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TECHNICAL REPORT

Response plan to control and manage the threat of multi- and extensively drug-resistant gonorrhoea in Europe

2019 update

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2019 update

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Abbreviations

AMR	Antimicrobial resistance
AST	Antimicrobial susceptibility testing
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EQA	External quality assessment
EU	European Union
Euro-GASP	European Gonococcal Antimicrobial Surveillance Programme
HIV	Human immunodeficiency virus
MDR NG	Multidrug-resistant *Neisseria gonorrhoeae*
NAAT	Nucleic acid amplification test
STI	Sexually transmitted infection
TESSy	The European Surveillance System
UK	United Kingdom
WGS	Whole-genome sequencing
XDR NG	Extensively drug-resistant *Neisseria gonorrhoeae*

Background

With 89 239 cases, gonorrhoea was the second most commonly reported bacterial sexually transmitted infection (STI) in European Union/European Economic Area (EU/EEA) in 2017[i]. Gonorrhoea is a serious public health problem as untreated infections may lead to severe secondary sequelae, including pelvic inflammatory disease, first-trimester miscarriages, ectopic pregnancy and infertility [1]. *N. gonorrhoeae* infections also facilitate HIV acquisition and transmission [2]. Successful treatment of cases reduces the risk of complications, but also serves as the main public health strategy for reducing transmission apart from condom use.

Over the past decades, *N. gonorrhoeae* has developed antimicrobial resistance (AMR) to several antimicrobial classes such as sulphonamides, penicillins, tetracyclines, macrolides, fluoroquinolones and more recently third-generation cephalosporins [3]. The first treatment failures connected to less potent oral third-generation cephalosporins were reported in Japan in 2000 [4]. Subsequently, further cases of treatment failure were reported from other Asian countries [5]. A report from Norway described the first two treatment failures with cefixime in the EU/EEA (2010 [6]), which were followed by treatment failures in England [7,8], Austria [9], France [10], Canada [11,12] and South Africa [13]. The report of the first extensively drug-resistant (XDR NG; as defined in [14]), highly ceftriaxone-resistant *N. gonorrhoeae* strain (H041) in Japan [15] triggered worldwide concerns as ceftriaxone is the last remaining option for empirical first-line monotherapy. Ceftriaxone treatment failures of pharyngeal gonorrhoea were reported in Japan [15], Sweden [16,17], Slovenia [18] and Australia [19,20]. The first case of genital infection of highly ceftriaxone-resistant *N. gonorrhoeae* in Europe was reported in France in 2011 [10] and two high-level ceftriaxone-resistant isolates were also reported from Spain in 2012 [21]. As a response to the public health concern due to spread of multidrug-resistant *N. gonorrhoeae* (MDR NG), including XDR NG, the European Centre for Disease Prevention and Control (ECDC), together with an international expert group, developed the 'Response Plan to Control and Manage the Threat of Multidrug-Resistant Gonorrhoea in Europe' in 2012 [22]. Furthermore, the 'European Guideline on the Diagnosis and Treatment of Gonorrhoea' was revised to recommend a first-line dual antimicrobial therapy consisting of a single 500 mg intramuscular dose of ceftriaxone plus a single 2 g oral dose of azithromycin [23]. Other international gonorrhoea management guidelines also were updated to recommend similar dual antimicrobial therapies with slightly different dosages [24–26].

It is a grave concern that the first treatment failure globally to dual antimicrobial therapy regimen recommended in the United Kingdom (500 mg of ceftriaxone plus 1 g of azithromycin), caused by a new XDR NG strain, was reported in 2016 in the UK [27]. In 2018, the first XDR NG strain with ceftriaxone resistance combined with high-level resistance to azithromycin was reported from England [28]. This strain also resulted in a failure to treat pharyngeal gonorrhoea with a single 1 g intramuscular dose of ceftriaxone plus 100 mg of doxycycline orally twice daily for seven days and subsequently also with a single 2 g intramuscular dose of spectinomycin. Two similar gonococcal isolates were identified in Australia several months later [29]. As a response, the ECDC together with an international expert group developed a rapid risk assessment on XDR NG in the UK and Australia (7 May 2018) [30]. Two of the three XDR NG cases reported in 2018 (one from the UK, one from Australia) likely acquired the infections in South East Asia and many of the previously identified ceftriaxone-resistant gonococcal strains have also been identified or acquired in Asia, especially in the Western Pacific region (frequently in Japan). There are limited quality-assured minimum inhibitory concentration-based antimicrobial susceptibility testing (AST) data for *N. gonorrhoeae* in this region and the regional distribution of XDR and ceftriaxone-resistant NG isolates is largely unknown. Accordingly, it is essential to enhance gonococcal AMR surveillance in this region. It is therefore crucial to further strengthen the collection of travel history of gonorrhoea patients, as well as the collaboration between the gonococcal AMR surveillance programmes in different regions globally. The need for collaboration at the EU/EEA level and collection of travel history data was also highlighted by XDR NG isolates detected in England in late 2018 and linked to travel of the case or a sexual partner to Ibiza [31].

The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) was established to inform public health and treatment guidelines on AST results in EU/EEA countries and reports on trends in gonococcal susceptibility [32]. These data are crucial for optimisation of treatment and to detect emerging resistance. Euro-GASP is implemented as a sentinel surveillance system, involves a network of laboratories in Member States and includes AST, an external quality assessment (EQA) programme and training. Euro-GASP has shown that resistance to cefixime decreased from 8.7% in 2010 to 2.0% in 2014 and since then has remained relatively stable (2.1% in 2016). Ciprofloxacin resistance has remained high, at 46.5% in 2016, and the level of azithromycin resistance was 7.2% in 2010 and 7.5% in 2016. Seven (0.3%) isolates displayed high-level resistance to azithromycin (MIC≥256 mg/L) in 2016, compared with five (0.2%) in 2015. No isolates displayed resistance to ceftriaxone in 2016, compared to one in 2015, five in 2014 (three of which were resistant to azithromycin) and seven in 2013 (one resistant to azithromycin) [33,34]. *N. gonorrhoeae* seems to retain resistance to several classes of antimicrobials, even when the antimicrobials in question have been discontinued in the treatment of gonorrhoea.

[i] ECDC atlas: http://atlas.ecdc.europa.eu/public/index.aspx?Dataset=27&HealthTopic=21

Euro-GASP data show a low and stable trend of cefixime and ceftriaxone resistance in the EU/EEA in recent years. This is encouraging and is likely in part due to the currently recommended and highly effective treatment with ceftriaxone, which in most settings is administered together with azithromycin in a dual-therapy regimen. However, the degree of resistance to azithromycin, although also currently stable, is of concern and threatens the effectiveness of this regimen. The spread of ceftriaxone and azithromycin co-resistance and treatment failures need to be closely monitored and detected in a timely manner, as the loss of the last remaining option for monotherapy of gonorrhoea, ceftriaxone, would have a significant impact on public health.

The ECDC 2012 response plan [22] complimented the WHO Global Action Plan [35], as well as national action plans subsequently published by the Centers for Disease Control and Prevention [36] and Public Health England [37]. Six years have passed since the initial ECDC response plan was published in 2012 [22] and even though *N. gonorrhoeae* still remains for the most part susceptible to ceftriaxone in Europe, the threat of untreatable gonorrhoea remains. The present ECDC 2019 response plan strives to further support Member States to develop and implement national strategies and interventions to control the threat of MDR and XDR gonorrhoea in a multidisciplinary approach. Importantly, preventing the emergence and spread of AMR in *N. gonorrhoeae* is just one aspect of gonorrhoea control that should always be part of comprehensive management strategies including appropriate treatment, diagnostics and testing algorithms (e.g. three-site testing in men who have sex with men), test of cure, notification and treatment of partners, enhanced focus on risk groups and STI prevention measures, including advocating for increased condom use [23,35].

2012 response plan

Objectives of 2012 response plan

The 2012 response plan detailed the response at the European level and was designed as a guide for Member States when planning national interventions. MDR *N. gonorrhoeae* (NG) and XDR NG were defined as by Tapsall et al [14].

The main goal of the public health response plan was to minimise the impact of MDR NG on the prevention and control of gonorrhoea in Europe and the specific components included:

- strengthening surveillance to obtain AMR profiles in a timely manner and with sufficient epidemiological information to inform national interventions
- implementing treatment failure monitoring to inform national and international authorities and professional societies in order to develop treatment guidelines and design national interventions; and
- establishing a communication strategy to increase awareness and disseminate the results from AMR surveillance in order to inform authorities, professional societies, physicians and potential patients about the threat of MDR NG.

Evaluation of 2012 response plan

To enable monitoring of the effectiveness of the 2012 response plan, the Euro-GASP network was requested to complete indicators described in the plan. It was requested that 2012 be used as the baseline year and progress for each indicator was evaluated against the situation in 2017. Responses were received from 22 countries (Table A1, Annex 2). The majority of countries reported to have a national gonococcal antimicrobial surveillance programme (82%) and STI clinic network (86%) in place, along with a platform[ii] to share the AMR data (73%). More than 60% of countries have assessed the laboratory capacity in their country but few countries had national training modules available (27%). Clinical management was less encouraging, with 50% or fewer countries reporting that they have reviewed clinical management guidelines, have a platform for reporting treatment failures and have agreed treatment failure case definitions in place. However, many countries likely use the European guidelines and case definitions. Few countries had a communication plan (32%) and fact sheets (41%), but more than half of the countries published data on MDR NG (59%), although it was unclear whether this included all AMR data or just multidrug resistance.

Indicators specific to Euro-GASP were also assessed. In 2017, the number of countries participating in Euro-GASP (n=27) and the EQA (n=28) was substantially higher compared to 2012 (Table A2, Annex 2) and shows good coverage across the EU/EEA. There was also a large increase (41%) in the number of isolates submitted to Euro-GASP over the same time period. Despite this, there was a slight decrease in the proportion of isolates submitted to Euro-GASP out of the overall number of reported gonorrhoea cases at the EU/EEA level (4% in 2012; 3% in 2016), a consequence of the large overall increase in the number of gonorrhoea cases over the period. Even though most countries report and have good completeness of reporting for age, gender and site of infection variables, there has been limited or no improvement in the proportion of countries reporting and the level of completeness for sexual orientation, as well as for many other variables. This is a key area that needs further improvement so better analysis can take place. Timely publication of Euro-GASP results is still an issue: even though the Euro-GASP network publishes a good number of peer-reviewed publications and reports, the time to publication remains too long. Data are now available in the ECDC atlas of infectious diseases within six months of reporting and a new brief report layout has been designed to help accelerate this process. Although reporting of treatment failures was established via the ECDC Epidemic Intelligence Information System (EPIS)-STI following the 2012 response plan, there were only two treatment failures in line with the case definition, officially reported in EPIS-STI and one additional case which was investigated and found not to fit the case definition.

The evaluation of the 2012 response plan also highlighted that management of treatment failures is still a gap across Europe which an updated response plan needs to address. In addition, future indicators should have clearer definitions, be more measurable and include specific examples, as there were differences in how certain the indicators were interpreted by Member States.

[ii] The 2012 response plan proposed the establishment of national platforms involving professional societies and disciplines involved in the prevention and control of gonorrhoea at the national level to allow for expert discussion, situation analysis and facilitate public health action and decision-making.

2019 response plan

Objectives of 2019 response plan

The 2019 response plan strives to further support Member States to develop and implement national strategies and interventions to control the threat of MDR and XDR NG in a multidisciplinary approach. In the context of this plan, any reference to MDR and XDR NG follows the definition by Tapsall et al [14] with the modification that azithromycin has been moved to Category I ('Antibiotics currently generally recommended in the treatment of gonorrhoea') and spectinomycin to Category II ('Antibiotics now less frequently used or else proposed for more extensive use') [38] (Annex 3 for full definitions). The public health response to this threat should include the following components:

- strengthen surveillance of gonococcal antimicrobial susceptibility in the EU/EEA Member States to
  - obtain AMR profiles in timely manner; and
  - provide sufficient epidemiological information to inform national treatment guidelines and public health interventions.
- ensure that appropriate capacity for culture and susceptibility testing in EU/EEA Member States is available or further developed
- implement suitable treatment failure monitoring procedures to inform national and international authorities so that targeted intervention strategies can be implemented to prevent the spread of MDR and XDR NG
- effectively disseminate results from AMR surveillance in order to increase awareness and inform authorities, professional societies, clinicians and other health care workers and persons at risk about threat of MDR and XDR NG; and
- introduce strategies to reduce the burden of gonorrhoea, such as implementation of appropriate gonorrhoea management, prevention, control and AMR policies/guidelines, including enhanced focus on high-risk groups, as well as mandatory reporting of gonorrhoea [23,35].

1 Strengthening antimicrobial surveillance

1.1 Euro-GASP expansion

Surveillance for AMR in *N. gonorrhoeae* isolates is essential in all EU/EEA countries to better inform appropriate treatment guidelines. Given the interconnected sexual networks and spread of gonococcal strains across Europe, a Europe-wide approach is essential in order to detect and monitor AMR strains and thus inform European and national treatment guidelines. Appropriate treatment is crucial to ensure successful patient management and interrupt transmission. Without reliable *N. gonorrhoeae* AST data, it is difficult to ascertain whether the correct treatment options are available in a country; inappropriate treatment can lead to the emergence of AMR, increased patient morbidity, increased acquisition of HIV and an overall bigger cost burden to the healthcare system.

In certain countries, antimicrobial drugs still appear to be easily available without prescription and this is becoming an even greater problem in many countries due to supply from international online pharmacies. The use of suboptimal medication as a second-line treatment can be common in certain countries [39]. These factors increase the risk of emergence of MDR and XDR NG.

In 2017, 27 of 31 EU/EEA countries participated in Euro-GASP. The reasons for non-participation are primarily the lack of available cultures to refer to Euro-GASP due to the use of nucleic acid amplification tests (NAATs), the differences in diagnostic procedures in STI clinics including syndromic approaches, and the lack of resources for performing culture. Even though participation in Euro-GASP has improved, there remain gaps in parts of central and eastern Europe which need to be addressed. Expanding Euro-GASP to more countries, increasing the number of isolates available for testing in some countries and improving representativeness are all important to further control emergence and spread of MDR NG strains in Europe.

ECDC has successfully recruited nine additional countries as of 2017 since it started coordinating Euro-GASP in 2009 by focusing on capacity building through the involvement of public health STI experts, STI clinics and laboratories. Participation in the EQA programme is essential to gain valid and comparable AST data to reliably detect emerging AMR and optimise patient management [40]. Gonococcal AST interpretation has been harmonised by the widespread use of the breakpoints stated by the European Committee on Antimicrobial Susceptibility Testing and further capacity building will ensure that participating laboratories produce unbiased and comparable data.

Training

Ensuring an acceptable quality of the data in the sentinel surveillance system requires a high standard of laboratory performance. The capacity to perform cultures has decreased in a number of countries with the increasing use of NAATs, which also likely affects the representativeness of surveillance systems. The number of isolates submitted to Euro-GASP should be monitored closely and any reductions (for example related to increased use of NAATs) should be investigated and a plan developed to preserve the use of culture for *N. gonorrhoeae* AST in the relevant countries.

ECDC offers STI laboratory training modules for STI laboratory staff in EU/EEA Member States in order to enhance the capacity to perform culture and antimicrobial susceptibility surveillance services. The level of training required is established by performance in EQAs and surveys assessing capacity and training needs in laboratory methods, diagnostics, and molecular typing including whole-genome sequencing (WGS). Training on specimen collection and management of treatment failure should also be provided for healthcare providers at the national level. A recent survey identified the following top three training needs within the Euro-GASP: analysis of WGS data, WGS laboratory techniques and *N. gonorrhoeae* laboratory procedures for culture, identification and AST.

Data completeness, representativeness and timeliness

Appropriate targeting of control measures at national and international levels depends on high quality antimicrobial susceptibility surveillance data linked to the basic epidemiological data in order to determine the key populations at risk of emerging MDR or XDR NG.

Reporting of epidemiological variables, including anatomic specimen site, gender, age, sexual orientation, previous infections, concurrently diagnosed STI and country of infection, is exceedingly important to understand the spread of infection. The completeness of these data in Euro-GASP 2017 continues to be low and Member States need to improve their reporting of these variables. The main reasons for the low completeness of these data involve technical and sometimes legal issues to link *N. gonorrhoeae* isolates with epidemiological and clinical data of the gonorrhoea cases. Summary reports by country reporting on data completeness following each annual data collection will be implemented with the Euro-GASP report covering 2018 data and this will enable the relevant countries to target specific reporting variables that need improvement.

The representativeness of Euro-GASP results was assessed in 2018 and showed that the prevalence of AMR reported by Euro-GASP appropriately reflects the AMR situation in the EU/EEA [41]. Euro-GASP can therefore provide robust resistance estimates to inform the European gonorrhoea management guideline [23] and national gonorrhoea guidelines. The representativeness of the data will be assessed from time to time to ensure that the isolates submitted continue to be representative of the epidemiological trends in Euro-GASP-participating countries. Further work is ongoing to determine if the Euro-GASP sample size remains adequate to provide a robust estimate of resistance prevalence, particularly in countries with high and increasing numbers of gonorrhoea cases.

Timely reporting of AMR and epidemiological data is essential in order to quickly identify emerging trends. Laboratories and epidemiologists participating in Euro-GASP should upload their national AMR and epidemiological data within agreed deadlines. ECDC will provide support and training for uploading data to the European Surveillance System (TESSy).

Actions

- Maintain and expand the number of countries participating in Euro-GASP surveillance and the EQA programme
- Ensure Euro-GASP maintains and improves representativeness of collected isolates and the correct sample sizes in different countries are established
- Increase the number of isolates from participating countries currently with low isolate numbers on the basis of the sample size estimations
- Provide ECDC STI laboratory training modules to support Euro-GASP and national GASPs based on identified Member State needs; and
- Improve the completeness of epidemiological characteristics and timeliness of reporting.

Indicators

1.1 Number and proportion of EU/EEA countries participating in Euro-GASP
1.2 Number and proportion of isolates (relating to total number of gonorrhoea cases) reported through Euro-GASP
1.3 Number of countries with at least one laboratory participating in the EQA programme
1.4
1.4.1 Number of countries that have participated in the ECDC laboratory training modules
1.4.2 Number of professionals from these countries that have participated in the ECDC laboratory training modules
1.5 Proportion of countries reporting epidemiological characteristics in Euro-GASP at an agreed threshold, particularly for sexual orientation
1.6 Completeness of Euro-GASP data with respect to key epidemiological characteristics
1.7 Euro-GASP reporting protocol reviewed annually

1.2 National antimicrobial surveillance

Euro-GASP provides important data at the European level, but is dependent on national GASPs or on specimen collections specifically designed for Euro-GASP in participating countries. The increased use of NAAT as the principal diagnostic method has made it difficult for many countries to continue to obtain samples for culture and AST.

Countries may consider the use of different strategies for effective gonococcal AMR surveillance at the national level. The following strategic options should be considered when setting up a national AMR surveillance system:

- establish a national platform involving all STI services (clinicians, laboratories, surveillance institutes; and public health authorities) and professional societies involved in the prevention and control of gonorrhoea at the national level to facilitate communication and promote surveillance and response to MDR NG.
- assess capacity for culture and AST and identify the minimum level of capacity needed to perform culture and AST for surveillance purposes. Training and technical support is available from ECDC for supporting such assessments and establishing training programmes, which should then be distributed nationally. Note: surveillance of AST of cultured gonococcal isolates can also be performed through participation in centralised testing in Euro-GASP.
- develop national sentinel surveillance programmes to monitor antimicrobial susceptibility on a representative proportion of samples; and
- collect prescription data for gonorrhoea treatment to better interpret AMR data.

Options for action at national level

- Develop and implement a national sentinel gonococcal antimicrobial surveillance programme (GASP) in accordance with methodologies and quality assurance in Euro-GASP [42] or ensure participation in Euro-GASP; and
- Collect data on current gonorrhoea treatment at the national level.

Indicators at national level

1.8 Presence of a national (sentinel) GASP or participation in Euro-GASP
1.9 Number of countries offering national training modules (laboratory and/or clinical)
1.10 Proportion of all STI clinics (sentinel sites) that have access to routine culture and antimicrobial susceptibility testing
1.11 Proportion of all (reported) gonorrhoea cases with antimicrobial susceptibility results available
1.12 Proportion of patients who received recommended gonorrhoea treatment

2 Clinical management and treatment failure monitoring

Clinical management

Clinicians have a crucial role in preventing the spread of AMR through appropriate clinical management, partner notification services and reporting cases of treatment failure. Clinicians who identify patients with suspected treatment failure from recommended therapeutic regimens need to request culture and AST testing of relevant clinical specimens and promptly report the case to appropriate public health authorities. Public health authorities at national level can investigate further and report to ECDC through the online treatment failure reporting tool. Possible or confirmed treatment failure should be appropriately investigated and treated, including sexual contacts of the index patient. Recent travel should also be recorded so any associated travel risk can be assessed and international responses initiated [30]. In order to collect accurate and comparable data, case definitions for treatment failures are suggested (see below). Annex 1 includes a proposed reporting form with the variables that will be collected on possible and confirmed cases of treatment failure.

By its mandate, ECDC does not establish treatment recommendations for gonorrhoea. However, ECDC supports the European STI Guideline Editorial Board and the European gonorrhoea treatment guideline. The 2012 European guideline on the diagnosis and treatment of gonorrhoea recommends a single 500 mg intramuscular dose of ceftriaxone plus a single 2 g oral dose of azithromycin as empirical first-line dual antimicrobial therapy for all cases of urogenital and extra-genital gonorrhoea [23]. Additional treatment options are recommended in case of failure to respond to recommended regimens. In addition, the 2012 guideline recommends a test of cure for all gonorrhoea cases to identify persisting infection and emerging resistance. Patients with persisting symptoms after treatment should be evaluated by culture and gonococcal isolates from these patients are tested for antimicrobial susceptibility. The 2012 guideline is currently being updated.

Case definitions for antibiotic treatment failure

Suitable follow-up of cases of suspected treatment failure are of considerable importance. The review and verification of such an event and subsequent initiation of adequate public health responses requires close collaboration between clinicians, laboratory staff and public health authorities.

A combination of appropriate clinical observations and laboratory examinations is required to verify treatment failures to recommended treatment regimens.

The suggested case definitions for confirmed and possible treatment failure are provided in Table 1.

Table 1. Working case definitions for confirmed and possible[a] treatment failure: clinical and laboratory criteria

1	A gonorrhoea patient who returns for test of cure or who has persistent symptoms after having received treatment for laboratory-confirmed gonorrhoea with the recommended therapeutic regimen (ceftriaxone 500–1000 mg plus azithromycin 1–2 g) or alternative regimens (ceftriaxone 500–1000 mg monotherapy; cefixime 400 mg plus azithromycin 1–2 g; or spectinomycin 2 g plus azithromycin 1–2 g) AND
2	Remains positive for one of the following tests for *N. gonorrhoeae*: • isolation of *N. gonorrhoeae* by culture taken at least 72 hours after completion of treatment[a] OR • positive nucleic acid amplification test (NAAT) taken two to three weeks after completion of treatment[b] AND
3	Reinfection is excluded as far as feasible AND
4	Resistance to antimicrobials used for treatment[a,c]: • ceftriaxone: MIC>0.12 mg/L • cefixime: MIC>0.12 mg/L • spectinomycin: MIC>64 mg/L Non-wild type for azithromycin: MIC>1.0 mg/L (ECOFF)

[a]: In case of possible treatment failure, no gonococcal isolate is available pre- and/or post-treatment (only diagnosed using NAATs) or the cultured isolate does not show phenotypic resistance to the antimicrobials used for treatment (failures to treat particularly pharyngeal gonorrhoea have been recorded with isolates that are phenotypically susceptible to the antimicrobials used for treatment).
[b]: Culture-negative and NAAT-positive specimens two weeks after treatment can be due to persistent nucleic acid (DNA/RNA) and in these cases, a repeated NAAT one week later should be considered. Where no cultured isolate is available, molecular testing to determine N. gonorrhoeae *multi-antigen sequence typing and AMR determinants in NAAT sample(s) should be performed.*
[c]: In case of confirmed treatment failure, pre- and post-treatment cultured isolates should show resistance to administered antimicrobials and be examined by WGS to confirm an indistinguishable genome sequence and presence of AMR determinants for the antimicrobials used for treatment.

Mechanisms for reporting of treatment failures

Standardised clinical and epidemiological data of treatment failures need to be collected and reported in real-time at the national level. Although Euro-GASP provides an overview of AMR gonococci in the EU/EEA, there is a need for developing comparable reporting mechanisms at national and international levels for treatment failures, with the possibility to distinguish between possible and confirmed cases.

The reporting of treatment failures within the European STI expert network will contribute to a better understanding of the spread of MDR and XDR NG across Europe and will facilitate the European response, particularly at a time of pressure on public health services. Furthermore, it will provide more accurate data to validate clinical breakpoints.

Cases of possible and confirmed treatment failure (in accordance with the case definitions as outlined above) should be reported through EPIS[iii] that will allow the secure exchange of information and data between members of the European STI expert network. A template for reporting is included in Annex 1. A member of the Euro-GASP team will follow up and gather more information to assess whether the treatment failure is possible, confirmed or whether it is a reinfection or delayed clearance of gonococcal DNA/RNA. If treatment failure is confirmed, then further laboratory support, such as WGS, as well as response support, such as advice on contact tracing, enhanced testing, communication and advice to travellers (if applicable), can be made available through ECDC. ECDC will provide support to countries that do not have the capacity to appropriately investigate treatment failures.

[iii] Alongside other ECDC platforms, EPIS is currently undergoing re-engineering aimed at improving technical functionalities. A name change is also possible.

Steps for reporting treatment failure or XDR or ceftriaxone-resistant *N. gonorrhoeae* isolate

Once treatment failure due to an MDR/XDR NG isolate is confirmed or an XDR or ceftriaxone-resistant isolate has been detected through other means such as surveillance or primary diagnostics, it is important that details are reported in real time through appropriate channels. Each country may have a different reporting structure, however the response can be based on the following suggestions:

- Ensure that detailed epidemiological data, including patient and recent sexual partner travel history, are collected for each confirmed case.
- If there are multiple cases or isolate has exceptional AMR profile, consider convening local incident team to investigate clinical management, epidemiology and microbiology.
- Consider performing rapid risk assessment[iv] to ensure risk of spread is assessed and mitigated.
- Alert local and national networks of laboratories and clinicians and remind them to follow correct guidance for *N. gonorrhoeae* testing, diagnostics and management.
- Inform/notify health department and any other appropriate bodies at national level.
- Ensure media department is informed in case of any media interest and prepare approved media responses (reactive lines) and background, including Q&As.
- In case infection was acquired abroad, notify country involved through Early Warning and Response System (EWRS) if in EU/EEA or WHO International Health Regulations (IHR) mechanism if outside EU/EEA.
- Report cases at EU/EEA level through EPIS and/or EWRS if criteria for reporting in EWRS are met and WHO IHR mechanism if relevant.
- Consider rapid publication of case details (e.g. submission of rapid communication to Eurosurveillance) for further dissemination to international community. Ensure all patient-identifiable information is removed from publically available documents and obtain consent for publication from patient(s) if possible.
- If applicable, provide additional advice to travellers and consider other public health interventions, such as social media awareness campaign.

Options for action

- Ensure national agreement and adoption of the case definitions on gonorrhoea treatment failure.
- Collect data regarding verified gonorrhoea treatment failures in order to inform the European guideline on the diagnosis and treatment of gonorrhoea and mitigate the spread of the strain.
- Online reporting template for treatment failures developed.

Indicators

2.1 ECDC represented in the European STI Guideline Editorial Board.
2.2 European access to an online reporting template for treatment failures supported by ECDC.
2.3 Number of reported verified gonorrhoea treatment failures to ECDC.

[iv] An e-learning course on production of rapid risk assessments is available from ECDC: http://ecdc.europa.eu/news-events/rapid-risk-assessment-e-learning-course

3 Monitoring effectiveness of response plan

Monitoring the effectiveness of the response plan should be done at national and European levels. To monitor the response at the national level, the table below and national-level indicators included in the previous sections can be used or adapted to local and national needs.

Table 2. Indicators for monitoring at national and EU/EEA levels

Component	Indicator	Indicator achieved/progress
Strengthen antimicrobial surveillance – EU level	1.1 Number and proportion of EU/EEA countries participating in Euro-GASP	
	1.2 Number of isolates reported through Euro-GASP	
	1.3 Number of laboratories participating in Euro-GASP EQA	
	1.4 Number of countries & professionals from these countries participating in the laboratory training	
	1.5 Proportion of countries reporting epidemiological characteristics in Euro-GASP	
	1.6 Completeness of Euro-GASP data for key epidemiological characteristics	
Strengthen antimicrobial surveillance – national level	1.8 Presence of a national representative isolate collection	
	1.9 Number of countries offering national training modules (laboratory and/or clinical)	
	1.10 Proportion of all STI clinics (sentinel sites) that have access to culture and antimicrobial susceptibility testing.	
	1.11 Proportion of all (reported) gonorrhoea cases tested with culture and with antimicrobial susceptibility results available.	
	1.12 Proportion of patients who received recommended gonorrhoea treatment	
Clinical management and treatment failure monitoring	2.1 ECDC contributes to public health aspects of revision of the gonorrhoea patient management guidelines	
	2.2 Online reporting template for probable and confirmed treatment failures developed	
	2.3 Number of reported verified gonorrhoea treatment failures to ECDC	
Control strategy and communications	3.1 Adoption of national plan to control MDR/XDR gonorrhoea or inclusion in gonorrhoea, STI, sexual health or other relevant strategy	
	3.2 Number of visits to ECDC Response Plan website	
	3.3 Number of peer-reviewed publications or other communications on antimicrobial resistant NG from Euro-GASP	

EU/EEA-level indicators that can be monitored through routinely collected data will be assessed by ECDC on an annual basis, while data for other indicators will be collected through specific surveys on a biennial basis.

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Annex 1. Template for report of treatment failure

Alert concerning *Neisseria gonorrhoeae* treatment failure

Reporting form

Please read the following instructions:
This form should be completed when a case of possible or confirmed *N. gonorrhoeae* treatment failure (see detailed case definitions in the ECDC Response Plan) is identified at national level. It is important that the form is submitted in a timely manner, so kindly report even if some data are not yet available. The form can be updated when additional confirmation or epidemiological information becomes available. • Please complete one report form for each treatment failure detected. • Please attach this report form by a notification in EPIS-STI within two weeks of being informed of the treatment failure.

1. General information

Reporter details		
Name		
Country reporting		
Name of reporting centre		
Telephone:		Email:

Treatment failure classification

☐ Confirmed treatment failure (cultured isolates show resistance to administered antimicrobials)
☐ Possible treatment failure

Case definition for treatment failure:

A gonorrhoea patient who returns for test of cure or who has persistent symptoms after having received treatment for laboratory-confirmed gonorrhoea with the recommended regimen (ceftriaxone 500 mg plus azithromycin 1-2 g) or alternative regimens (ceftriaxone 500-1000 mg monotherapy; cefixime 400 mg plus azithromycin 1-2 g; or spectinomycin 2 g plus azithromycin 1-2 g)
AND
remains positive for one of the following tests for *N. gonorrhoeae*:

- isolation of *N. gonorrhoeae* by culture taken at least 72 hours after completion of treatment;

OR

- positive nucleic acid amplification test (NAAT) taken two to three weeks after completion of treatment

AND
reinfection has been excluded, as far as feasible.

AND*
Resistance to antimicrobials used for treatment:

- ceftriaxone: MIC>0.12 mg/L
- cefixime: MIC>0.12 mg/L

Non wild-type for azithromycin: MIC>1. mg/L (ECOFF)

** In a case of confirmed treatment failure, the pre- and post-treatment cultured isolates should show resistance to administered antimicrobials and be examined by whole genome sequencing to confirm an indistinguishable genome sequence and presence of AMR determinants for the antimicrobials used for treatment.*

Case details	
Date of first notification of the treatment failure to the reporting centre:	
Age	
Gender	
Sexual orientation	
Is the case likely to have acquired the infection in the country of diagnosis/reporting?	
If no, in which country?	

Diagnostics and treatment – first visit	
Was the case symptomatic?	
Site of infection	
Date of first visit	
Which tests at which anatomic sites were used for diagnosis (include results)?	
If culture was performed, please list available MICs for:	Ceftriaxone: Cefixime: Azithromycin: Gentamicin: Ciprofloxacin: Spectinomycin: Other antibiotics tested:
What was the treatment prescribed on initial diagnosis (drug, route of administration, dosage)?	

Diagnostics and treatment – second visit	
Date of return to clinic	
Which tests at which anatomic sites were used for diagnosis (include results)?	
If culture was performed, please list available MICs for:	Ceftriaxone: Cefixime: Azithromycin: Gentamicin: Ciprofloxacin: Spectinomycin: Other antibiotics tested:
What treatment was prescribed following the second visit (drug, route of administration, dosage)?	
Was a test of cure performed after re-treatment?	
If yes, which test was used and what was the result?	
Is any support required from the STI network for further laboratory investigations?	

Please provide a short description of the circumstances of the event and on public health measures taken including on partner management:

Annex 2. Indicator tables

Table A1. Indicator responses from 22* Euro-GASP participating countries, as of 2017

Component	Indicator	Number of countries where indicator met	%
Strengthen surveillance	National Gonococcal Antimicrobial Surveillance Programme in place	18	81.8
	STI clinic network established (sentinel or other)	19	86.4
	National platform for sharing of information/data on gonorrhoea resistance established	16	72.7
	Assessment of laboratory capacity performed	14	63.6
	National training modules (laboratory and/or clinical) available	6	27.3
Clinical management	Case definitions for gonorrhoea treatment failure agreed and implemented	10	45.5
	National treatment failure reporting/monitoring implemented	9	40.9
	Gonorrhoea clinical management guidelines reviewed and revised	11	50.0
	Recommended culture and AMR testing for cases of suspected treatment failure	17	77.3
Communication strategy	National communication plan agreed	7	31.8
	Fact sheet adjusted and disseminated	9	40.9
	National publications or communications on MDR *Neisseria gonorrhoeae*	13	59.1

** Responses received from Austria, Belgium, Croatia, Cyprus, Denmark, Estonia, Finland, Germany, Hungary, Iceland, Latvia, Liechtenstein, Luxembourg, Malta, The Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia, Sweden and the United Kingdom.*

Table A2. Euro-GASP indicators, 2012 vs. 2017

Component	Indicator	Indicators 2012 [43]	Indicators 2017 [44]	Indicator achieved/progress
Strengthen surveillance	Number of countries participating in Euro-GASP	20/30	27/31	Increased by 7 countries
	Number of isolates reported through Euro-GASP	1 927 (4% of reported gonorrhoea cases)	3 248 (3% of reported gonorrhoea cases)	Increased by 41% (1 321 isolates)
	Number of laboratories participating in Euro-GASP EQA	15	28	Increased by 13 laboratories
	Number of countries participated in the laboratory training	N/A (13 in 2014)	14	Increased by one country
	Proportion of countries reporting epidemiological characteristics (mode of transmission) in Euro-GASP	16/20 (80%; based on transmission data)	17/27 (63%) based on transmission	Increased by one country (based on transmission data)
	Completeness of Euro-GASP data for key epidemiological characteristics*	85.9% completeness on average; 51.2% for mode of transmission	87.7% completeness on average; 61.6% for mode of transmission	Increased by 1.8% for key variables and 10.4% increase for mode of transmission
	Time between Euro-GASP data collection and publication of interim and annual report	12 months	2017 not yet published, but 2016 – 12 months	Remained constant
Clinical management	Number of cases of treatment failure reported in EPIS-STI (using the template)		Only two cases reported in EPIS-STI since publication of 2012 response plan	True number of treatment failures unknown, but number is an underestimate based on treatment failures reported in literature.
Communication strategy	Number of publications or communications on MDR NG			9 peer-reviewed Euro-GASP publications, four in progress. Reports: molecular typing report, annual EQAs and Euro-GASP reports, laboratory capacity survey, training surveys, response plan.

** Percentage completeness average taken across all countries for age, gender, mode of transmission and site of infection.*

Annex 3. Definitions of MDR and XDR *Neisseria gonorrhoeae* (adapted from [14,38])

Antibiotics used for gonorrhoea treatment are grouped in three categories (Table A3):

- Category I: antibiotics in current and wide use to treat gonorrhoea
- Category II: antibiotics less frequently used or little used but proposed for more extensive use; and
- Category III: antibiotics that are now superseded or else regarded as inappropriate.

MDR NG are defined as those resistant to one of the antibiotic classes listed in category I, plus two or more in category II. XDR NG are defined as those resistant to two or more of the antibiotic classes in category I and three or more in category II.

Table A3. Classification of antibiotics in current use, proposed for use or else discontinued for use in treatment of gonorrhoea

Category I. Antibiotics currently generally recommended for treatment of gonorrhoea • Extended-spectrum cephalosporins (ESCs) – Injectable ESCs: ceftriaxone and others less frequently used, such as cefodizime, cefotaxime and ceftizoxime – Oral ESCs: cefixime and others less frequently used, such as ceftibuten, cefpodoxime proxetil, cefdinir and cefditoren • Azithromycin
Category II. Antibiotics now less frequently used or else proposed for more extensive use • Penicillins • Fluoroquinolones (ciprofloxacin is the most widely used example) • Aminoglycosides (kanamycin was more widely used and gentamicin is proposed) • Carbapenems • Spectinomycin (not available in many countries)
Category III. Other antibiotics, now superseded or else regarded as inappropriate • Chloramphenicol and thiamphenicol • Tetracyclines • Rifampicin • Co-trimoxazole • Erythromycin

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