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World Health Organization Global Gonococcal Antimicrobial Surveillance Program (WHO GASP): review of new data and evidence to inform international collaborative actions and research efforts

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Abstract

Antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* is a serious public health problem, compromising the management and control of gonorrhoea globally. Resistance in *N. gonorrhoeae* to ceftriaxone, the last option for first-line empirical monotherapy of gonorrhoea, has been reported from many countries globally, and sporadic failures to cure especially pharyngeal gonorrhoea with ceftriaxone monotherapy and dual antimicrobial therapies (ceftriaxone plus azithromycin or doxycycline) have been confirmed in several countries. In 2018, the first gonococcal isolates with ceftriaxone resistance plus high-level azithromycin resistance were identified in England and Australia. The World Health Organization (WHO) Global Gonococcal Antimicrobial Surveillance Program (GASP) is essential to monitor AMR trends, identify emerging AMR and provide evidence for refinements of treatment guidelines and public health policy globally. Herein we describe the WHO GASP data from 67 countries in 2015–16, confirmed gonorrhoea treatment failures with ceftriaxone with or without azithromycin or doxycycline, and international collaborative actions and research efforts essential for the effective

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Conflicts of interest

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management and control of gonorrhoea. In most countries, resistance to ciprofloxacin is exceedingly high, azithromycin resistance is present and decreased susceptibility or resistance to ceftriaxone has emerged. Enhanced global collaborative actions are crucial for the control of gonorrhoea, including improved prevention, early diagnosis, treatment of index patient and partner (including test-of-cure), improved and expanded AMR surveillance (including surveillance of antimicrobial use and treatment failures), increased knowledge of correct antimicrobial use and the pharmacokinetics and pharmacodynamics of antimicrobials and effective drug regulations and prescription policies (including antimicrobial stewardship). Ultimately, rapid, accurate and affordable point-of-care diagnostic tests (ideally also predicting AMR and/or susceptibility), new therapeutic antimicrobials and, the only sustainable solution, gonococcal vaccine(s) are imperative.

Additional keywords:

antimicrobial resistance; azithromycin; ceftriaxone; gonorrhoea; *Neisseria gonorrhoeae*; treatment

Introduction

In 2016, the World Health Organization (WHO) estimated 86.9 million cases of gonorrhoea, which remains a global public health concern, among adults worldwide.[1–5] Effective and accessible antimicrobial treatment is essential for gonorrhoea management, but antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* has emerged to all previous first-line therapeutic drugs.[3–6] The extended-spectrum cephalosporin (ESC) ceftriaxone is the last option for empirical first-line gonorrhoea monotherapy, but decreased susceptibility or resistance (DS/R) has been reported worldwide,[3–24] and sporadic failures to cure especially pharyngeal gonorrhoea with ceftriaxone monotherapy have been confirmed in several countries.[9,22,25–30] From 2011, dual antimicrobial therapy (ceftriaxone 250–500 mg plus azithromycin 1–2 g) was introduced for empirical first-line therapy in many countries.[5,31–34] Worryingly, the first failure of treating pharyngeal gonorrhoea with dual therapy was reported in 2016,[35] international spread of ceftriaxone-resistant gonococcal strains was confirmed in 2015–19[15–21] and the first strain with resistance to ceftriaxone plus high-level azithromycin resistance was isolated in England and Australia in 2018.[22–24]

In 2012, the WHO published a global action plan to control the spread and impact of AMR in *N. gonorrhoeae*.[3,36] This plan is linked to the WHO global action plan on AMR.[37] The gonococcal global action plan stresses the key priorities, including: advocacy for increased awareness on correct antimicrobial use; effective drug regulations and prescription policies; effective early prevention, diagnosis, sexual partner notification, treatment, including test of cure (TOC), and control of gonorrhoea; research into alternative and especially novel treatment options and vaccine(s); and strengthened regular, quality-assured and comparable AMR surveillance nationally and internationally, including systematic monitoring of treatment failures and research into the use of molecular AMR prediction methods.[3,36] Gonococcal AMR surveillance is essential to identify emerging AMR, monitor AMR trends and to provide evidence for revisions of global, regional and national gonorrhoea management guidelines and public health strategies and policies.

This paper describes WHO Global Gonococcal Antimicrobial Surveillance Program (GASP) data from 67 countries in 2015–16, reviews reported confirmed gonorrhoea treatment failures with ceftriaxone with or without azithromycin or doxycycline, highlights the crucial need for molecular AMR surveillance and describes international collaborative actions and research efforts essential for the effective management and control of gonorrhoea.

WHO GASP

Since 2009, WHO GASP,[6] initially established in 1990,[38] has been significantly expanded. WHO GASP consists of reference laboratories globally that are networked with other international and national programs, such as the European Gonococcal Antimicrobial Surveillance Program (Euro-GASP),[7,8] the US Gonococcal Isolate Surveillance Project (GISP; https://www.cdc.gov/std/gisp/, accessed 28 June 2019),[39,40] the Canadian GASP,[41] the Gonococcal Antimicrobial Susceptibility Surveillance Program–Argentina(GASSP),[42] the UK Gonococcal Resistance to Antimicrobials Surveillance Program (GRASP)[43] and the Australian Gonococcal Surveillance Program (AGSP).[44]

The WHO recommends that gonorrhoea management guidelines are revised based on recent and quality-assured gonococcal AMR surveillance data and first-line empirical gonorrhoea treatment be discontinued when the level of treatment failures and/or *in vitro* AMR reach 5%.[3–6] However, the evidence for the ≥5% AMR threshold is limited, and proportions of ≥1% and >3% resistance in high-frequency transmitting populations have also been suggested.[45,46] It is important to consider whether dual therapy is used, making the threshold for single antimicrobial suboptimal, and the availability of new antimicrobials. Further, the prevalence and local epidemiology of gonorrhoea and AMR, aetiological diagnostics or syndromic management, transmission frequency, sexual partner tracing strategies and treatment strategies and cost are important.[4,47,48]

WHO GASP data in 2015–16

The structure, sampling and testing methodologies, quality assurance (QA) and quality control (QC) practices, including the well-characterised 2016 WHO gonococcal reference strains for intra- and interlaboratory comparisons,[49–51] of WHO GASP have been described previously.[6] Briefly, the aims of WHO GASP include collecting ≥100 representative gonococcal isolates per country and year, ideally using quantitative methods for determination of the minimum inhibitory concentration (MIC) of antimicrobials (agar dilution method or MIC gradient strip tests, such as Etest (bioMérieux, Marcy-l'Étoile, France)) and using validated and standardised interpretative criteria (i.e. most WHO GASP countries use the breakpoints stated by the European Committee on Antimicrobial Susceptibility Testing (EUCAST; www.eucast.org, accessed 28 June 2019) or the Clinical and Laboratory Standards Institute (CLSI; www.clsi.org, accessed 28 June 2019)).

From 1 January 2015 to 31 December 2016, 67 countries reported gonococcal AMR data to the WHO (Geneva, Switzerland) for ceftriaxone (63 countries), cefixime (42 countries), azithromycin (62 countries) and/or ciprofloxacin (67 countries). Fifty-two (77.6%) countries reported data in both 2015 (56 countries; 83.6%) and 2016 (62 countries; 92.5%). The

number of countries reporting data for at least one antimicrobial annually was the same as in 2014 (52 countries).

In 2015–16, as in 2014, the WHO European Region (EUR)[52] had the highest number of reporting countries (30 countries; including 26 European Union (EU)/European Economic Area (EEA) countries), followed by the Western Pacific Region (WPR;[53] 13 countries), Region of Americas (including Latin America, Caribbean[54,55] and North America with the US[39,40] (www.cdc.gov/std/gisp/default.htm) and Canada;[41] 11 countries), South-east Asian Region (SEAR;[56] 6 countries), African Region (AFR;[57] 6 countries) and the Eastern Mediterranean Region (EMR; 1 reporting country).

Of countries monitoring susceptibility to ceftriaxone (63 countries), cefixime (42 countries), azithromycin (62 countries) and/or ciprofloxacin (67 countries), 23.8%, 45.2%, 80.6% and 100% of countries respectively reported isolates showing DS/R in 2015–16 (Table 1).

The most recent WHO GASP data are summarised in Figs 1–4.

Ceftriaxone and cefixime

In 2015–16, 64 countries reported on susceptibility to ceftriaxone and/or cefixime, which is significantly more countries compared with 2014 (45 countries; $P < 0.05$). Thirty-two (50%) countries reported DS/R to either of these ESCs, which is a significant decrease from the 66% of countries in 2009–14[6] ($P < 0.05$). In 2016, 58 countries reported data on susceptibility to ceftriaxone and 22.4% (13/58) reported isolates with DS/R (Fig. 1). Thirty-nine countries reported data on susceptibility to cefixime and 48.7% (19/39) reported isolates with DS/R (Fig. 2).

In the Euro-GASP,[7,8,58] 2660 isolates from 25 EU/EEA countries in WHO EUR were tested in 2016. No isolates were resistant to ceftriaxone, compared with one (0.05%) in 2015 and five (0.23%) in 2014.[8] Furthermore, no resistance to ceftriaxone was found in 2015–16 in the non-EU/EEA WHO EUR countries of Belarus (36 isolates), Kyrgyzstan ($n = 72$), Russia ($n = 293$) and Ukraine ($n = 58$; Fig. 1). Cefixime-resistant isolates were detected in 56% (14/25) of the EU//EEA countries, but the overall resistance was stable at 2.1% (1.7% in 2015, 2.0% in 2014). Twenty-four per cent of countries ($n = 6$; Croatia (11.1%), Luxembourg (10.0%), Hungary (8.5%), Belgium (8.1%), Germany (6.4%) and Poland (5.2%)) reported ≥5% resistance. As in 2015, cefixime resistance was highest among heterosexual males(2.2%), followed by females (2%) and men who have sex with men (MSM; 0%).[8] No cefixime resistance was detected in Ukraine, but cefixime resistance was detected in Belarus(22.2%) and Kyrgyzstan (1.4%; Fig. 2).

In the WHO WPR in 2016, DS/R to ceftriaxone was reported by 83.3% (10/12) of countries reporting on ceftriaxone susceptibility in 9763 isolates, an increase from 71% (5/7) in 2014. Six countries (China, Japan, Mongolia, Singapore, Republic of Korea and Vietnam) reported DS/R in ≥5% of isolates. Only two countries (New Caledonia and Cambodia) reported all isolates as susceptible to ceftriaxone in 2016 (Fig. 1).[59] However, only two isolates were tested in Cambodia.

In the WHO SEAR, DS/R to ceftriaxone was reported in one (Myanmar) of the countries (n = 5) reporting ceftriaxone susceptibility data in 907 isolates in 2016. However, only five isolates were tested in Myanmar. Only susceptible isolates were found in Bhutan, India, Sri Lanka and Thailand (Fig. 1).[59,60]

In the WHO Region of Americas, DS/R to ceftriaxone in 2016 was reported in three (33.3%) of the nine countries reporting on ceftriaxone susceptibility in 12 887 isolates in 2016 (Peru (2.4%), Canada (1.8%; vs 2.7% in 2014[41]) and the US (0.3%; vs 0.4% in 2014; Fig. 1). Notably, in 2014, DS/R to ceftriaxone was confirmed in Argentina and reported from Bolivia (disc diffusion results not confirmed by MIC determination).[6,61] DS/R to cefixime in 2016 was documented in Argentina (1.4%), Canada (0.3%; vs 1.1% in 2014[41]) and the US (0.3%; declined from 0.9% in 2012; www.cdc.gov/std/gisp/default.htm, accessed 28 June 2019). All isolates in Brazil,[62] Chile and Paraguay (and Peru in 2015) were susceptible to cefixime (Fig. 2). In 2013–14, DS/R to cefixime was reported also in Chile and Uruguay.[6]

In 2016, only four of 47 WHO AFR countries (8.5%) provided ceftriaxone susceptibility data for 496 isolates and no DS/R was reported from Cote d'Ivoire,[63] South Africa or Zimbabwe.[64] However, one of 35 isolates (3.0%) from Madagascar showed DS/R to ceftriaxone, but this single isolate was not confirmed using MIC determination (Fig. 1). Notably, DS/R to ceftriaxone has been reported from South Africa and Uganda.[6] In 2016, no DS/R to cefixime was detected in Cote d'Ivoire,[63] Malawi, South Africa or Zimbabwe (Fig. 2).[64]

In the WHO EMR, only Pakistan (4.5%; 1/22) provided ceftriaxone and cefixime susceptibility data for 64 isolates in 2016 and no DS/R to these ESCs was found (Figs 1, 2).

Azithromycin

In 2016, 59 countries reported data on azithromycin susceptibility and 83.0% (49/59) of countries reported resistant isolates, which is similar ($P > 0.05$) to the 81% (47/58) and 78% (35/45) reported in 2009–14 and 2014 respectively. In 2016, 29 (49.1%) countries reported ≥5% azithromycin resistance (Fig. 3), which is significantly ($P < 0.05$) higher than in 2014 (28.9%; 13/45).[6]

In the WHO EUR, azithromycin-resistant isolates were detected in 84% (21/25) of Euro-GASP countries, but the overall resistance in the EU/EEA was stable at 7.5% (7.1% in 2015 and 7.9% in 2014).[7,8] Fifty-two per cent (13/25) of Euro-GASP countries reported ≥5% resistance.[8] As in 2015, azithromycin resistance was most common among heterosexual males (7.6%), followed by MSM (5.6%) and females (5.3%).[8] The azithromycin resistance levels in Belarus, Russia and Ukraine were 13.9%, 6.5% and 4.0% respectively; however, no resistance was found in Kyrgyzstan (Fig. 3).

In the WHO WPR, 75.0% (9/12) of settings reported azithromycin-resistant isolates in 2016, compared with 78% (7/9) in 2014. Five settings reported ≥5% resistance (Australia, Cambodia (only two isolates tested), China, Hong Kong, Japan and New Zealand) and three countries reported <5% resistance (Brunei, Mongolia and Singapore; Fig. 3).[59]

In the WHO SEAR, azithromycin resistance was detected in all six countries reporting in 2016, compared with 83% (5/6) in 2014. Three (50%) countries (India, Myanmar and Indonesia) reported ≥5% resistance (Fig. 3), but only three and five isolates were tested with a disc diffusion method in Myanmar and Indonesia respectively.

In the WHO Region of Americas, azithromycin resistance was identified in all eight countries reporting in 2016. Five (62.5%) countries (Brazil,[62] Canada, Columbia, Cuba and Peru) reported ≥5% resistance, whereas three (37.5%) reported <5% resistance (Argentina, Chile and the US; 3.6% vs 2.5% in 2014;[6] Fig. 3).

In the WHO AFR, Cote d'Ivoire[63] and Malawi reported azithromycin-resistant isolates (2.0% and 12.6% respectively) in 2016, whereas no azithromycin resistance was detected in Madagascar or South Africa. Notably, ≥5% azithromycin resistance was reported in Uganda in 2014, South Africa in 2013 and Kenya in 2014[6] and 2015 (Fig. 3).

In the WHO EMR, 4.7% of isolates in Pakistan were resistant to azithromycin in 2016 (Fig. 3).

Ciprofloxacin

In 2016, the highest ciprofloxacin resistance levels were recorded in the WHO SEAR (94.2%) and WPR (72.0%). In these WHO regions, nine of the 19 reporting countries (47.4%) reported >90% resistance and six (33.3%) countries reported >80% resistance. Also in the WHO AFR (69.1%), EMR (Pakistan: 96.9%) and EUR (45.4%), three countries reported >90% resistance, namely Madagascar, Pakistan and Kyrgyzstan respectively. Countries belonging to all the remaining WHO regions reported ≥70% ciprofloxacin resistance (Argentina, Cuba, Peru, Cote D'Ivoire,[63] Malawi, South Africa, Iceland, Luxembourg;[7,8] Fig. 4).

Confirmed gonorrhoea treatment failures with ceftriaxone, with or without azithromycin or doxycycline, and characterised ceftriaxone-resistant strains

Confirmed failures to cure gonorrhoea with ceftriaxone alone or combined with azithromycin or doxycycline are summarised in Table 2. Sporadic failures to cure gonorrhoea with ceftriaxone (250–1000 mg) have been confirmed during the past decade in Japan, Australia, Slovenia, Sweden and the UK.[9,21,25–30] In 2016, the first global failure to cure pharyngeal gonorrhoea with dual therapy (ceftriaxone 500 mg plus azithromycin 1 g) was confirmed in England.[35] An internationally spreading ceftriaxone-resistant gonococcal strain caused a failure to cure pharyngeal gonorrhoea with ceftriaxone 250 × mg 1 (plus doxycycline) in 2017 in France[19] and with ceftriaxone 1 g × 1 in 2018 in England.[21] In 2018, the first global gonococcal strain with ceftriaxone resistance plus high-level azithromycin resistance caused a treatment failure of pharyngeal gonorrhoea with ceftriaxone (1 g; plus doxycycline) in England.[22] All confirmed gonorrhoea treatment failures, except one recent case in the UK,[21] have been pharyngeal infection, a site where gonorrhoea is usually asymptomatic, tissue penetration of several antimicrobials is limited

and new genetic AMR determinants can be acquired from coexisting non-gonococcal *Neisseria* species.[65,66] Gonococcal infections acquired in the WHO WPR and SEAR represent most of the confirmed ceftriaxone treatment failures, but several have been acquired also in the EUR.[9,19,21,22,25–30,35] The burden of ceftriaxone treatment failures is unknown, and it is essential to enhance gonococcal surveillance, including verification of treatment failures after treatment with recommended ceftriaxone and ESC plus azithromycin dual therapies. The WHO recommends, where feasible, examination of pre- and post-treatment isolates for MICs of relevant antimicrobials, molecular epidemiological genotype, molecular AMR determinants and documentation of all treatments administered and excluding reinfection.[3,6,45,67]

The ceftriaxone MICs of strains causing the confirmed ceftriaxone treatment failures ranged from 0.016 to 4 mg L^{-1}. To cure gonorrhoea, 20–24 h of free ceftriaxone above MIC ($fT_{>MIC}$) is required.[68] According to Monte Carlo simulations, with doses of ceftriaxone 500 mg × 1 and ceftriaxone 1 g × 1, sufficient $fT_{>MIC}$ (≥20 h) will not be reached in up to 5% of individuals infected with gonococcal strains with ceftriaxone MICs of ≥0.06 and ≥0.125 mg L^{-1} respectively.[68] This agrees with observations regarding the relatively low ceftriaxone MICs of strains causing several of the confirmed treatment failures (Table 2). The low ceftriaxone MICs (0.016–0.03 mg L^{-1}) of strains causing some of these failures (Table 2) probably reflects a low bioavailability of ceftriaxone and the difficulties in curing pharyngeal gonorrhoea.[4,9,25–30,65,67] Enhanced understanding of the pharmacokinetic and pharmacodynamic properties of current and novel antimicrobials in anogenital and pharyngeal gonorrhoea is critical. Promisingly, a murine genital tract infection model recently showed that the pharmacokinetic and pharmacodynamic relationships for ESCs in mice reflected those in humans with *in vivo* efficacy against an ESC-susceptible strain requiring an $fT_{>MIC}$ of >20–24 h.[69] Furthermore, hollow-fibre bioreactor models[70] are under development for gonococci.

The first extensively drug-resistant (XDR)[67] gonococcal strains with high-level ceftriaxone resistance were reported from Japan, France and Spain in 2011–12.[9–11] No additional cases caused by these strains were detected, and it was subsequently verified that their resistance-determining mosaic penicillin-binding protein 2 (PBP2) caused reduced fitness *in vitro* and in mice,[71] which likely limited their spread. Worryingly, the failure to treat pharyngeal gonorrhoea with ceftriaxone in 2017 in France[19] and in 2018 in England[21] (Table 2) was caused by an internationally spreading ceftriaxone-resistant strain (FC428), initially identified in 2015 in Japan.[15] FC428 subclones have been reported in Australia, Canada, Denmark, France, Ireland, England, Japan, China and Singapore in 2017–19.[15–21,72] This is the first ceftriaxone-resistant gonococcal clone maintaining an adequate fitness and spreading internationally. FC428andmost ofitssubclones[15–21,72] have originated from the WHO SEAR and WPR. The FC428 clade contains the ceftriaxone resistance-mediating mosaic *penA*-60.001 allele,[73] which may have originated from *Neisseria cinerea*.[74] The first gonococcal strain with ceftriaxone resistance plus high-level azithromycin resistance (WHO Q) identified in 2018 in England (infection acquired in Thailand) and Australia (one associated with travel to the SEAR) also harboured mosaic *penA*-60.001.[22–24] This further indicates that the ceftriaxone resistance-mediating mosaic *penA*-60.001 does not

substantially decrease the fitness of strains, enabling the international spread of ceftriaxone resistance.

Molecular surveillance of AMR in *Neisseria gonorrhoeae*

N. gonorrhoeae has used almost all known AMR mechanisms (enzymatic antimicrobial destruction or modification, modification or protection of antimicrobial targets, increased export (e.g. through MtrCDE efflux pump) and decreased uptake (e.g. through the porin PorB)).[4] Some AMR determinants, particularly target alterations, directly cause AMR, whereas others require combination with other AMR determinants to cause AMR. The AMR determinants conferring resistance to currently and previously recommended treatment options have been detailed elsewhere.[4,75,76]

To enhance WHO GASP, it is essential to strengthen the gonococcal culture capacity internationally. It is also imperative to continue to develop and use appropriate molecular tests to detect gonococcal AMR determinants to predict AMR, particularly where gonococcal culture is unavailable. Many polymerase chain reaction (PCR) assays have been developed for this purpose.[4,77–81] However, the prediction of susceptibility or resistance to antimicrobials other than ciprofloxacin and testing of clinical, especially extragenital, specimens have limitations, and few assays have been appropriately validated and quality assured.[77] PCRs detecting specific ceftriaxone-resistant strains such asH041,[9] F89[10] and FC428[15] have been developed.[82–84] The *N. gonorrhoeae* Sequence Typing for Antimicrobial Resistance (NG-STAR; https://ngstar.canada.ca, accessed 28 June 2019), examining seven AMR determinants, has standardised the nomenclature of AMR determinants and can be used to track AMR strains and indirectly AMR prediction.[73] Whole-genome sequencing (WGS) can elucidate the emergence, transmission and evolution of AMR and national and international spread of AMR gonococcal strains, but can also be used to predict AMR with relatively adequate accuracy.[85,86] It was recently reported that rapid, real-time sequencing using the small hand-held MinION (Oxford Nanopore Technologies, Oxford, UK) can relatively accurately sequence genomes and predict resistance to ciprofloxacin and azithromycin, as well as DS/R to ESCs in gonococcal isolates.[87] Unfortunately, genetic AMR prediction will never completely replace phenotypic AMR testing, which also detects AMR due to unknown AMR determinants.

In the future, molecular point-of-care (POC) tests detecting *N. gonorrhoeae* and AMR determinants for multiple antimicrobials will be available. These POC tests could be used for prompt diagnosis, AMR surveillance and to guide individualised treatments.[77–80,88]

Discussion

In 2015–16, WHO GASP documented sustained high levels of ciprofloxacin resistance, stable relatively high resistance to azithromycin and the emergence of DS/R to ESCs. Major concerns remain regarding the lack of AMR data in many countries worldwide, especially in the WHO AFR (12.8% of countries reporting any data in 2015–16) and EMR (4.5%), but also in the WHO Region of Americas (31.4%), WPR(44.8%), SEAR (54.5%) and EUR (55.6%; 83.9% in the EU/EEA[7,8]). Further, there are concerns regarding the

representativeness of data due to low numbers of isolates (<100 isolates tested annually), selection of isolates, limited information about the total number of isolates and gonococcal diagnostic tests (culture and nucleic acid amplification tests (NAAT)), and the methodologies used in several countries. Critically, many countries with limited gonococcal AMR surveillance have high gonorrhoea incidences, suboptimal gonorrhoea diagnosis, over-the-counter access to antimicrobials, as well as limited availability of optimal antimicrobial treatment (e.g. high-quality ceftriaxone or dual therapy with ceftriaxone plus azithromycin). These factors combine to create the prerequisites for the emergence and spread of gonococcal AMR.[4,67] To develop evidence-based treatment guidelines based on validated surveillance information, it is crucial to strengthen the WHO GASP and other GASPs (both more countries and more representative isolates), including the use of only MIC determination (agar dilution or MIC gradient strip tests) instead of different disc diffusion methods, and to monitor treatment failures. Strengthened AMR surveillance is especially urgent in the WHO AFR, where some progress has been made recently,[63,64,89] and in the EMR. In the SEAR and WPR, there has been a substantial increase in the number of countries providing surveillance data for both ceftriaxone and azithromycin, and in ceftriaxone MIC testing across the Asia–Pacific;[59] however, much more needs to be done in these regions because many ceftriaxone-resistant strains have originated from this region.[15–23]

To enhance WHO GASP, political engagement and financial commitment nationally and internationally is essential. An increased awareness among politicians (e.g. at national Ministries of Health) and healthcare professionals (at clinics, laboratories and public health organisations) that regular, representativeness and quality-assured gonococcal AMR surveillance should be the foundation of national AMR action plans to control gonorrhoea, part of routine diagnostics and/or surveillance and used to refine treatment recommendations is imperative. Additional gonococcal reference laboratories need to be established, and clinical and laboratory training must be provided regarding: (1) sample collection, transportation and preservation; (2) laboratory methodologies, including culture and AMR testing; and (3) appropriate QA, including use of internal QCs and external quality assessment (EQA).[90–92] Appropriate research evaluating the precision, opportunities and cost-effectiveness of molecular AMR assays is important. These methods can supplement the phenotypic AMR surveillance and substantially increase the sample size in countries where gonococcal culture is limited. In remote Australia, molecular AMR assays have been used to enhance gonococcal AMR surveillance for several years.[79,81–84] However, the limitations of molecular AMR prediction should be considered (e.g. cross-reactions with non-gonococcal species in clinical, particularly pharyngeal, specimens, suboptimal sensitivity and specificity in the AMR prediction for several key antimicrobials and that new AMR determinants will be undetected).[4,77–80] Continued research to describe novel AMR determinants, and ideally their induction or selection, evolution and biological fitness, is imperative. In the future, new rapid molecular POC tests, including gonococcal detection and AMR prediction, will guide individualised treatment at the first healthcare visit.[4,77–80] These rapid POC tests will improve the management and control of gonorrhoea and gonococcal AMR by directing appropriate treatment and sparing last-line antimicrobials, thus mitigating the emergence and spread of AMR. WGS is revolutionising knowledge of

AMR, AMR prediction and the transmission of AMR gonococcal strains, and is informing the development of gonococcal diagnostics and a vaccine.[51,85–87,93–100] It cannot be excluded that rapid, real-time sequencers, such as the hand-held MinION or similar sequencer, will be used for gonococcal detection and prediction of AMR in the future, including at POC.[87] However, currently, the wider use of WGS is limited by its complexity and cost.

The main limitations of WHO GASP (and most other GASPs) include the limited number of countries, particularly in the WHO AFR and EMR, the low number and suboptimal representativeness (geographically, from all risk groups, sexes and anatomical sites) of isolates, the use of disc diffusion methods for AMR testing in some countries, the lack of standardised global QA including QCs and EQA, the lack of harmonised breakpoints for decreased susceptibility and/or resistance, the limited epidemiological data for gonorrhoea patients (except in Euro-GASP[7,8,58] and US GISP[39,40]), the limited information on treatment and treatment failures and the delays in publication of AMR data, limiting the value of the data, particularly for early warning of AMR emergence. The WHO, together with the liaised GASPs, is continuously addressing these limitations. For example, training is regularly provided in GASP methodologies to culture more representative samples of gonococcal isolates. MIC determination (agar dilution or different MIC gradient strip tests, which also differ substantially in performance and quality[101]) is increasingly used and supported, and all ceftriaxone resistance identified by disc diffusion methods should be verified by MIC determination at national or international reference laboratories. Regional WHO reference centres assist with WHO reference strains[49–51] for QA and ideally EQA, and the most frequently used CLSI (CLSI; www.clsi.org, accessed 28 June 2019) and EUCAST (EUCAST; www.eucast.org, accessed 28 June 2019) resistance breakpoints are increasingly harmonised in collaboration with GASPs. However, the suboptimal correlates between existing resistance breakpoints and treatment outcomes, particularly for azithromycin, need to be improved, making surveillance of treatment failures essential. Finally, in some sentinel countries (e.g. the Philippines and Thailand[60]), the WHO in collaboration with the US Centers for Disease Control and Prevention has initiated an enhanced GASP (EGASP) aiming to collect standardised and quality-assured epidemiological and clinical information, including treatment failures, linked to AMR data, as collected in Euro-GASP and GISP.[7,8,39,40,58]

In general, improved prevention, including primary prevention, testing (to also detect asymptomatic urogenital gonorrhoea in women and extragenital gonorrhoea in both sexes), management (including TOC) and control of gonorrhoea, ideally linked to general HIV and sexually transmissible infection (STI) prevention,[3,36] and public health guidelines and policies are essential. Key prevention actions include: education regarding symptomatic and asymptomatic STIs; promotion of safe sexual behaviours, including increased condom use; behaviour change communication programs; enhanced sexual partner notification and treatment; expansion of targeted interventions, including screening in some settings for vulnerable populations (sex workers, MSM, adolescents and STI patients and their sexual partners); and think-out-of-box research, such as using antiseptic mouthwash to prevent pharyngeal gonorrhoea.[102] However, the only sustainable solution for gonorrhoea control is adequate uptake of a sufficiently effective gonococcal vaccine. In the recent decade,

significant progress in gonococcal vaccine development has been made, and increased research should be strongly promoted.[103–109]

Until a gonococcal vaccine is available, gonorrhoea control will need to rely on appropriate, timely and affordable antimicrobial treatment in combination with prevention strategies, diagnosis and surveillance. In 2016, the WHO published new guidelines for gonorrhoea treatment.[5] In countries lacking recent, local and quality-assured gonococcal AMR data (and TOC), the WHO recommends dual therapy (ceftriaxone 250 mg plus azithromycin 1 g OR cefixime 400 mg plus azithromycin 1 g).[5] Where feasible, the regimen with ceftriaxone plus azithromycin is preferable, and this regimen appears to be highly effective (very few ceftriaxone-resistant strains also show resistance to azithromycin). This recommendation is similar to the recommendations of dual antimicrobial therapy in many other regional or national gonorrhoea treatment guidelines.[31–34] Notably, evidence for the selection of gonococcal resistance to azithromycin by the use of ceftriaxone plus azithromycin therapy for gonorrhoea is limited.[110,111] Gonococcal azithromycin resistance is likely mostly a consequence of the widespread use of azithromycin monotherapy to treat respiratory tract infections, chlamydia and/or non-gonococcal urethritis.[8,111] Nevertheless, new antimicrobials for monotherapy and/or inclusion in a dual therapy, which should be considered for all novel antimicrobials, for urogenital and extragenital gonorrhoea is essential. Antimicrobials such as lefamulin,[112,113] SMT-571,[114] gepotidacin[115–117] and especially zoliflodacin[118–122] must be studied further.[123,124]

In conclusion, gonococcal AMR remains a major global public health concern, which compromises treatment and control of gonorrhoea. WHO GASP, including its liaised GASPs, provides invaluable data regarding decreased susceptibility and resistance to therapeutically relevant antimicrobials. However, WHO GASP must continue to be significantly improved and sustainable, and national and international leadership and political and financial commitment are imperative. The inclusion of gonococcal AMR in the Global AMR Surveillance System (GLASS) (http://www.who.int/antimicrobial-resistance/global-action-plan/surveillance/glass/en/, accessed 28 June 2019) demonstrates the relevance of this public health threat and will also support the expansion of WHO GASP. Countries must strengthen their gonococcal AMR surveillance programs in the context of their national AMR programs, taking the opportunity of the investment in development of microbiology laboratory capacity. Work to improve the monitoring of antimicrobial use, the conservation and regulation of antimicrobials, monitoring prescription policies and enhancing awareness of the correct use of antimicrobials is also underway internationally. Research efforts should be of highest priority, including developing novel antimicrobials for gonorrhoea treatment (in conjunction with strategies to conserve these and other antimicrobials), gonococcal vaccine(s) and new diagnostic tests (including POC tests for simultaneous detection of gonococci and AMR) for diagnosis and surveillance.

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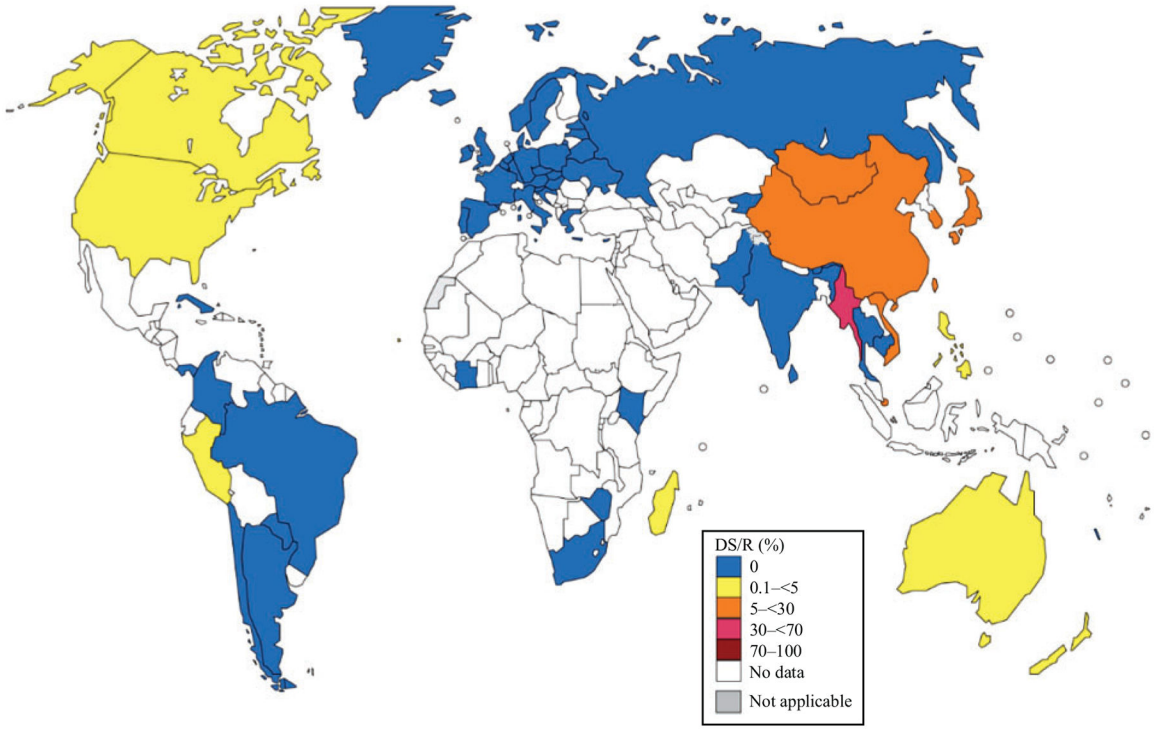

Fig. 1.

Percentage of isolates with decreased susceptibility or resistance (DS/R) to ceftriaxone reported to the World Health Organization Global Gonococcal Antimicrobial Surveillance Program in 2016 (for Cyprus, Kenya and Panama, data were only available from 2015). Note, the areas in grey are disputed territories (e.g. Western Sahara, Jammu and Kashmir) and no antimicrobial resistance data were available from these regions.

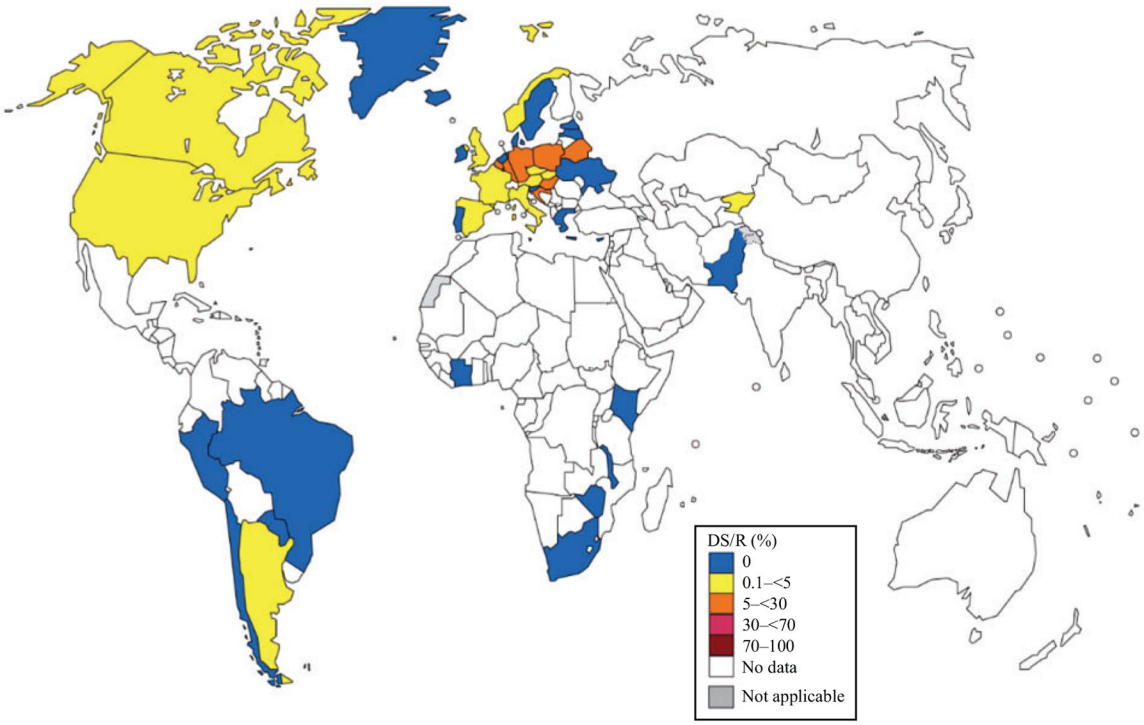

Fig. 2.

Percentage of isolates with decreased susceptibility or resistance (DS/R) to cefixime reported to the World Health Organization Global Gonococcal Antimicrobial Surveillance Program in 2016 (for Cyprus, Kenya and Peru, data were only available from 2015). Note, the areas in grey are disputed territories (e.g. Western Sahara, Jammu and Kashmir) and no antimicrobial resistance data were available from these regions.

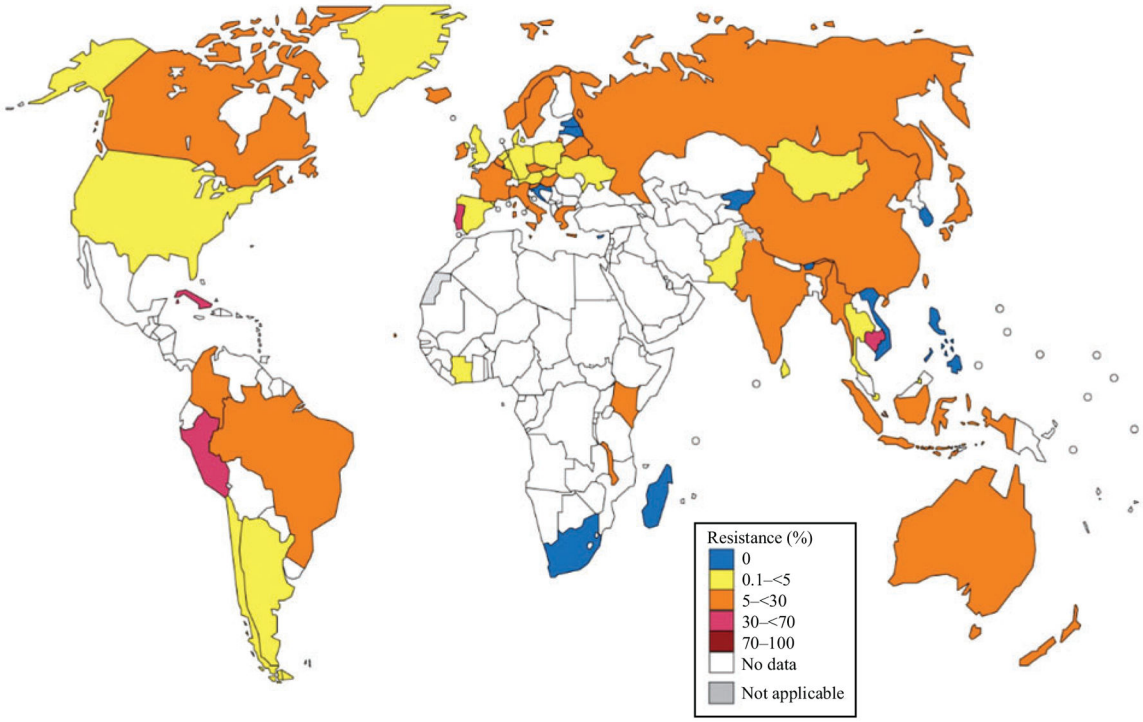

Fig. 3.

Percentage of isolates with resistance to azithromycin reported to World Health Organization Global Gonococcal Antimicrobial Surveillance Program in 2016 (for Cyprus and Kenya, data were only available from 2015). Note, the areas in grey are disputed territories (e.g. Western Sahara, Jammu and Kashmir) and no antimicrobial resistance data were available from these regions.

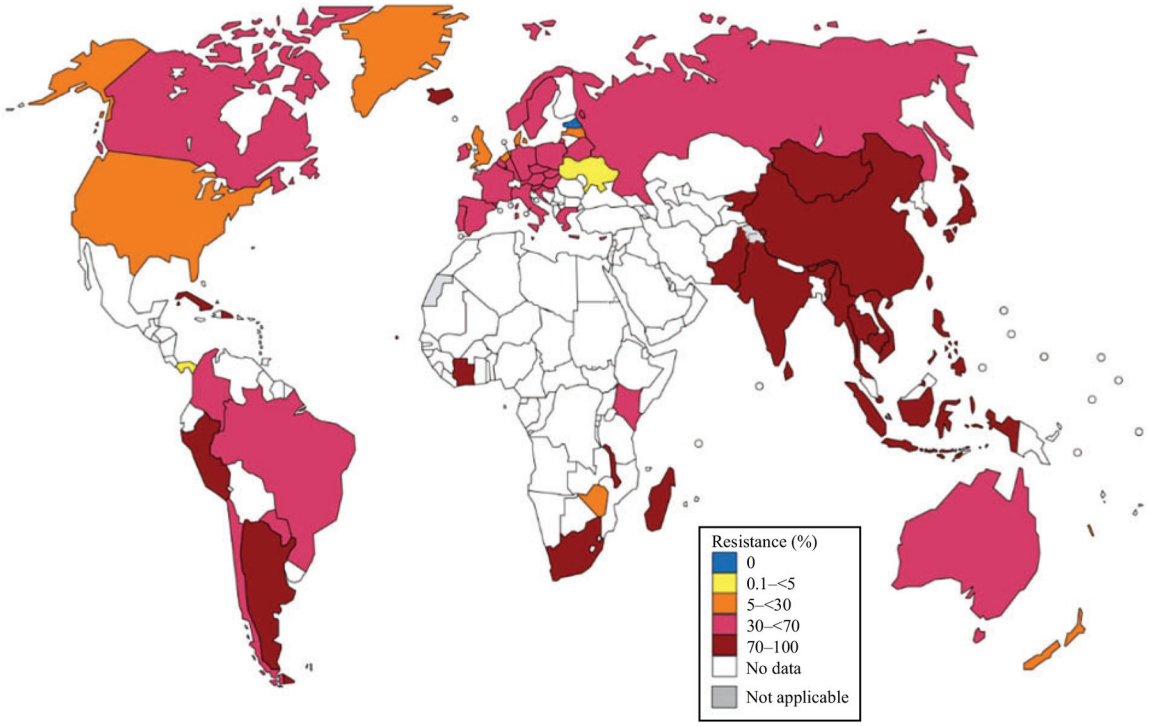

Fig. 4.

Percentage of isolates with resistance to ciprofloxacin reported to World Health Organization Global Gonococcal Antimicrobial Surveillance Program in 2016 (for Cyprus, Dominican Republic, Kenya and Panama, data were only available from 2015). Note, the areas in grey are disputed territories (e.g. Western Sahara, Jammu and Kashmir) and no antimicrobial resistance data were available from these regions.

Table 1.

Number of countries in different World Health Organization (WHO) regions reporting *Neisseria gonorrhoeae* isolates with resistance (R) to azithromycin and ciprofloxacin, and decreased susceptibility or resistance (DS/R) to ceftriaxone and/or cefixime in 2015–16

	WHO Regions							No. countries reporting R or DS/R (%)
	Africa	Americas	Eastern Mediterranean	Europe	South-east Asia	Western Pacific	Total	
Ceftriaxone[A]								
No. countries reporting:	5	10	1	30	5	12	63	
≥5% DS/R[B]	0	0	0	0	1	6	7	15 (23.8)
<5% DS/R	1	3	0	0	0	4	8	
Susceptibility	4	7	1	30	4	2	48	
Cefixime[A]								
No. countries reporting:	5	7	1	29	0	0	42	
≥5% DS/R[B]	0	0	0	7	0	0	7	19 (45.2)
<5% DS/R	0	3	0	9	0	0	12	
Susceptibility	5	4	1	13	0	0	23	
Azithromycin								
No. countries reporting:	5	8	1	30	6	12	62	
≥5% R[B]	2	5	0	15	3	6	30	50 (80.6)
<5% R	1	3	1	9	2	3	20	
Susceptibility	2	0	0	6	1	3	12	
Ciprofloxacin								
No. countries reporting:	6	11	1	30	6	13	67	
>90% R[C]	0	1	1	1	5	4	12	
≥5% R[B]	6	10	1	29	6	13	65	67 (100)
<5% R	0	1	0	1	0	0	2	
Susceptibility	0	0	0	0	0	0	0	

[A] Decreased susceptibility or resistance to ceftriaxone and cefixime were combined due to the different antimicrobial resistance testing methods (minimum inhibitory concentration (MIC) determination using agar dilution or MIC gradient strip tests, or disc diffusion methods) and breakpoints used.

[B] Resistance level where the WHO recommends discontinuing a first-line empirical antimicrobial regimen in the gonorrhoea treatment.

[C] Arbitrary resistance level illustrating the extremely high level of ciprofloxacin resistance particularly in the WHO South-east Asian and Western Pacific regions.

Table 2.

Characteristics of confirmed gonorrhoea treatment failures with ceftriaxone (250–1000 mg × 1) or ceftriaxone (250–1000 mg × 1) plus azithromycin or doxycycline, and the gonococcal strains causing the failures

Country (no. cases; country of infection), year	Therapy	MIC of CRO/AZM (mg L^{-1})	CRO $fT_{>MIC}$ (h)[A]	ML ST ST/NG-MAST ST/NG-STAR type/PBP2 allele	Site of failure	Final successful treatment
Australia (*n* = 2; Australia), 2007[28]	CRO 250 mg × 1	0.016–0.03/ND	41.4–50.3	ND/5, 2740/ND/ND	Pharynx	CRO 500 mg × 1/CRO 1 g × 1
Japan (*n* = 1; Japan), 2009[9]	CRO 1 g × 1	4.0/1	0	7363/4220/226/37.001 (mosaic)	Pharynx	None[B]
Sweden (*n* = 1; Japan), 2010[30]	CRO 250 mg × 1 and CRO 500 mg × 1	0.125–0.25/0.5	15.6–32.8	1901/2958/1399/71.001 (mosaic)	Pharynx	CRO 1 g × 1
Australia (*n* = 1; Australia), 2010[29]	CRO 500 mg × 1	0.03–0.06/0.25–0.5	41.3–49.9	ND/4950 (genogroup 1407)/ND/ND	Pharynx	AZM 2 g × 1
Slovenia (*n* = 1; Serbia), 2011[26]	CRO 250 mg × 1	0.125/0.5	24.3	1901/1407/90/34.001 (mosaic)	Pharynx	CRO 250 mg × 1 plus AZM 1 g × 1
Australia (*n* = 2; Australia), 2011[27]	CRO 500 mg × 1	0.03–0.06	41.3–49.9	1901/225, new variant of 225/ND/ND	Pharynx	CRO 1 g × 1 plus AZM 2 g × 1/CRO 1 g × 1
Sweden (*n* = 3; Sweden), 2013–2014[25]	CRO 500 mg × 1	0.064–0.125/1–2	32.8–41.3	1901/3149, 3149, 4706 (genogroup 1407)/90/34.001 (mosaic)	Pharynx	CRO 1 g × 1
UK (*n* = 1; Japan), 2014[35]	CRO 500 mg × 1 plus AZM 1 g × 1	0.25/1	24.3	1901/12133/22/10.001 (mosaic)	Pharynx	CRO 1 g × 1 plus AZM 2 g × 1
France (*n* = 1; France), 2017[19]	CRO 250 mg × 1 plus DOX 100 mg × 2 daily, 7 days	0.5/0.5	6.6	1903/3435/233/60.001 (mosaic)	Pharynx	Lost to follow-up
UK (*n* = 1; Thailand), 2018[22]	CRO 1 g × 1 plus DOX 100 mg × 2 daily, 7 days	0.5/>256	24.3	12039/16848/996/60.001 (mosaic)	Pharynx	ETP 1 g × 1, 3 days
UK (*n* = 1; UK[C]), 2018[21]	CRO 1 g × 1	1/0.5	15.6	1903/1614/233/60.001 (mosaic)	Rectum, urogenital tract	ETP 1 g × 1, 3 days

AZM, azithromycin; CRO, ceftriaxone; DOX, doxycycline; ETP, ertapenem; MIC, minimum inhibitory concentration; MLST, multilocus sequence typing; ND, not determined; NG-MAST, *Neisseria gonorrhoeae* multi-antigen sequence typing; NG-STAR, *Neisseria gonorrhoeae* sequence typing antimicrobial resistance; PBP2, penicillin-binding protein 2; ST, sequence type

[A] Simulation of time of free ceftriaxone above the MIC ($fT_{>MIC}$) based on mean pharmacokinetic parameter values. Data are from Chisholm *et al.*[68]

[B] The infection was considered to have resolved spontaneously within 3 months.

[C] Link to Ibiza, Spain.