would recognize both meningococcal and gonococcal MIP and would produce cross-species bactericidal action	Gonococcal strains P9-17 (expressing M35 Ng-MIP, titers of 64–512) and 12CFX T 003 (expressing M10 Ng-MIP, titers of 8–16) were inhibited by antisera to M2 rT-Nm-MIP, while FA1090 was not (expressing M8 Ng-MIP)
Cash et al. 2015; Price et al. 2005)	A and B transferrin-binding proteins (tbpA and tbpB)	To evaluate the mice immunized intranasally with recombinant transferrin-binding proteins (rTbpA and rTbpB) conjugated to rCtb and their anti-Tbp immune responses	Both are widely expressed and can elicit a systemic vaginal antibody response in mice, even though these antibodies have a minimal impact on the animals' ability to survive
Shewell et al. (2013)	Nitrite reductase AniA	To determine the immunogenicity of AniA glycoforms in *N. meningitidis* C311	Antisera produced against a shortened, non-glycosylated, recombinant form of the AniA protein are capable of inhibiting nitrite reductase activity
Zhu et al. (2011)	Protein B (PorB) of the outer membrane porin	To test the effectiveness of vaccinations against either viral replicon particles (VRPs) or outer membrane vesicles (OMVs)	Extremely conserved and intriguing, but not producing significant effective vaccine research thus far. Correlates with immunity when a Th1 response is elicited, but not when an antibody response

example, a recent study has identified potential new drug targets for tuberculosis in *Mycobacterium tuberculosis* P450 enzymes through an in silico interaction analysis with azole drugs (Kumar 2020).

Several strategies have been developed to combat resistance in *N. gonorrhoeae* isolates. The global health agency, WHO has formulated a comprehensive global action plan to tackle the spread and impact of antimicrobial resistance in *N. gonorrhoeae* (Lewis 2014*).* Additionally, several countries have also established their national action plans to address this issue. The key strategies and priorities to optimize the treatment include global, regional, and national surveillance, diagnostics, public health initiatives and research, antimicrobials, and therapeutic regimens (Unemo et al. 2019b; WHO (World Health Organization) 2012).

Conclusion

Some factors that define the importance of gonorrhea for public health include the prevalence of the disease among people of reproductive age, which has a significant detrimental effect on fertility, the increased risk of multiple infections with other known STIs, the lack of a gonococcal vaccine, and N. gonorrhea's progressive drug resistance.

N. gonorrhoeae is found to be one of the longest-surviving bacteria pathogens in human history. Up until today, it remains one of the global health problems. Shortly after antimicrobials were implemented in clinical practice, the antimicrobial resistance of these pathogens became significant. Seen, drug designing to develop new antibacterial agents and vaccines faced challenges as these bacterial pathogens can adapt to the microenvironments of the human host. Due to the ability to survive when detected by the immune system, it can be generally assumed that there will be no immunity against recurrent infection.

Since this bacterial pathogen can change in response to its host, unraveling how it causes the disease is a more complicated task. A lack of symptoms is associated with infection in women, although men show signs of illness. However, this continues to be accepted as gospel. We also learn that experimental research to obtain the tissue culture has limits. Therefore, we have very little information about the host and this bacteria pathogen. To fulfill the therapeutic challenge of treating gonorrhea, the antibiotic pipeline will need to be supplied with new, effective pharmacological therapies due to the acquisition and propagation of antimicrobial resistance determinants among naturally competent gonococcal strains. This implies that more research is required. Possible therapeutic targets and vaccination candidates could be located using a bioinformatics integration strategy.

In summary, it is imperative to develop new antimicrobial agents to combat gonorrhea effectively. The integration of genomic, transcriptomic, and proteomic analyses, coupled with advancements in drug chemistry and high-throughput screening of compound libraries, along with insights derived from physiological experiments, can facilitate the identification of novel bacterial targets and offer prospects for the rational development of novel drugs.

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