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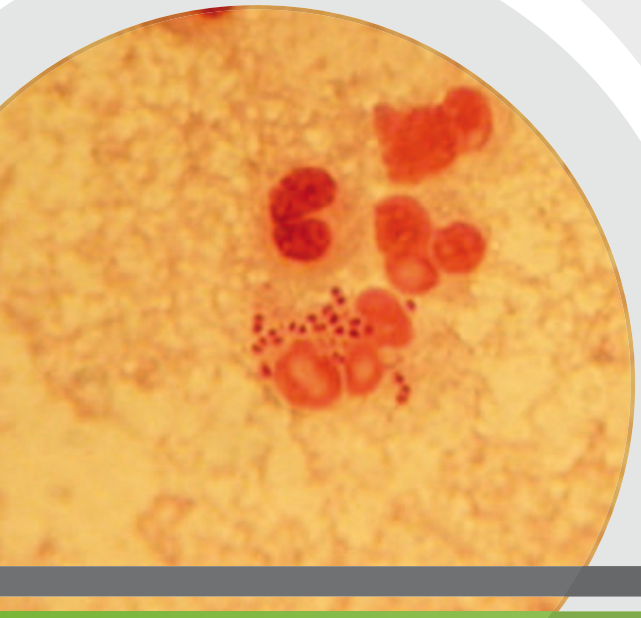

SPECIAL REPORT

Response plan to control and manage the threat of multidrug-resistant gonorrhoea in Europe

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This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated and produced by Gianfranco Spiteri and Marita van de Laar, Programme for STIs, including HIV/AIDS and blood-borne infections.

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Contents

Abbreviations

AMR	Antimicrobial resistance
EEA	European Economic Area
EPIS	Epidemic Intelligence Information System
EQAS	External quality assurance scheme
EU	European Union
Euro-GASP	European Gonococcal Antimicrobial Surveillance Programme
HIV	Human immunodeficiency virus
HPA	Health Protection Agency, UK
IUSTI	International Union against Sexually Transmitted Infections
MDR NG	Multidrug-resistant *Neisseria gonorrhoeae*
MSM	Men who have sex with men
NAAT	Nucleic acid amplification test
STI	Sexually transmitted infections
SW	Sex workers
TESSy	The European Surveillance System
UK	United Kingdom

Background

Resistance in gonorrhoea

With 32 028 cases, gonorrhoea was the second most commonly reported bacterial STI in Europe in 2010 [1]. Gonorrhoea is a serious public health problem as untreated infections may lead to severe secondary sequelae, including pelvic inflammatory disease, first trimester abortions, ectopic pregnancy, and infertility [2]. *N. gonorrhoeae* infections also play a role in facilitating HIV transmission [3]. The average cost per case of gonorrhoea has been estimated to be 266 USD for women and 53 USD for men [4]. Successful treatment of cases reduces the risk of complications, but also serves as the main public health strategy for reducing transmission.

Over the past decades, *N. gonorrhoeae* has developed resistance to several antimicrobial drugs such as sulphonamides, penicillin, tetracyclines and quinolones. Current treatment guidelines in most European countries recommend the use of single-dose injectable (ceftriaxone) or oral (cefixime) third-generation cephalosporins [5]. The first treatment failures connected to less potent third-generation cephalosporins were reported in Japan in 2000 [6]. Subsequently, further cases of treatment failure were reported from other countries [7]. A recent report described the first two treatment failures with cefixime in the EU/EEA (2010 in Norway [8]), followed by three cases of treatment failure in England [9, 10] and one case in Austria in 2011 [11]. The recent report of a highly ceftriaxone-resistant *N. gonorrhoeae* strain H041 in Japan [12] triggered worldwide concerns as ceftriaxone is the last remaining option for empirical first-line treatment. Ceftriaxone treatment failure of pharyngeal gonorrhoea [13] has been recently reported in Sweden; the first case of genital infection of highly ceftriaxone-resistant *N. gonorrhoeae* in Europe was reported in France in 2011 [14]. A suspected ceftriaxone-resistant strain has also been reported from Spain [15]. The *in vitro* susceptibility to cefixime has also rapidly decreased, and results from the European gonococcal antimicrobial surveillance programme (Euro-GASP) show that susceptibility to ceftriaxone is decreasing [16-19]. *N. gonorrhoeae* also seems to retain resistance to several classes of antimicrobials, even when the antimicrobials in question were discontinued.

In recent years, nucleic acid amplification tests (NAATs) have increasingly been replacing culture as a diagnostic test for gonorrhoea across Europe. Although NAATs are generally more sensitive and quicker than culture, this has resulted in the loss of expertise and capacity in a number of countries to perform culture and antimicrobial resistance (AMR) testing. This move towards an increased use of NAATs has therefore resulted in a lack of AMR data in a number of EU/EEA countries. The lack of use of commercially available transport medium which is suitable both for NAAT and culture retrieval is of serious concern and jeopardises the possibility of producing national AMR profiles for gonococci to inform treatment guidelines.

This lack of AMR data implies that national authorities and professional medical associations may not be able to develop appropriate treatment guidelines for gonorrhoea. This is particularly relevant when alternative therapies for cephalosporin-resistant *N. gonorrhoeae* are becoming more and more limited.

European Gonococcal Antimicrobial Surveillance Programme

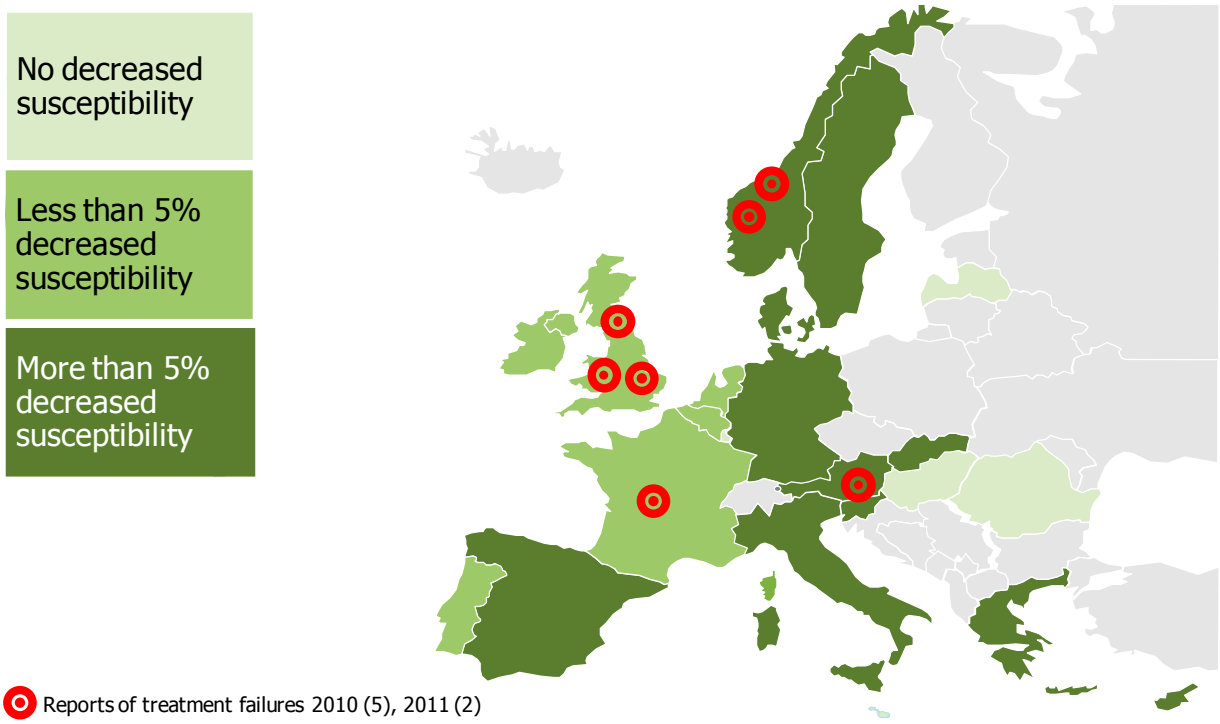
The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) has been set up to inform public health and treatment guidelines on AMR testing results in EU/EEA countries and reports on trends in gonococcal AMR across Europe [16]. These data are crucial for optimisation of treatment and to detect emerging resistance. Euro-GASP is implemented as a sentinel surveillance system through the European STI expert network and involves a network of laboratories in Member States. Euro-GASP includes AMR testing twice a year, an external quality assessment programme, and training for laboratory staff.

Table 1 shows the main results from Euro-GASP 2010. The most worrying result is the increase in the percentage of isolates with decreased susceptibility to cefixime and the increase in the number of countries where this phenotype was identified between 2009 and 2010. Patient characteristics of isolates with decreased susceptibility did not differ greatly when compared to the overall population, except for age: patients with decreased susceptibility to cefixime were more likely to be older. Rates of ciprofloxacin and azithromycin resistance have both decreased since 2009, but remain high across Europe (53% and 7%, respectively). Between 2009 and 2011, the external quality assessment programme has consistently shown high comparability between participants, which in turn gives confidence with respect to gonococcal antimicrobial susceptibility data from Euro-GASP [16].

Table 1: Key results from Euro-GASP in 2009 and 2010

	2009	2010
Number of participating countries	17	21
Number of isolates tested	1471	1766
Percentage of isolates with decreased susceptibility to cefixime (MIC > 0.12 mg/L)	4%	9%
Number of countries where decreased susceptibility to cefixime was detected	10	17

Figure 1: Decreased susceptibility to cefixime (MIC > 0.12mg/L) and reported cefixime treatment failures, 2010



The rapid increase and spread of decreased susceptibility to cefixime is extremely concerning as this is a recommended therapy for gonorrhoea across Europe, as is ceftriaxone. Euro-GASP has also detected increases from 2009 onwards in the higher MIC categories for ceftriaxone, which could be due to the molecular mechanisms that confer decreased susceptibility to cefixime also conferring decreased susceptibility to ceftriaxone. The lack of alternative therapies, decreasing susceptibility to the cephalosporins, and numbers of treatment failures across Europe show that the gonococcal population needs to be monitored carefully, and a European public health response plan needs to be developed, as the loss of both cefixime and ceftriaxone as treatment options for gonorrhoea would have a significant impact on public health.

Public health response

Objectives of the response plan

This response plan is designed to contribute to preventing the spread of multidrug-resistant *Neisseria gonorrhoeae* (MDR NG) in the EU/EEA in the context of the possible emergence of untreatable gonorrhoea. MDR NG is defined as by Tapsall et al [20]. The plan details the response at European level and is designed as a guide for Member States when planning national interventions.

The main goal of the public health response plan is to minimise the impact of MDR NG on the prevention and control of gonorrhoea in Europe.

Specific objectives include:

- Strengthening the surveillance of gonococcal antimicrobial susceptibility in the EU/EEA Member States to inform national treatment guidelines;
- Ensuring that a minimum capacity for culture and susceptibility testing in EU/EEA Member States is either available or developed;
- Establishing a strategy to rapidly detect patients diagnosed with gonorrhoea who experience a clinical treatment failure following treatment with recommended cephalosporins, including the clinical management of affected patients and their sexual partners;
- Outlining a set of recommended public health actions to be implemented at the national level, following the detection of MDR NG cases; and
- Increasing the awareness of policy makers, clinicians, patients, and key populations.

Components of the response plan

The response plan strives to support Member States to develop and implement national interventions to control the threat of multidrug-resistant gonorrhoea in a multidisciplinary approach. The public health response has the following components:

- 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 multidrug-resistant gonorrhoea.

1 Strengthening antimicrobial surveillance

1.1 A strategy for expanding Euro-GASP

It is imperative that AMR testing results for *N. gonorrhoeae* isolates are obtained from all EU/EEA countries to inform the AMR profiles to be able to develop appropriate treatment guidelines. Given the movement of strains across Europe, a Europe-wide approach is essential in order to detect and monitor resistant strains and thus informs European treatment guidelines. Appropriate treatment must be administered to ensure successful patient management and to interrupt transmission. Without proper *N. gonorrhoeae* AMR data it is difficult to ascertain whether the correct treatment options are available in a country; inappropriate treatment can lead to the emergence of resistance, increased patient morbidity, increased acquisition of HIV, and an overall bigger cost burden to the healthcare system.

In 2011, 21 out of 30 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 NAATs), the differences in diagnostic procedures in STI clinics, and the lack of resources for performing culture. Participation from central and eastern EU/EEA countries should be improved, as very limited information is available on the AMR profile in these countries. In some countries, antimicrobial drugs seem to be easily available without prescription and the use of suboptimal medication as a second-line treatment seems to be common [21]. These factors increase the risk of emergence of MDR NG. Expanding Euro-GASP to more countries is therefore important to further control emergence and spread of MDR NG strains in Europe.

ECDC has developed a strategy to enable individual Member States to join Euro-GASP in 2012 and 2013 by focusing on capacity building through the involvement of public health STI experts, STI clinics and laboratories. A suitable specimen collection and laboratory protocol will be developed through international cooperation. ECDC will provide training to STI laboratory staff if needed. Participation in the external quality assessment programme is part of the capacity building strategy in order to gain valid and comparable susceptibility data to reliably detect emerging resistance and optimise patient management. Capacity building will ensure that participating laboratories produce unbiased and comparable data. A further goal is the harmonisation of the methods and interpretative criteria.

Actions

- Inclusion of two additional Member States in Euro-GASP 2012.
- Ensuring that all Euro-GASP laboratories participate in the EQA programme.
- Ensuring further dissemination of Euro-GASP results though the members of the European STI network.

Indicators

- Number of countries participating in Euro-GASP.
- Number of isolates reported through Euro-GASP.
- Number of laboratories participating in the EQA programme.

1.2 National antimicrobial surveillance

Euro-GASP provides important data at the European level but is dependent on national gonococcal surveillance systems or on specimen collection specifically designed for Euro-GASP participation. The increased use of NAAT as the principal diagnostic method in many countries has made it difficult for many countries to obtain samples for culture and susceptibility testing.

Countries may consider the use of different strategies for effective AMR gonococcal surveillance at the national level. The following strategies are helpful when setting up a national AMR surveillance system:

- Establishment of a national platform involving all professional societies and disciplines involved in the prevention and control of gonorrhoea at the national level. The platform will allow for expert discussion, review of the current situation and facilitates public health action and decision making. Public health authorities could lead the platform and involve decision making staff. The national platform would also offer the opportunity to rapidly disseminate national AMR results from Euro-GASP and thus ensure the further dissemination of these results.

- As a minimum measure, Member States should encourage links between clinicians providing STI services; local, regional and national laboratories; surveillance institutes; and public health authorities to facilitate communication and promote surveillance and response to MDR NG.
- The capacity to perform culture has decreased in a number of countries with the increasing use of NAAT. Member States should assess their capacity for culture and susceptibility testing and identify the minimum level of capacity needed to perform culture and susceptibility testing for sentinel surveillance purposes. A small network of clinics with laboratories could be formed to allow specimen collection through the development of referral pathways. Alternatively, networks could be established by laboratories that perform culture thus ensuring that these laboratories collect clinical data. Such networks could function as sentinel sites for surveillance purposes. Additionally, countries could invest in increasing the capacity for culture. Training and technical support is available from ECDC for supporting such assessments and establishing these programmes.
- Countries should consider the development of national sentinel surveillance programmes to monitor antimicrobial susceptibility. Laboratories participating in these programmes should perform culture and susceptibility testing on a proportion of samples. Such sentinel systems could allow countries to collect data which inform the development of treatment guidelines and also make it possible to participate in Euro-GASP.
- Surveillance activities at the national level should be facilitated by the implementation of transport media which allow both NAAT and subsequent culturing. Such media would enable countries to use NAAT as the primary diagnostics tool, and still culture NAAT-positive samples, thus eliminating the need for additional samples.
- In addition to AMR surveillance activities, countries could be encouraged to perform surveys in order to determine the various prescribed gonorrhoea treatments. These surveys would help the interpretation of AMR data and guide sensitization activities conducted among prescribers.

Actions at the national level

- Promoting the establishment of a national platform for expert consultation across different disciplines involved in gonorrhoea control.
- Developing and implementing a national sentinel gonococcal antimicrobial susceptibility programme (GASP) which provides information on a limited number of gonococcal isolates against a panel of antimicrobials linked to the epidemiological characteristics of the patient.
- Ensuring specimen collection for GASP thorough a small network of laboratories or a system of transferring samples to a reference laboratory (minimum requirement).
- Supporting the implementation at the national level of transport media for gonococci which allow dual usage of NAAT and subsequent culture and antimicrobial susceptibility testing.

Indicators

- National (sentinel) GASP in place.
- Proportion of all STI clinics (sentinel sites) that have access to culture and antimicrobial susceptibility testing.
- Proportion of all (reported) gonorrhoea cases tested with culture and with antimicrobial susceptibility results available.

1.3 Training

ECDC continues to offer 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 services. Training on sampling and treatment failure should be provided for healthcare providers at national level.

Actions

- Providing ECDC laboratory training modules to a number of Member States.
- Countries offering training for laboratories and/or clinicians at the national level.

Indicators

- Number of countries participating (or have participated) in the ECDC laboratory training modules.
- Number of countries offering national training modules (laboratory and/or clinical).

1.4 Improving data completeness and timeliness

AMR surveillance could be further improved by including epidemiological data linked to gonococcal isolates to understand the key populations at risk of emerging MDR NG. This would also help to target control measures at national and international levels.

Reporting of epidemiological variables, including specimen site, sex, age, sexual orientation, previous infections and concurrent STI diagnosed is important to understand the spread of infection. The completeness of this data in Euro-GASP 2009 and 2010 (annual reports) is low and the number of Member States reporting these variables needs to be increased.

The need for complete data should be discussed at the national level. Different methods need to be considered in order to improve the current situation: one available option is the development of a national form for reporting the epidemiological characteristics (within the sentinel surveillance context) together with detailed AMR results at the national level.

Collection of information on the presence or absence of symptoms needs to be considered. This would allow the monitoring of trends for symptomatic and asymptomatic cases separately, particularly in women, and thus help distinguish the spread of the disease from the strengthening of screening due to the growing use of NAAT for the diagnosis of gonorrhoea.

Additionally, the representativeness of Euro-GASP results needs to be assessed in order to ensure that Euro-GASP specimens (currently originating mainly from male patients and with specimens mainly of genital origin [22]) are representative of the epidemiological trends in a country.

Timely reporting of AMR and epidemiological data is essential in order to quickly identify emerging trends. Laboratories and epidemiologists participating in Euro-GASP will be encouraged to upload their national AMR and epidemiological data in a timely manner. ECDC will provide support and training for uploading data to The European Surveillance System (TESSy).

Actions

- Improving the completeness of epidemiological characteristics at national level.
- Assessing the representativeness of Euro-GASP in 2012–2013.
- Ensuring that AMR and epidemiological data are reported in a timely manner to TESSy.
- Assessing the time required for Euro-GASP reports and recommending improvements.

Indicators

- Proportion of countries reporting epidemiological characteristics in Euro-GASP.
- Indicators for improving representativeness developed following the first assessment.
- Completeness of Euro-GASP data with respect to key epidemiological characteristics.
- Time interval between Euro-GASP sample collection period and publication of Euro-GASP reports (interim and final).

2 Clinical management and treatment failure monitoring

2.1 Clinical management

Clinicians have a crucial role in preventing the spread of antimicrobial resistance through appropriate clinical management, partner notification services, and reporting cases of treatment failure. Clinicians who identify patients with suspected cephalosporin treatment failure need to request culture and susceptibility testing of relevant clinical specimens and report the case to local public health authorities.

Close collaboration between the clinicians, laboratories and local public health authorities is essential in order to ensure that cases with probable or confirmed treatment failure are appropriately investigated and treated. Close coordination is also necessary to ensure that partners are being notified, investigated and treated appropriately. Clinicians noticing clusters of treatment failures should also be encouraged to report to local public health authorities so that appropriate investigations and interventions can be undertaken. Local or regional health authorities should contact national authorities (particularly the STI departments managed by formal STI focal points) who can then share data on such cases at the European level.

In order to collect accurate and comparable data, we suggest case definitions for treatment failures (see below). For keeping track of treatment failure in a country, a structured collection of clinical and epidemiological information is suggested and needs to be implemented at country level. Annex 1 includes a proposed reporting form with the variables that will be collected on probable and confirmed cases of treatment failure. The data collected through this system will inform the development of national and European treatment guidelines.

European clinical management guidelines are currently under revision by IUSTI. Current guidelines provide indications for performing a test of cure, for example: persistence of symptoms; re-exposure of infection; possible AMR resistance to therapy; national or local practice; pharyngeal infection [5]. The growing number of reports of gonorrhoea treatment failures and third-generation cephalosporin MICs should be reason enough for countries to consider test-of-cure cultures for all gonorrhoea cases. Countries need to ensure that patients with persisting symptoms after treatment are evaluated by culture and that gonococcal isolates are tested for antimicrobial susceptibility. Updated guidelines are also needed for the management of gonorrhoea treatment failures. These guidelines should include alternative regimens in case of multidrug resistance.

Action

- ECDC and IUSTI to review guidance on the management of gonorrhoea treatment failures and recommendations for a test of cure.

Indicators

- Gonorrhoea patient management guidelines reviewed and revised.
- Number of countries recommending culture and antimicrobial susceptibility testing for cases of suspected treatment failure.

2.2 Case definitions for antibiotic treatment failure

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 are required to verify treatment failures with recommended cephalosporin treatment regimens.

A patient who fulfils all criteria described in Table 2 is defined as a confirmed case of treatment failure.

Table 2: Working case definition for confirmed treatment failure: clinical and laboratory criteria

1	A gonorrhoea patient who returns for test of cure or who has persistent genital symptoms after having received treatment for laboratory-confirmed gonorrhoea with a recommended cephalosporin regimen (ceftriaxone or cefixime in appropriate dose) AND
2	remains positive for one of the following tests for *N. gonorrhoeae*: • presence of intracellular Gram-negative diplococci on microscopy taken at least 72 hours after completion of treatment; OR • 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
3	denies sexual contact during the post-treatment follow-up period AND
4	decreased susceptibility to cephalosporin used for treatment*: • cefixime: MIC>0.12 mg/L** • ceftriaxone: MIC>0.12 mg/L**

** Ideally, the pre- and post-treatment isolates should be examined with an appropriate and highly discriminatory molecular epidemiological typing method (to confirm an identical strain) and with genetic methods (to confirm the resistance determinants in order to show that the strain is truly resistant).*

*** These thresholds are in accordance with EUCAST tentative breakpoints.*

The MIC breakpoints for intermediate susceptibility and resistance to cefixime and ceftriaxone are tentative due to the lack of sufficient clinical data. Accordingly, treatment failures, in particular of pharyngeal gonorrhoea, may occur with *N. gonorrhoeae* isolates that show MICs below the breakpoints given in Table 2. Thus, the working case definition for possible treatment failure, which is described in Table 3, does not take into account the MIC value of the *N. gonorrhoeae* strains suspected to cause the clinical failure. In these instances it is important that MIC values are determined, recorded and reported in order to identify treatment failures occurring below the described breakpoints.

Table 3: Working case definition for probable treatment failure: clinical and laboratory criteria

1	A gonorrhoea patient who returns for test of cure or who has persistent genital symptoms after having received treatment for laboratory-confirmed gonorrhoea with a recommended cephalosporin regimen (ceftriaxone or cefixime in appropriate dose) AND
2	remains positive for one of the following tests for *N. gonorrhoeae*: • presence of intracellular Gram-negative diplococci on microscopy taken at least 72 hours after completion of treatment; OR • 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
3	denies sexual contact during the post-treatment follow-up period

Actions

- Ensuring national agreement of the above case definitions.
- Dissemination of the case definitions to all EU/EEA Member States.
- Encouraging the dissemination of the case definitions at the national level.

Indicator

- Number of countries adopting the case definitions for gonorrhoea treatment failure.

2.3 Mechanisms for reporting of treatment failures

Standardised clinical and epidemiological data of treatment failures should be collected and reported in a timely manner at the national level. Although Euro-GASP provides an overview of antimicrobial-resistant gonococci in the EU, there is a need for developing a reporting mechanism that functions as an (inter)national reporting system for treatment failures, with the possibility to distinguish between probable 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 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 establish clinical breakpoints.

Cases of probable and confirmed treatment failure (in accordance with the case definitions as outlined above) should be reported through the Epidemiological Intelligence Information System for STI (EPIS-STI), an online application which allows the secure exchange of information and data between the members of the European STI expert network. A template for reporting is included in Annex 1.

The algorithm below shows the sequence of steps when a clinician detects a treatment failure. This will allow clinicians and public health services at the national or international level to monitor the spread of resistant gonorrhoea in a timely manner, recognize factors leading to AMR, identify populations associated with increased AMR, and facilitate further control interventions.

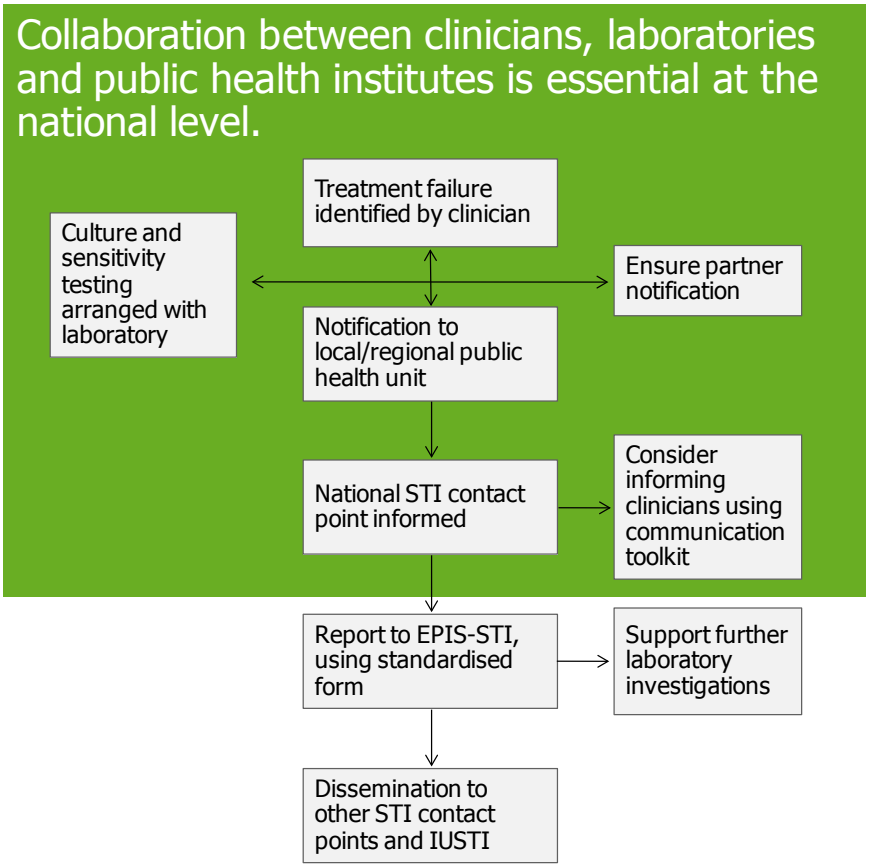
Actions

- Agreement with experts on the reporting template for probable and confirmed treatment failures.
- Further developing EPIS-STI in order to facilitate the reporting of cases of treatment failure.

Indicators

- Number of countries implementing treatment failure monitoring.
- Number/proportion of cases of treatment failure reported in EPIS-STI (and in publications).
- Number/proportion of treatment failures reported in EPIS-STI using the agreed reporting template.

Figure 2: Flowchart for the reporting of probable and confirmed treatment failure



3 Communication strategy

It is essential to increase the awareness of the threat connected to the emergence of cephalosporin-resistant *N. gonorrhoeae* in a number of groups:

- Engaging politicians and policy makers in order to prioritise the issue and ensure that resources are available for culture and susceptibility testing.
- Awareness among clinicians and other healthcare providers is needed in order to ensure optimal patient treatment and to enable the early identification of treatment failures. This can be achieved through direct communication with clinicians and microbiologists (see templates for a letter and fact sheets in Annexes 2 and 3) or through publications in national medical journals with a wide readership.
- The importance of maintaining the capacity of culturing *N. gonorrhoeae* and conducting antimicrobial susceptibility testing needs to be emphasised to microbiologists and laboratory staff in order to ensure that AMR data will remain available.
- People at increased risk for acquiring MDR NG (e.g. men who have sex with men, sex workers, and youths) need to be aware of the threat of resistant gonorrhoea. Prevention messages should be targeted at these groups. This can be achieved by distributing leaflets in dedicated clinical settings.

The timely dissemination of surveillance information to those who plan public health programmes and those who develop local, regional and national policies will ensure an optimal response to the threat of MDR NG.

A communication strategy can be developed at the national level and discussed within the multidisciplinary platform suggested above. It is important to engage clinicians, laboratories, professional societies and public health authorities in the development and agreement. As a minimum measure, a communication strategy should contain a plan for the dissemination of the most recent data on gonorrhoea and AMR patterns.

Actions

- Establish a communication strategy at national level.
- Producing a template for a letter to medical professionals and adjusting it to national standards.
- Producing a fact sheet on multidrug-resistant *N. gonorrhoea* (templates provided) for publication at national level.
- Encouraging and supporting Member States in writing publications on the threat of cephalosporin-resistant *N. gonorrhoeae* for national and international medical journals.

Indicator

- Number of countries with a national communication strategy.
- Number of national and international publications/communications on MDR NG.

4 Monitoring the effectiveness of the response plan

Monitoring the effectiveness of the response plan can be done at national but also at European level. To monitor the response at national level, the table below could be used or adapted to local and national needs. It includes the main components of the public health response plan.

Table 4: Monitoring and evaluation, selected indicators at the national level

Component	Indicator	Achieved yes/no	Strength	Weakness	Comments
Strengthen surveillance	National GASP in place				
	Sentinel network established				
	National platform established				
	Assessment of laboratory capacity				
Clinical management	Case definitions agreed and implemented				
	National treatment failure reporting				
Communication strategy	National communication plan agreed				
	Fact sheet adjusted and disseminated				

ECDC will monitor the indicators in order to measure the effectiveness of the response plan (SMART indicators).

Table 5: Selected indicators to be monitored at international level

Component	Indicator	Indicator achieved/ progress	Strength	Weakness	Comments
Strengthen surveillance	Number of countries participating in Euro-GASP				
	Number of isolates reported through Euro-GASP				
	Number of laboratories participating in Euro-GASP EQA				
	Number of countries participated in the laboratory training				
	Number of countries offering national training modules (laboratory and/or clinical)				

Component	Indicator	Indicator achieved/ progress	Strength	Weakness	Comments
	Proportion of countries reporting epidemiological characteristics in Euro-GASP				
	Completeness of Euro-GASP data for key epidemiological characteristics				
	Time between Euro-GASP data collection and publication of interim and annual report				
Clinical management	Gonorrhoea guidelines reviewed and revised				
	Number of countries recommending culture and AMR testing for cases of suspected treatment failure				
	Number of countries adopting the case definitions for gonorrhoea treatment failure				
	Number of countries implementing treatment failure monitoring				
	Number/proportion of cases of treatment failure reported in EPIS-STI (using the template)				
Communication strategy	Number of national publications or communications on MDR NG				

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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 probable or confirmed *N. gonorrhoeae* treatment failure 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	
☐ Probable treatment failure	☐ Confirmed treatment failure
Case definition for probable treatment failure: A gonorrhoea patient who returns for test of cure or who has persistent genital symptoms after having received treatment for laboratory-confirmed gonorrhoea with a recommended cephalosporin regimen (ceftriaxone or cefixime in appropriate dose) AND remains positive for one of the following tests for *N. gonorrhoeae*: • presence of intracellular Gram-negative diplococci on microscopy taken at least 72 hours after completion of treatment; OR • 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 denies sexual contact during the post-treatment follow-up period.	**Case definition for confirmed treatment failure:** A gonorrhoea patient who returns for test of cure or who has persistent genital symptoms after having received treatment for laboratory-confirmed gonorrhoea with a recommended cephalosporin regimen (ceftriaxone or cefixime in appropriate dose) AND remains positive for one of the following tests for *N. gonorrhoeae*: • presence of intracellular Gram-negative diplococci on microscopy taken at least 72 hours after completion of treatment; OR • 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 denies sexual contact during the post-treatment follow-up period AND decreased susceptibility to cephalosporin used for treatment*: • cefixime: MIC>0.12 mg/L** • ceftriaxone: MIC>0.12 mg/L**
Did the patient have any type of sexual contact between the start of treatment and the second visit?	

Description of the event	
Please provide a short description of the circumstances of the event:	
Date of first notification of the treatment failure to the reporting centre:	

Case details	
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?	

Other comments. Please add any information considered relevant on the event or on public health measures taken.

Annex 2. Letter to clinicians

Dear Colleague,

Antimicrobial resistant gonorrhoea is spreading in the EU/EEA. It is becoming exceedingly difficult to treat, and there is a real possibility that gonorrhoea will become an untreatable infection. Therefore ECDC, in collaboration with international experts, has prepared an EU/EEA response plan to inform and guide clinicians, microbiologists, epidemiologists and public health professionals.

It is imperative that we work together to create heightened awareness of antimicrobial resistance to ensure that treatment failures are quickly detected and treated appropriately. Public health control of gonorrhoea will be a challenge in the coming years, and it is essential that we have a combined approach to combat the problem.

Major steps include:

- the appropriate use of new diagnostic tests;
- sustained knowledge on how to culture *Neisseria gonorrhoeae*;
- the collection of a representative sample of viable isolates;
- the provision of timely surveillance data;
- vigilance for emerging resistance; and
- enhanced prevention measures.

To assist you, we have prepared the enclosed fact sheets on antimicrobial resistance and treatment failure.

Yours sincerely,

Annex 3. Facts in brief

Multidrug-resistant gonorrhoea

Gonorrhoea may soon become an untreatable disease.

Sulphonamides, penicillin, tetracyclines and quinolones are already unsuitable as treatment options due to resistance. Current treatment guidelines in most European countries recommend the use of single-dose injectable (ceftriaxone) or oral third-generation cephalosporins (e.g. cefixime). Treatment is often administered before antimicrobial sensitivity results are available.

There is an increasing number of reports about treatment failures to cefixime and ceftriaxone (Japan, Austria, Norway, UK, France, Spain) and ceftriaxone (Japan, Sweden). Overall, the susceptibility to cefixime (map) and ceftriaxone in Europe is decreasing, and once cefixime and ceftriaxone become unsuitable for treatment, there are no options left for empirical treatment.

Awareness of gonorrhoea treatment failures needs to be increased in the medical community.

At a more practical level, doctors need to:

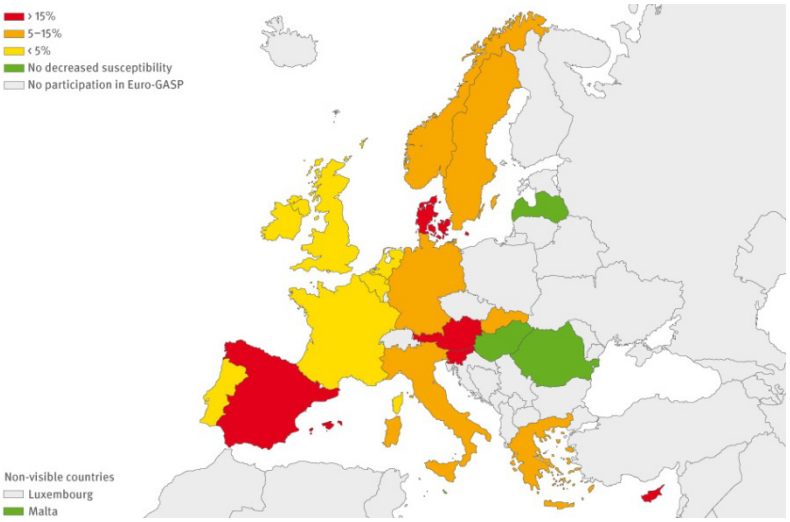
- comply with treatment regimens and guidelines (often based on the European IUSTI guidelines);
- interact with microbiologists and public health experts after suspected treatment failure;
- ask patients to return for a test of cure more frequently, particularly if at risk for treatment failure; and
- ensure that contacts of gonorrhoea cases are traced and managed appropriately.

Public health efforts should emphasise:

- effective prevention (e.g. condom use);
- the continued availability of culture and susceptibility testing as part of gonorrhoea diagnostics; and
- improved reporting of demographic and behavioural surveillance data for gonorrhoea cases.

For more information, consult the 'ECDC response plan' at http://www.ecdc.europa.eu

Map: Decreased susceptibility to cefixime (MIC > 0.12 mg/L) across Europe, 2010



Annex 4: Fact sheet

Epidemiological information on multidrug-resistant gonorrhoea

Neisseria gonorrhoeae has developed resistance to several antimicrobial drugs over the years. Drugs such as sulphonamides, penicillin, tetracyclines and quinolones are now unsuitable as treatment options. Current treatment guidelines in most European countries recommend the use of single-dose injectable (ceftriaxone) or oral (cefixime) third-generation cephalosporins.

Since 2000, however, treatment failures with the use of third-generation cephalosporins have been reported in Japan. In Europe there were reports of treatment failures with cefixime standard treatment in England and Norway in 2010. In 2011, the first *N. gonorrhoeae* strain with decreased susceptibility to cefixime and subsequent treatment failure was reported in Austria. The recent emergence of the highly ceftriaxone-resistant *N. gonorrhoeae* strain H041 in Japan triggered worldwide concerns as ceftriaxone is the last remaining option for empirical first-line treatment. The first case of genital infection of highly cefixime- and ceftriaxone-resistant *N. gonorrhoeae* in Europe was reported in France and a suspected ceftriaxone-resistant strain was reported in Spain. Ceftriaxone treatment failure of pharyngeal gonorrhoea has been reported in Sweden.

The results from the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) have shown that susceptibility to cefixime and ceftriaxone is decreasing in Europe. In 2009, 17 EU/EEA countries participated in Euro-GASP and more than 1300 gonococcal isolates were tested against a panel of relevant antimicrobials. Five percent of the tested isolates had decreased susceptibility to cefixime; decreased susceptibility was detected in 10 countries.

In 2010, decreased susceptibility to cefixime has increased rapidly to nine percent (of over 1700 tested isolates) and is now present in 21 countries, of which 11 reported a decreased susceptibility of more than 5 %. In four countries, decreased susceptibility was above 15 %. A total increase of 4 % was reported over 2009 and 2010.

Map: Decreased susceptibility to cefixime (MIC > 0.12 mg/L) across Europe, 2010