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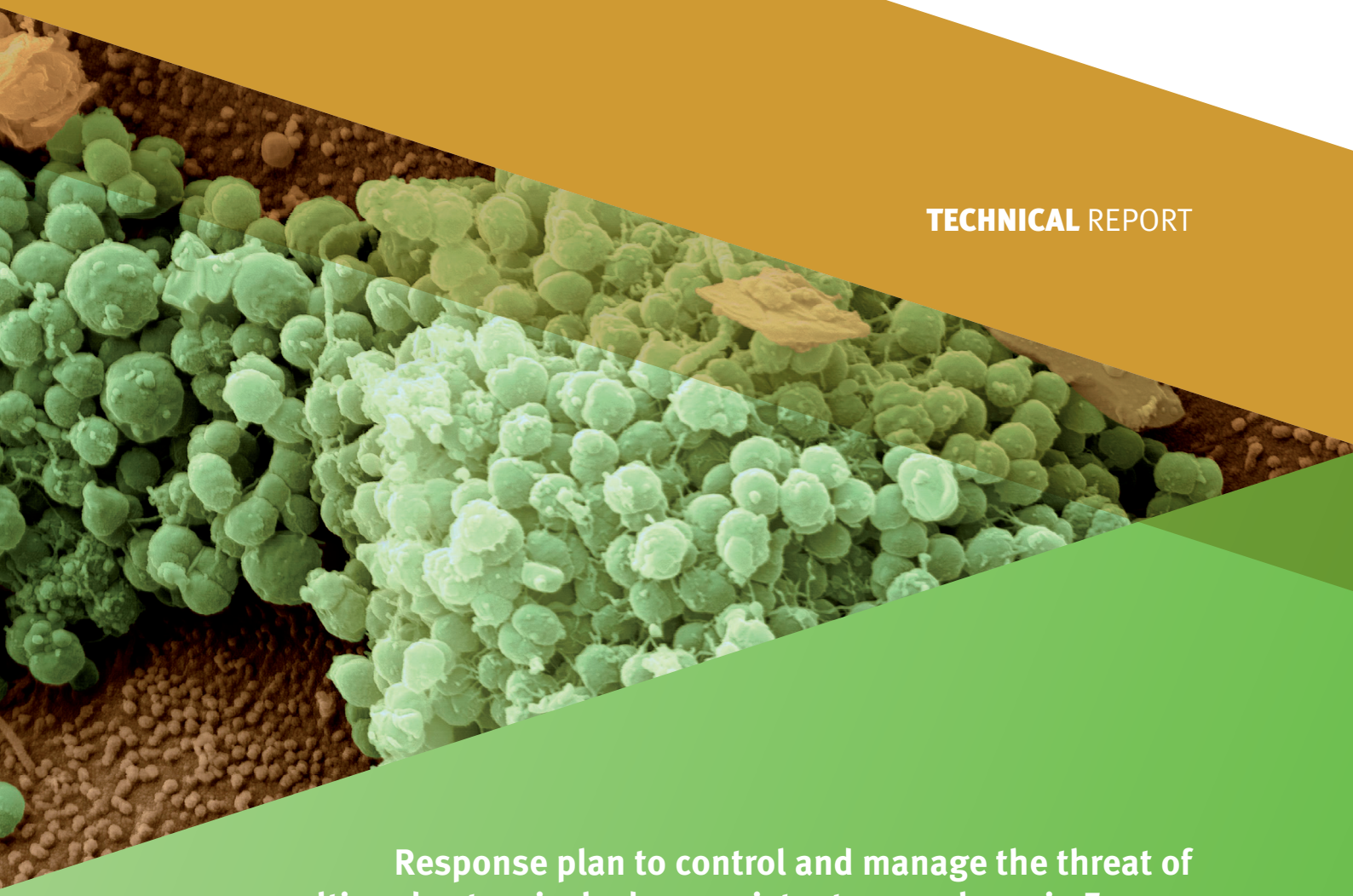

TECHNICAL REPORT

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

Indicator monitoring 2019

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Response plan to control and manage the threat of multi- and extensively drug-resistant gonorrhoea in Europe – Indicator monitoring 2019

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Abbreviations

AMR	Antimicrobial resistance
AST	Antimicrobial susceptibility testing
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EPIS	Epidemic Intelligence Information System
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*

1. Background

Gonorrhoea remains a serious public health problem and is one of the most common sexually transmitted infections (STIs) in European countries [1]. Successful treatment of *Neisseria gonorrhoeae* infections reduces the risk of complications – such as pelvic inflammatory disease, first-trimester miscarriage, ectopic pregnancy and infertility [2] – and reduces the risk of HIV acquisition and transmission [3].

Over time, *N. gonorrhoeae* has developed antimicrobial resistance (AMR) to sulphonamides, penicillins, tetracyclines, macrolides, fluoroquinolones and, more recently, third-generation cephalosporins [4]. Third-generation cephalosporin treatment failures were first reported in Japan in 2000 [5], followed by further cases reported from Asia [6]. The first cases of treatment failure in the European Union/European Economic Area (EU/EEA) were reported from Norway in 2010 [7]. Subsequently, such treatment failures have been reported in the United Kingdom (UK) [8,9], Austria [10], France [11], Canada [12,13] and South Africa [14]. Initial treatment failures were to less potent third-generation cephalosporins, such as cefixime, but in 2009 the first extensively drug-resistant (as defined in [15], see Annex 1), highly ceftriaxone-resistant *N. gonorrhoeae* strain (H041) was identified in Japan [16]. Further ceftriaxone treatment failures of pharyngeal gonorrhoea were reported in Japan [16] before the first cases were identified in EU/EAA countries, including Sweden [16,17] and Slovenia [18], as well as in Australia [19,20]. The first case of genital infection with highly ceftriaxone-resistant *N. gonorrhoeae* in Europe was reported in France in 2011 [11] and two high-level ceftriaxone-resistant isolates of the same strain were also reported from Spain in 2012 [21], all of which belonged to sequence type (ST) 1407.

As ceftriaxone is the last remaining option for empirical first-line monotherapy, these treatment failures triggered worldwide concern and led to the development of the 'Response plan to control and manage the threat of multidrug-resistant gonorrhoea in Europe' in 2012 [22] by ECDC together with an international expert group. Also in 2012, 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 were also updated to recommend similar dual antimicrobial therapies with slightly different dosages [24-26].

In 2016, the first treatment failure globally to dual antimicrobial therapy (500 mg of ceftriaxone plus 1 g of azithromycin) was reported in the UK [27]. This was followed, in 2018, by the first extensively drug-resistant *N. gonorrhoeae* (XDR NG) strain with ceftriaxone resistance combined with high-level resistance to azithromycin being reported from the UK [28]. This XDR NG strain caused a treatment failure of pharyngeal gonorrhoea with a single 1 g intramuscular dose of ceftriaxone plus 100 mg of doxycycline orally, twice daily for seven days, followed by a single 2 g intramuscular dose of spectinomycin. The pharyngeal infection was finally cured with 1 g ertapenem intravenously, daily for three days. Two gonococcal isolates belonging to the same XDR NG strain were identified in Australia several months later [29], with both the Australian and the UK infections linked to infections in Southeast Asia. In response, a rapid risk assessment on XDR NG in the UK and Australia was published by ECDC on 7 May 2018 [30]. The rapid risk assessment identified the following needs: to strengthen gonococcal AMR surveillance in the Western Pacific region of Asia, to enhance collaboration between the gonococcal AMR surveillance programmes in different regions globally and to collect travel history data of gonorrhoea patients in the EU/EAA.

The ECDC response plan [22] published in 2012 complemented the World Health Organization(WHO) Global Action Plan [31], as well as national action plans subsequently published by the US Centers for Disease Control and Prevention [32] and Public Health England [33]. In 2019, the first update to the ECDC response plan was published [34]. It reviewed the effectiveness of the 2012 response plan, updated the indicators with data from 2017 and evaluated the achievements and progress made during the intervening years. In September 2020, EU/EEA countries were invited to provide information on the indicators for 2019, using 2017 as a baseline. Twenty-six of 31 EU/EEA countries provided data in response to this request. The present report seeks to once again review the progress made over the preceding two years, using the data collected for 2019.

2. Monitoring the implementation of the response plan – 2019

2.1 Strengthening antimicrobial surveillance

Euro-GASP expansion

Europe-wide surveillance for AMR in *N. gonorrhoeae* isolates is essential given the interconnected sexual networks and spread of gonococcal strains across Europe. Appropriate treatment is crucial to ensure successful patient management and to interrupt transmission. The use of suboptimal medication increases the risk of emergence of multidrug-resistant *N. gonorrhoeae* (MDR NG) and XDR NG (as defined in [15]; see Annex 1). Therefore, detection and monitoring of AMR strains is essential for informing both European and national treatment guidelines. The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) provides EU/EEA Member States with access to quality-assured antimicrobial susceptibility testing (AST), regular external quality assessment, expert advice (including country visits) and laboratory training.

In 2019, 26 of 31 EU/EEA countries participated in Euro-GASP (Table A2, Annex 2). Although participation has increased since the initial response plan was published in 2012, one fewer laboratory reported data in 2019 compared to 2017 due to a lack of available cultures to refer to Euro-GASP. This was due to increased use of nucleic acid amplification tests (NAATs). Although 84% of EU/EEA countries are currently represented in the programme, there remain gaps in parts of central and eastern Europe.

The number of isolates reported through Euro-GASP in 2019 remained at approximately 3% of annually reported cases, with an overall increase of 28.3% (918 isolates) since 2017. The large increase in isolate numbers was mainly due to a high number of isolates submitted from just two countries, so representativeness may be an issue for this dataset.

Since 2017, ECDC has successfully recruited nine additional laboratories from EU candidate countries to participate in the external quality assessment (EQA) programme. The EQA is essential to gain valid and comparable AST data to reliably detect emerging AMR and optimise patient management [35]. Gonococcal AST interpretation has been harmonised by the widespread use of the breakpoints stated by the European Committee on Antimicrobial Susceptibility Testing [36] and further capacity building will ensure that participating laboratories produce unbiased and comparable data.

Training

Training is important to ensure high-quality data in the sentinel surveillance system. For this reason, ECDC offers STI laboratory training modules for STI laboratory staff in EU/EEA Member States. A 2018 survey identified the following top three training needs among countries participating in Euro-GASP: analysis of whole genome sequencing (WGS) data, WGS laboratory techniques and *N. gonorrhoeae* laboratory procedures for culture, identification and AST. In response to these needs, a training course on *N. gonorrhoeae* laboratory procedures for culture, identification and AST was scheduled to take place in March 2020 for 12 participants from 12 different countries. Unfortunately, due to the COVID-19 pandemic, the training course has been postponed indefinitely. Two of the 26 countries participating in Euro-GASP had national training modules available in 2019 (Table A2, Annex 2).

2.2 Data completeness and timeliness

Reporting of epidemiological variables is exceedingly important to understand the spread of infection, to identify key populations at risk of emerging MDR NG or XDR NG, and to ensure appropriate targeting of control measures at national and international levels.

Compared to 2017, the completeness of epidemiological data in Euro-GASP decreased by 4.5% for key variables and by 13.4% for mode of transmission in 2019 (Table A3, Annex 2). A possible reason for these decreases could be the COVID-19 pandemic, which may have taken priority over surveillance work and may have impacted epidemiologists' capacity to source data for the Euro-GASP isolates. There is still one country that has 100% completeness for key variables and a further nine with over 90% completeness.

Since 2018, a summary of epidemiological data completeness has been included in the annual Euro-GASP report, enabling countries to visualise the specific reporting variables that need improvement. Barriers to improvements include technical and sometimes legal issues to linking *N. gonorrhoeae* isolates with epidemiological and clinical data of the gonorrhoea cases.

Timely data reporting is necessary to quickly identify emerging trends. However, Euro-GASP data collection faced unprecedented external circumstances in 2019 due to the COVID-19 pandemic, which had considerable impact on the timeliness of AMR and epidemiological data reporting.

2.3 National antimicrobial surveillance

The success of Euro-GASP is reliant upon national gonococcal antimicrobial surveillance programmes or on specimen collections specifically designed for Euro-GASP in participating countries to provide data to inform at the EU/EEA level. The increased use of NAAT as a principal diagnostic method has made it difficult for many countries to continue to obtain samples for culture and AST, and this has led to one country no longer being able to participate. Only 22 of the 26 country respondents reported access to culture and AST at their STI clinics and the proportion of clinics with access within a country varied from 71% to 100%. Of the 20 countries that could estimate the proportion of all gonorrhoea cases that had culture and AST data available, the proportion ranged from 5% to 100% (Table A2, Annex 2).

3. Clinical management and treatment failure monitoring

3.1 Clinical management

Reporting cases of suspected treatment failure and ensuring that these cases are followed up with culture and AST is crucial for preventing the spread of AMR. Clinicians play a vital role in this through appropriate clinical management, partner notification services and prompt reporting of treatment failure cases to the appropriate public health authorities. National public health authorities should further investigate these cases, record their recent travel histories and ensure that sexual contacts of the index patient are tested and that the online treatment failure reporting tool is used to report the case to ECDC. Working case definitions for confirmed and possible treatment failures (clinical and laboratory criteria) are suggested in Table 1. A proposed reporting form with the variables that should be collected on possible and confirmed cases of treatment failure is given in Annex 3.

ECDC supports the European STI Guideline Editorial Board and the European gonorrhoea treatment guidelines. The 2012 European gonorrhoea treatment guidelines recommended 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]. At the time of reporting, five of the 26 country respondents had no official national guidelines and followed the WHO or the 2012 European gonorrhoea treatment guidelines instead (Table A2, Annex 2). Seven countries' national guidelines differed from the 2012 European guidelines with regard to first-line therapy: instead of recommending the aforementioned dual therapy, they suggested ceftriaxone monotherapy, which is more in line with the European gonorrhoea treatment guidelines that were published in 2020 [36]. Availability of data on treatment used for gonorrhoea patients varies widely, not only between countries but also between types of clinics within countries. Treatment data from private clinics is especially lacking.

Table 1. Working case definitions for confirmed and possible* 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 500–1 000 mg plus azithromycin 1–2 g) or alternative regimens (ceftriaxone 500–1 000 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* OR • positive nucleic acid amplification test (NAAT) taken two to three weeks after completion of treatment[ł] AND
3	Reinfection is excluded as far as feasible AND
4	Resistance to antimicrobials used for treatment*,+: • 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)

** In a 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 pharyngeal gonorrhoea in particular have been recorded with isolates that are phenotypically susceptible to the antimicrobials used for treatment).*
[ł] 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.*
+ In a 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.

3.2 Mechanisms for reporting treatment failures

Only 19% (5/26) of country respondents had an online form for reporting possible and confirmed treatment failures, although paper forms were used in two additional countries (Table A2, Annex 2). A template for reporting possible treatment failures is given in Annex 3. Cases of treatment failure (as defined in Table 1) should be reported through the European surveillance portal for infectious diseases (EpiPulse), which allows for the secure

exchange of information and data between members of the European STI expert network. The case can then be further investigated to confirm treatment failure or whether it is a reinfection or a delayed clearance of gonococcal DNA/RNA. ECDC provides support to countries that do not have the capacity to appropriately investigate treatment failures and offers advice on contact tracing, enhanced testing (such as WGS), designing communication strategies and advising travellers (if applicable). In 2019, no suspected or confirmed treatment failures were reported to ECDC by the 26 respondent countries, although eight countries responded that this data was unknown. However, during this period nine ceftriaxone-resistant strains were detected in the UK: three in England and six unconfirmed (i.e. no confirmatory testing was done at the UK reference laboratory and no treatment outcome or epidemiological data were available) strains in Northern Ireland.

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Annex 1. Definitions of MDR and XDR *Neisseria gonorrhoeae*

Antibiotics used for gonorrhoea treatment are grouped into three categories (Table A1, adapted from [15,37]). 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 listed in Category I and three or more in Category II.

Table A1. Classification of antibiotics in current use, proposed for use or discontinued for use in the 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 proposed for more extensive use • Penicillins • Fluoroquinolones (ciprofloxacin is the most widely used example) • Aminoglycosides (gentamicin has been proposed) • Carbapenems • Spectinomycin (not available in many countries)
Category III. Other antibiotics, now superseded or regarded as inappropriate • Chloramphenicol and thiamphenicol • Tetracyclines • Rifampicin • Co-trimoxazole • Erythromycin

Annex 2. Indicator tables

Table A2. Indicator responses from 26* Euro-GASP participating countries, as of 2019

Component	Indicator	Indicator achieved
Strengthen antimicrobial surveillance – national level	1.8 Presence of a national representative isolate collection	21 countries (80.8%)
	1.9 Number of countries offering national training modules (laboratory and/or clinical)	2 countries (7.7%)
	1.10 Proportion of all STI clinics (sentinel sites) that have access to culture and antimicrobial susceptibility testing	Range: 71–100%; average: 97.3%[ǂ] (4 countries reported variable unknown or NA)
	1.11 Proportion of all (reported) gonorrhoea cases tested with culture and with antimicrobial susceptibility results available	Range: 5–100%; average: 38.5%[ǂ] (6 countries reported variable unknown or NA)
	1.12 Proportion of patients who received recommended gonorrhoea treatment[+]	Range: 35–100%; average: 93.2%[ǂ] (14 countries reported variable unknown or NA)
Clinical management and treatment failure monitoring	2.1 ECDC contributes to public health aspects of revision of the gonorrhoea patient management guidelines	5 countries (19.2%)
	2.2 Online reporting template for possible and confirmed treatment failures developed	5 countries (19.2%)
	2.3 Number of reported verified gonorrhoea treatment failures to ECDC	0 countries (0.0%)
Control strategy and communications	3.1. Adoption of a national plan to control MDR/XDR NG or inclusion of MDR/XDR NG in gonorrhoea, STI, sexual health or other relevant strategy	6 countries (23.1%)
	3.3 Number of peer-reviewed publications or other communications on antimicrobial-resistant NG from Euro-GASP	two reports, 47 peer-reviewed publications, one book chapter (from 46.2% of countries)[#]

** Responses received from Belgium, Croatia, Cyprus, Czechia, Denmark, Estonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.*

[ǂ] Average percentage based on positive responses received (excluding the responses 'unknown' and 'NA').

[+] Recommended gonorrhoea treatment: 19 countries report recommending ceftriaxone plus azithromycin and seven countries ceftriaxone only. Fourteen countries follow European guidelines.

[#] Twelve out of 26 country respondents had at least one publication in 2019.

Table A3. Euro-GASP indicators (2012, 2017–2019) and developments (2017 vs 2019), EU/EEA level

Component	Indicator	2012	2017	2018	2019	Progress 2017 vs 2019
Strengthen surveillance	1.1 Number and proportion of EU/EEA countries participating in Euro-GASP	20/30 (66.7%)	27/31 (87.1%)	27/31 (87.1%)	26/31 (83.9%)	Decreased by one country
	1.2 Number of isolates reported through Euro-GASP	1 927 (4% of reported gonorrhoea cases)	3 248 (3% of reported gonorrhoea cases)	3 299 (3% of reported gonorrhoea cases)	4 166 (total reported gonorrhoea cases currently unavailable)	Increased by 28.3% (918 isolates)
	1.3 Number of laboratories participating in Euro-GASP EQA	15	28	34	37	Increased by nine laboratories
	1.4.1 Number of countries that have participated in the ECDC laboratory training modules	NA*	14	NA	NA‡	30 countries participated in a 2018 survey on training needs
	1.5 Proportion of countries reporting epidemiological characteristics in Euro-GASP (based on mode of transmission)	16/20 (80.0%)	17/27 (63.0%)	20/27 (74.0%)	22/26 (84.6%)	Increased by three countries
	1.6 Completeness# of Euro-GASP data for key epidemiological characteristics	85.9% (51.2% for mode of transmission)	87.7% (61.6% for mode of transmission)	88.5% (63.1% for mode of transmission)	83.2% (48.2% for mode of transmission)	Decreased by 4.5% (13.4% for mode of transmission)
	Supplemental indicator: Time between Euro-GASP data collection and publication of (interim) annual report	12 months	8 months	9 months	Not yet published	Time from final data collection to publications has remained below 12 months
Clinical management	2.3 Number of reported verified gonorrhoea treatment failures to ECDC (as available in EPIS-STI)	NA	Only two cases reported in EPIS-STI since publication of 2012 response plan	One in the UK	None	Treatment failures are reported to ECDC; numbers remain low
Communication strategy	3.2 Number of visits to ECDC Response Plan website	NA	NA	NA	NA	293 in 2019 (7 October†–31 December 2019) and 262 in 2020
	3.3 Number of peer-reviewed publications or communications on antimicrobial resistant NG from Euro-GASP (total over all years, publications written by Euro-GASP hub/ECDC)	NA	NA	NA	NA	12 peer-reviewed publications (not all about MDR NG) and three in progress. Other communications: molecular typing report, annual EQAs and Euro-GASP reports, laboratory capacity survey, training survey, response plan [38].

** Thirteen in 2014.*
‡ Twelve were planned for 2020, but have been postponed indefinitely due to the COVID-19 pandemic.
 # Percentage completeness average was taken across all countries for age, gender, mode of transmission and site of infection.
† Date of publication of the updated response plan.

Annex 3. 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 the 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 to a notification in EpiPulse 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 500-1000 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
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
- spectinomycin: MIC>64 mg/L

Non wild-type for azithromycin: MIC>1.0 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	
Sex	
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:

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