



## RAPID RISK ASSESSMENT

# Extensively drug-resistant (XDR) *Neisseria gonorrhoeae* in the United Kingdom and Australia

7 May 2018

### Main conclusions and options for response

The first three cases of infection with extensively drug-resistant (XDR) *Neisseria gonorrhoeae* displaying resistance to ceftriaxone (MIC = 0.5 mg/L) and high-level resistance to azithromycin (MIC >256 mg/L) at a global level were reported by the United Kingdom (one case) and Australia (two cases) in February and March 2018, respectively. The case from the UK and one case from Australia were travel-associated and both acquired gonorrhoea in South-East Asia. These strains are the first global reports of high-level azithromycin resistant *N. gonorrhoeae* which is also resistant to ceftriaxone as well as most other alternative antimicrobials. Consequently, they are resistant to the first line dual therapy for gonorrhoea (ceftriaxone intramuscularly and azithromycin orally) recommended by European, Australian, World Health Organisation and other guidelines. They highlight the increasing threat of multidrug- (MDR) and extensively drug-resistant (XDR) gonorrhoea in the context of limited therapeutic alternatives, lack of vaccine and limited surveillance capacity in many regions globally.

Effective response to this threat will require strengthened collaboration between clinicians, microbiologists, epidemiologists and public health authorities at national and international level through the adoption of measures to preserve ceftriaxone and azithromycin as viable treatment options for gonorrhoea. The recently reported cases indicate a need to continue to increase awareness of the issue among the public, clinicians, laboratory staff, epidemiologists and other healthcare and public health professionals.

Prevention efforts need to be focused on measures to reduce the overall number of gonorrhoea cases, by emphasising the importance of safer sex practices, in particular the use of condoms [1], and following any national guidelines on STI testing after unprotected sexual activity with new or casual partners. Considering that two of the three XDR gonorrhoea cases reported here were travel-related, provision of information on safer sex practice should be considered as routine advice for travellers. All patients diagnosed with gonorrhoea, need to be reminded of the importance of partner notification and attending for test of cure.

Clinicians need to ensure that all gonorrhoea cases are managed according to national and/or international guidelines, be aware of the possibility of further cases which are resistant to ceftriaxone and azithromycin, ensure that tests of cure are performed for all diagnosed cases, and submit samples for culture and antimicrobial susceptibility testing from all suspected or proven positive sites of infection. In case of XDR gonorrhoea, clinicians should consider taking pharyngeal samples irrespective of reported sexual practices. Sexual health services also need to ensure that partner notification is undertaken for all cases. Particular attention should be paid to effective detection and treatment of pharyngeal gonorrhoea, which is frequently more difficult to eradicate compared to urogenital infections.

Antimicrobial resistance surveillance for *N. gonorrhoeae* in EU/EEA countries and globally, needs to continue to be prioritised and strengthened. Reporting of treatment failures should be implemented and/or strengthened at the national and European level to enable rapid implementation of interventions to prevent the spread of MDR- and XDR *N. gonorrhoeae*. Timely sharing of data between national authorities on treatment failures will also facilitate a more effective global response.

## Source and date of request

ECDC internal decision, 25 April 2018.

## Public health issue

The first three cases of infection with XDR *Neisseria gonorrhoeae* resistant to ceftriaxone and with high-level resistance to azithromycin (HLAziR; minimum inhibitory concentration of  $\geq 256$  mg/L.) on a global scale were reported in the United Kingdom (one) and Australia (two) [2,3]. These extensively drug-resistant isolates (see footnote\* and ref [4] for definition) were not susceptible in vitro to the empiric first-line dual antimicrobial therapy recommended in the EU/EEA (ceftriaxone 500 mg intramuscularly together with azithromycin 2g orally as a single dose), or in Australia (ceftriaxone 500mg IM plus azithromycin 1g orally) and showed resistance to most commonly used antibiotics. Ceftriaxone and azithromycin in varying doses is widely recommended as the first-line treatment for *N. gonorrhoeae* and these strains are also resistant to most alternative available treatments [5]. There are currently very limited treatment options for such cases and the spread of ceftriaxone-resistant and HLAziR *N. gonorrhoeae* would have a significant public health impact. In its list of priority antibiotic-resistant bacteria to guide research, discovery and development of new antimicrobials, the World Health Organization (WHO) has identified *N. gonorrhoeae* as a high priority [6].

Two of the reported cases (one from the UK and one from Australia) are believed to have acquired the infection in South-East Asia, from where limited antimicrobial resistance surveillance data for *N. gonorrhoeae* are available. The regional distribution of isolates with this phenotype is therefore not known.

A large proportion of gonorrhoea cases in the EU/EEA are diagnosed through nucleic acid amplification testing (NAAT) and therefore antimicrobial resistance data are often not available. Furthermore, despite the European guideline specifying the need to perform a test of cure following treatment of each case (in particular for pharyngeal infections) [5], it is likely that in many cases a test of cure is not performed, [7,8], increasing the risk of further spread of antimicrobial-resistant *N. gonorrhoeae* isolates. Microbiological culture and antimicrobial susceptibility testing of *N. gonorrhoeae* isolates is crucial to detect MDR and XDR isolates and inform treatment guidelines.

This rapid risk assessment aims to assess the risk of XDR *Neisseria gonorrhoeae* spreading further in the EU/EEA and provide some options for response.

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The views expressed in this document by CDC experts are those of the reviewers and do not necessarily represent the official position of the US CDC.

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\* In this document, MDR and XDR *N. gonorrhoeae* are defined as by Tapsall et al. [4]. In brief, MDR-*N. gonorrhoeae*, are defined as those infections resistant to one of the category I antibiotics (which includes injectable extended spectrum cephalosporins, oral extended-spectrum cephalosporins and spectinomycin) and at least two of the antibiotic classes listed in category II (which includes penicillins, fluoroquinolones, azithromycin, aminoglycosides and carbapenems). XDR-*Neisseria gonorrhoeae* are defined as those resistant to two or more of the antibiotic classes in category I and three or more in category II.

## Disease background information

### Gonorrhoea

Gonorrhoea is the second most commonly reported bacterial STI in Europe, with 75 349 confirmed cases reported in 2016 [9] and as such it poses a serious and growing public health problem. In men, urethral infection usually leads to dysuria and urethral discharge and may be complicated by epididymitis. Among women, genital tract infection is frequently asymptomatic, but when symptoms occur they include dysuria, increased or altered vaginal discharge, lower abdominal pain and, in rare cases, intermenstrual bleeding or menorrhagia. Among men and women, rectal and pharyngeal infections are relatively frequent and mostly asymptomatic. Untreated infections may lead to severe secondary sequelae among women, including pelvic inflammatory disease, first trimester abortions, ectopic pregnancy, and infertility [5,10]. *N. gonorrhoeae* infections also play a role in facilitating HIV acquisition and transmission [11]. Successful treatment of cases reduces the risk of complications, but also serves as the main public health strategy for reducing transmission.

### Travel-associated gonorrhoea

Travel-associated gonorrhoea accounts for a large proportion of gonorrhoea cases reported in the EU/EEA. Although, in general, data reported to the European Surveillance System (TESSy) on travel-associated gonorrhoea are of low completeness, an analysis of data reported by Nordic countries (which report high levels of completeness for the country of infection) showed that, between 2008 and 2013, 25.5% of reported gonorrhoea cases were acquired abroad, most commonly in Thailand (31%) followed by the Philippines (8%) and Spain (7%) [12]. Data from the UK Gonococcal Resistance to Antimicrobial Surveillance Programme (GRASP) shows that 10% of all cases and 20% of men who have sex with men diagnosed with gonorrhoea in this sentinel surveillance programme reported having had sex abroad [13]. A separate study in Sweden found that Thailand was the country with the highest incidence of STI among travellers (34 per million travellers) [14]. Among Finnish travellers, the risk of gonorrhoea was highest among those travelling to Asia and Oceania (11 per 100 000 travellers).

### Antimicrobial resistance in *Neisseria gonorrhoeae*

In recent decades, *N. gonorrhoeae* has developed resistance to several antimicrobial classes such as sulphonamides, penicillins, tetracyclines, macrolides, fluoroquinolones and, more recently, the third-generation cephalosporins [15]. The first treatment failures with less potent, oral third-generation cephalosporins were reported in Japan in 2000 [16]. Subsequently, further cases of treatment failure were reported from other Asian countries [17]. A report from Norway described the first two treatment failures with the most potent oral cephalosporin, cefixime in the EU/EEA (2010 [18]), which were followed by similar treatment failures in England [19,20], Austria [21], France [22], Canada [23,24], and South Africa [25]. The report of a highly ceftriaxone-resistant (MIC=2 µg/ml) *N. gonorrhoeae* strain H041 in Japan [26] triggered worldwide concerns as ceftriaxone, which is administered parenterally, is the last remaining option for empirical, first-line monotherapy of *N. gonorrhoeae*. Ceftriaxone treatment failures of pharyngeal gonorrhoea have been reported in Japan [26], Sweden [27,28], Slovenia [29], and Australia [30,31], and the first case of genital infection of highly ceftriaxone-resistant *N. gonorrhoeae* in Europe was reported in France in 2011 [22]. High-level ceftriaxone-resistant isolates have also been reported from Spain [32], and the first reported treatment failure globally to a recommended dual antimicrobial therapy regimen (ceftriaxone 500 mg plus azithromycin 1 g) was identified in the UK in late 2014 [33]. Some additional sporadic isolates with ceftriaxone resistance have also been characterised in more detail in recent years, including isolates from Australia in 2013 and 2017 [34,35] Argentina in 2014 [36], Japan in 2014 and 2015 [37,38], Denmark in 2017 [37,38] and Canada in 2017 [39]. In 2012, the European Centre for Disease Prevention and Control (ECDC) published a Response Plan to Control and Manage the Threat of Multidrug-Resistant Gonorrhoea in Europe, outlining recommendations and possible strategies to control the threat of multidrug-resistant gonorrhoea across Europe [40]. In 2017, WHO published results from its Global Gonococcal Antimicrobial Surveillance Programme (WHO GASP) and issued a call for international collaborative action to respond to the threat [41].

### Antimicrobial resistance surveillance for *N. gonorrhoeae*

#### EU/EEA

The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) has been established to inform public health and treatment guidelines on antimicrobial susceptibility testing (AST) results in EU/EEA countries and reports on trends in gonococcal susceptibility [42]. These data are crucial for optimisation of treatment and to detect emerging antimicrobial resistance. Euro-GASP is implemented as a sentinel surveillance system and involves a network of laboratories in EU/EEA countries and includes AST, an external quality assessment programme, molecular typing and training. Euro-GASP uses resistance breakpoints as defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [43] and therefore defines ceftriaxone resistance as >0.125 mg/L and azithromycin resistance as >0.5 mg/L. Results from Euro-GASP have shown that, in participating EU/EEA countries, resistance to cefixime decreased from 8.7% in 2010 to 2.1% in 2016. Ciprofloxacin resistance remained

high, at 47% in 2016, and the level of azithromycin resistance has remained stable at around 7–8% between 2014 and 2016. However, seven isolates were HLAziR in 2016, compared with only one in 2014. No isolate displayed resistance to ceftriaxone in 2016, compared to one in 2015, five in 2014 and seven in 2013 [44,45].

*N. gonorrhoeae* seems to retain resistance to several groups of antimicrobials, even when such antimicrobials are no longer used for the treatment of gonorrhoea.

The low and stable proportions of cefixime-resistant or ceftriaxone-resistant isolates in the EU/EEA is encouraging and is most probably partly due to the currently recommended highly-effective dual-therapy regimen (ceftriaxone plus azithromycin). However, the proportion of isolates with resistance to azithromycin is of concern and threatens the effectiveness of this regimen.

Trends and drifts in susceptibility to antimicrobial agents used for the treatment of gonorrhoea in England and Wales are monitored through GRASP. It was established in 2000 and is based on a collaboration between Public Health England (PHE), 27 genitourinary medicine clinics throughout England and Wales, and regional primary diagnostic laboratories [46].

During 2015–2016, GRASP did not detect any isolates with resistance to ceftriaxone. The proportion of isolates with azithromycin resistance decreased from 9.8% to 4.7%, whereas the proportion of isolates with cefixime resistance increased for the second consecutive year from 0.4% to 1.7%. Ciprofloxacin resistance decreased from 41.9% to 33.7%, and penicillin resistance from 17.6% to 13.9%.

Among referred isolates between January 2015 and June 2017, PHE confirmed two cases of ceftriaxone resistance (MIC >0.125 mg/L), 325 cases of azithromycin resistance (MIC >0.5 mg/L), 81 of which were HLAziR (MIC ≥256 mg/L), and one case of treatment failure after dual therapy with ceftriaxone and azithromycin (reported in April 2015) [33]. The HLAzR cases were part of an ongoing outbreak [47]. There had been no other treatment failures following therapy with ceftriaxone and azithromycin confirmed by PHE before the current XDR case reported here [2,13].

In Scotland, surveillance for *N. gonorrhoeae* antimicrobial resistance is performed through the Gonococcal Antibiotic Surveillance in Scotland system (GASS) [48]. There was no resistance observed to ceftriaxone and no treatment failures were reported. Resistance to azithromycin was seen in 0.9% of isolates (n=10), two of which were HLAziR. Resistance to cefixime and ciprofloxacin in Scotland have remained stable (0.5% and 34.9% respectively).

## Australia

The Australian Gonococcal Surveillance Programme (AGSP), established in 1981, is run by the National Neisseria Network (NNN) and supported by the Australian Government. The NNN is a collaboration of *Neisseria* reference laboratories in each state and territory that perform phenotypic and genotypic testing on clinical isolates of pathogenic *Neisseria*. Clinical isolates from males and females are referred from both public and private sector laboratories to NNN laboratories for testing, representing as wide a section of the community as possible [49]. In 2017, 7 835 clinical *N. gonorrhoeae* isolates were tested for antimicrobial resistance, 28% of the 28 399 cases of gonococcal infection notified in Australia in that year [50]. In 2017, 0.04% of GC isolates had ceftriaxone MIC values ≥0.125 mg/L (decreased susceptibility). There were two isolates reported with a ceftriaxone MIC value of 0.5 mg/L, the highest MIC value obtained in Australia since the A8806 isolate reported in 2013 [35]. In 2013–2015, azithromycin resistance in Australia was reported in 2.1–2.6% of isolates, increasing to 5.0% in 2016 and 9.3% in 2017 [51]. Four isolates were HLAziR (MIC value ≥256 mg/L) in 2017. Ciprofloxacin resistance (MIC ≥1 mg/L) was detected in 27.5% of isolates, which was lower than in 2014 (36%), and had been decreasing since 2008 (54%) [34].

## South-East Asia and Western Pacific

WHO, in collaboration with the United States Centers for Disease Control and Prevention (US CDC), has been supporting efforts to develop antimicrobial resistance surveillance for *N. gonorrhoeae* in the South-East Asian and Western Pacific Region through initiatives such as the Enhanced Gonococcal Antimicrobial Surveillance Program (EGASP) [52]. The first site, implemented in 2015, was in Bangkok, Thailand. The first results from this site were reported in 2017. Resistance to cefixime, ceftriaxone, azithromycin and gentamicin was not reported; however, 96% of isolates were resistant to ciprofloxacin [53]. Another study in Thailand using isolates from 2008 to 2014 also did not report resistance to cefixime, ceftriaxone or azithromycin [54].

Antimicrobial resistance surveillance data on *N. gonorrhoeae* from South-East Asia are limited. Nevertheless, decreased susceptibility to ceftriaxone was reported by nine out of 18 laboratories participating in WHO GASP between 2009 and 2012 [55]. The proportion of isolates reported to be of decreased susceptibility to ceftriaxone ranged from 0.1% to 84%, whereas azithromycin resistance was observed in <5% of isolates overall. This study included sites in Bhutan, India, Sri Lanka and Thailand.

Other studies on antimicrobial resistance in South-East Asia or the Western Pacific Region reported the following:

- In Indonesia, among 79 *N. gonorrhoeae* isolates tested in 2014, none was resistant to ceftriaxone or cefixime, and only one was resistant to azithromycin [56]. In contrast, 98.8% isolates were resistant to doxycycline and 97.6% to ciprofloxacin.
- In Hanoi, Vietnam, among 108 *N. gonorrhoeae* isolates tested in 2011, high proportions of resistance to antimicrobials previously recommended for gonorrhoea treatment were found, including 98% resistance to ciprofloxacin, 82% to tetracycline and 48% to penicillin. In addition, 11% of isolates were resistant to azithromycin, 5% to ceftriaxone and 1% to cefixime [57].
- In Vientiane, Laos, among 158 *N. gonorrhoeae* isolates collected between 2011 and 2015, no resistance was observed to ceftriaxone and spectinomycin, however 90% were resistant to penicillin, 99% to tetracycline and 85% to ciprofloxacin [58].
- In Japan, a study of 2 471 *N. gonorrhoeae* isolates collected from nine regions between 2000 and 2015 showed that, each year, between 0% and 20% of isolates had a ceftriaxone MIC  $\geq 0.25$  mg/L. The highest proportion of ceftriaxone-resistant isolates were detected in 2011 (22.3%), 2007 (20%), 2010 (16.9%) and 2006 and 2015 (12.9%). Six isolates had a ceftriaxone MIC of 0.5 mg/L. Azithromycin resistance ( $\geq 1$  mg/L) has been observed in 10–40% of isolates each year since 2004; 18.8% of isolates were resistant to azithromycin in 2015 [59]. Another study with 677 isolates from Fukuoka collected between 2010 and 2013 reported a significant increase in azithromycin-resistant isolates from 1.8% in 2010 to 22.6% in 2013. Ceftriaxone resistance was not detected in this study, although there was a significantly increasing trend in isolates with decreased susceptibility to ceftriaxone (MIC = 0.12 mg/L) from 0% in 2010 to 6.6% in 2013 [60].
- In China, results of antimicrobial susceptibility testing of 3 849 isolates collected from patients with a confirmed positive *N. gonorrhoeae* culture during clinic visits in the period 2013–2017 in seven provinces, indicated that 2.3% (87/3,827; 95% CI 1.9%–2.8%) of the isolates were both resistant to azithromycin (defined as MIC  $\geq 1.0$  mg/l) and showed decreased susceptibility to ceftriaxone (defined as MIC  $\geq 0.125$  mg/l). The prevalence of resistance to azithromycin and decreased susceptibility to ceftriaxone increased in this sample of patients from 1.9% in 2013 to 3.3% in 2016 (chi-squared test for trend,  $P = 0.03$ ) [61].

In the Western Pacific Region, WHO GASP included 23 laboratories from 11 countries in 2015 [62]. The proportion of resistance to ciprofloxacin is very high throughout the region; azithromycin resistance is frequently reported, particularly in China (16–30% of isolates) and Japan (16–30% of isolates); and decreased susceptibility or resistance to ceftriaxone is also common in 16–30% of isolates in Japan and Korea reported to be ceftriaxone-resistant.

In a recent review [41], WHO GASP reported that (2014 data):

- In the WHO Western Pacific Region, five out of seven countries reporting ceftriaxone susceptibility data reported decreased susceptibility or resistance to ceftriaxone, and three of these (Hong Kong SAR (China), Japan, and Korea) reported decreased susceptibility or resistance in  $\geq 5\%$  of isolates. Prior to 2014, China, Mongolia, and Tonga have also reported  $\geq 5\%$  of isolates with decreased susceptibility or resistance to ceftriaxone. Out of seven countries in the region reporting azithromycin resistance, three (Japan, Hong Kong (China), and Mongolia) reported  $\geq 5\%$  resistance and four (Australia, New Zealand, Singapore, and Vietnam) reported  $< 5\%$  resistance. Two (Korea and the Philippines) reported no resistance.
- In the WHO South-East Asian Region, three (Bhutan, India, and Indonesia) of six reporting countries detected decreased susceptibility or resistance to ceftriaxone, with India and Indonesia reporting  $\geq 5\%$  decreased susceptibility or resistance. Azithromycin resistance was reported by five out of six reporting countries, four of which reported less than 5% resistance whereas Indonesia reported  $\geq 5\%$ .

## Event background information

On 23 March 2018, the UK reported on the Early Warning and Response System of the European Union (EWRS) the detection of a *N. gonorrhoeae* isolate resistant to ceftriaxone (MIC = 0.5 mg/L) and with high-level resistance to azithromycin (MIC  $> 256$  mg/L).

The isolate was from a heterosexual man who had attended sexual health services in England in early 2018. He reported being in a relationship with a regular female partner in the UK and having had a female sexual contact in South-East Asia in the month prior to symptom onset. The case was empirically treated with ceftriaxone (1 g) and subsequently with spectinomycin (2 g). At test of cure, the urine was negative on NAAT but a pharyngeal swab culture was positive, indicating treatment failure as reinfection was excluded [2]. Antimicrobial susceptibility testing showed that the isolate was only susceptible to spectinomycin and possibly gentamicin (MIC = 2 mg/L) as there is no defined resistance breakpoint for gentamicin. The ertapenem MIC was low (0.032 mg/L), suggesting that this antimicrobial could be effective, although there is also no defined resistance breakpoint for ertapenem. The patient was therefore treated with intravenous ertapenem for three days, which cured the infection [63].

Identification of sexual partners and follow-up was coordinated by the UK incident management team which concluded that the isolate had probably not spread further within the UK. Efforts to contact the partner in South-East Asia are ongoing. While cases of HLAziR (MIC  $> 256$  mg/L) *N. gonorrhoeae* had previously been detected in

the UK (England and Wales) (81 cases between January 2015 and June 2017 as part of an ongoing outbreak [47]), this was the first isolate which was also resistant to ceftriaxone. PHE reminded clinical laboratories to continue to refer *N. gonorrhoeae* isolates with resistance to ceftriaxone (MIC >0.125 mg/L) or to azithromycin (MIC >0.5 mg/L) to the PHE Reference Bacteriology for confirmation and general practitioners to refer all suspected cases of gonorrhoea to genitourinary medicine services for appropriate management, as per national guidance [64]. The need to ensure sexual healthcare pathways that facilitate prompt diagnosis, culture for antimicrobial susceptibility testing, effective treatment, test of cure, partner notification, and a full sexually transmitted infection screen was also highlighted by PHE.

On 5 April, Australia notified WHO of two isolates of XDR *N. gonorrhoeae* that appeared to be phenotypically the same as the isolate reported by PHE. The two isolates exhibited resistance to ceftriaxone (MIC = 0.5 mg/L), high-level resistance to azithromycin (MIC >256 mg/L) and were also resistant to benzylpenicillin and ciprofloxacin. The isolates were reported to be susceptible to gentamicin and spectinomycin.

These two isolates were from two Australian patients - one diagnosed in Western Australia and one in Queensland - with no identified epidemiological links [3]. One case reported having acquired the infection from a sex worker in South-East Asia. This was the first time XDR *N. gonorrhoeae* had been detected in Australia. Australian authorities have initiated epidemiological investigations and response activities including contact tracing, dissemination of prevention messages and clinical advice on case management, in order to contain spread.

## ECDC threat assessment for the EU

These events give significant cause for concern considering the lack of alternative treatments for gonorrhoea. Although the isolates were reported to be susceptible to spectinomycin and possibly to gentamicin (no resistance breakpoint defined by EUCAST or CLSI), spectinomycin is (a) not easily available in many EU/EEA countries, (b) known to be less effective for pharyngeal gonorrhoea and the UK case failed treatment at the pharynx despite the isolate being susceptible, and (c) *N. gonorrhoeae* has the potential to rapidly develop resistance to spectinomycin [65,66]. Gentamicin has been found to be effective as combination treatment with azithromycin [67]; however, there is limited evidence on the effectiveness of gentamicin monotherapy since the studies available are generally small and of low quality [68,69]. In particular, there is a lack of data on the efficacy of gentamicin when treating pharyngeal and rectal gonorrhoea. The 'Gentamicin in the Treatment of Gonorrhoea' (G-TOG) study, which compared gentamicin 240 mg with ceftriaxone 500 mg (each as a single intramuscular dose combined with azithromycin 1g orally) and was reported at the STI and HIV World Congress in 2017, showed that gentamicin was not as effective as ceftriaxone and had lower clearance rates, particularly in the pharynx (80% versus 96%) and the rectum (90% versus 98%) [70]. Ertapenem was used to treat the UK case reported above; however there is no published clinical trial on its efficacy in treating gonorrhoea, although reported MICs have been generally low [71].

Alternative treatment options described in the current European guideline published by the International Union against Sexually Transmitted Infections - Europe (IUSTI) on diagnosis and treatment of gonorrhoea when extended-spectrum cephalosporin resistance is identified include ceftriaxone (1g) as a single intramuscular dose plus azithromycin (2g) orally, or gentamicin (240 mg) as a single intramuscular dose plus azithromycin (2g) orally [1]. In addition, gemifloxacin (320 mg) orally plus azithromycin (2g) orally has also been found to be effective in treating urogenital gonorrhoea [72]. Although this trial was not powered to provide estimates of the efficacy for treatment of rectal or pharyngeal infection, it cured the few extra-genital infections detected in the study [72]. The combinations of gentamicin/azithromycin and gemifloxacin/azithromycin are included in the 2015 CDC gonorrhoea treatment guidelines as alternatives in the setting of cephalosporin allergy [73]. High-level resistance to azithromycin means that the above-mentioned three treatment options would, in practice, correspond to monotherapy of XDR *N. gonorrhoeae* and the first option might not be effective, as in the UK case where treatment with 1g ceftriaxone failed. The IUSTI European guideline is currently under revision and will provide additional options for treatment of cases resistant to both ceftriaxone and azithromycin, although the alternative options and the evidence base are extremely limited.

Antimicrobial resistance surveillance data for *N. gonorrhoeae* in South-East Asia are limited. It is therefore difficult to assess how widely XDR, MDR and HLAziR *N. gonorrhoeae* isolates are distributed. Considering the substantial number of gonorrhoea cases in the EU/EEA acquired abroad, and specifically, in South-East Asia, it is likely that more cases have been and are being imported into the EU/EEA, particularly if such XDR *N. gonorrhoeae* strains are widely distributed and biologically fit. Detection of all imported XDR *N. gonorrhoeae* cases is extremely difficult for a number of reasons, including the asymptomatic nature of many cases, the limited use of culture in many countries, lack of implementation of test of cure [7,8], and challenges in tracing all partners. Further spread of XDR *N. gonorrhoeae* in the EU/EEA in a similar manner to the spread of HLAziR strains seen in the UK [47] would threaten the effectiveness of the currently recommended dual treatment and increase the reliance on antimicrobials for which data on effectiveness is very limited. This could lead to an increase in the number of cases of gonorrhoea as, apart from primary prevention, effective treatment is the main way to control gonorrhoea. In addition, the incidence of serious complications, such as pelvic inflammatory disease, first trimester abortions, ectopic pregnancy, and infertility could potentially increase. Finally, prolonged cases of gonorrhoea in HIV co-infected patients, not on antiretroviral therapy, raise the likelihood of increased HIV transmission in situations where barrier and/or biomedical HIV prevention methods are not in use.

Whole genome sequencing to assess the genetic relationship between the three isolates detected in the UK and in Australia, is currently underway to assess the relationship to other ceftriaxone-resistant isolates and to identify resistance determinants.

## Conclusions and options for response

Under the current circumstances where there are limited options for treatment, an effective response will require strengthened collaboration between clinicians, microbiologists, epidemiologists and public health authorities at national and international level in adopting measures to preserve ceftriaxone and azithromycin as viable treatment options for gonorrhoea.

Measures to increase awareness of the issue among the public, clinicians, laboratory staff, epidemiologists and other healthcare and public health professionals are a priority. Results from antimicrobial resistance surveillance need to be effectively communicated to increase awareness of the threat of MDR and XDR gonorrhoea among authorities, professional societies, physicians, and persons at risk of gonorrhoea, and to inform treatment guidelines. Prevention efforts need to be focused on measures to reduce the overall number of gonorrhoea cases, through emphasising the importance of safer sex practices, in particular the use of condoms, and following any national guidelines on STI testing following unprotected sexual activity with new or casual partners. Provision of information on safer sex practice should be considered as routine advice for travellers. All patients diagnosed with gonorrhoea need to be reminded of the importance of partner notification and attending for test of cure.

In addition, clinicians need to ensure that all gonorrhoea cases are managed according to national and/or international guidelines, be aware of the possibility of further cases which are resistant to ceftriaxone and azithromycin, ensure that tests of cure are performed for all diagnosed cases, as recommended by the European guidelines [5] or similar national guidelines, and to submit samples for culture and antimicrobial susceptibility testing from all suspected or proven sites of infection. In the event of XDR gonorrhoea, clinicians should consider taking pharyngeal samples irrespective of reported sexual practices. Sexual health services also need to ensure that partner notification is undertaken for all cases. If required, the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) [42,44] can provide expert technical and microbiological support in the event of ceftriaxone-resistant and/or azithromycin-resistant isolates being detected. In general, increased attention to effective detection and treatment of pharyngeal gonorrhoea, which is frequently more difficult to eradicate compared to urogenital infections, is crucial.

Antimicrobial resistance surveillance for *N. gonorrhoeae* in EU/EEA countries, and globally, needs to continue to be prioritised and strengthened. Timely antimicrobial resistance profiles with sufficient epidemiological information will enable early detection and investigation of treatment failures, and will inform national and international treatment guidelines.

Reporting of treatment failures should be implemented and/or strengthened at the national and European level to enable rapid intervention so as to prevent the spread of antimicrobial-resistant *N. gonorrhoeae*. Timely sharing of data on treatment failure among international partners will also facilitate a more effective global response. The benefit of using readily existing platforms at European level, such as ECDC's Epidemic Intelligence Information System for Sexually Transmitted Infections (EPIS STI), should be explored among partners.

These cases highlight the need for novel antimicrobials for the treatment of gonorrhoea as well as prioritisation of an effective vaccine. In the long-term, the development of new antimicrobials and an effective vaccine could make a significant impact on the control of antimicrobial resistance and gonorrhoea. Although some progress has been made on the former, with three antimicrobials currently completing phase II or phase III trials, a vaccine for gonorrhoea remains some way away, despite recent developments [74-77]. Increased advocacy to prioritise and fund research in novel gonorrhoea treatment options and vaccine development is required [41].

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