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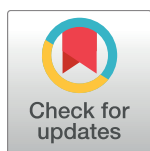
ESSAY

Multidrug-resistant gonorrhoea: A research and development roadmap to discover new medicines

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Summary points

- The number of gonorrhoea cases is rising in many settings worldwide, and an increasing proportion of cases are multidrug-resistant. The choice of antimicrobials that can be used for treatment of gonorrhoea is very limited, and resistance has even been reported to extended-spectrum cephalosporins, which are the mainstay of currently recommended antimicrobial therapy. Currently, only 3 new chemical entities are in different stages of clinical development for treatment of gonorrhoea.
- In 2016, the Global Antibiotic Research and Development Partnership (GARDP) was launched by the World Health Organization (WHO) and Drugs for Neglected Disease *initiative*, which hosts and provides governance for GARDP.
- GARDP has worked together with experts from different regions to draft “ideal” and “acceptable” Target Product Profiles for the treatment of gonorrhoea, reflecting medical need.
- Amongst other activities to combat antimicrobial resistance, GARDP has developed a plan to meet the urgent need for new drugs to treat gonorrhoea.

Abbreviations: AMR, antimicrobial resistance; DND*i*, Drugs for Neglected Diseases *initiative*; ESBL, extended-spectrum β -lactamase; ESC, extended-spectrum cephalosporin; GARDP, Global Antibiotic Research and Development Partnership; GASP, Gonococcal Antimicrobial Surveillance Programme; MDR, multidrug-resistant; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSM, men who have sex with men; PID, pelvic inflammatory disease; PK/PD, pharmacokinetic/pharmacodynamic; R&D, research and development; STI, sexually transmitted infection; TPP, Target Product Profile; XDR, extensively drug-resistant; YLD, years lived with disability.

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- Over the next 7 years, this research and development proposal includes the following: exploring the introduction of a new clinical entity against gonorrhoea; the identification of existing, suitable partner drugs; the recovery of previously abandoned, out-of-favor, and withdrawn antibiotics; and the development of simplified treatment guidelines for the empiric management of sexually transmitted infections.

Gonorrhoea: A growing, worldwide disease burden

Gonorrhoea is among the most common sexually transmitted infections (STIs), with an estimated 78 million new cases in 2012 [1]. Countries with good surveillance have reported increases in cases of gonorrhoea, such as an 11% rise between 2014 and 2015 in the United Kingdom [2], a doubling of cases among MSM (men who have sex with men) in France between 2013 and 2015 [3], a 5% rise between 2013 and 2015 in the United States [4], and an increase of 29%–146% in almost all Australian states between 2010 and 2014 [5], all reflecting longer-term trends. Decreasing condom use [6], increased urbanization and travel, poor infection detection rates, and inadequate or failed treatment [7] all contribute to this increase.

Gonorrhoea affects high-, middle-, and low-income countries. The African region has the highest rates of gonococcal infections worldwide, with some 50 and 100 new infections per 1,000 women and men, respectively, every year [8]. In the US, it is the second most frequently reported notifiable infectious disease, accounting for 395,000 cases in 2015, a 13% increase from 2014 [4]; in Canada, a similar rise (15%) was reported.

Gonorrhoea is a debilitating disease, which was responsible for an estimated 445,000 years lived with disability (YLD) in 2015 [9].

Urogenital gonorrhoea may be asymptomatic in 40% of men [10] and manifests most commonly as urethritis [11]. It is also asymptomatic in more than half of women [12]. In men, untreated urethral infection can lead to epididymitis, reduced fertility, and urethral stricture. In women, when present, symptoms are nonspecific and include abnormal vaginal discharge, dysuria, lower abdominal discomfort, and dyspareunia. The lack of discernible symptoms [13] results in unrecognized and untreated infections, which can lead to serious complications. Overall, 10%–20% of female patients develop pelvic inflammatory disease (PID) and, consequently, are at risk for infertility [14]. Pregnancy complications associated with gonorrhoea include chorioamnionitis, premature rupture of membranes, preterm birth, ectopic pregnancies, and spontaneous abortions [13,15,16]. Perinatal transmission occurs in 30%–40% of gonorrhoea cases and occurs predominantly in low- and middle-income countries, where 3%–15% of mothers are infected. Infants of mothers with gonococcal infection can be infected at delivery, resulting in neonatal conjunctivitis (ophthalmia neonatorum). Such untreated conjunctivitis may lead to scarring and blindness.

Extra-genital infections are common in both sexes and frequently occur in the absence of urogenital infection [17,18]. Rectal infections are usually asymptomatic but can manifest as rectal and anal pain or discharge. Pharyngeal infections are mostly asymptomatic, but mild sore throat and pharyngitis may occur. Although bacterial concentrations are generally lower than in other infection sites, the pharynx is thought to be a favorable site for resistance emergence due to acquisition of resistance traits from commensal *Neisseria* spp. [19]. Disseminated gonococcal infections with gonococcal arthritis also occur. Because they are frequently

asymptomatic, extra-genital infections often remain untreated, despite their key role in disease transmission.

Coinfection with other major STIs—HIV, Herpes Simplex Virus, *Chlamydia trachomatis*, *Mycoplasma genitalium*, and syphilis—are common and may result in synergistic effects on transmission and disease severity.

Almost all antibiotic classes used against gonorrhea have lost their efficacy because of resistance [20]. Sulfonamides, penicillins, early-generation cephalosporins, tetracyclines, macrolides, and fluoroquinolones can no longer be relied upon. The extended-spectrum cephalosporins (ESCs, i.e., cefixime and ceftriaxone), which represent the last remaining option for first-line empirical monotherapy, are also under threat, with resistance reported worldwide [7,21–24]. The WHO Gonococcal Antimicrobial Surveillance Programme (GASP) found that resistance is spreading especially in Asia, North America, Europe, Latin America and the Caribbean, and Australia, with large data gaps in Africa and Central Asia [25]. Reports of treatment failures with ESC are on the rise [26–38], and the first case of treatment failure with a dual therapy has recently been reported [7]. Fluoroquinolone, high-level azithromycin, and cephalosporin resistance have now been found in several countries [19,39–41].

N. gonorrhoeae displays extraordinary genetic versatility to achieve antimicrobial resistance (AMR), allowing horizontal gene transfer events with nonpathogenic *Neisseria* species that reside in different anatomical sites, particularly the pharynx [42–44].

The acquisition of multiple AMR traits, except perhaps for fluoroquinolone [45], does not appear to affect biological fitness, resulting in the persistence of strains that are multidrug-resistant (MDR) or extensively drug-resistant (XDR) even in the absence of antimicrobial selection pressure [45–47]. In the context of gonorrhea, MDR denotes resistance to current guideline treatments [48,49] including oral ESC, plus resistance to 2 or more of macrolides, fluoroquinolones, penicillins, tetracycline, aminoglycosides, and carbapenems. XDR denotes resistance to both oral and intramuscular ESCs or resistance to 1 type of ESC and spectinomycin, with resistance to 3 or more of macrolides, fluoroquinolones, penicillins, tetracycline, aminoglycosides, and carbapenems [48,49]. WHO recommends adapting treatment guidelines in areas with over 5% resistance.

Most patients are managed in the community, and because of limited diagnostic access and capabilities in many settings, gonorrhea treatment is empiric (i.e., symptom-based, without identification of the causative organism or definition of its antimicrobial susceptibility profile) and syndromic, in accordance with WHO guidance [50]. Treatment is based on the presence of easily recognized signs (e.g., urethral or vaginal discharge) and the provision of antibiotics that deal with the majority of, or the most serious, organisms responsible for the syndrome. With increasing resistance to ESC monotherapy, several countries have now adopted combination therapy with ESC plus azithromycin [51,52]. However, whether dual therapy actually delays resistance emergence is not supported by strong evidence [53], and strains resistant to either ESC or azithromycin are already in circulation [26–36,38]. In some regions of Africa and Latin America, less costly fluoroquinolones are still recommended, although they have been removed from WHO guidelines, and extensive resistance has been described [54–57].

Effective treatment of pharyngeal infections (regardless of resistance) is more difficult than treatment of urogenital infections; while the average cure rate for urogenital infection is 96%, rates drop to 79% and 84% (males and females) for oropharyngeal infections [58,59]. This may relate to insufficient drug exposure in the latter site. Worryingly, these infections most likely act as a reservoir, and persistence of pathogens at these sites jeopardize global efforts to slow the spread of resistant gonorrhea.

Insufficient research and development for an urgent public health threat

As a disease that is not usually deadly but affects millions of people, gonorrhoea control initiatives lack sufficient coordination and investment. With increasingly limited treatment options in the wider context of AMR, there is now growing concern that the threat of untreatable gonorrhoea will become a reality. In February 2017, WHO listed *N. gonorrhoeae* among “High Priority” pathogens for research and development (R&D) of new antibiotics [60]. While hospital-acquired pathogens may have been highest on the list because of the high rates of mortality they cause, *N. gonorrhoeae* was notably included because infections are extremely widespread, cause substantial morbidity with a significant health cost for countries, can affect pregnant women and their babies, and develop AMR at a particularly rapid pace. Gonorrhoea was also listed by the US Centers for Disease Control and Prevention (CDC) in the top “Urgent Threat” category of 18 drug-resistant threats to the US [61] and is included in similar AMR priority lists in the UK and Canada.

The current pipeline for gonorrhoea treatments is severely depleted, with only 3 new chemical entities in various stages of clinical development. Two of these candidates are also being developed for other indications.

1. Solithromycin (Cempra Inc.) is an oral fluoroketolide with activity against gram-positive and fastidious gram-negative bacteria, including *N. gonorrhoeae*, *M. genitalium*, and *C. trachomatis* [62–64]. It targets 3 different prokaryotic ribosomal sites and showed good efficacy in a Phase II study [65], with a 100% efficacy for genital, oral, and rectal sites of infection in men and women. A Phase III trial is ongoing.
2. Zoliflodacin (Entasis Therapeutics) is a first-in-class spiropyrimidinetrione topoisomerase II inhibitor with activity against several pathogens, including *N. gonorrhoeae*, and *C. trachomatis* [66,67]. Zoliflodacin has been shown to be highly effective in vitro against a large collection of geographically and genetically diverse *N. gonorrhoeae* isolates [68]. Results from a Phase II trial showed high efficacy against urogenital infections (98%–100% microbiological cure rate, dependent on dose; clinicaltrials.gov NCT02257918). Over 90% of participants were male.
3. Gepotidacin (GlaxoSmithKline) is another bacterial topoisomerase II inhibitor, a novel triazaacenaphthylene with good in vitro activity against a wide range of drug-resistant bacteria, including MRSA (methicillin-resistant *Staphylococcus aureus*), ESBL (extended-spectrum β -lactamases)-producing *Enterobacteriaceae*, and *N. gonorrhoeae* [69]. A Phase II trial was recently completed, and 96.7% and 94.8% cure rates were achieved with doses of 1500 mg and 3000 mg, respectively (clinicaltrials.gov NCT02294682). As before, over 90% of the participants were male.

A global surveillance plan is outlined by Wi and colleagues in parallel with this R&D agenda [70].

The spread and incidence of gonococcal AMR is of great concern and has outpaced the development of new medicines, raising the prospect of untreatable gonorrhoea [71,72]. A business-as-usual scenario will prevent achievement of the Global Health Sector STI Strategy’s target, approved by the World Health Assembly in 2016, of a 90% reduction in the incidence of gonorrhoea by 2030. The frequency of asymptomatic infections, rapidly changing antimicrobial susceptibility patterns, variety of AMR mechanisms, and, paradoxically, progress against HIV (resulting in a reduced use of condoms) make the control of AMR gonorrhoea particularly challenging.

Commercial drug development for infectious diseases suffers from “market failure.” There are multiple reasons for this relating to how antibiotics are prescribed and sold, but also

because stewardship initiatives may be diametrically at odds with the race against the “patent clock” to recoup drug development costs. Finally, there is competition from cheap generics, and the increasing need to combine antibiotics with other drugs, which brings formulation, costs, regulatory, and profitability challenges. Thus, there is an urgency to replenish the antibiotic drug discovery pipeline. In the shorter term, for gonorrhoea, there is a need to advance, prioritize, and evaluate the 3 new molecules in the clinical pipeline, investigate new antimicrobial combinations, and reconsider the use of existing antibiotics. Moreover, for both new and existing drugs, there is a lack of clinical efficacy data on oropharyngeal infections.

The unmet treatment needs can be summarized as:

- No sustainable therapeutic option for MDR and XDR gonorrhoea
- No evidence-based and sufficiently effective treatment for extra-genital infections, particularly oropharyngeal infections
- No evidence-based treatment for complications arising from initial urogenital infections

An R&D proposal for gonorrhoea

At the 68th World Health Assembly in 2015, WHO adopted the Global Action Plan on Antimicrobial Resistance. One of the Plan’s initiatives was the launch of the Global Antibiotic Research and Development Partnership (GARDP; www.gardp.org) in May 2016 [73]. GARDP is hosted and governed by the Drugs for Neglected Diseases *initiative* (DNDi) and has set up several programs aimed at developing new treatments in the short- to medium-term for STIs, neonatal sepsis, and an antimicrobial memory-recovery initiative. The latter aims to retrieve drugs and drug candidates (and associated expertise) whose use or development were halted in the past for reasons that no longer apply (e.g., Pharma portfolio considerations).

To better define the essential characteristics of new treatments for gonorrhoea, and efficiently steer R&D activities, GARDP and WHO convened an international STI expert panel in mid-2016, who agreed on a Target Product Profile (TPP; [Table 1](#)). The requirements were split for short- and long-term targeted treatment, with each being further divided between “ideal” and “acceptable” profiles. Based on the needs identified above, and in line with the consensus TPP, GARDP has developed a comprehensive R&D strategy that is broken down into 4 complementary components.

Component 1: Accelerate the development of a new chemical entity

As part of this first component, GARDP will seek to accelerate development and registration of 1 new molecule for the treatment of uncomplicated gonorrhoea and, in particular, to support the conduct of late-development activities (i.e., Phase III and IV trials). GARDP also aims to work with the patent holders to optimize the profile of the molecule along the lines of the TPPs.

To support access, stewardship, and conservation of the molecule, and keeping in mind the necessity to integrate it within existing guidelines, GARDP would then investigate possible combinations of the new molecule with existing antibiotics. In vitro studies would be initiated to investigate synergies, antagonisms, and activity against other STIs.

Finally, GARDP will seek to explore the clinical efficacy of the new therapeutic entity, alone or in combination, on (1) extra-genital gonorrhoea and (2) patients coinfecting with other STIs. This may entail investigating increased dosage or multiple-dose regimens, conducting additional pharmacokinetic/pharmacodynamic (PK/PD) investigations and gathering additional clinical data through subsequent trials in high-risk groups.

Table 1. Consensus Target Product Profile (TPP) developed by the gonorrhoea expert group.

	Short-term (up to 5 years)		Long-term (up to 10 years)	
	Ideal	Acceptable	Ideal	Acceptable
Indication	(First-line) treatment of uncomplicated, urogenital gonorrhoea (susceptible and MDR)	(First-line) treatment of uncomplicated, urogenital gonorrhoea (susceptible and MDR)	(First-line) treatment of urogenital gonorrhoea (susceptible and MDR, complicated and uncomplicated)	(First-line) treatment of urogenital gonorrhoea (susceptible and MDR)
	First-line treatment of extra-genital gonorrhoea (ano-rectal and oro-pharyngeal)		First-line treatment of extra-genital gonorrhoea (ano-rectal and oro-pharyngeal)	Treatment of <i>Chlamydia</i> infections
Activity against coinfecting STI pathogens	<i>Chlamydia trachomatis</i>		<i>Chlamydia trachomatis</i> , <i>Mycoplasma genitalium</i>	<i>Chlamydia trachomatis</i>
Patient population	Adults and adolescents (aged 10–19 years)		Adults, children, and adolescents	
Clinical efficacy	97% (95% CI, 95–100)	95% (95% CI, 90–100)	97% (95% CI, 95–100)	95% (95% CI, 90–100)
Activity against ESC and macrolide-resistant NG strains	Yes		Yes	
Mechanism of action (target site, -cidal versus static; broad-spectrum versus narrow-spectrum)	Bactericidal/static	Bactericidal/static	Unique mechanism	
	Intracellular activity	–	Bactericidal/static	Bactericidal/static
	No cross-resistance	Limited cross-resistance	Intracellular activity	–
			No cross-resistance	Limited cross-resistance
Safety and tolerability	Well tolerated in pregnancy and lactation	–	Well tolerated in pregnancy and lactation	–
	No patient monitoring required post treatment	Minimal outpatient monitoring required post treatment	No patient monitoring required post treatment	Minimal outpatient monitoring required post treatment
Contra-indications	None	Pregnancy and lactation	None	Pregnancy and lactation
Drug–Drug Interaction profile	None	Minimal	None	Minimal
Route of Administration/ formulation	Oral/IM, separated combination		Fixed-dose combination for orals	Copackaged loose combination
Dosing Schedule	Single dose	Multiple doses	Single dose	Multiple doses
Treatment duration	1 day	Up to 5 days	Up to 3 days	Up to 5 days
Stability	Heat stable, 3-year shelf-life in climatic region IV ^a	Heat stable, 3-year shelf-life	Heat stable, 3-year shelf-life in climatic region IV	Heat stable, 3-year shelf-life
Cost (price/day of therapy)	Equivalent to current treatment regimens		Equivalent to current treatment regimens	
Time to patient availability	5 years	7 years	7 years	10 years

ESC, extended-spectrum cephalosporin; IM, intramuscular injection; IV, intravenous injection; MDR, multidrug-resistant; NG, *Neisseria gonorrhoeae*; STI, sexually transmitted infection.

^aHot tropic/humid climate, simulated with 30°C and 65% relative humidity.

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Component 2: Evaluate the potential of existing antibiotics and their combinations

Several existing antibiotics have shown good antigonococcal properties in vitro and, for some, in patients: gentamicin, kanamycin, ertapenem, and fosfomycin. However, their efficacy remains to be confirmed in randomized clinical trials. Adequate PK/PD studies for these antibiotics are lacking, and more data are needed on their MIC (minimum inhibitory concentration) and the relationship between the MICs, PK/PD, and clinical outcomes. More data are

also required for their utility in treating extra-genital and complicated infections. Other antibiotics have been abandoned but may deserve further investigation. The aminocyclitol spectinomycin was commercialized in the 1960s as a specific treatment for gonorrhea. Resistance rapidly emerged in some settings [74–76], and spectinomycin use was discontinued. But resistance is currently rare worldwide [20] and spectinomycin retains excellent activity against most gonococcal isolates. It is used in some European countries, China, and South Korea, but its availability in other regions is limited.

GARDP will aim to better understand the opportunities and liabilities of existing drugs and seek to identify optimal combinations through *in vitro* studies. Clinical efficacy of these combinations will be confirmed through trials involving groups with high STI burdens and sites in different countries that represent varied patterns of resistance.

Component 3: Explore copackaging and development of fixed-dose combinations

Management of STIs often entails the coadministration of 2 or more antibiotics in order to cover all possible etiological agents. Copackaged products or fixed-dose combinations thus offer many practical advantages such as facilitating control over prescription, distribution, and administration of antibiotic combinations and reduce production costs. In addition, such combinations may increase compliance, and this may help to limit the emergence of AMR. Finally, fixed drug combination and/or copackaging offer a clear advantage in terms of stewardship. As part of this third component, GARDP will explore combinations and/or copackaging for the optimal combinations of new and/or existing antibiotics identified through the first 2 components.

Component 4: Support the development of simplified treatment guidelines and foster conservation

To ensure the appropriate use of new treatments, GARDP and WHO will work with pharmaceutical companies, regulators, and other stakeholders to ensure that the newly developed antibiotics/combinations are globally accessible while at the same time used in an appropriate manner. The partners will support the development of evidence-based, regional/national treatment guidelines. This may entail carrying out observational studies and resistance surveys, in collaboration with WHO, to inform the integration of optimal combinations in STI guidelines. It may also involve observational studies to support the use of developed treatments in vulnerable populations (e.g., pregnant women and adolescents). GARDP will also work with partners to promote the appropriate use of new treatments by healthcare providers and patients by educating key stakeholders, supporting the conduct of pilot implementation studies, and monitoring of treatment use and emergence of resistance.

Conclusions

The number of gonococcal infections is rapidly rising worldwide. Most worrisome, *N. gonorrhoeae* is an important member of the bacterial community that spreads AMR. Just 3 new clinical entities are in various stages of clinical development for treatment of gonorrhea today, in a therapeutic area that lacks a strong commercial interest. GARDP, a joint initiative founded by WHO and DNDi, has begun to document ideal and acceptable profiles of antimicrobials for gonorrhea treatment. Four R&D routes have been outlined that require donor support: introduction of a new molecule for gonorrhea, identification of ideal combination partners among existing antibiotics, formulation of new fixed drug combinations, and establishment of a

stewardship framework for the distribution and use of the new treatments. GARDP intends to work with its partners and other stakeholders to complete this roadmap and bring at least 1 new treatment into clinical practice by 2023.

References

1. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. *PLoS ONE*. 2015; 10:12:e0143304. <https://doi.org/10.1371/journal.pone.0143304> PMID: 26646541; PubMed Central PMCID: PMC4672879.
2. Public Health England. Sexually transmitted infections and chlamydia screening in England, 2015. Health Protection Report. 2016;10(22) Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/559993/hpr2216_stis_CRRCTD4.pdf.
3. Santé Publique France. Bacterial sexually transmitted infections in France: recent trends and characteristics in 2015 [French]. *Bulletin épidémiologique hebdomadaire*. 2016;41-42(29 Nov) Available from: http://invs.santepubliquefrance.fr/beh/2016/41-42/_41-42_1.html.
4. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance. Available from: <https://www.cdc.gov/std/stats15/std-surveillance-2015-printpdf>. 2015.
5. The Kirby Institute for infection and immunity in society. HIV, viral hepatitis and sexually transmissible infections in Australia. Available from: http://kirbyunsw.edu.au/sites/default/files/hiv/resources/SERP_2016-Annual-Surveillance-Report_UPD170116pdf. 2016; Annual Surveillance Report 2016.
6. Paz-Bailey G, Mendoza MC, Finlayson T, Wejnert C, Le B, Rose C, et al. Trends in condom use among MSM in the United States: the role of antiretroviral therapy and seroadaptive strategies. *AIDS (London, England)*. 2016; 30(12):1985–90. <https://doi.org/10.1097/QAD.0000000000001139> PMID: 27149088.
7. Fifer H, Natarajan U, Jones L, Alexander S, Hughes G, Golparian D, et al. Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhoea. *N Engl J Med*. 2016; 374(25):2504–6. <https://doi.org/10.1056/NEJMc1512757> PMID: 27332921.
8. World Health Organization. Report on global sexually transmitted infection surveillance 2013. Sexual and reproductive health. 2014; Available from: http://apps.who.int/iris/bitstream/10665/112922/1/9789241507400_eng.pdf?ua=1.
9. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016; 388(10053):1545–602. Epub 2016/10/14. [https://doi.org/10.1016/S0140-6736\(16\)31678-6](https://doi.org/10.1016/S0140-6736(16)31678-6) PMID: 27733282.
10. Handsfield HH, Lipman TO, Harnisch JP, Tronca E, Holmes KK. Asymptomatic gonorrhoea in men. Diagnosis, natural course, prevalence and significance. *N Engl J Med*. 1974; 290(3):117–23. <https://doi.org/10.1056/NEJM197401172900301> PMID: 4202519.
11. Harrison WO, Hooper RR, Wiesner PJ, Campbell AF, Karney WW, Reynolds GH, et al. A trial of minocycline given after exposure to prevent gonorrhoea. *N Engl J Med*. 1979; 300(19):1074–8. <https://doi.org/10.1056/NEJM197905103001903> PMID: 107450.
12. Van Der Pol B. Sexually transmitted infections in women. *Scand J Clin Lab Invest Suppl*. 2014; 244:68–74; discussion 3. <https://doi.org/10.3109/00365513.2014.936691> PMID: 25083897.
13. Maxwell GL, Watson WJ. Preterm premature rupture of membranes: results of expectant management in patients with cervical cultures positive for group B streptococcus or *Neisseria gonorrhoeae*. *Am J Obstet Gynecol*. 1992; 166(3):945–9. PMID: 1550170.
14. Tsevat DG, Wiesenfeld HC, Parks C, Peipert JF. Sexually transmitted diseases and infertility. *Am J Obstet Gynecol*. 2017; 216(1):1–9. <https://doi.org/10.1016/j.ajog.2016.08.008> PMID: 28007229; PubMed Central PMCID: PMC5193130.
15. Liu B, Roberts CL, Clarke M, Jorm L, Hunt J, Ward J. Chlamydia and gonorrhoea infections and the risk of adverse obstetric outcomes: a retrospective cohort study. *Sex Transm Infect*. 2013; 89(8):672–8. <https://doi.org/10.1136/sextrans-2013-051118> PMID: 24005255.
16. Donders GG, Desmyter J, De Wet DH, Van Assche FA. The association of gonorrhoea and syphilis with premature birth and low birthweight. *Genitourin Med*. 1993; 69(2):98–101. PMID: 8509101; PubMed Central PMCID: PMC1195038.
17. Koedijk FD, van Bergen JE, Dukers-Muijers NH, van Leeuwen AP, Hoebe CJ, van der Sande MA, et al. The value of testing multiple anatomic sites for gonorrhoea and chlamydia in sexually transmitted infection centres in the Netherlands, 2006–2010. *Int J STD AIDS*. 2012; 23(9):626–31. <https://doi.org/10.1258/ijsa.2012.011378> PMID: 23033514.

18. van Liere GA, Hoebe CJ, Dukers-Muijrs NH. Evaluation of the anatomical site distribution of chlamydia and gonorrhoea in men who have sex with men and in high-risk women by routine testing: cross-sectional study revealing missed opportunities for treatment strategies. *Sex Transm Infect.* 2014; 90(1):58–60. <https://doi.org/10.1136/sextrans-2013-051248> PMID: 24106338.
19. Unemo M, Nicholas RA. Emergence of multidrug-resistant, extensively drug-resistant and untreatable gonorrhoea. *Future Microbiol.* 2012; 7(12):1401–22. <https://doi.org/10.2217/fmb.12.117> PMID: 23231489; PubMed Central PMCID: PMC3629839.
20. Unemo M, Shafer WM. Antimicrobial resistance in *Neisseria gonorrhoeae* in the 21st century: past, evolution, and future. *Clin Microbiol Rev.* 2014; 27(3):587–613. <https://doi.org/10.1128/CMR.00010-14> PMID: 24982323; PubMed Central PMCID: PMC4135894.
21. Camara J, Serra J, Ayats J, Bastida T, Carnicer-Pont D, Andreu A, et al. Molecular characterization of two high-level ceftriaxone-resistant *Neisseria gonorrhoeae* isolates detected in Catalonia, Spain. *J Antimicrob Chemother.* 2012; 67(8):1858–60. <https://doi.org/10.1093/jac/dks162> PMID: 22566592.
22. Ohnishi M, Golparian D, Shimuta K, Saika T, Hoshina S, Iwasaku K, et al. Is *Neisseria gonorrhoeae* initiating a future era of untreatable gonorrhoea?: detailed characterization of the first strain with high-level resistance to ceftriaxone. *Antimicrob Agents Chemother.* 2011; 55(7):3538–45. <https://doi.org/10.1128/AAC.00325-11> PMID: 21576437; PubMed Central PMCID: PMC3122416.
23. Unemo M, Golparian D, Nicholas R, Ohnishi M, Gallay A, Sednaoui P. High-level cefixime- and ceftriaxone-resistant *Neisseria gonorrhoeae* in France: novel penA mosaic allele in a successful international clone causes treatment failure. *Antimicrob Agents Chemother.* 2012; 56(3):1273–80. <https://doi.org/10.1128/AAC.05760-11> PMID: 22155830; PubMed Central PMCID: PMC3294892.
24. Lahra MM, Enriquez RP. Australian Gonococcal Surveillance Programme, 1 April to 30 June 2016. *Commun Dis Intell Q Rep.* 2016; 40(4):E557–E9. PMID: 28043233.
25. World Health Organization. Report on global sexually transmitted infection surveillance 2015. Available from: <http://apps.who.int/iris/bitstream/10665/249553/1/9789241565301-eng.pdf>. 2016.
26. Lewis DA, Sriruttan C, Muller EE, Golparian D, Gumede L, Fick D, et al. Phenotypic and genetic characterization of the first two cases of extended-spectrum-cephalosporin-resistant *Neisseria gonorrhoeae* infection in South Africa and association with cefixime treatment failure. *J Antimicrob Chemother.* 2013; 68(6):1267–70. <https://doi.org/10.1093/jac/dkt034> PMID: 23416957.
27. Lewis D, Sriruttan C, Coetzee JD. Detection of multidrug-resistant gonorrhoea in the Gauteng province. *S Afr J Infect Dis.* 2012; 27(4):199–200.
28. Golparian D, Ohlsson A, Janson H, Lidbrink P, Richtner T, Ekelund O, et al. Four treatment failures of pharyngeal gonorrhoea with ceftriaxone (500 mg) or cefotaxime (500 mg), Sweden, 2013 and 2014. *Euro Surveill.* 2014; 19(30):20862. PMID: 25108533.
29. Allen VG, Mitterni L, Seah C, Rebbapragada A, Martin IE, Lee C, et al. *Neisseria gonorrhoeae* treatment failure and susceptibility to cefixime in Toronto, Canada. *JAMA.* 2013; 309(2):163–70. <https://doi.org/10.1001/jama.2012.176575> PMID: 23299608.
30. Unemo M, Golparian D, Syversen G, Vestrheim DF, Moi H. Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010. *Euro Surveill.* 2010; 15(47):19721. PMID: 21144442.
31. Ison CA, Hussey J, Sankar KN, Evans J, Alexander S. Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010. *Euro Surveill.* 2011; 16(14):19833. PMID: 21492528.
32. Unemo M, Golparian D, Stary A, Eigentler A. First *Neisseria gonorrhoeae* strain with resistance to cefixime causing gonorrhoea treatment failure in Austria, 2011. *Euro Surveill.* 2011; 16(43):19998. PMID: 22085601.
33. Singh AE, Gratrix J, Martin I, Friedman DS, Hoang L, Lester R, et al. Gonorrhoea Treatment Failures With Oral and Injectable Expanded Spectrum Cephalosporin Monotherapy vs Dual Therapy at 4 Canadian Sexually Transmitted Infection Clinics, 2010–2013. *Sex Transm Dis.* 2015; 42(6):331–6. <https://doi.org/10.1097/OLQ.0000000000000280> PMID: 25970311.
34. Tapsall J, Read P, Carmody C, Bourne C, Ray S, Limnios A, et al. Two cases of failed ceftriaxone treatment in pharyngeal gonorrhoea verified by molecular microbiological methods. *J Med Microbiol.* 2009; 58(Pt 5):683–7. <https://doi.org/10.1099/jmm.0.007641-0> PMID: 19369534.
35. Chen MY, Stevens K, Tideman R, Zaia A, Tomita T, Fairley CK, et al. Failure of 500 mg of ceftriaxone to eradicate pharyngeal gonorrhoea, Australia. *J Antimicrob Chemother.* 2013; 68(6):1445–7. <https://doi.org/10.1093/jac/dkt017> PMID: 23390207.
36. Read PJ, Limnios EA, McNulty A, Whiley D, Lahra MM. One confirmed and one suspected case of pharyngeal gonorrhoea treatment failure following 500mg ceftriaxone in Sydney, Australia. *Sexual health.* 2013; 10(5):460–2. <https://doi.org/10.1071/SH13077> PMID: 24028864.

37. Unemo M, Golparian D, Potocnik M, Jeverica S. Treatment failure of pharyngeal gonorrhoea with internationally recommended first-line ceftriaxone verified in Slovenia, September 2011. *Euro Surveill.* 2012; 17(25):20200. PMID: [22748003](https://pubmed.ncbi.nlm.nih.gov/22748003/).
38. Unemo M, Golparian D, Hestner A. Ceftriaxone treatment failure of pharyngeal gonorrhoea verified by international recommendations, Sweden, July 2010. *Euro Surveill.* 2011; 16(6):19792. PMID: [21329645](https://pubmed.ncbi.nlm.nih.gov/21329645/).
39. Grad YH, Harris SR, Kirkcaldy RD, Green AG, Marks DS, Bentley SD, et al. Genomic Epidemiology of Gonococcal Resistance to Extended-Spectrum Cephalosporins, Macrolides, and Fluoroquinolones in the United States, 2000–2013. *J Infect Dis.* 2016; 214(10):1579–87. <https://doi.org/10.1093/infdis/jiw420> PMID: [27638945](https://pubmed.ncbi.nlm.nih.gov/27638945/); PubMed Central PMCID: PMC5091375.
40. Vidovic S, Caron C, Taheri A, Thakur SD, Read TD, Kusaliik A, et al. Using crude whole-genome assemblies of *Neisseria gonorrhoeae* as a platform for strain analysis: clonal spread of gonorrhea infection in Saskatchewan, Canada. *J Clin Microbiol.* 2014; 52(10):3772–6. <https://doi.org/10.1128/JCM.01502-14> PMID: [25056324](https://pubmed.ncbi.nlm.nih.gov/25056324/); PubMed Central PMCID: PMC4187769.
41. Uehara AA, Amarin EL, Ferreira Mde F, Andrade CF, Clementino MB, de Filippis I, et al. Molecular characterization of quinolone-resistant *Neisseria gonorrhoeae* isolates from Brazil. *J Clin Microbiol.* 2011; 49(12):4208–12. <https://doi.org/10.1128/JCM.01175-11> PMID: [21976763](https://pubmed.ncbi.nlm.nih.gov/21976763/); PubMed Central PMCID: PMC3232978.
42. Ito M, Deguchi T, Mizutani KS, Yasuda M, Yokoi S, Ito S, et al. Emergence and spread of *Neisseria gonorrhoeae* clinical isolates harboring mosaic-like structure of penicillin-binding protein 2 in Central Japan. *Antimicrob Agents Chemother.* 2005; 49(1):137–43. <https://doi.org/10.1128/AAC.49.1.137-143.2005> PMID: [15616287](https://pubmed.ncbi.nlm.nih.gov/15616287/); PubMed Central PMCID: PMC538884.
43. Ameyama S, Onodera S, Takahata M, Minami S, Maki N, Endo K, et al. Mosaic-like structure of penicillin-binding protein 2 Gene (penA) in clinical isolates of *Neisseria gonorrhoeae* with reduced susceptibility to cefixime. *Antimicrob Agents Chemother.* 2002; 46(12):3744–9. PubMed Central PMCID: PMC132769. <https://doi.org/10.1128/AAC.46.12.3744-3749.2002> PMID: [12435671](https://pubmed.ncbi.nlm.nih.gov/12435671/)
44. Osaka K, Takakura T, Narukawa K, Takahata M, Endo K, Kiyota H, et al. Analysis of amino acid sequences of penicillin-binding protein 2 in clinical isolates of *Neisseria gonorrhoeae* with reduced susceptibility to cefixime and ceftriaxone. *J Infect Chemother.* 2008; 14(3):195–203. <https://doi.org/10.1007/s10156-008-0610-7> PMID: [18574654](https://pubmed.ncbi.nlm.nih.gov/18574654/).
45. Kunz AN, Begum AA, Wu H, D'Ambrozio JA, Robinson JM, Shafer WM, et al. Impact of fluoroquinolone resistance mutations on gonococcal fitness and in vivo selection for compensatory mutations. *J Infect Dis.* 2012; 205(12):1821–9. <https://doi.org/10.1093/infdis/jis277> PMID: [22492860](https://pubmed.ncbi.nlm.nih.gov/22492860/); PubMed Central PMCID: PMC3415892.
46. Warner DM, Shafer WM, Jerse AE. Clinically relevant mutations that cause derepression of the *Neisseria gonorrhoeae* MtrC-MtrD-MtrE Efflux pump system confer different levels of antimicrobial resistance and in vivo fitness. *Mol Microbiol.* 2008; 70(2):462–78. <https://doi.org/10.1111/j.1365-2958.2008.06424.x> PMID: [18761689](https://pubmed.ncbi.nlm.nih.gov/18761689/); PubMed Central PMCID: PMC2602950.
47. Warner DM, Folster JP, Shafer WM, Jerse AE. Regulation of the MtrC-MtrD-MtrE efflux-pump system modulates the in vivo fitness of *Neisseria gonorrhoeae*. *J Infect Dis.* 2007; 196(12):1804–12. <https://doi.org/10.1086/522964> PMID: [18190261](https://pubmed.ncbi.nlm.nih.gov/18190261/).
48. Tapsall JW, Ndowa F, Lewis DA, Unemo M. Meeting the public health challenge of multidrug- and extensively drug-resistant *Neisseria gonorrhoeae*. *Expert Rev Anti Infect Ther.* 2009; 7(7):821–34. <https://doi.org/10.1586/eri.09.63> PMID: [19735224](https://pubmed.ncbi.nlm.nih.gov/19735224/).
49. Tapsall J. Multidrug-resistant *Neisseria gonorrhoeae*. *CMAJ.* 2009; 180(3):268–9. <https://doi.org/10.1503/cmaj.081721> PMID: [19188616](https://pubmed.ncbi.nlm.nih.gov/19188616/); PubMed Central PMCID: PMC2630337.
50. World Health Organization. Global strategy for the prevention and control of sexually transmitted infections: 2006–2015. Available from: http://apps.who.int/iris/bitstream/10665/43853/1/9789241563475_eng.pdf. 2007.
51. Maldonado NG, Takhar SS. Update on Emerging Infections: news from the Centers for Disease Control and Prevention. Update to the CDC's Sexually Transmitted Diseases Treatment Guidelines, 2010: Oral cephalosporins no longer a recommended treatment for gonococcal infections. *Ann Emerg Med.* 2013; 61(1):91–5. <https://doi.org/10.1016/j.annemergmed.2012.10.015> PMID: [23260686](https://pubmed.ncbi.nlm.nih.gov/23260686/).
52. Bignell C, Unemo M, European STIGEB. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. *Int J STD AIDS.* 2013; 24(2):85–92. <https://doi.org/10.1177/0956462412472837> PMID: [24400344](https://pubmed.ncbi.nlm.nih.gov/24400344/).
53. Rice LB. Will use of combination cephalosporin/azithromycin therapy forestall resistance to cephalosporins in *Neisseria gonorrhoeae*? *Sex Transm Infect.* 2015; 91(4):238–40. <https://doi.org/10.1136/sextrans-2014-051730> PMID: [25926405](https://pubmed.ncbi.nlm.nih.gov/25926405/).

54. Lagace-Wiens PR, Duncan S, Kimani J, Thiong'o A, Shafi J, McClelland S, et al. Emergence of fluoroquinolone resistance in *Neisseria gonorrhoeae* isolates from four clinics in three regions of Kenya. *Sex Transm Dis.* 2012; 39(5):332–4. <https://doi.org/10.1097/OLQ.0b013e318248a85f> PMID: 22504591; PubMed Central PMCID: PMC3328140.
55. Deguchi T, Saito I, Tanaka M, Sato K, Deguchi K, Yasuda M, et al. Fluoroquinolone treatment failure in gonorrhea. Emergence of a *Neisseria gonorrhoeae* strain with enhanced resistance to fluoroquinolones. *Sex Transm Dis.* 1997; 24(5):247–50. PMID: 9153731.
56. Dillon JA, Trecker MA, Thakur SD, Gonococcal Antimicrobial Surveillance Program Network in Latin A, Caribbean. Two decades of the gonococcal antimicrobial surveillance program in South America and the Caribbean: challenges and opportunities. *Sex Transm Infect.* 2013; 89 Suppl 4:iv36–41. <https://doi.org/10.1136/sextrans-2012-050905> PMID: 24243878.
57. Starnino S, Group G-LW, Galarza P, Carvallo ME, Benzaken AS, Ballesteros AM, et al. Retrospective analysis of antimicrobial susceptibility trends (2000–2009) in *Neisseria gonorrhoeae* isolates from countries in Latin America and the Caribbean shows evolving resistance to ciprofloxacin, azithromycin and decreased susceptibility to ceftriaxone. *Sex Transm Dis.* 2012; 39(10):813–21. <https://doi.org/10.1097/OLQ.0b013e3182631c9f> PMID: 23001269.
58. Weinstock H, Workowski KA. Pharyngeal gonorrhea: an important reservoir of infection? *Clin Infect Dis.* 2009; 49(12):1798–800. <https://doi.org/10.1086/648428> PMID: 19911969.
59. Moran JS. Treating uncomplicated *Neisseria gonorrhoeae* infections: is the anatomic site of infection important? *Sex Transm Dis.* 1995; 22(1):39–47. PMID: 7709324.
60. World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Available from: http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1. 2017.
61. Centers for Disease Control and Prevention. Antibiotic resistance trends in the United States, 2013. Available from: <https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>. 2013.
62. Roblin PM, Kohlhoff SA, Parker C, Hammerschlag MR. *In vitro* activity of CEM-101, a new fluoroketolide antibiotic, against *Chlamydia trachomatis* and *Chlamydia (Chlamydoxiphila) pneumoniae*. *Antimicrob Agents Chemother.* 2010; 54(3):1358–9. <https://doi.org/10.1128/AAC.01343-09> PMID: 20038627; PubMed Central PMCID: PMC2825974.
63. Waites KB, Crabb DM, Duffy LB. Comparative *in vitro* susceptibilities of human mycoplasmas and ureaplasmas to a new investigational ketolide, CEM-101. *Antimicrob Agents Chemother.* 2009; 53(5):2139–41. <https://doi.org/10.1128/AAC.00090-09> PMID: 19258276; PubMed Central PMCID: PMC2681567.
64. Golparian D, Fernandes P, Ohnishi M, Jensen JS, Unemo M. *In vitro* activity of the new fluoroketolide solithromycin (CEM-101) against a large collection of clinical *Neisseria gonorrhoeae* isolates and international reference strains, including those with high-level antimicrobial resistance: potential treatment option for gonorrhea? *Antimicrob Agents Chemother.* 2012; 56(5):2739–42. <https://doi.org/10.1128/AAC.00036-12> PMID: 22354296; PubMed Central PMCID: PMC3346660.
65. Hook EW 3rd, Golden M, Jamieson BD, Dixon PB, Harbison HS, Lowens S, et al. A Phase 2 Trial of Oral Solithromycin 1200 mg or 1000 mg as Single-Dose Oral Therapy for Uncomplicated Gonorrhea. *Clin Infect Dis.* 2015; 61(7):1043–8. <https://doi.org/10.1093/cid/civ478> PMID: 26089222.
66. Huband MD, Bradford PA, Otterson LG, Basarab GS, Kutschke AC, Giacobbe RA, et al. *In vitro* antibacterial activity of AZD0914, a new spiroprimidinetriene DNA gyrase/topoisomerase inhibitor with potent activity against Gram-positive, fastidious Gram-negative, and atypical bacteria. *Antimicrob Agents Chemother.* 2015; 59(1):467–74. <https://doi.org/10.1128/AAC.04124-14> PMID: 25385112; PubMed Central PMCID: PMC4291388.
67. Kohlhoff SA, Huband MD, Hammerschlag MR. *In vitro* activity of AZD0914, a novel DNA gyrase inhibitor, against *Chlamydia trachomatis* and *Chlamydia pneumoniae*. *Antimicrob Agents Chemother.* 2014; 58(12):7595–6. <https://doi.org/10.1128/AAC.03920-14> PMID: 25288086; PubMed Central PMCID: PMC4249501.
68. Unemo M, Ringlander J, Wiggins C, Fredlund H, Jacobsson S, Cole M. High *in vitro* susceptibility to the novel spiroprimidinetriene ETX0914 (AZD0914) among 873 contemporary clinical *Neisseria gonorrhoeae* isolates from 21 European countries from 2012 to 2014. *Antimicrob Agents Chemother.* 2015; 59(9):5220–5. <https://doi.org/10.1128/AAC.00786-15> PMID: 26077246; PubMed Central PMCID: PMC4538562.
69. Biedenbach DJ, Bouchillon SK, Hackel M, Miller LA, Scangarella-Oman NE, Jakielaszek C, et al. *In Vitro* Activity of Gepotidacin, a Novel Triazaacenaphthylene Bacterial Topoisomerase Inhibitor, against a Broad Spectrum of Bacterial Pathogens. *Antimicrob Agents Chemother.* 2016; 60(3):1918–23. <https://doi.org/10.1128/AAC.02820-15> PMID: 26729499; PubMed Central PMCID: PMC4776004.

70. Wi T, Lahra MM, Ndowa F, Bala M, Dillon JR, Ramon-Pardo P, et al. Antimicrobial resistance in *Neisseria gonorrhoeae*: Global surveillance and a call for international collaborative action. *PLoS Med*. 2017; 14:7:e1002344. <https://doi.org/10.1371/journal.pmed.1002344> PMID: 28686231.
71. Unemo M, Jensen JS. Antimicrobial-resistant sexually transmitted infections: gonorrhoea and *Mycoplasma genitalium*. *Nat Rev Urol*. 2017; 14(3):139–52. <https://doi.org/10.1038/nrurol.2016.268> PMID: 28072403.
72. Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. *N Engl J Med*. 2012; 366(6):485–7. <https://doi.org/10.1056/NEJMp1112456> PMID: 22316442.
73. The Global Antibiotic Research and Development Partnership (GARDP) www.gardp.org. 2016.
74. Boslego JW, Tramont EC, Takafuji ET, Diniega BM, Mitchell BS, Small JW, et al. Effect of spectinomycin use on the prevalence of spectinomycin-resistant and of penicillinase-producing *Neisseria gonorrhoeae*. *N Engl J Med*. 1987; 317(5):272–8. <https://doi.org/10.1056/NEJM198707303170504> PMID: 2955222.
75. Ashford WA, Potts DW, Adams HJ, English JC, Johnson SR, Biddle JW, et al. Spectinomycin-resistant penicillinase-producing *Neisseria gonorrhoeae*. *Lancet*. 1981; 2(8254):1035–7. PMID: 6118488.
76. Stolz E, Zwart HG, Michel MF. Activity of eight antimicrobial agents in vitro against *N. Gonorrhoeae*. *Brit J Vener Dis*. 1975; 51(4):257–64. PMID: 125618; PubMed Central PMCID: PMC1046560.