Review

Antimicrobial Resistance of Neisseria gonorrhoeae in Sub-Saharan Populations

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Abstract: Neisseria gonorrhoeae has become a significant global public health problem due to growing infection rates and antibiotic resistance development. In 2012, N. gonorrhoeae positive samples isolated from Southeast Asia were reported to be the first strains showing resistance to all first-line antibiotics. To date, N. gonorrhoeae’s antimicrobial resistance has since been identified against a wide range of antimicrobial drugs globally. Hence, the World Health Organization (WHO) listed N. gonorrhoeae’s drug resistance as high-priority, necessitating novel therapy development. The persistence of N. gonorrhoeae infections globally underlines the need to better understand the molecular basis of N. gonorrhoeae infection, growing antibiotic resistance, and treatment difficulties in underdeveloped countries. Historically, Africa has had minimal or rudimentary N. gonorrhoeae monitoring systems, and while antimicrobial-resistant N. gonorrhoeae is known to exist, the degree of resistance is unknown. This review looks at the gender-related symptomatic gonorrhoeae disease and provides an overview of the essential bacterial factors for the different stages of pathogenesis, including transmission, immune evasion, and antibiotic resistance. Finally, we deliberate on how molecular epidemiological studies have informed our current understanding of sexual networks in the Sub-Saharan region.

Keywords: Neisseria gonorrhoeae; antimicrobial-resistance; gonococcal infection; drug-resistance; sexually transmitted infection; gonorrhoeae; molecular typing; public health; sexual health

1. Introduction

Neisseria gonorrhoeae, a Gram-negative diplococcus beta proteobacterium, is the causative agent of gonorrhoeae, one of the most prevalent sexually transmitted infections (STIs) worldwide [1–3]. Although N. gonorrhoeae infections are rarely fatal, the disease has a high prevalence, particularly among men. On the other hand, females are more prone to complications during infection, such as the development of pelvic inflammatory diseases [3,4]. Urogenital infections are generally asymptomatic, and more than half (>50) of all females are likely to report at least one urogenital infection in their lifetime [5]. N. gonorrhoeae causes damage to the upper genital tract in females and the less frequently observed epididymitis in males [6,7]. These infections can lead to reproductive difficulties and even infertility for both men and women [8]. High-risk populations for N. gonorrhoeae infection include sexual networks that engage in unprotected sex with multiple partners, commercial sex workers, men who have sex with men, and young heterosexuals [9,10]. Recently, there has been a 19% increase in new cases of gonococcal infections worldwide [7]. According to the WHO, there is a 2.6–5.0% annual increase of reported N. gonorrhoeae infections in females aged between 15–49 years in Sub-Saharan Africa [11,12]. According to additional modelling research, Sub-Saharan Africa is the only region with such significant STI incidences [13,14]. It has been widely reported that females are more susceptible to infection than males for various reasons, specifically that male and female genital tract sensitivity to infection differ, and transmission from males to females is more successful [4,15]. Secondly, most infections in females are asymptomatic and remain untreated [5,10,16]. Females with an undiagnosed
infection are likely to develop pelvic inflammatory disease, which may lead to ectopic pregnancy, tubal infertility, or persistent pelvic discomfort [6,17,18]. In addition to epidemiological data, it is physiologically possible that certain STIs, including N. gonorrhoeae, promote human immunodeficiency virus (HIV) acquisition and enable transmission [4,19]. Identifying and managing STIs and other reproductive tract infections have been highlighted as essential components for excellent sexual and reproductive health services [14]. Health services have been included as part of government services in several African countries. There has been a rise in new and untreated instances of N. gonorrhoeae infections due to treatment failures and the disease’s asymptomatic qualities [20,21]. Asymptomatic infections may present high levels of surface antigenic variation; this variation, along with antibiotic resistance, are critical characteristics that have caused N. gonorrhoeae to pose a global health problem [3,22]. The lack of microbiological STI identification in low-resource settings implies that STI-related symptoms should be managed using a syndrome-based approach [23]. This form of therapy is also used to treat patients who present gonococcal symptoms; however, these do not need a positive N. gonorrhoeae identification from the laboratory [21]. If patients are suspected to be infected with N. gonorrhoeae, they are instantly given drug-combination treatment without any diagnostic tests [24]. This syndrome-based approach has well-established financial advantages and antimicrobial resistance development drawbacks [25]. N. gonorrhoeae has a very effective genetic resistance mechanism to antimicrobials used to treat infections [26]. In recent years, there has been a surge in antimicrobial resistance globally [17]. Antimicrobial resistance affects all countries, regardless of their financial status or development, and it has been suggested that surveillance and sharing of information must be established to enable informed treatment options for infected individuals [22,26]. As a result, inadequate treatment recommendations for the local context are often due to the lack of quality data [2,27]. Multidrug-resistant N. gonorrhoeae has emerged, and resistance mechanisms have been rapidly evolving [11,28]. Recent studies suggest that acquired resistance determinants may occur through extracellular DNA absorption [29]. Various forms of resistance acquisition exist, including chromosome-mediated, plasmid-mediated, and multidrug-resistant efflux pump resistance [7]. In 2019, Chen and colleagues argued that the development of non-beta-lactamase resistance towards penicillin, cephalosporins, and azithromycin resistance by gonococci, requires overexpression of the mtrCDE-encoded efflux pump [30]. Misuse of treatment drugs is the most significant and essential factor contributing to antibiotic resistance [10,31]. Currently, the first-line therapies for urinary tract infections or acute respiratory tract infections are amoxicillin, sulfamethoxazole, or trimethoprim [32], whereas bloodstream infections are treated with a combination of ampicillin and gentamicin or ceftriaxone [11,33]. Recent research has discovered a significant degree of N. gonorrhoeae resistance to frequently used antibiotics in Sub-Saharan countries [33]. Buder and colleagues found that approximately 90% of N. gonorrhoeae isolates were resistant to chloramphenicol, an antimicrobial agent used to treat N. gonorrhoeae infection [34]. Therefore, it is critical to assess the present state of antibiotic resistance and identify information gaps to plan appropriate continental responses. New treatment therapies and vaccines need to be developed to keep up with the ever-emerging drug-resistant N. gonorrhoeae strains; currently, we have limited alternative therapeutic options [26,35]. The development of novel treatments focusing on the non-variable host cell structures encountered by gonococci during adhesion, colonisation, and invasion is critical to mounting a suitable defence against the diseases [22,36].

2. Gonococcal Pathogenesis

Despite the historical prevalence of N. gonorrhoeae in the human population and the significant severity and frequency with which adverse complications accompany disease (particularly in females), we have only recently begun to understand N. gonorrhoeae pathogenesis in human hosts [3,36]. The lack of animal models closely resembling human infection impedes the overall understanding of the underlying mechanisms involved in gonococcal pathogenesis [35]. Although numerous animal models have been established,
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none replicate the complete range of diseases produced by *N. gonorrhoeae* at any particular location inside the human body [37]. As a result, researchers studying *gonococcal* pathogenesis have depended on human volunteers, organ cultures, and immortalised or malignant tissue culture cell lines [36]. According to recent studies, the proclivity of gonococci to undergo both phase and antigenic change in a random process would be subject to varied selective environmental forces depending on the model system used [38].

*N. gonorrhoeae* colonises the cells efficiently once adhered to the mucosal epithelium by extracellular replication and nutrition acquisition from the surrounding extracellular environment. *N. gonorrhoeae* must interact with, and even compete with, indigenous bacteria for nutrition. Indeed, in order to defend itself against bacterial diseases, *N. gonorrhoeae* needs to absorb elements, such as iron, zinc, and manganese, which are restricted by the human host, a process known as nutritional immunity. The influx of neutrophils during spontaneous colonisation may increase nutrition acquisition by generating serum component leakage and tissue injury, as well as exposing *N. gonorrhoeae* to intracellular nutrient pools after phagocytosis, thus supplying nutrients for bacterial growth. To survive and multiply, *N. gonorrhoeae* must adapt to changing environmental conditions within the host’s vaginal canal, rectum, and oropharynx. The limitations of current *N. gonorrhoeae* experimental models have prevented gains in specific knowledge of the pH, nutrient, and oxygen concentrations in the varying ecological niches of the genital mucosa; however, the range of adaptive mechanisms acquired and maintained by the bacterium over evolutionary time indicates the main contributing environmental changes that may affect survival during infection. These techniques regulate global transcriptional changes using transcriptional regulators and two-component systems, translational regulation using regulatory short RNAs (sRNAs), and clonal variation using phase variation. The development of a primary human male urethral epithelial cell culture system and the human male experimental challenge paradigm have considerably increased our understanding of the particular variables involved in the early pathogenesis processes of *N. gonorrhoeae* colonisation urethral epithelium [35,39]. These models do not account for the cellular and molecular processes that occur during long-term infection. Furthermore, clinical findings and data show that male infection models cannot be generalised to relate to infection in females [26]. A suitable in vitro cell culture model is required for studying the entire infection, including adhesion, transmigration, and transport to deeper tissue layers [40]. In other studies, co-culturing human dermal fibroblasts with human colorectal carcinoma, endometrial epithelial, and male uroepithelial cells resulted in three independent 3D tissue models based on porcine small intestinal submucosa (SIS) scaffold [40]. Transepithelial electrical resistance (TEER) and FITC-dextran assays revealed that the created monolayer had high barrier integrity. Based on the histological, immunohistochemical, and ultrastructural investigations, the 3D SIS scaffold-based models closely resemble the major characteristics of the site of gonococcal infection in human hosts, including mucus production, tight junctions, and microscopic structures [40]. The established 3D tissue models were infected with various *N. gonorrhoeae* strains and derivatives with varying adhesion and invasion phenotypes. In response to infection, tight junctions were disrupted in a strain- and cell-type-dependent manner, and interleukin production increased [40]. Three independent 3D co-cultured tissue models of human HEC-1-B, SV-HUC-1, and T84 with human fibroblast cells on a biological decellularised scaffold were established. This was the first report on developing a 3D tissue model for studying *Neisseria* sp. infections, which included co-culturing of epithelial and fibroblast cells [41]. The models provided physiologically relevant conditions containing both connective tissue with fibroblasts and polarised epithelial monolayers of mucosal surfaces and thus represent a significant advancement in the modelling of *N. gonorrhoeae* infection [17]. The severity of complications of *N. gonorrhoeae* infection in females has previously limited human research to mostly male participants [5]. Microscopic studies of clinical biopsies and male urethral exudates have offered some insight into effective *N. gonorrhoeae* infection as it occurs in vivo, but these analyses are not without limitations in that they are susceptible to personal observation and interpretation [26,42]. Furthermore, the findings obtained
cannot be linked to any specific time point post-infection [40]. Primary cell and organ culture methods have also been created to study *N. gonorrhoeae* interaction throughout the lower and upper female genital tracts; however, these systems are site-specific, making a worldwide examination of the female genital tract impossible [36]. The female genital tract comprises a diverse combination of epithelia, resulting in a complicated environment that is difficult to duplicate in vitro [35]. As a result, data collected from primary cell and organ culture may only give a hazy picture of *gonococcal* pathogenesis as it happens in vivo at any point throughout the female genital canal. The development of a female mouse model of genital tract infection has been and will continue to be an essential tool for studying *gonococcal* pathogenesis in an immunologically defined setting [43]. However, it is currently unclear whether data obtained from the mouse model of female genital tract infection is reflective of infection as it occurs within the human female genital tract because mice lack the expression of several human-specific receptors (e.g., CR3, CD46, and CEACAM), which are thought to play critical roles in potentiating *gonococcal* disease [44,45]. Furthermore, large amounts of oestrogen are necessary to induce infection in mice, and the significance of induced oestrogen to the findings obtained is unknown [43]. To explore molecular variables involved in *gonococcal* pathogenesis, researchers frequently utilise immortal and malignant cell lines [36]. These systems are helpful because they are widely available, simple to maintain, and adaptable. Immortality and ongoing laboratory care cause these cell lines’ protein and receptor expression patterns to frequently change [36,40]. Furthermore, changing protein expression can result in additive or synergistic alternative functional responses within these immortal cells compared to their respective parental tissues [36]. It is also worth noting that certain cell lines widely used in the research of *gonococcal* pathogenesis have unclear or irrelevant origins [46]. As a result, extrapolating data obtained from the use of immortal cell lines concerning *gonococcal* infection at any specific site within a human host is complex, and caution should be exercised when concluding these studies because immortal cell lines may not be truly representative of the epithelia encountered by the *N. gonorrhoeae* in vivo [26,36,43]. However, the use of immortal cells has considerably increased our understanding of human and *N. gonorrhoeae* elements that may play a role in disease potentiation in vivo [46].

### 3. Antimicrobial Resistance of *N. gonorrhoeae* in Africa

In 2016, the WHO stated that the global rate of new *N. gonorrhoeae* infections was 19 per 1000 females and 24 per 1000 males [4]. This implies that over 75 million people are exposed to the infection each year, and of these numbers, Africa has the highest incidence of *gonococcal* infections [6,16]. The most considerable prevalence of infection and disease sequelae in these developing countries occurs amongst teens and young adults, given the link between increased risk of *N. gonorrhoeae* infection and HIV type 1 [13,19]. Data from 102 studies reporting on the epidemiology of *N. gonorrhoeae* in various contexts and countries in Sub-Saharan Africa, from 2005 to 2014 [47]. All investigations were conducted in countries with moderate-to-high HIV prevalence [47,48]; see Figure 1. Significant variations were noted in the number of studies in each Sub-Saharan country, with South Africa (18%), Tanzania (17%), and Kenya (12%) representing the bulk of studies [47]. Another study with a total of 147 *gonorrhoeae* prevalence studies from 56 countries globally was found. The global pooled mean prevalence of current *gonorrhoeae* infection was estimated to be 2.2% (95% CI 1.3% to 3.2%), with Africa having the greatest incidence at 5.0% (95% CI 1.9% to 9.3%) [49]. Furthermore, the identified articles only represented a small fraction of the Sub-Saharan population; there were no data points for a significant number of countries (49). The little attention devoted to *N. gonorrhoeae* epidemiology in the Sub-Saharan population is mirrored further in that only seven studies reported on infection incidence estimates between 2005 and 2014 [16]. Many African countries lack comprehensive data collection methods for STIs, indicating a widespread lack of national STI surveillance systems [4,50]. The broad acceptance of the syndromic approach to the diagnosis and management of STIs has resulted in genital specimens for laboratory analysis no longer being routinely
collected when patients come in with genital symptoms [10]. Nonetheless, the benefits of the syndromic approach may be observed because several bacterial STIs, such as urethritis, syphilis, and chancroid, have decreased over time [16]. Following reports of \textit{N. gonorrhoeae} antimicrobial resistance to quinolones, the WHO has recommended that countries conduct more systematic and frequent monitoring of \textit{N. gonorrhoeae} antimicrobial resistance [33].

The WHO organised a three-day workshop in Harare, Zimbabwe, to assess how far countries had progressed in adopting national surveillance systems for \textit{N. gonorrhoeae} antimicrobial resistance [4,50]. Only 11 Sub-Saharan countries were represented during this event, namely, Benin, Cameroon, Ethiopia, Ghana, Kenya, Madagascar, Nigeria, South Africa, Tanzania, Uganda, and Zimbabwe. Although the response to the request for monitoring \textit{N. gonorrhoeae} antimicrobial resistance in Africa has been lethargic, several studies have been undertaken in certain countries, and other countries are prepared for implementation [50]. In Cameroon, a retrospective study (2012–2018) isolated a total of 449 \textit{N. gonorrhoeae} strains, with a large proportion of them resistant to ciprofloxacin (64.4%), benzylpenicillin (80.1%), and tetracycline (58.4%). Ciprofloxacin resistance grew dramatically from 15.0% in 2012 to 79.5% in 2018 (\(p\)-value = 0.0001). Resistance to benzylpenicillin has decreased significantly (\(p\)-value = 0.002) since 2016, but resistance to tetracycline has remained steady. The prevalence of resistance to ceftriaxone (1.8%), azithromycin (2.1%), and spectinomycin (2.0%) was modest [51]. The last identified study of \textit{N. gonorrhoeae} antimicrobial resistance in the Central African Republic was in 1984 (males) and 1999 (females).
In 1984, 460 male gonorrhoeae patients were randomised to receive either $4.0 \times 10^6$ units procaine penicillin + 1 g probenecid or 2 g spectinomycin. Ninety-one per cent of these patients returned for follow-up; the failure rate was 4.8% with the penicillin schedule and 6.2% with the spectinomycin schedule (difference not statistically significant). Seven (1.5%) of the 460 patients were infected with penicillinase-producing *Neisseria gonorrhoeae* (PPNG) strains [52]. In 1999, participants were subjected to a regular gynaecological checkup at the health centre, which included *gonorrhoeae* testing. Cervical secretions and blood samples were sent to the National STD Reference Centre for *Neisseria gonorrhoeae* testing. Overall, 34% of the study women had at least one sexually transmitted illness, and *N. gonorrhoeae* was found in 3.1% of these women [53]. In Zambia, for *Chlamydia Trachomatis* and *N. gonorrhoeae*, correlations with sociodemographic and clinical risk variables are investigated independently. Cross-sectional research of high-risk women in two Zambian cities, Lusaka and Ndola, has been conducted using multivariate logistic regression (MLR) models to evaluate relationships between putative *Chlamydia Trachomatis* and/or *N. gonorrhoeae* risk variables. With a prevalence of 6.8%, *N. gonorrhoeae* was related to younger age, lower education, concurrent *Trichomonas vaginalis*, bacterial vaginosis, and incident syphilis infection [54]. In Sudan, pregnant women who visited the Khartoum Teaching Hospital Antenatal Clinic between January and October 1999 were invited to take part in this prospective cross-sectional research. A total of 151 patients were recruited for the research and underwent the stated interviews, examinations, and investigations. *N. gonorrhoeae* was found in three (2%) of the women [55]. There is currently a significant lack of data on gonococcal infections and AMR in Sudan [56]. In Botswana, a cross-sectional investigation of 703 prenatal care attendees in Botswana was conducted, and specimens were obtained for *N. gonorrhoeae* diagnosis. *N. gonorrhoeae* was discovered in 3% of the attendants. There are no acceptable care measures for *N. gonorrhoeae* in pregnant women in Botswana, a condition that is likely to be replicated in other Sub-Saharan African nations [57]. In Benin, 206 samples were identified as *N. gonorrhoeae* positive, with antibiotic resistance found in 52 of the isolates [58]. Antimicrobial resistance surveillance has been conducted in all nine provinces in South Africa, namely Gauteng, the Northern Cape, Mpumalanga, the Western Cape, the Free State, the Eastern Cape, the North West Province, KwaZulu Natal, and Limpopo [11]. These investigations revealed a widespread ciprofloxacin resistance in *N. gonorrhoeae*, while cephalosporins remained effective. However, two instances of cefpodoxime-resistant *N. gonorrhoeae* isolates were identified in the Gauteng province [11,18]. The two isolates also showed reduced sensitivity to azithromycin and gentamicin and a higher than expected minimum inhibitory concentration (MIC) for ceftriaxone [59]. Another study isolated *N. gonorrhoeae* strains from 42 immunocompromised males presenting *gonorrhoeae* symptoms at public healthcare institutions in Johannesburg, South Africa [59]. Almost one-third of the isolates were categorised as multidrug-resistant (resistant to more than three drugs) [11,59]. Ciprofloxacin-resistance was found in nearly 80% of the patients, and azithromycin-resistance was found in 15% of the strains. Fortunately, no evidence of cefixime-resistance or ceftriaxone-resistance was identified. Ciprofloxacin-resistance was reported to be consistently high across the entire country, whereas azithromycin-resistance was not [11,18,59]. Recent research from the province of KwaZulu-Natal discovered azithromycin resistance in 68% of *N. gonorrhoeae* bacteria, with 71% being multidrug-resistant [60]. Surveillance locations, on the other hand, revealed azithromycin resistance in fewer than 5% of samples [61]. These disparities necessitate a concerted effort to establish the extent of azithromycin resistance across the country. Forty-one papers were discovered in another search aimed to analyse recent publications on the incidence of *N. gonorrhoeae* infections in Africa; see summary in Table 1. In these studies, a total of 15,546 people were examined, with 1250 (7.9%) primarily infected with *N. gonorrhoeae*. In comparison to females, the incidence of *N. gonorrhoeae* infection, see Table 1 and Figure 2, and infection incidences were found to be more prone in the age group 21–25 years. Men were found to have a greater frequency than women in Nigeria, Ethiopia, and Ghana.
Table 1. Infections caused by \textit{N. gonorrhoeae} in 15 Sub-Saharan African nations.

| Country                | Sample Size | Male Participants | Male +GC | Female Participants | Female +GC |
|------------------------|-------------|-------------------|----------|---------------------|------------|
| Benin                  | 81          | 0                 | 0        | 81                  | 1          |
| Burkina Faso           | 367         | 0                 | 0        | 367                 | 13         |
| Cameroon               | 79          | 40                | 40       | 39                  | 39         |
| Central African Republic | 30        | 28                | 28       | 2                   | 2          |
| Ethiopia               | 907         | 274               | 17       | 633                 | 26         |
| Ghana                  | 3079        | 539               | 173      | 2540                | 108        |
| Guinea                 | 237         | 0                 | 0        | 237                 | 9          |
| Kenya                  | 3696        | 2895              | 9        | 801                 | 15         |
| Madagascar             | 126         | 95                | 95       | 31                  | 31         |
| Mali                   | 114         | 0                 | 0        | 114                 | 5          |
| Nigeria                | 2868        | 777               | 61       | 2091                | 87         |
| South Africa           | 3495        | 2639              | 156      | 856                 | 220        |
| Sudan                  | 151         | 0                 | 0        | 151                 | 3          |
| Zambia                 | 116         | 0                 | 0        | 116                 | 43         |
| Zimbabwe               | 200         | 0                 | 0        | 200                 | 48         |
| Total                  | 15546       | 7287              | 579      | 8259                | 650        |

Figure 2. Prevalence of \textit{N. gonorrhoeae} infections in 15 Sub-Saharan countries listed in Table 1.
4. Evolution of Antimicrobial Resistance

4.1. Sulphonamides

Sulphonamides were first used to treat *N. gonorrhoeae* in the 1930s; however, by 1944, 75% of World War II soldiers in the Italian army had experienced treatment failure with these drugs. Sulphonamide antimicrobials compete with the dihydropteroate synthetase (DHPs) enzyme in the production of folic acid [17]. Resistance is established by increasing the production of the standard substrate, p-aminobenzoic acid, or by creating a mutant DHPs with a poor affinity for the antibiotic [62]. In the 1960s, combination therapy with trimethoprim was offered as an alternative to increasing the efficacy of sulphonamide in treating uncomplicated *N. gonorrhoeae* infections. Trimethoprim prevents susceptible *N. gonorrhoeae* from converting dihydrofolate to tetrahydrofolate in the metabolic pathway performed by the dihydrofolate reductase (DHFR) enzyme [33]. *N. gonorrhoeae* DHFR, on the other hand, has a low affinity for trimethoprim and may be genetically changed, making the bacterium less susceptible to this antibiotic [32]. Until the 1970s, the synergic combination of sulphonamides and trimethoprim was utilised to treat *gonorrhoeae* in high and multi-dose treatment schemes. These drugs inhibit bacterial folic acid synthesis by targeting the bacterial dihydropteroate synthase (DHPS) enzymes [17]. Over synthesis of p-aminobenzoic acid, which dilutes the antimicrobial agent, or changes in the *folP* gene (point mutations or the presence of a mosaic gene containing DNA sequences from commensal *Neisseria* spp.), which encodes the drug target DHPS, can cause sulphonamide resistance [63]. The modifications to DHPS result in a significantly reduced affinity for sulphonamide agents as well as bacteriostatic activity [21].

4.2. Penicillin

Penicillin was introduced as an antibacterial therapy for *N. gonorrhoeae* in 1943, notably when sulphonamide treatment failed. Penicillin worked by inhibiting the bacterial cell wall production by binding to transpeptidase enzymes in the periplasm of penicillin-binding proteins (PBP). Therefore, penicillin resistance mechanisms in *N. gonorrhoeae* were linked to reduced sensitivity by cumulative chromosomal changes in various genes associated with cell wall production (*penA* and *penA1*) or structures influencing periplasmic drug concentration [17]. However, in the 1960s, penicillin had reduced susceptibility against *Neisseria gonorrhoeae*. In the 1970s, *N. gonorrhoeae* isolates had MICs of up to 128 g/mL, thus ending the penicillin era; however, in the 1960s, penicillin had reduced susceptibility against *N. gonorrhoeae* therapy [64]. The newly discovered resistance mechanism was a plasmid-mediated β-lactamase (*bla*) gene type TEM (*blaTEM*), and the isolates were dubbed penicillinase-producing *N. gonorrhoeae* (PPNG). The plasmids carried by *N. gonorrhoeae* *blaTEM* are genetically similar but have various sizes, insertion, or deletion sites and are termed according to their epidemiological origin. The African (5588 bp) is one of the most frequently reported *bla*-plasmids in *N. gonorrhoeae* isolates [60].

4.3. Tetracycline

In the 1950s, tetracycline was offered as a therapeutic alternative for *N. gonorrhoeae* in individuals allergic to penicillin. Overexpression of *penB* and *mtr* in *N. gonorrhoeae* isolates inhibited tetracycline action, thus establishing an emergence of tetracycline-resistant *Neisseria gonorrhoeae* [65]. In 1985, the first *N. gonorrhoeae* isolates with high-level tetracycline resistance (MIC 24–32 g/mL) were isolated; this was said to be a result of the expression of the TetM protein. The emergence of this resistance was the initiation of the quinolone era in *N. gonorrhoeae* therapy. Tetracyclines limit aminoacyl-tRNA binding to the mRNA-ribosome complex, mostly through binding to the 30S ribosomal subunit, and hence reduce protein synthesis, resulting in a bacteriostatic effect [17,28]. Chromosomally-mediated tetracycline resistance in gonococci is caused by mutations that change the structure of the ribosomal protein (target), which interacts with resistance determinants to enhance efflux and reduce the inflow of tetracycline [62].
4.4. Quinolone

Ciprofloxacin was developed in 1983 and released to the market in the late 1980s. Initially, ciprofloxacin was used to treat *N. gonorrhoeae* in a single dosage of 250 mg [17]. However, the Centers for Disease Control and Prevention (CDC) initially recommended 500 mg of ciprofloxacin in a single dose treatment. Although isolates with reduced susceptibility (MIC 0.25 g/mL) had been detected before 1989, and despite numerous therapeutic failures reported during the 1990s, ciprofloxacin therapy continued to be used at the exact dosage globally for an additional 10–25 years depending on the country [66]. Quinolones interfere with the activity of DNA gyrase and topoisomerase IV, two topoisomerases that are required for DNA replication, transcription, recombination, and repair [67]. Quinolone antibiotics create a drug–enzyme–DNA complex and then release double-stranded DNA breaks. Resistance to ciprofloxacin in *N. gonorrhoeae* is mediated by mutations in the quinolone resistance-determining region (QRDR), situated near the topoisomerase’s DNA binding site. Bacterial DNA gyrase and topoisomerase IV are type II topoisomerases that are required for DNA metabolism [66]. They work by breaking and reconnecting double-stranded DNA in an ATP-dependent process. Quinolones provide bactericidal effects via inhibiting DNA gyrase and topoisomerase IV [17].

4.5. Azithromycin

In the early 1980s, azithromycin was proposed as a potential treatment for *Neisseria gonorrhoeae*. This macrolide inhibits peptidyl transferase polypeptide chain elongation by interacting with the P site of the 50S ribosomal subunit. Various elements may influence azithromycin activity in *Neisseria gonorrhoeae*. One of these is the overexpression of the efflux pump *mtrCDE*, which is guided by the same molecular processes that have been found to reduce *N. gonorrhoeae* sensitivity to penicillin, raising the azithromycin MIC to 0.5 g/mL [64]. The development of mutations in the L4 ribosomal protein is another cause of azithromycin resistance development. Resistance to azithromycin develops when mutations occur directly in this 23S rRNA domain [29]. Mutations of *A2143G* or *C2599T* found in one to four *rrl* gene alleles encoding the 23S RNA result in azithromycin resistance [3]. In recent years, *N. gonorrhoeae* with a high level of azithromycin resistance has evolved. The first incidence occurred in 2001, and since then, high-level azithromycin resistance has been detected in many Sub-Saharan countries [33]. By attaching to the 50S ribosomal subunit, macrolides impair protein synthesis by impeding peptidyl-tRNA translocation, blocking the peptide exit channel in 50S subunits by interacting with 23S rRNA, and causing ribosomes to release incomplete polypeptides [17].

4.6. Ceftriaxone

Previously, ceftriaxone was the drug of choice for *N. gonorrhoeae* infections. Ceftriaxone aids by binding to *PBP2* with great affinity; however, recently, it has been noted that *N. gonorrhoeae* sensitivity to this antibiotic declined rapidly, and resistance rates have reached 30%. Changes in the *penB*, *mtrR*, and *penC* genes enhance ceftriaxone resistance, and mutations in the *penA* gene, which encodes *PBP2*, appear to be the primary ceftriaxone resistance determinant [26]. The changed *PBP2* has a lower affinity for ceftriaxone, and resistance to ceftriaxone is characterised by MIC > 0.5 µg/mL by CDC, and most ceftriaxone resistance has been related to the presence of different patterns of *PBP2* [17]. The rise of ceftriaxone-resistance in *N. gonorrhoeae* and the lack of a new therapeutic option for *N. gonorrhoeae* prompted dual therapy regimens using ceftriaxone and azithromycin. Cephalosporins, like other -lactam antibiotics, block peptidoglycan cross-linking inside the bacterial cell wall by binding the -lactam ring to PBPs (transpeptidases), resulting in bactericidal action [2]. Cephalosporin resistance in gonococci is caused mostly by mutations that alter the target proteins (PBPs), but it can also be attributed to increased efflux and decreased inflow of cephalosporin [17].

All these molecular determinants and mechanisms of *Neisseria gonorrhoeae* resistance are shown in Table 2, and Figure 3 summarises the history of discovered and introduced
antimicrobials, the evolution of resistance, including genetic resistance determinants, and changes in the recommended first-line antimicrobial(s).

Table 2. Molecular determinants and mechanisms of *N. gonorrhoeae* resistance to antimicrobials currently or previously used to treat gonorrhoeae.

| Antimicrobial Class | Resistance Determinants/Mechanisms |
|---------------------|-----------------------------------|
| Sulphonamide        | Overproduction of p-aminobenzoic acid, diluting the sulphonamide. Target affinity is reduced when *folP* (encoding the sulphonamide target DHPS) is mutated. SNPs or a mosaic *folP* gene containing sequences from commensal *Neisseria* spp. comprise the *folP* mutations [26]. |
| Penicillin          | *PenA* mutations (encoding the main lethal target *PBP2*). Traditionally, the mutations were a single amino acid insertion D345 in *PBP2* and 4 to 8 concomitant mutations in the *PBP2* carboxyl-terminal region, which reduced *PBP2* acylation rate and susceptibility by a factor of 6 to 8. Many mosaic *penA* alleles with up to 70 amino acid changes, reducing *PBP2* acylation, have been described in the last decade. Overexpression and increased efflux from the *MtrCDE* efflux pump are caused by mutations in *mtrR*, the promoter (most commonly a single nucleotide [A] deletion in the 13-bp inverted repeat sequence), or the coding sequence (most commonly a G45D substitution). *PorB1b* SNPs, such as those encoding G120K and G120D/A121D mutations in *PorB1b* loop 3, reduce influx (penB resistance determinants). Surprisingly, the penB phenotype is only seen in strains carrying the mtrR resistance determinant [17,26]. |
| Tetracycline        | Mutations in *penB* and *mtrR* (see above). |
| Quinolone           | *gyrA* SNPs in the QRDR, such as S91F, D95N, and D95G, reduce quinolone binding to DNA gyrase. *ParC* SNPs in the QRDR, such as D86N, S88P, and E91K, reduce quinolone binding to topoiso merase IV [66,67]. |
| Macrolides (Azithromycin) | C261TT and A2059G, 23S rRNA SNPs (in 1 to 4 alleles) result in a 23S rRNA target (peptidyltransferase loop of domain V) with a lower affinity for the 50S ribosomal macrolide target [29]. |
| Cephalosporins (Ceftriaxone) | Mosaic *penA* alleles encoding mosaic *PBP2s* with a lower rate of *PBP2* acylation. These proteins have up to 70 amino acid changes and are the result of horizontal transfer of partial *penA* genes from primarily commensal *Neisseria* spp. A311V, I312M, V316T, V316P, T483S, A501P, A501V, N512Y, and G545S are mosaic *PBP2* mutations known to contribute to resistance. Other epistatic mutations in the mosaic *penA* allele are required for resistance mutations [17,65]. |

Figure 3. International history of discovered and recommended antimicrobials, as well as the evolution of resistance in *N. gonorrhoeae*, including the emergence of genetic resistance determinants.
5. Future Treatment Objectives

The lack of antimicrobial surveillance by most Sub-Saharan countries creates an avenue of multi-drug resistance development that can impact the entire continent [33]. To combat this, training facilities and laboratories for healthcare practitioners and laboratory personnel need to be established. It is also critical to provide quality assurance for each participating laboratory and establish several centers to offer backup for antimicrobial resistance monitoring [33,68]. Ceftriaxone and azithromycin are now licensed as dual-antimicrobial therapies in the United States and Europe, and they should be explored in all cases where thorough, quality-assured local AMR surveillance data are missing, or no other superior treatment regime is available [64,69]. As a result, resistance to ceftriaxone has grown rapidly in many instances and spreading swiftly in countries where azithromycin is often used, and gonococcal strains with reduced sensitivity to ceftriaxone are already circulating globally [70]. Increased understanding of the structure and evolution of bacterial targets for antimicrobials, or those involved in resistance, as well as how these targets will evolve and whether these mechanisms will have fitness costs or benefits, will allow for the development of more effective and long-lasting antimicrobials [3,16,34]. According to WHO guidelines, first-line antimicrobial therapy should be highly effective, commonly accessible, cost-effective, nontoxic, administered in a single dose, and cure at least 95% of infected patients within 24 h [71]. Various health organisations around the world have developed treatment guidelines for gonorrhoea, which typically include a single oral or intramuscular dose of a third-generation cephalosporin (250–500 mg intramuscular (IM) ceftriaxone or 400 mg per os-oral (PO) cefixime) in combination with a single oral dose of 1–2 g azithromycin [69]. Genomic, transcriptomic, and proteomic research, along with breakthroughs in medicinal chemistry and high-throughput screening of chemical libraries, as well as insights acquired from physiological tests, will discover novel bacterial targets and create chances for rational drug design [70,72]. Recent studies have shown a potential alternative for gonorrhoeae infections, Zoliflodacin (AZD0914 or ETX0914) [73]. This is an investigational spiropyridinetrione antimicrobial agent qualified as an infectious disease product and subsequently as a fast-track agent for the development of oral treatment for N. gonorrhoeae infections [67]. The mechanism of action of zoliflodacin varies from that of currently available treatments. It inhibits microbial biosynthesis by prohibiting the development of the cleaved covalent gyrase complex and the formation of fused circular DNA, both of which are necessary for biosynthesis [73]. The susceptibility of ciprofloxacin-resistant and ceftriaxone-resistant N. gonorrhoeae and fluoroquinolone-resistant and vancomycin-resistant Staphylococcus aureus isolates to zoliflodacin demonstrates the urgently desired efficacy of this drug. Since 2019, researchers have been studying the safety of zoliflodacin for the treatment of uncomplicated gonorrhoeae [73]. Antimicrobial resistance and antimicrobial consumption surveillance, improved aetiological diagnostics, improved antimicrobial resistance mutation surveillance, rapid point-of-care tests for detection of N. gonorrhoeae, and antimicrobial resistance or susceptibility to inform individualised N. gonorrhoeae treatment are all goals of these studies.

6. Limitations

The current review’s shortcomings include omitting non-English language publications since papers from French-speaking African nations may have been overlooked. It is difficult to analyse the data representativeness since it is conceivable that many of the Sub-Saharan countries are not included in this review due to a lack of relevant data.

7. Conclusions

In the few cases where surveillance was conducted in the Sub-Sahara, recruitments yielded low numbers. The reasons for these low recruitment rates are that most men with urethral discharge prefer to see private doctors or buy their medication from street vendors. Furthermore, where samples have been collected, there are insufficient means of transportation of samples to a processing laboratory, as well as delays by laboratory
staff in processing the isolates [3,49]. Thus, while the antimicrobial resistance levels of \textit{N. gonorrhoeae} may increase globally, in the context of the Sub-Sahara, some cases should be interpreted with caution due to the small sample sizes of the isolates tested. \textit{N. gonorrhoeae} surveillance and monitoring in Sub-Saharan populations are needed, and a comprehensive approach should be considered to achieve progress toward WHO global health sector plan goals. The Sub-Saharan region has a statistically significant degree of antibiotic resistance to a wide range of antibiotics [33]. This probability should necessitate quality microbiological identification and susceptibility testing so that national and international organisations can track the scope of this antimicrobial resistance concern. The global health community should assist these countries in addressing the highlighted areas of concern to prevent the public health hazard linked with the emergence of antimicrobial resistance. The absence of an effective prophylactic against \textit{N. gonorrhoeae} infections further necessitates the development of new strategies to expand the pool of novel effective drug candidates.

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**References**

1. Unemo, M.; Shafer, W.M. Antibiotic resistance in \textit{Neisseria gonorrhoeae}: Origin, evolution, and lessons learned for the future. \textit{Ann. N. Y. Acad. Sci.} 2011, 1230, E19–E28. [CrossRef] [PubMed]

2. Whittles, L.K.; White, P.J.; Paul, J.; Didelot, X. Epidemiological Trends of Antibiotic Resistant Gonorrhoeae in the United Kingdom. \textit{Antibiotics} 2018, 7, 60. Available online: https://www.mdpi.com/2079-6382/7/3/60 (accessed on 14 September 2021). [CrossRef] [PubMed]

3. Unemo, M.; Seifert, H.S.; Hook, E.W.; Hawkes, S.; Ndowa, F.; Dillon, J.-A.R. \textit{Gonorrhoeae}. \textit{Nat. Rev. Dis. Prim.} 2019, 5, 79. Available online: https://www.nature.com/articles/s41572-019-0128-6 (accessed on 15 September 2021). [CrossRef]

4. World Health Organization. \textit{WHO Guidelines for the Treatment of Neisseria Gonorrhoeae}. WHO Library Catalog Data. 2016. Available online: https://apps.who.int/iris/bitstream/handle/10665/246114/9789241549691-eng.pdf (accessed on 15 September 2021).

5. Biggel, M.; Heytens, S.; Latour, K.; Bruyndonckx, R.; Goossens, H.; Moons, P. Asymptomatic bacteriuria in older adults: The most fragile women are prone to long-term colonization. \textit{BMC Geriatr.} 2019, 19, 1–11. Available online: https://bmcgeriatr.biomedcentral.com/articles/10.1186/s12877-019-1181-4 (accessed on 8 November 2021). [CrossRef] [PubMed]

6. Kularatne, R.; Maseko, V.; Gumede, L.; Radebe, F.; Kufa-Chakezha, T. \textit{Neisseria Gonorrhoeaee Antimicrobial Resistance Surveillance in Gauteng Province, South Africa}. 2018. Available online: https://www.nicd.ac.za/wp-content/uploads/2018/08/Neisseria-gonorrhoeaee-AMR-surveillance.pdf (accessed on 15 September 2021).

7. Kirkcaldy, R.D.; Weston, E.; Segurado, A.C.; Hughes, G. Epidemiology of Gonorrhea: A Global Perspective. \textit{Sex. Health} 2019, 16, 401. Available online: https://www.publish.csiro.au/SH/SH19061 (accessed on 14 September 2021). [CrossRef] [PubMed]

8. Tsevat, D.G.; Wiesenfeld, H.C.; Parks, C.; Peipert, J.F. Sexually Transmitted Diseases and Infertility. \textit{Am. J. Obstet. Gynecol.} 2017, 216, 1. Available online: https://www.sciencedirect.com/science/article/abs/pii/S0002937816305737 (accessed on 8 November 2021). [CrossRef]

9. Chesson, H.W.; Mayaud, P.; Aral, S.O. Sexually Transmitted Infections: Impact and Cost-Effectiveness of Prevention. Disease Control Priorities, 2017. Available online: https://www.ncbi.nlm.nih.gov/books/NBK525195/ (accessed on 14 September 2021).

10. Mabonga, E.; Parkes-Ratanshi, R.; Riedel, S.; Nabweyambo, S.; Mbabazi, O.; Taylor, C.; Manabe, Y.C. Complete ciprofloxacin resistance in gonococcal isolates in an urban Ugandan clinic: Findings from a cross-sectional study. \textit{Int. J. STD AIDS} 2019, 30, 256. Available online: https://journals.sagepub.com/doi/abs/10.1177/0956462418799017 (accessed on 14 September 2021). [CrossRef]

11. Maduna, L.D.; Kock, M.M.; Van der Veer, B.M.; Radebe, O.; McIntyre, J.; Van Alphen, L.B.; Peters, R.P. Antimicrobial Resistance of \textit{Neisseria gonorrhoeae} Isolates from High-Risk Men in Johannesburg, South Africa. \textit{Antimicrob. Agents Chemother.} 2020, 64, e00906-20. Available online: https://pubmed.ncbi.nlm.nih.gov/32868325/ (accessed on 15 September 2021). [CrossRef]
12. Workneh, M.; Hamill, M.M.; Kakooza, F.; Mande, E.; Wagner, J.; Mbabazi, O.; Mugasha, R.; Kajumbula, H.; Walwema, R.; Zenilman, J.; et al. Antimicrobial Resistance of Neisseria Gonorrhoeae in a Newly Implemented Surveillance Program in Uganda. Surveillance Report. JMI R Public Health Surveil. 2020, 6, e17009. Available online: https://pubhealth.jmir.org/2020/2/e17009 (accessed on 8 November 2021). [CrossRef]

13. Kharsany, A.B.M.; Karim, Q.A. HIV Infection and, A.I.D.S in Sub-Saharan Africa: Current Status, Challenges and Opportunities. Open AIDS J. 2016, 10, 34. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4893541/ (accessed on 8 November 2021). [CrossRef][PubMed]

14. Torrone, E.A.; Morrison, C.S.; Chen, P.L.; Kwok, C.; Francis, S.C.; Hayes, R.J.; Looker, K.J.; McCormack, S.; McGrath, N.; van de Wijger, J.H.; et al. Prevalence of sexually transmitted infections and bacterial vaginosis among women in sub-Saharan Africa: An individual participant data meta-analysis of 18 HIV prevention studies. PLoS Med. 2018, 15, e1002511. Available online: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002511 (accessed on 8 November 2021). [CrossRef][PubMed]

15. van Eyk, A. The treatment of sexually transmitted infections. S. Afr. Fam. Pract. 2016, 58, 12–22. [CrossRef]

16. Kularatne, R.S.; Niit, R.; Rowley, J.; Kufa-Chakezha, T.; Peters, R.P.H.; Taylor, M.M.; Johnson, L.E.; Korenromp, E.L. Adult gonorrhoea, chlamydia and syphilis prevalence, incidence, treatment and syndromic case reporting in South Africa: Estimates using the Spectrum-STI model, 1990–2017. PLoS ONE 2018, 13, e0205863. Available online: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0205863 (accessed on 8 November 2021). [CrossRef][PubMed]

17. da Costa-Lourenço, A.P.R.; dos Santos, K.T.B.; Moreira, B.M.; Fracalanzza, S.E.L.; Bonelli, R.R. Antimicrobial resistance in Neisseria gonorrhoeae: History, molecular mechanisms and epidemiological aspects of an emerging global threat. Braz. J. Microbiol. 2017, 48, 617. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5628311/ (accessed on 14 September 2021). [CrossRef]

18. Kularatne, R.; Maseko, V.; Gumede, L.; Kufa, T. Trends in Neisseria gonorrhoeae Antimicrobial Resistance over a Ten-Year Surveillance Period, Johannesburg, South Africa, 2008–2017. Antibiotics 2018, 7, 58. [CrossRef][PubMed]

19. Guvenc, F.; Kaul, R.; Gray-Owen, S.D. Intimate Relations: Molecular and Immunologic Interactions Between Neisseria gonorrhoeae and H.I.V-1. Front. Microbiol. 2020, 11, 1299. [CrossRef][PubMed]

20. Lovett, A.; Duncan, J.A. Human Immune Responses and the Natural History of Neisseria gonorrhoeae Infection. Front. Immunol. 2018, 9, 3187. [CrossRef][PubMed]

21. Springer, C.; Salen, P. Gonorrhea. Med. Monatsschr. Pharm. 2021, 44, 342–345.

22. Quillin, S.J.; Seifert, H.S. Neisseria gonorrhoeae host-adaptation and pathogenesis. Nat. Rev. Microbiol. 2018, 16, 226. [CrossRef][PubMed]

23. Glasgow, K.E. Lack of Sexually Transmitted Infection Treatment Accuracy When Relying on Syndromic Management in an Urgent Care Setting. Sex. Transm. Dis. 2020, 47, 625–627. Available online: https://pubmed.ncbi.nlm.nih.gov/32815903/ (accessed on 8 November 2021). [CrossRef]

24. Cyr, S.S.; Barbee, L.; Workowski, K.A.; Bachmann, L.H.; Pham, C.; Schlanger, K.; Torrone, E.; Weinstock, H.; Kersh, E.N.; Thorpe, P. Update to CDC’s Treatment Guidelines for Gonococcal Infection. 2020. MMWR Morb. Mortal. Wkly. Rep. 2020, 69, 1911–1916. Available online: https://www.cdc.gov/mmwr/volumes/69/wr/mm6950a6.htm (accessed on 8 November 2021). [CrossRef][PubMed]

25. Ventola, C.L. The Antibiotic Resistance Crisis: Part 1: Causes and Threats. Pharm. Ther. 2015, 40, 277.

26. Unemo, M. Current and Future Antimicrobial Treatment of Gonorrhoeae—The Rapidly Evolving Neisseria Gonorrhoeae Continues to Challenge. BMC Infect. Dis. 2015, 15, 364. [CrossRef][PubMed]

27. Hook, E.W.; Kirkcaldy, R.D., III. A Brief History of Evaluating Diagnostics and Therapy for Gonorrhea: Lessons Learned. Clin. Infect. Dis. 2018, 67, 1294. [CrossRef]

28. Elkashif, A.; Seleem, M.N. Investigation of auranofin and gold-containing analogues antibacterial activity against multidrug-resistant Neisseria gonorrhoeae. Sci. Rep. 2020, 10, 5602. [CrossRef][PubMed]

29. Pham, C.D.; Sharpe, S.; Schlanger, K.; St. Cyr, S.; Holderman, J.; Steece, R.; Sore, O.O.; Masinde, G.; Arno, J.; Schmerer, M.; et al. Emergence of Neisseria gonorrhoeae Strains Harboring a Novel Combination of Azithromycin-Attenuating Mutations. Antimicrob. Agents Chemother. 2019, 63, e02313-18. [CrossRef]

30. Chen, S.; Connolly, K.L.; Rouquette-Loughlin, C.; Andrea, A.D.; Jerse, A.E.; Shafer, W.M. Could Dampening Expression of the Neisseria gonorrhoeaeemtrCDE-Encoded Efflux Pump Be a Strategy to Preserve Currently or Resurrect Formerly Used Antibiotics to Treat Gonorrhoea? mBio 2019, 10, e01576-19. [CrossRef][PubMed]

31. Thangamani, S.; Mohammad, H.; Abushabha, M.F.N.; Sobreira, T.J.P.; Hedrick, V.E.; Paul, L.N.; Seleem, M.N. Antibacterial activity and mechanism of action of auranofin against multi-drug resistant bacterial pathogens. Sci. Rep. 2016, 6, 1–13. Available online: https://www.nature.com/articles/srep22571 (accessed on 14 September 2021). [CrossRef][PubMed]

32. Fourie, J.L.; Ciaasen, F.M.; Myburgh, J.J. Causative pathogens and antibiotic resistance in community-acquired urinary tract infections in central South Africa. SAMJ S. Afr. Med. J. 2021, 111, 124–128. Available online: http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S0256-95742021000200011&lng=en&nrm=iso&tlng=en (accessed on 15 September 2021). [CrossRef][PubMed]
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33. Tadesse, B.T.; Ashley, E.A.; Ongarello, S.; Havumaki, J.; Wijegoonewardena, M.; González, I.J.; Dittrich, S. Antimicrobial resistance in Africa: A systematic review. BMC Infect. Dis. 2017, 17, 1–17. Available online: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-017-2173-1 (accessed on 15 September 2021). [CrossRef] [PubMed]

34. Buder, S.; Dudareva, S.; Jansen, K.; Loenenbach, A.; Nikisins, S.; Sailer, A.A.; Guhl, E.; Kohl, P.K.; Bremer, V. Antimicrobial resistance of Neisseria gonorrhoeae in Germany: Low levels of cefalosporin resistance, but high azithromycin resistance. BMC Infect. Dis. 2018, 18, 1–11. Available online: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-018-2944-9 (accessed on 14 September 2021). [CrossRef] [PubMed]

35. Xu, X.X.; Leontyev, D.; Kaul, R.; Gray-Owen, S.D. Neisseria gonorrhoeae co-infection exacerbates vaginal, H.I.V shedding without affecting systemic viral loads in human, C.D.34+ engraved mice. PLoS ONE 2013, 8, e0119672. Available online: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0119672 (accessed on 14 September 2021).

36. Lenz, J.D.; Dillard, J.P. Pathogenesis of neisseria gonorrhoeaeand the host defense in ascending infections of human fallopian tube. Front. Immunol. 2018, 9, 2710. [CrossRef] [PubMed]

37. Thangamani, S.; Maland, M.; Mohammad, H.; Pascuzzi, P.E.; Avramova, L.; Koehler, C.M.; Hazbun, T.R.; Seleen, M.N. Repurposing Approach Identifies Auranofin with Broad Spectrum Antifungal Activity That Targets Mia40-Erv1 Pathway. Front. Cell Infect. Microbiol. 2017, 8, 4. [CrossRef] [PubMed]

38. Russell, M.W. Immune Responses to Neisseria gonorrhoeae: Challenges and Opportunities with Respect to Pelvic Inflammatory Disease. J. Infect. Dis. 2021, 224 (Suppl. S2), S96–S102. Available online: https://academic.oup.com/jid/article/224/Supplement_2/S96/6352151 (accessed on 8 November 2021). [CrossRef] [PubMed]

39. Russell, M.W.; Jerse, A.E.; Gray-Owen, S.D. Progress Toward a Gonococcal Vaccine: The Way Forward. Front. Immunol. 2019, 10, 2417. [CrossRef] [PubMed]

40. Heydarian, M.; Yang, T.; Schweinlin, M.; Steinke, M.; Walles, H.; Rudel, T.; Kozjak-Pavlovic, V. Biomimetic human tissue model for long-term study of Neisseria gonorrhoeae infection. Front. Microbiol. 2019, 10, 1740. [CrossRef] [PubMed]

41. Liu, Y.; Ma, W.; Liu, B.; Wang, Y.; Chu, J.; Xiong, G.; Shen, L.; Long, C.; Lin, T.; He, D.; et al. Urethral reconstruction with autologous urine-derived stem cells seeded in three-dimensional porous small intestinal submucosa in a rabbit model. Stem. Cell Res. Ther. 2017, 8, 1–14. Available online: https://stemcellres.biomedcentral.com/articles/10.1186/s13287-017-0500-y (accessed on 8 November 2021). [CrossRef]

42. Budkaw, J.; Chumworathayi, B.; Pientong, C.; Ekalakasananan, T. Prevalence and factors associated with gonorrhoea infection with respect to anatomic distributions among men who have sex with men. PLoS ONE 2019, 14, e0211682. Available online: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0211682 (accessed on 8 November 2021). [CrossRef]

43. Raterman, E.L.; Jerse, A.E. Female Mouse Model of Neisseria gonorrhoeae Infection. Methods Mol. Biol. 2019, 1997, 413–429. Available online: https://pubmed.ncbi.nlm.nih.gov/31119637/ (accessed on 8 November 2021).

44. Jerse, A.E.; Wu, H.; Packiam, M.; Vonck, R.A.; Begum, A.A.; Garvin, L.E. Estradiol-treated female mice as surrogate hosts for neisseria gonorrhoeae genital tract infections. Front. Microbiol. 2011, 2, 107. [CrossRef] [PubMed]

45. Sanay, A. Identification of Cellular Factors Involved in Neisseria Gonorhoeae Induced Enhanced H-1 Transmission in a Cervical Tissue Based Organ Culture Model. Available online: https://www.proquest.com/openview/4cd893651b29715033e569ed133b/1?pq-origsite=gscholar&cbl=18750 (accessed on 8 November 2021).

46. Rouquette-Loughlin, C.E.; Zalucki, Y.M.; Dhulipala, V.L.; Balthazar, J.T.; Doyle, R.G.; Nicholas, R.A.; Begum, A.A.; Raterman, E.L.; Jerse, A.E.; Shafer, W.M. Control of gdhR Expression in Neisseria gonorrhoeae via Autoregulation and a Master Repressor (MtrR) of a Drug Efflux Pump Operon. mBio 2017, 8, e00449-17. Available online: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0240052/ (accessed on 8 November 2021). [CrossRef]

47. Dubbink, J.H.; Verweij, S.P.; Struthers, H.E.; Uouburg, S.; McIntyre, J.A.; Morré, S.A.; Peters, P.R. Genital Chlamydia trachomatis and Neisseria gonorrhoeae infections among women in sub-Saharan Africa: A structured review. Int. J. STD AIDS 2018, 29, 806–824. Available online: https://pubmed.ncbi.nlm.nih.gov/29486628/ (accessed on 8 November 2021). [CrossRef] [PubMed]

48. Kirkcaldy, R.D. Neisseria gonorrhoeae Antimicrobial Susceptibility Surveillance—The Gonococcal Isolate Surveillance Project, 27 Sites, United States, 2014. Morb. Mortal. Wkly. Rep. Survell. Summ. 2019, 65, 1–24.

49. Kassa, Z.Y.; Hussien, S.; Hadra, N.; Mokes, Y.; Bonja, F. Prevalence of Neisseria gonorrhoeae infection among women of reproductive age in sub-Saharan Africa: A systematic review and meta-analysis. Eur. J. Contracept. Reprod. Health Care 2020, 25, 365–371. [CrossRef] [PubMed]

50. Wi, T.; Lahra, M.M.; Ndowa, F.; Bala, M.; Dillon, J.A.R.; Ramon-Pardo, P.; Eremin, S.R.; Bolan, G.; Unemo, M. Antimicrobial resistance in Neisseria gonorrhoeae: Global surveillance and a call for international collaborative action. PLoS Med. 2017, 14, e1002344. [CrossRef] [PubMed]

51. Crucitti, T.; Belinga, S.; Fonkoua, M.C.; Abanda, M.; Mbanouzen, W.; Sokeng, E.; Nzouankeu, A. Sharp increase in ciprofloxacin resistance of Neisseria gonorrhoeae in Yaounde, Cameroon: Analyses of a laboratory database period 2012–2018. Int. J. STD AIDS 2020, 31, 579–586. Available online: https://journals.sagepub.com/doi/abs/10.1177/0956462419897227 (accessed on 8 November 2021). [CrossRef] [PubMed]

52. Meheus, A.; Widy-Wirsik, R.; D’Costa, J.; Van Dyck, E.; Delgadillo, R.; Piot, P. Treatment of gonorrhoeae in males in the Central African Republic with spectinomycin and procaine penicillin. Bull. World Health Organ. 1984, 62, 89–94. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6232015/?tool=EBI (accessed on 8 November 2021).
53. Blankhart, D.; Müller, O.; Gresenguet, G.; Weis, P. Sexually transmitted infections in young pregnant women in Bangui, Central African Republic. Int. J. STD AIDS 1999, 10, 609–614. Available online: https://pubmed.ncbi.nlm.nih.gov/10492429/ (accessed on 8 November 2021). [CrossRef]

54. Connolly, S.; Wall, K.M.; Parker, R.; Kilembe, W.; Inambao, M.; Visouiu, A.M.; Sharkey, T.; Hunter, E.; Allen, S. Sociodemographic Factors and STIs associated with Chlamydia trachomatis and Neisseria gonorrhoeae infections in Zambian female sex workers and single mothers. Int. J. STD AIDS 2020, 31, 364–374. Available online: https://journals.sagepub.com/doi/full/10.1177/0956462419894453 (accessed on 8 November 2021). [CrossRef]

55. Ortashi, O.M.; El Khditir, I.; Herieka, E. Prevalence of, HIV, syphilis, Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis and candidiasis among pregnant women attending an antenatal clinic in Khartoum, Sudan. J. Obstet. Gynaecol. 2009, 24, 513–515. [CrossRef]

56. Abdelrahim, N.A.; Ahmed, H.I.; Fadl-Elmula, I.M.; Bayoumi, M.A.; Homeida, M.M. Sexually transmitted infections other than, H.I.V/AIDS among women of low socio-economic class attending antenatal clinics in Khartoum, Sudan. Int. J. STD AIDS 2017, 28, 781–787. Available online: https://pubmed.ncbi.nlm.nih.gov/27582306/ (accessed on 9 November 2021). [CrossRef] [PubMed]

57. Romoren, M.; Sundby, J.; Velaauthapillai, M.; Rahman, M.; Klouman, E.; Hjortdahl, P. Chlamydia and gonorrhoea in pregnant Batswana women: Time to discard the syndromic approach? BMC Infect. Dis. 2007, 7, 1–11. Available online: https://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-7-27 (accessed on 11 November 2021). [CrossRef]

58. Wynn, A.; Ramogola-Masire, D.; Gaolebale, P.; Moshashane, N.; Sickboy, O.; Duque, S.; Williams, E.; Doherty, K.; Klausner, J.D.; Morroni, C. Prevalence and treatment outcomes of routine Chlamydia trachomatis, Neisseria gonorrhoeae and Trichomonas vaginalis testing during antenatal care, Gaborone, Botswana. Sex Transm. Infect. 2018, 94, 230–235. [CrossRef] [PubMed]

59. Peters, R.; Maduna, L.D. Drug-Resistant Gonorrhoeae is a Growing Threat: A South African Case Study the Conversation. 2020. Available online: https://theconversation.com/drug-resistant-gonorrhoeae-is-a-growing-threat-a-south-african-case-study-148012 (accessed on 14 September 2021).

60. Rambaran, S.; Naidoo, K.; Dookie, N.; Moodley, P; Sturm, A.W. Resistance Profile of Neisseria gonorrhoeae in KwaZulu-Natal, South Africa Questioning the Effect of the Currently Advocated Dual Therapy. Sex. Transm. Dis. 2019, 46, 266–270. [CrossRef] [PubMed]

61. Maharaj, S. The Effect of HIV and Neisseria Gonorrhoeae on the Tight Junctions of Cervical Epithelial Cells. 2020. Available online: https://link.springer.com/article/10.1007/s00430-019-00651-4 (accessed on 14 September 2021). [CrossRef] [PubMed]

62. Munita, J.M.; Arias, C.A. Mechanisms of Antibiotic Resistance. Microbiol. Spectr. 2016, 4, 464–472. [CrossRef]

63. Unemo, M.; Shafer, W.M. Antimicrobial Resistance in Neisseria gonorrhoeae in the 21st Century: Past, Evolution, and Future. Clin. Microbiol. Rev. 2014, 27, 587. [CrossRef]

64. Młynarczyk-Bonikowska, B.; Majewska, A.; Malejczyk, M.; Młynarczyk, G.; Majewski, S. Multiresistant Neisseria gonorrhoeae: A new threat in second decade of the XXI century. Med. Microbiol. Immunol. 2019, 209, 95–108. Available online: https://link.springer.com/article/10.1007/s00430-019-00651-4 (accessed on 14 September 2021). [CrossRef] [PubMed]

65. Kivata, M.W.; Mbuchi, M.; Eyase, F.; Bulimo, W.D.; Kyanya, C.K.; Oundo, V.; Mbinda, W.M.; Sang, W.; Andagalu, B.; Soge, O.O.; et al. Plasmid mediated penicillin and tetracycline resistance among Neisseria gonorrhoeae isolates from Kenya. BMC Infect. Dis. 2020, 20, 1–11. Available online: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05398-5 (accessed on 9 November 2021). [CrossRef]

66. d’Atanasio, N.; de Joannon, A.C.; Sante, L.D.; Mangano, G.; Ombrato, R.; Vitiello, M.; Bartella, C.; Magarini, B.; Soge, O.O.; et al. Antibacterial activity of novel dual bacterial, D.N.A type, I.I. topoisomerase inhibitors. PLoS ONE 2020, 15, e0228509. Available online: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0228509 (accessed on 15 September 2021). [CrossRef]

67. Huband, M.D.; Bradford, P.A.; Otterson, L.G.; Basarab, G.S.; Kutschke, A.C.; Giacobbe, R.A.; Potter, M.E.; et al. In Vitro Antibacterial Activity of, A.Z.D0914, a New Spiropyrimidinetrione, D.N.A Gyrase/Topoisomerase Inhibitor with Potent Activity against Gram-Positive, Fastidious Gram-Negative, and Atypical Bacteria. Antimicrob. Agents Chemother. 2015, 59, 467. [CrossRef]

68. Massongo, M.; Ngando, L.; Pefura Yone, E.W.; Nzouankeu, A.; Mbanzouen, W.; Fonkoua, M.C.; Ngandjio, A.; Chatchueng, J.; Barger, D.; Tejiokem, M.C. Trends of Antibacterial Resistance at the National Reference Laboratory in Cameroon: Comparison of the Situation between 2010 and 2017. Biomed. Res. Int. 2021, 2021. Available online: https://www.hindawi.com/journals/bmri/2021/9957112/ (accessed on 15 September 2021). [CrossRef]

69. Suay-Garcia, B.; Pérez-Gracia, M.T. Future Prospects for Neisseria gonorrhoeae Treatment. Antibiotics 2018, 7, 49. [CrossRef] [PubMed]

70. Yang, F.; Yan, J. Antibiotic Resistance and Treatment Options for Multidrug-Resistant Gonorrhoea. Infect. Microbes Dis. 2020, 2, 67–76. Available online: https://journals.lww.com/imd/FullText/2020/06000/Antibiotic_Resistance_and_Treatment_Options_for_6.aspx (accessed on 9 November 2021). [CrossRef]

71. León-Buitimea, A.; Garza-Cárdenas, C.R.; Garza-Cervantes, J.A.; Lerma-Escalera, J.A.; Morones-Ramírez, J.R. The Demand for New Antibiotics: Antimicrobial Peptides, Nanoparticles, and Combinatorial Therapies as Future Strategies in Antibacterial Agent Design. Front. Microbiol. 2020, 11, 1669. [CrossRef] [PubMed]
72. Bradford, P.A.; Miller, A.A.; O’Donnell, J.; Mueller, J.P. Zoliflodacin: An Oral Spiropyrimidinetrione Antibiotic for the Treatment of Neisseria gonorrhoeae, Including Multi-Drug-Resistant Isolates. *ACS Infect. Dis.* 2020, 6, 1332–1345. Available online: https://pubs.acs.org/doi/full/10.1021/acsinfecdis.0c00021 (accessed on 15 September 2021). [CrossRef] [PubMed]

73. Taylor, S.N.; Marrazzo, J.; Batteiger, B.E.; Hook, E.W.; Seña, A.C.; Long, J.; Wierzbicki, M.R.; Kwak, H.; Johnson, S.M.; Lawrence, K.; et al. Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea. *N. Engl. J. Med.* 2018, 379, 1835–1845. [CrossRef]