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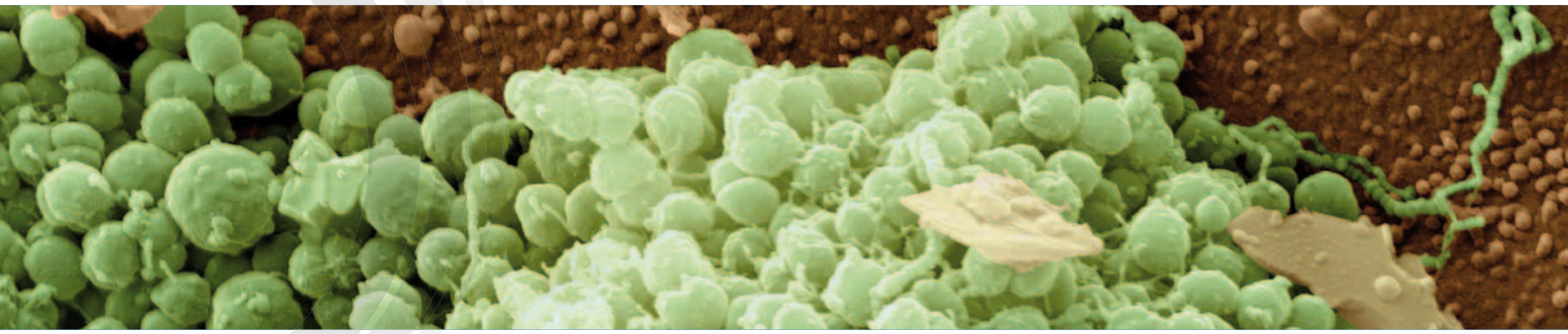

Gonococcal antimicrobial susceptibility surveillance in Europe

2010

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This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by Marita van de Laar and Gianfranco Spiteri, and produced by the Health Protection Agency, Centre for Infections, London, United Kingdom.

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Contents

Abbreviations

AMR	Antimicrobial resistance
CFU	Colony-forming unit
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute, Wayne, PA, USA
DS	Decreased Susceptibility
DV	Dermatovenerology
EEA	European Economic Area
EQA	External quality assessment
ESSTI	European Surveillance of Sexually Transmitted Infections Project
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
Euro-GASP	European Gonococcal Antimicrobial Surveillance Programme
GC	Gonococcal
GE	Genital pathogens scheme
GUM	Genitourinary medicine
GP	General practitioner
GRASP	Gonococcal Resistance to Antimicrobials Surveillance Programme
HPA	Health Protection Agency
MIC	Minimum inhibitory concentration
MSM	Men who have sex with men
PPNG	Penicillinase-producing *Neisseria gonorrhoeae*
SRGA	Swedish Reference Group for Antibiotics
STI	Sexually transmitted infection
UK-NEQAS	United Kingdom National External Quality Assessment Service
WHO	World Health Organization

Executive summary

Since 2009, the European STI surveillance network has been working to strengthen the surveillance of gonococcal susceptibility in European Union/European Economic Area (EU/EEA) Member States by the continued development and implementation of sentinel surveillance of antimicrobial-resistant gonorrhoea and an external quality assurance (EQA) scheme for gonococcal antimicrobial susceptibility.

During 2010, the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) evolved from annual to biannual testing, where participating laboratories were requested to collect gonococcal isolates during two periods (May/June and November/December). During the first collection, Euro-GASP followed the centralised testing model, where susceptibility testing was performed on all isolates centrally by E-test or agar dilution for the following therapeutically relevant antimicrobials: cefixime, ceftriaxone, ciprofloxacin, azithromycin, spectinomycin and gentamicin. During the second collection period, participating laboratories that fulfilled set criteria were invited to take part in decentralised testing, where susceptibility testing was performed in the participant's own laboratory.

In 2010, 21 EU/EEA Member States participated in Euro-GASP, nine of which participated in decentralised testing. A total of 1766 isolates were collected and tested. The majority of gonococci (83%) were collected from men. The age range of the patients was less than one year to 76 years, with a median of 29 years; 34% of patients were younger than 25 years. Men who have sex with men (MSM) and male heterosexuals were significantly older than women. The site of specimen was mainly genital (85%), followed by rectal (11%) and pharyngeal (4%). When information on previous diagnosis of gonorrhoea was available, 21% had previously been diagnosed with gonorrhoea. There was a significant increase in the number of patients being concurrently diagnosed with chlamydia (22%; 14% in 2009). When sexual orientation was known, 61% stated that they were heterosexual and 40% were MSM. HIV status data was collected from the second half of 2010 only; of the 16% of HIV-positive cases from the HIV-known status dataset, all were MSM.

Eighteen countries participated in the gonococcal antimicrobial resistance EQA scheme. The EQA has continued to show high comparability between participants, which in turn gives confidence in respect to gonococcal antimicrobial susceptibility in Euro-GASP, particularly for decentralised testing.

Euro-GASP has identified a significant increase in the proportion of tested isolates that show decreased susceptibility to cefixime, dropping from 4% in 2009 to 9% in 2010, using a cut-off of >0.125 mg/L. Isolates with this phenotype were detected in 17 countries; seven more than the previous year. The patient characteristics of those isolates with decreased susceptibility do not differ greatly when compared to the overall population, except for age, where patients with decreased susceptibility to cefixime were more likely to be older. Rates of ciprofloxacin and azithromycin resistance have both decreased since 2009, but still remain high (53% and 7%, respectively). The minimum inhibitory concentration (MIC) distribution of gentamicin continues to offer hope that gentamicin could be used for therapy in the future. Overall the distribution of resistance is similar across the patient groups and specimen types, other than an association between concurrent chlamydia infection, age and ciprofloxacin susceptibility and also between HIV-positive status and ciprofloxacin susceptibility.

The rapid increase and spread of decreased susceptibility to cefixime is extremely concerning as cefixime is a recommended therapy for gonorrhoea across Europe, as is ceftriaxone. The increases from 2009 onwards in the higher MIC of ceftriaxone could be due to the molecular mechanisms that confer decreased susceptibility to cefixime. These molecular mechanisms could also confer decreased susceptibility to ceftriaxone, and selection pressure imposed by the use of ceftriaxone for the treatment of gonorrhoea may also play a part. Decreasing susceptibility to the cephalosporins and increasing numbers of treatment failures across Europe show that the European gonococcal population needs to be monitored carefully, as the loss of both cefixime and ceftriaxone as treatment options for gonorrhoea would be a major public health concern. Continued surveillance is essential to inform treatment guidelines, thereby preventing onward transmission and reducing patient morbidity.

1 Introduction

Since 2009, the European Centre for Disease Prevention and Control (ECDC) is co-ordinating the enhanced surveillance of sexually transmitted infections (STI) in the European Union and the European Economic Area (EU/EEA). The STI microbiology project – which is part of European STI surveillance – has been contracted with an international team lead by the Health Protection Agency (United Kingdom) and includes the Statens Serum Institut (Denmark) and Örebro University Hospital (Sweden).

The main objectives of the STI microbiology project are:

- to improve the quality of laboratory surveillance of gonorrhoea, syphilis, congenital syphilis and infection with *Chlamydia trachomatis* (including Lymphogranuloma venereum) in EU/EEA Member States; and
- to strengthen the surveillance of *Neisseria gonorrhoeae* antimicrobial susceptibility in EU/EEA Member States, including an external quality assessment (EQA) scheme and training.

1.1 Background

The emergence and spread of antimicrobial resistance (AMR) in *N. gonorrhoeae* is a serious threat to the treatment and control of gonorrhoea. The therapeutic agents currently recommended in Europe [1], extended-spectrum cephalosporins, are amongst the last agents to remain broadly effective [2].

Ever since decreased susceptibility to cephalosporins was first recognised in 2001 in Japan [3], there has been rapid spread of isolates displaying this decreased susceptibility across Europe [4–7]. As there are no new or alternative treatment options available, the loss of cephalosporins for the treatment of gonorrhoea would be a major public health concern, particularly in light of the documented treatment failures in Japan [8;9] and more recently in Norway, Sweden and the United Kingdom [10–13].

In 2009, the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) was implemented as a sentinel surveillance programme in 17 EU countries. The major findings were [6]:

- Five per cent of tested isolates had decreased susceptibility to cefixime, using a cut-off of ≥0.25 mg/L.
- Ceftriaxone is still a suitable option for therapy; however the upward drift in the MIC for ceftriaxone needs careful and regular monitoring.
- Rates of ciprofloxacin and azithromycin resistance were high across Europe (63% and 13%, respectively).
- The minimum inhibitory concentration (MIC) distribution of gentamicin suggests that this antimicrobial could be used for therapy in the future.

1.2 Objectives

With 5% of isolates (tested in Euro-GASP 2009) already displaying decreased susceptibility to cefixime, and the recent documented treatment failures, the need to monitor *N. gonorrhoeae* AMR in the EU/EEA Member States is clear.

It is the overall aim of the STI microbiology project to strengthen the surveillance of gonococcal antimicrobial susceptibility in the EU/EEA Member States. The following objectives are focused on achieving this aim:

- Developing and implementing sentinel surveillance of gonococcal antimicrobial susceptibility to a range of therapeutically relevant antimicrobials.
- Improving the timeliness of surveillance to allow more frequent reporting of developments in gonococcal antimicrobial susceptibility across Europe.
- Linking susceptibility data with epidemiological information to better understand the risk factors associated with emerging resistance patterns.
- Implementing an external quality assessment (EQA) scheme for antimicrobial susceptibility testing across Europe.
- Providing training in gonococcal antimicrobial susceptibility testing, thereby facilitating a standardised methodology across Europe.

This report presents the results from the 2010 gonococcal antimicrobial susceptibility surveillance and a summary of the 2010–2011 EQA scheme.

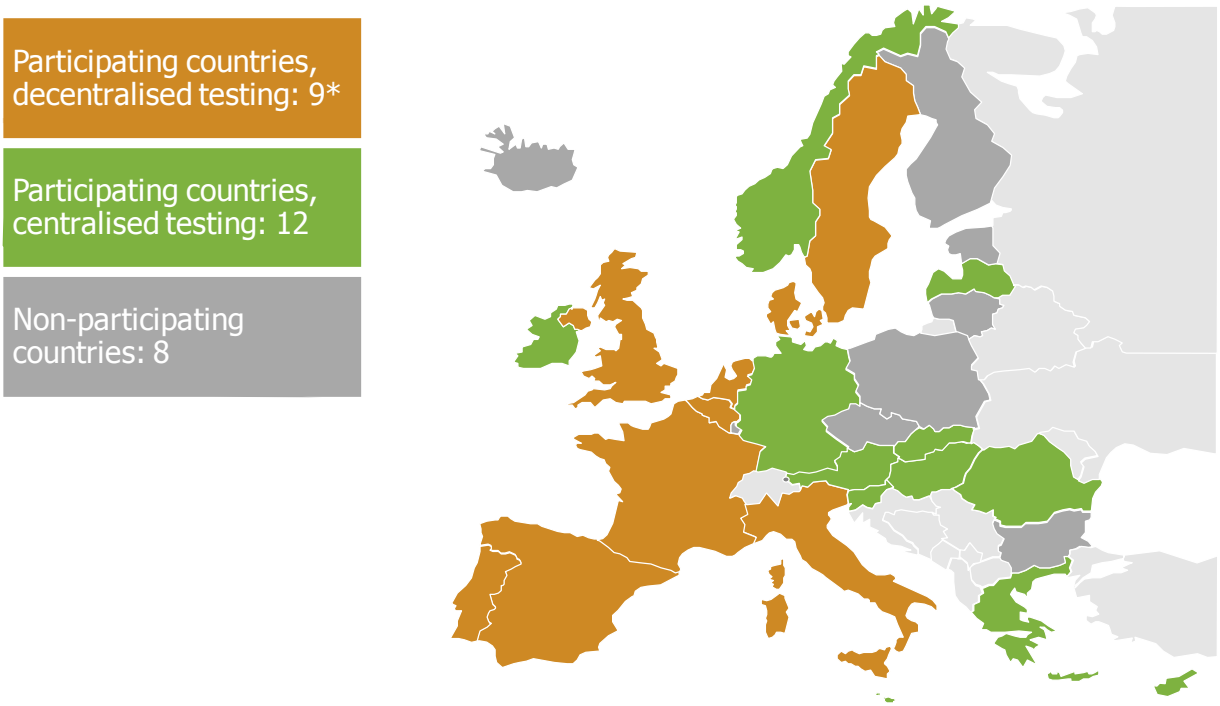
2 Methods

In 2010, Euro-GASP changed with the advent of biannual and decentralised testing. For the biannual testing, participating laboratories were requested to collect gonococcal isolates during two periods; May/June and November/December. During the first collection in May/June 2010 Euro-GASP followed the centralised testing model, where susceptibility testing was performed on all isolates centrally, using the same methodology (see 2.4). During the second collection period, participating laboratories, who fulfilled set criteria, were invited to take part in decentralised testing, where susceptibility testing was performed in the participants own laboratory. Subsequently, countries were requested to upload their results in the European Surveillance System (TESSy). Full details on the framework for Euro-GASP and the criteria for decentralised testing can be found in Annex 1.

2.1 Participating laboratories

The nominated contact points for STI surveillance in EU/EEA countries were invited to participate in the strain collection as part of Euro-GASP. The laboratory contact points in 21 countries agreed to participate (Map 1). The new participants in 2010 were Cyprus, Ireland, Hungary and Romania.

Map 1: Countries participating in Euro-GASP, 2010



** As of November 2010. Norway participated in May/June collection only.*
Cyprus, Hungary and Romania participated from November/December only.

2.2 National protocol

Each country referring gonococcal isolates or susceptibility data was requested to provide additional information on the implementation of Euro-GASP at national level (Annex 2). This information is critical in interpreting data and in ensuring accurate linking of laboratory and epidemiological data.

2.3 Strain collection

Each country was asked to contribute 110 isolates each year, with the aim of retrieving and testing 100 isolates from each country. For countries where 100 isolates represents less than 10% of the total number of cases of gonorrhoea (Spain, The United Kingdom, and the Netherlands), it was requested that up to a maximum of 200 isolates should be collected. The aim was for laboratories to collect half the isolates in May/June and the remainder

in November/December. However for the United Kingdom, the first collection was in July and the second in September to coincide with the collection period of the national Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) in England and Wales. Laboratories were requested to collect one isolate from each patient in the following order of preference when multiple sites were infected:

Males: Pharyngeal, rectal, urethral, other

Females: Pharyngeal, cervical, other anogenital (high vaginal swab (HVS)/rectal/urethral), other

For centralised testing, pure cultures 18–24 hours old, were saved on Microbank beads and stored at −70°C. The isolates were then sent frozen on dry ice to one of the following three laboratories for susceptibility testing: Health Protection Agency, London, United Kingdom; Statens Serum Institut, Copenhagen, Denmark; or Örebro University Hospital, Örebro, Sweden.

2.4 Susceptibility testing

Centralised susceptibility testing was performed using either a breakpoint technique that allows for isolates to be categorised as susceptible or resistant (including intermediate resistance where applicable), or E-tests to determine the minimal inhibitory concentration (MIC) to allow monitoring of drift in susceptibility.

The antimicrobials that were tested included those currently recommended for treatment (cefixime, ceftriaxone and spectinomycin), those considered potential alternatives (azithromycin and gentamicin) and those previously used for treatment (ciprofloxacin and penicillin, enzyme-mediated high-level resistance only).

The following methodologies were used for the individual antimicrobial agents:

- azithromycin (breakpoint);
- ciprofloxacin (breakpoint);
- cefixime (E-test);
- ceftriaxone (E-test);
- gentamicin (agar dilution/E-test);
- penicillinase production (nitrocefin); and
- spectinomycin (breakpoint);

Further details on the testing methodology and breakpoints can be found in Annex 3.

Decentralised susceptibility testing: Laboratories participating in decentralised testing performed susceptibility testing in their own laboratories (Annex 1) and the results were interpreted using the Euro-GASP breakpoints (Annex 2). For 2010, Belgium, Spain and the Netherlands did not test gentamicin, and the Netherlands did not test spectinomycin.

2.5 Background variables

During the first collection period in 2010 the following data for each isolate were collected where available: date specimen obtained; specimen site, sex, age, sexual orientation, previously diagnosed with gonorrhoea, and concurrent STI diagnosed this episode.

During the second collection period in 2010, additional variables were collected when data collection was implemented in the European Surveillance System (TESSy) through the development of the GONO AMR metadata; place of residence, clinical service type, HIV status and probable country of infection. The full variable list and variable codes are described in Annex 4.

2.6 Data collection and analysis

In the first round of data collection in 2010, the AMR data and the background variables were collected via an Excel spreadsheet and the data imported into Access. For the second collection period in 2010, data generated by centralised testing were prepared in the appropriate TESSy format and sent to the national contacts where additional epidemiological data were appended where available. After the creation of a data source for the GONOAMR data (Annex 5), the data were uploaded using the GONOAMR metadata in TESSy by each Member State and then approved. Data from centres performing decentralised testing were uploaded to TESSy in the same manner. The dataset was trimmed to the number of isolates specified in the reporting protocol for those countries that submitted excess isolate data.

Statistical analysis: Statistical analysis was performed in Stata v11.2. The Z-test was used to determine the p-value of the difference between epidemiological and AMR data collected in 2009 versus 2010, and to determine differences in age categories. A univariate analysis was performed to investigate associations between patient characteristics and antimicrobial resistance or decreased susceptibility. The odds ratios (OR) and 95% confidence

intervals (CI) were calculated where datasets contained sufficient numbers. A Pearson's chi-squared test was used to test if these odds ratios were significantly different from one. For small cell numbers, Fisher's exact test was performed. A multivariable analysis used logistic regression to model the odds of associations between ciprofloxacin susceptibility and concurrent chlamydia infection controlling for other variables. Significance for all tests was set at p=0.05.

Completeness of data: In Table 1 the completeness of data reporting is presented for both collection periods in 2010 and for the second collection period only, when extra variables were collected. The completeness of reporting for 'gender' and 'age' was high (over 98%), along with 'site of infection' and 'place of residence' at 95% and 83%, respectively. For the 'place of residence' variable it should be noted that 349 of the 720 entries were at the country level only. The remaining variables ranged from 30.4% for 'probable country of infection', to 70% for 'clinical service type'. The number of collected known variables for 'mode of transmission', 'previous gonorrhoea' and 'concurrent STI' are greater in the second collection period than the first, however the number of known 'site of infection' variables are less. Overall, there is not a great difference in the completeness of reporting between two data collection periods.

Table 1: Completeness of reporting, Euro-GASP 2010

Variables	Number and % of variables, first collection period, 2010 (n=900)		Number and % of variables, second collection period, 2010 (n=866)		Number and % of variables, TOTAL 2010 (n=1766)	
	No	**%**	**No**	**%**	**No**	**%**
Gender	892	99.1	857	99.0	1749	99
Age	889	98.8	851	98.3	1740	98.5
Mode of transmission	485	53.9	516	59.6	1001	56.7
Site of infection	873	97.0	810	93.5	1683	95.3
Previous gonorrhoea	336	37.3	355	41.0	691	39.1
Concurrent STI	360	40.0	419	48.4	779	44.1
Place of residence	**Not collected**		720	83.1	720	83.1
Clinical service type			610	70.4	610	70.4
Country of birth			392	45.3	392	45.3
Probable country of infection			263	30.4	263	30.4
HIV status			310	35.8	310	35.8

3 Results

3.1 Isolate and patient data

A total of 1766 isolates were collected over the 2010 collection period; 900 during the first collection period, and 866 during the second collection period. The number of isolates tested from each country varied from nine (Romania) to 222 (United Kingdom) (Table 2). The level of coverage (number of isolates tested compared to the number of reported cases as part of the enhanced epidemiological surveillance of STI in 2010) ranged from 1% (United Kingdom and Hungary) to 81% (Portugal), and four countries had 5% or less collection coverage (Hungary, Romania, Spain, and the United Kingdom). To monitor the progress of Euro-GASP the percentage of isolates tested in 2009 Euro-GASP is also displayed in Table 2. There has been a decrease in the percentage of isolates tested in Euro-GASP 2010 in five countries (Austria, France, Greece, Slovenia, and Sweden) due to a higher number of gonorrhoea cases reported in 2010 as compared to 2009 [14]. The decrease in the percentage of isolates tested in Malta was due to less isolates available for testing, and Norway only participated in the first 2010 collection period. The large increase from 13% to 70% in Slovakia is due to the participating laboratory collecting more isolates for Euro-GASP. The remaining countries had a similar level to 2009. Further work is required to support strain collection in Hungary, Latvia, Romania and Spain to increase the number of tested isolates with respect to representativeness. Even though the numbers of tested isolates in the Netherlands and the United Kingdom have doubled since 2009, the overall number of reported gonorrhoea cases in these countries is too large for Euro-Gasp to achieve any greater representation.

Table 2: Number of isolates tested in Euro-GASP 2010 and number of reported gonorrhoea cases, 2010

Country	Number of isolates tested	Number of cases reported[14]	% isolates tested 2010	% isolates tested 2009
Austria	110	339	32	77
Belgium	110	752	15	15
Cyprus†	12	23	52	N/A
Denmark	96	482	20	20
France	111	463	24	32
Germany	109	No data	--	--
Greece	97	312	31	67
Hungary†	14	1170	1	N/A
Ireland	88	614	14	N/A
Italy	105	251	42	48
Latvia	20	343	6	3
Malta	29	47	62	92
Netherlands	215	2815	8	5
Norway††	46	411	11	54
Portugal	72	89	81	75
Romania†	9	479	2	N/A
Slovakia	88	125	70	13
Slovenia	28	44	64	80
Spain	101	1944	5	5
Sweden	84	840	10	18
United Kingdom*	222	18580	1	1
Total	**1766**	**30123**	**6**	**6**

† Second collection period only; †† first collection period only

** 2010 isolates from the United Kingdom were only from England and Wales.*

Information on the source of the data as described by the 'National Protocols for the implementation of Euro-GASP, 2010' and /or the data source variable in TESSy is described in Table 3. National protocols were received from all countries except Hungary, Malta and Norway.

Table 3: Characteristics of national protocols for the implementation of Euro-GASP, 2010

Country	Coverage	Specimen Source	Comprehensiveness	Sampling method
Austria	Regional/capital area	STI clinics, DV clinics, GPs, hospitals	Sentinel	Consecutively but from a selective population
Belgium	National	GPs, hospitals, STI clinics, gynaecologists	Comprehensive	Consecutively
Cyprus	Regional	STI clinics, GPs, hospitals		Selectively
Denmark	National	STI clinics, DV clinics, GPs, hospitals	Comprehensive	Consecutively
France	National	GPs, STI clinics and hospitals	Sentinel	Consecutively
Germany	National	Medical practices, outpatients, hospital laboratories, public health departments, STI ambulances and Federal armed forces.	Other	Consecutively
Greece	National	STI clinics and general hospitals	Mainly STI clinics; general hospitals also report sporadic cases	Consecutively
Hungary*	Regional		Sentinel	
Ireland	Regional/capital area	STI clinic and STI outreach services	Other	Consecutively
Italy	Regional	STI clinics, hospitals, university/hospital microbiology units, DV clinics	Comprehensive	Consecutively
Latvia	National	STI clinics/inpatients	Other	Consecutively
Malta				
Netherlands	Regional/Amsterdam	STI clinic	Sentinel	Consecutively
Norway				No data source – did not participate in second collection
Portugal	National	STI clinics, DV clinics, GPs, hospitals, family planning clinics	Sentinel	Consecutively
Romania	Regional/capital area	DV clinics, outpatients	Other	Selectively
Slovakia	Regional	DV, urology and gynaecology practices.	Comprehensive	Consecutively
Slovenia	Regional	DV clinics	Other	Consecutively
Spain	National	STI clinics and hospitals	Sentinel	Consecutively
Sweden	National	STI clinics	Comprehensive	Consecutively
United Kingdom	Regional	GUM/STI clinics, GPs and outpatients	Sentinel	Consecutively

Comprehensive: Reporting is based on cases occurring within the whole population of the geographical area where the surveillance system is set up (national, regional, etc.).

Sentinel: Reporting is based on a selected group of physicians/hospitals/laboratories/or other institutions' notifications and/or cases occurring within a selected group of population defined by age group, gender, exposure or other selection criteria.

Other: Reporting is based on a part of the population or group of physicians (or other institutions) which is not specified, for example reporting of some laboratories with no selection criteria.

** Data for Hungary collected from the data source.*

The majority of gonococci (82%, n=1441) were collected from men. Gender was unknown for 17 cases (Table 4). The age range of the patients was 12 days to 76 years, with a mode and median age of 22 and 29 years, respectively; a total of 34% (599) of patients were younger than 25 years when age was known (Table 4). MSM were significantly older than females ($p<0.01$), with the highest and lowest number of <25-year-olds in the female (60%) and MSM patient groups (19.6%) (Table 5). Males are still significantly older than females if MSM and unknowns are excluded from the analyses ($p<0.01$).

Site of specimen was mainly genital (85%, n=1373), followed by rectal (18 female, 172 male), pharyngeal (19 female, 40 male) and other; site of infection was unknown for 83 cases.

Table 4: Overall patient characteristics, 2009–2010

	2009, Number (%)	2010, Number (%)	Difference in proportion (95% CI)	P value of difference (Z-test)
Total number of isolates	1366	1766		
Sex				
Male	1123 (83.7)	1441 (82.4)	1.3 (-1.4–3.9)	0.344
Female	219 (16.3)	308 (17.6)	1.3 (-1.4–3.9)	0.344

	2009, Number (%)	2010, Number (%)	Difference in proportion (95% CI)	P value of difference (Z-test)
Unknown	24	17		
Age (years)				
<25	422 (32.0)	599 (34.4)	2.5 (-0.9–5.8)	0.154
≥25	898 (68.0)	1141 (65.6)	2.5 (-0.9–5.8)	0.154
Unknown	46	26		
Mode of transmission				
Heterosexual (male and female)	431 (63.2)	605 (60.5)	2.7 (-2.0–7.4)	0.264
Female heterosexual	117 (17.2)	179 (17.9)	0.7 (-3.0–4.4)	0.694
Male heterosexual	314 (46.1)	426 (42.6)	3.4 (-1.4–8.3)	0.163
Men who have sex with men	251(36.8)	395 (39.5)	2.7 (-2.0–7.4)	0.264
Unknown	684	766**		
Site of infection				
Genital	1164 (86.5)	1426 (84.7)	1.8 (-0.7–4.3)	0.159
Pharyngeal	34 (2.5)	62 (3.5)	1.2 (-0.1–2.4)	0.07
Anorectal	138 (10.3)	191 (11.4)	1.1 (-1.2–3.3)	0.339
Other	9 (0.7)	7 (0.4)	0.3 (0.3–0.9)	0.34
Unknown	21	80		
Previously diagnosed				
Yes	84 (18.1)	145 (21)	2.8 (-1.9–7.4)	0.236
No	379 (81.9)	546 (79)	2.8 (-1.9–7.4)	0.236
Unknown	903	1075		
Concurrent STI				
Concurrent chlamydia	78 (14.3)	172 (22.1)	7.8 (3.6-11.9)	0.0004
Concurrent other STI (not HIV)	35 (6.4)	28† (3.6)	2.8 (0.5-5.4)	0.0177
No concurrent STI	433 (79.3)	579 (74.3)	4.9 (0.3-9.5)	0.0357
Unknown	820	987		
HIV status*				
Positive	N/D	48 (15.5)		
Negative	N/D	262 (84.5)		
Unknown	N/D	556		
Known HIV status – all males (718)	N/D	256 (35.7)		
Known HIV status – male heterosexual (229)	N/D	110 (48)		
Known HIV status – MSM (204)	N/D	127 (62.3)		
Known HIV status – all females (139)	N/D	54 (38.9)		
Known HIV status – female heterosexual (83)	N/D	50 (60.2)		

N/D: no data

Percentages calculated from known values.

** Data from 866 patients*

*** Includes one individual with unknown gender but with known mode of transmission; heterosexual*

† Includes two individuals with two concurrent STIs

Information on previous diagnosis of gonorrhoea was available for 39% (677) of cases, of which 21% (145) had a previous infection and 79% (546) did not. Information on concurrent STI was available for 44% (779) of cases; 22% (172) of patients had concurrent chlamydia, 4% (28) were infected with another STI, and 74% (579) were not co-infected with other STIs.

Information on mode of transmission was available for 56% (1000) of the cases, of which 61% (605) of the *N. gonorrhoeae* infections were heterosexually acquired (29.6% females and 70.4% males) and 40% (395) were from MSM. Forty-seven males with unknown mode of transmission had *N. gonorrhoeae* isolated from the pharynx or anogenital region.

HIV status data was collected from the second half of 2010 only; of the 16% (48) of HIV-positive cases from the HIV-known status dataset (310/866), all were MSM. HIV status data is more complete for MSM (62%) than for male heterosexuals (48%) and similar for female heterosexuals (60%).

There is little change in the epidemiological data when compared with 2009 (Table 3), other than with concurrent STI. The percentage of patients with concurrent chlamydia increased significantly from 14% in 2009 to 22% in 2010 ($p<0.01$), and there was a significant decrease in concurrent infections with other STI ($p<0.02$) and no concurrent STI ($p<0.05$). The same number of countries (n=13; Norway reported in 2009 only, and Ireland in 2010 only) reported on concurrent STI in 2009 and 2010, so the increase in the number of patients with a concurrent STI is not necessarily due an increase in reporting. Further country-specific data is presented in Annex 6 (Table A6.1).

Table 5: Patient age distribution, 2010

Variable	Number†	Age (years)			
		Range	Mode	Median	<25 (%)
All patients	1740	0*–76	22	29	599 (34.4)
Gender					
Male	1427	1–76	23	30	413 (28.9)
Female	305	0*–69	21	23	183 (60)
Mode of transmission					
Heterosexual (all)	602	15–72	22	26	252 (41.9)
Male heterosexual	423	16–72	22	28	143 (33.8)
MSM	392	16–69	27	32	77 (19.6)

† = where information is available

** = 12 days*

A breakdown of clinical service type, country of birth, place of residence and probable country of infection is shown in Table A6.2 (Annex 6). All three variables were collected in the second collection period only. To aid clinical service type analysis, the 14 coded variables were merged into six groups (Tables 6 and 7). The majority of patients attended a dedicated STI or sexual health clinic (73%) when the clinical service type was known.

Table 6: Description of clinical service type coding and subsequent grouping

Coded value	Description	Grouping
COMB	Combined service	STI and sexual health clinics
ANC	ANC	Antenatal
FPC	Family planning clinic	STI and sexual health clinics
ED	Hospital emergency department	outpatient clinic
GYN	Gynaecology clinic	outpatient clinic
ID	Infectious disease clinic	outpatient clinic
URO	Urology	outpatient clinic
O	Other	Other
GP	General practitioner	Primary Care
OPC	Other primary care	Primary Care
DV	Dermatology-venereology clinic	STI and sexual health clinics
STI	Dedicated STI clinic	STI and sexual health clinics
YTH	Youth clinics	STI and sexual health clinics
UNK	Unknown	Unknown

Table 7: Grouping of clinical service type coding

Grouping	Total
STI and sexual health clinics	444
Antenatal	0
Outpatients clinic	36
Other	42
Primary care	88
Unknown	256

Information on country of birth was supplied by 11 countries (Cyprus, Denmark, Greece, Hungary, Italy, Malta, the Netherlands, Portugal, Romania, Slovakia, and Slovenia), of which Denmark, Greece, Italy and the Netherlands reported patients that acquired gonorrhoea in their country but had a different country of birth, with the Netherlands having the largest number of nationalities (n=21). Of the 392 completed variables for country of birth, 87% (n=340) of patients were diagnosed with gonorrhoea in the same reporting country as their country of birth. The most common countries reported as different country of birth to the reporting country were Suriname (eight

patients), Romania and Albania (five patients) and Bulgaria (three patients). Probable country of infection data was supplied by eight countries (Denmark, France, Greece, Hungary, Italy, Latvia, Romania, and the United Kingdom), of which Denmark, Greece, Hungary, Italy, and the United Kingdom report patients acquiring gonorrhoea outside the reporting country. The majority of cases (94%; 247/263), most probably acquired gonorrhoea in the same country that reported the case. Most common countries reported as probable country of infection, that were different to the reporting country were Thailand (five patients) and Spain (three patients).

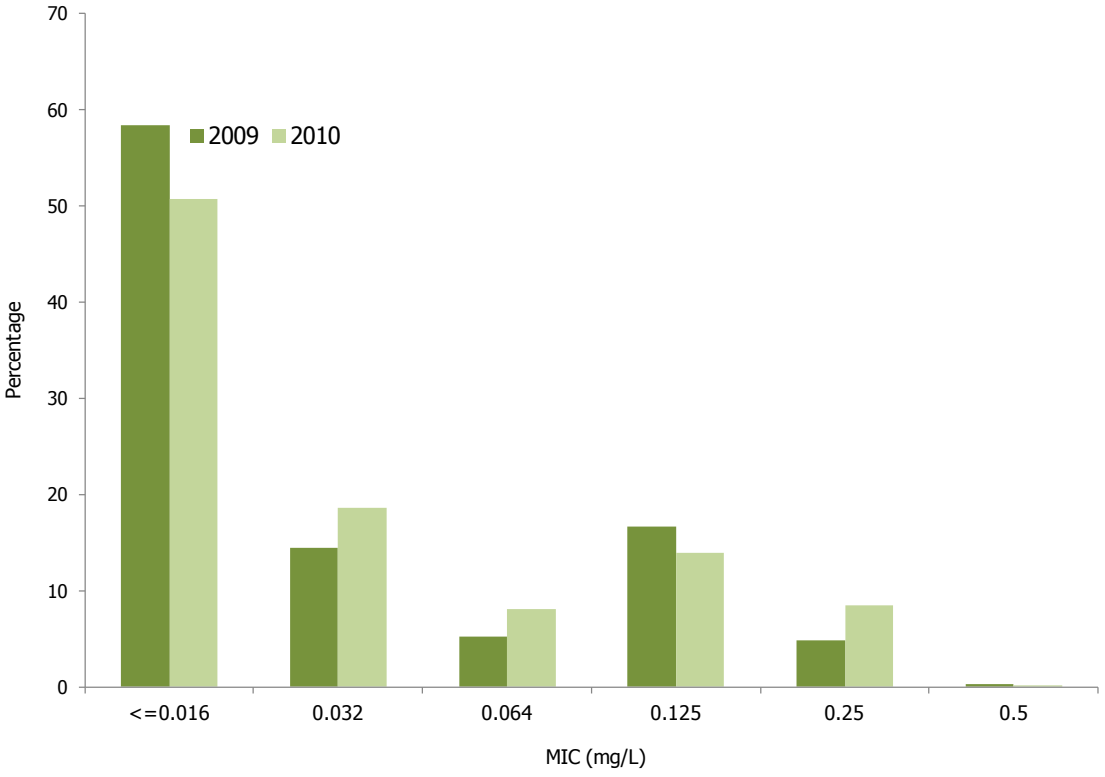
3.2 Antimicrobial resistance

The European guidelines for first-line empirical treatment of gonorrhoea [1] changed in 2009 to recommend usage of third-generation cephalosporins (either the oral agent cefixime or the parenteral agent ceftriaxone) or spectinomycin. Surveillance of susceptibility of these agents is therefore essential to ensure efficient patient management.

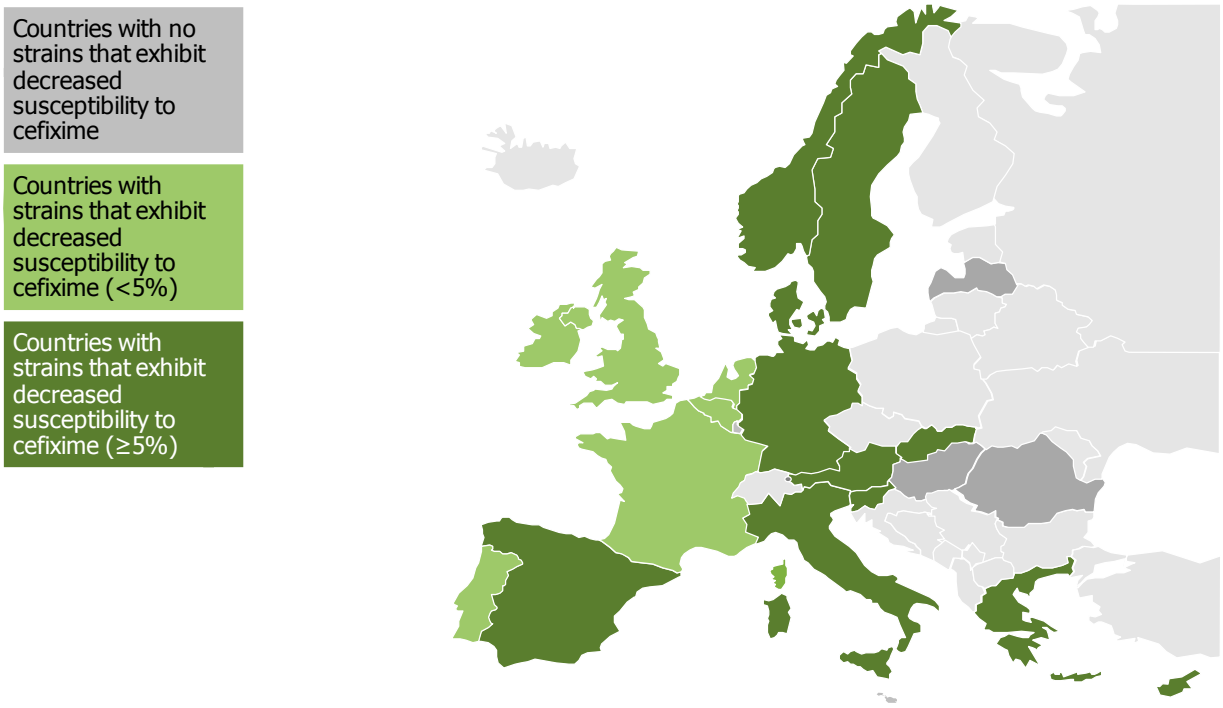
Ceftriaxone and cefixime

Nine per cent of the isolates (n=153) displayed decreased susceptibility (≥0.25 mg/L) to cefixime (Figure 1). The majority of isolates showed low MICs of ≤0.016, but it is of concern that the proportion of isolates displaying an MIC of >0.125 mg/L appears to have increased since 2009, given the documented relationship between treatment failure and MICs of this level [11;12]. There is an alarming 4% increase ($p<0.01$) in the number of isolates displaying decreased susceptibility to cefixime since Euro-GASP 2009 (Figure 1). This increase is not due to the additional countries in Euro-GASP in 2010 (Cyprus, Hungary, Ireland, and Romania), as the percentage of isolates displaying decreased susceptibility in Euro-GASP when these countries are removed is the same: 8.7% (143/1643).

Figure 1: Distribution of MIC with respect to cefixime in Euro-GASP, 2009–2010



Map 2: Geographical distribution of gonococcal isolates with respect to susceptibility to cefixime, 2010



Decreased susceptibility to cefixime was detected in 17 countries (Table 8), seven more than in 2009 (only confined to: Austria, Italy, Denmark, Slovenia, Belgium, Sweden, Germany, France, Norway, and the Netherlands). Eleven of these (65%) had more than 5% decreased susceptibility (Table 8). Five countries even reported a more than 15% decreased susceptibility. Decreased susceptibility to cefixime was not detected in four countries, all of which supplied low specimen numbers (Malta, Latvia, Hungary, and Romania). Map 2 displays the widespread geographical distribution of these isolates with decreased susceptibility to cefixime.

Most of the isolates displaying decreased susceptibility to cefixime were from men (84%) and were predominantly heterosexually acquired (39%), when sexual orientation was known (Table 8). However, as in Euro-GASP 2009, there were differences across countries with respect to sexual orientation of the cases, as the isolates were either from predominately MSM or heterosexuals in each country (Table 8). Eight individuals had concurrent chlamydia infection, one had concurrent syphilis, and two patients were HIV positive. The patient characteristics of those with isolates displaying decreased susceptibility to cefixime are quite similar as compared to the overall population. The exception is with age, as there is strong evidence of an association with decreased susceptibility to cefixime: individuals above 25 years are more likely to be infected with a strain displaying decreased susceptibility to cefixime (odds ratio <25 years to ≥25 years=1.62, CI 1.11–2.38, p=0.012). There was no evidence of an association with gender (odds ratio male to female=0.782; CI 0.489–1.25, p=0.305) and sexual orientation (odds ratio heterosexual to MSM= 0.72; CI 0.454–1.15, p=0.165). It should be noted that the number of unknown variables is large and so interpretations should be viewed with caution.

Table 8: Countries with isolates displaying decreased susceptibility (DS) to cefixime and epidemiological information, 2010

Country	Total number of isolates tested	Isolates with DS to cefixime		Age				Gender						Sexual orientation					
				Age		<25 years		Males		Females		Unknown		MSM		Heterosexual		Unknown	
		No.	(%)	Mean	Mode	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Austria	110	25	22.7	36	34	5	20.0	17	68.0	8	32.0	0	0.0	1	4.0	21	84.0	3	12.0
Belgium	110	4	3.6	35	39	1	25.0	2	50.0	2	50.0	0	0.0	1	25.0	0	0.0	3	75.0
Cyprus	12	6	50.0	25.6	n/a	1	16.7	5	83.3	0	0.0	1	16.7	0	0.0	0	0.0	6	100.0
Denmark	96	20	20.8	27.3	17	11	55.0	17	85.0	3	15.0	0	0.0	5	25.0	13	65.0	2	10.0
France	111	2	1.8	24.5	n/a	1	50.0	2	100.0	0	0.0	0	0.0	0	0.0	0	0.0	2	100.0
Germany	109	13	11.9	32.6	n/a	4	30.8	13	100.0	0	0.0	0	0.0	2	15.4	2	15.4	9	69.2
Greece	97	13	13.4	39.9	26	0	0.0	13	100.0	0	0.0	0	0.0	1	7.7	12	92.3	0	0.0
Ireland	88	4	4.5	32.3	n/a	1	25.0	4	100.0	0	0.0	0	0.0	0	0.0	0	0.0	4	100.0

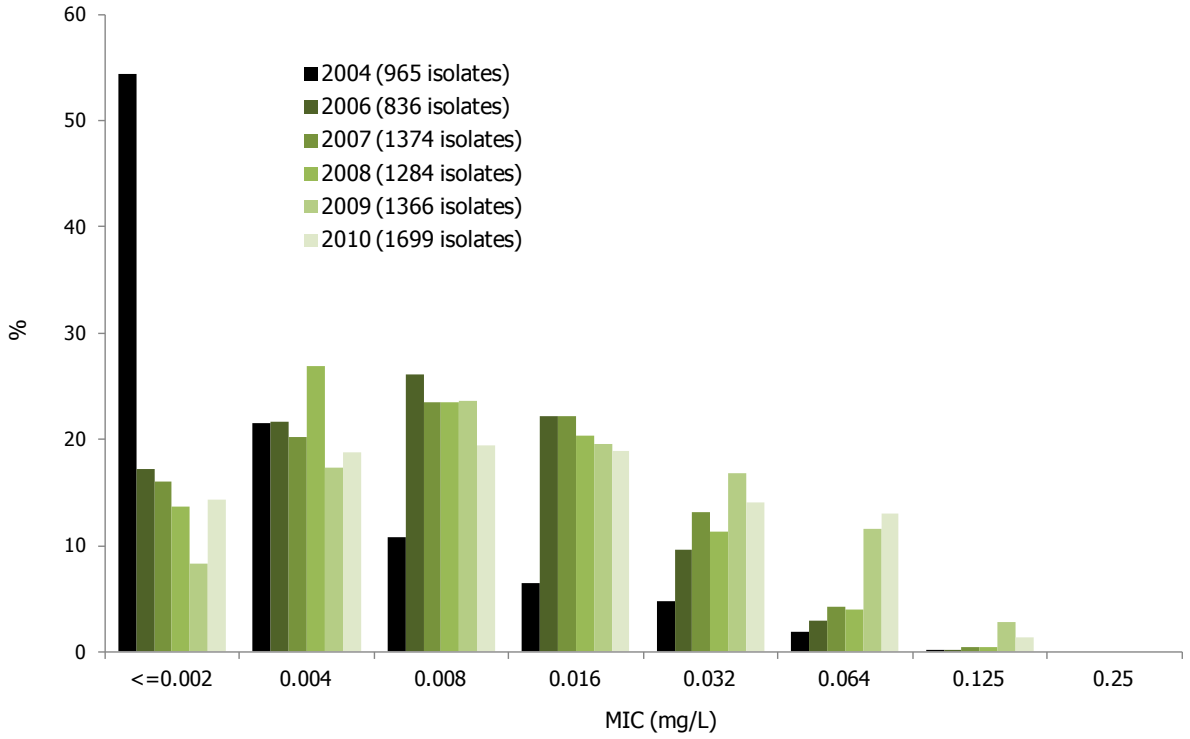
Country	Total number of isolates tested	Isolates with DS to cefixime		Age				Gender						Sexual orientation					
				Age		<25 years		Males		Females		Unknown		MSM		Heterosexual		Unknown	
		No.	(%)	Mean	Mode	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Italy	105	6	5.7	40.5	n/a	1	16.7	5	83.3	1	16.7	0	0.0	3	50.0	3	50.0	0	0.0
Netherlands	215	7	3.3	40	n/a	0	0.0	6	85.7	0	0.0	1	14.3	6	85.7	0	0.0	1	14.3
Norway	46	3	6.5	37	38	0	0.0	3	100.0	0	0.0	0	0.0	0	0.0	0	0.0	3	100.0
Portugal	72	1	1.4	26	n/a	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0
Slovakia	88	13	14.8	30.2	25	3	23.1	11	84.6	2	15.4	0	0.0	0	0.0	7	53.8	6	46.2
Slovenia	28	7	25.0	29.6	23	3	42.9	7	100.0	0	0.0	0	0.0	6	85.7	0	0.0	1	14.3
Spain	101	16	15.8	31.9	23	6	37.5	12	75.0	4	25.0	0	0.0	0	0.0	0	0.0	16	100.0
Sweden	84	6	7.1	41	n/a	1	16.7	4	66.7	2	33.3	0	0.0	0	0.0	0	0.0	6	100.0
United Kingdom	222	7	3.2	31.6	n/a	0	0.0	7	100.0	0	0.0	0	0.0	4	57.1	2	28.6	1	14.3
Total	**1694**	153	9.0	33.3	34	38	24.8	129	84.3	22	14.4	2	1.3	29	19.0	60	39.2	64	41.8

N/A – not enough data to establish a modal age

** Total of countries that have isolates with decreased susceptibility to cefixime. Overall prevalence across Europe is 8.7% (153/1766)*

No decreased susceptibility to ceftriaxone (≥0.25 mg/L) was detected in 2010 (Figure 2). The increases from 2009 onwards in the higher MIC categories could be due to selection pressure imposed by the use of ceftriaxone for the treatment of gonorrhoea and/or to the molecular mechanisms that additionally confer decreased susceptibility to cefixime.

Figure 2: Distribution of MIC for ceftriaxone, 2004–10



Note: 67 isolates were not analysed in the ceftriaxone MIC distribution as the MIC result of <0.016 mg/L was generated using an E-test with a higher MIC scale.

Other antimicrobials

The overall gonococcal resistance for ciprofloxacin, azithromycin and penicillin (high-level resistance only) is presented below (Table 9).

Table 9: Resistance to ciprofloxacin, azithromycin and penicillin antimicrobials, 2010

Country	Number of isolates tested	Resistance						Method of testing
		Ciprofloxacin		Azithromycin		PPNG		
		No.	**%**	**No.**	**%**	**No.**	**%**	
Austria	110	68	62	11	10	4	4	Centralised
Belgium	110	66	60	3	3	16	15	Decentralised – MIC
Cyprus†	12	12	100	0	0	0	0	Centralised
Denmark	96	66	69	16	17	16	17	Decentralised – E-test
France	111	36	32	0	0	4	4	Decentralised – E-test
Germany	109	64	59	9	8	5	5	Centralised
Greece	97	62	64	6	6	6	6	Centralised
Hungary†	14	11	79	0	0	0	0	Centralised
Ireland	88	31	35	1	1	6	7	Centralised
Italy	105	61	58	9	9	11	10	Decentralised – E-test
Latvia	20	2	10	1	5	0	0	Centralised
Malta	29	24	83	0	0	0	0	Centralised
Netherlands	215	87	40	9	4	12	6	Decentralised – E-test
Norway††	46	16	35	12	26	8	17	Centralised
Portugal	72	27	38	4	6	1	2^	Decentralised – E-test
Romania†	9	7	78	2	22	1	11	Centralised
Slovakia	88	80	91	26	30	1	1	Centralised
Slovenia	28	20	71	5	18	3	11	Centralised
Spain	101	61	60	10	10	6	6	Decentralised – MIC
Sweden	84	58	69	2	2	37	44	Decentralised – E-test
United Kingdom	222	71	32	1	0	13	6	Decentralised – MIC
Total	**1766**	930	53	127	7	150	9*	
95% CI		50.3–55		5.51–7.89		7.23–9.89		
Median		58		4		5		

† Second collection period only

†† First collection period only

CI = confidence interval of the total % mean

^ Calculated from 51 isolates with penicillinase results

** Calculated from 1745 isolates with penicillinase results*

Ciprofloxacin

Resistance (≥1 mg/L) in 2010 ranged from 10% (Latvia) to 100% (Cyprus); the mean was 53% (Table 9). Resistance rates for ciprofloxacin still remain high although rates have decreased significantly ($p<0.0002$, Z-test) for the first time by 10% between 2009 (62.7%) and 2010 (52.7%) (Figure 3).

Azithromycin

There is considerable variation in azithromycin resistance (≥1 mg/L) as the resistance levels ranged from 0% (Cyprus, France, Hungary, Malta, and the United Kingdom) to 30% (Slovakia), with a mean of 7% (Table 9). No isolates displayed high-level resistance to azithromycin (>256 mg/L). There is no apparent trend between 2004 and 2010; azithromycin resistance increased from 2% in 2008 to 13% in 2009 but has decreased significantly ($p<0.0002$, Z-test) to 7% in 2010 (Figure 3). As in previous years, the modal MIC of resistant isolates to azithromycin was 1 mg/L, which is the breakpoint used for categorising resistance. Isolates with an MIC on the breakpoint are just one doubling dilution from giving a susceptible category, which may explain the fluctuating resistance rates observed from 2004 to 2010.

Penicillin

High-level plasmid-mediated resistance to penicillin (penicillinase-producing *N. gonorrhoeae*, (PPNG)) ranged from 0% (Cyprus, Hungary and Malta) to 44% (Sweden), with a mean of 8.6% (Table 9). High-level resistance to penicillin (penicillinase-producing *N. gonorrhoeae*, PPNG) has remained fairly constant over the years at 8.6–13% (Figure 3), however the 6% decrease from 2009 (12.6%) to 2010 (8.6%) is significant ($p=0.0003$, Z-test).

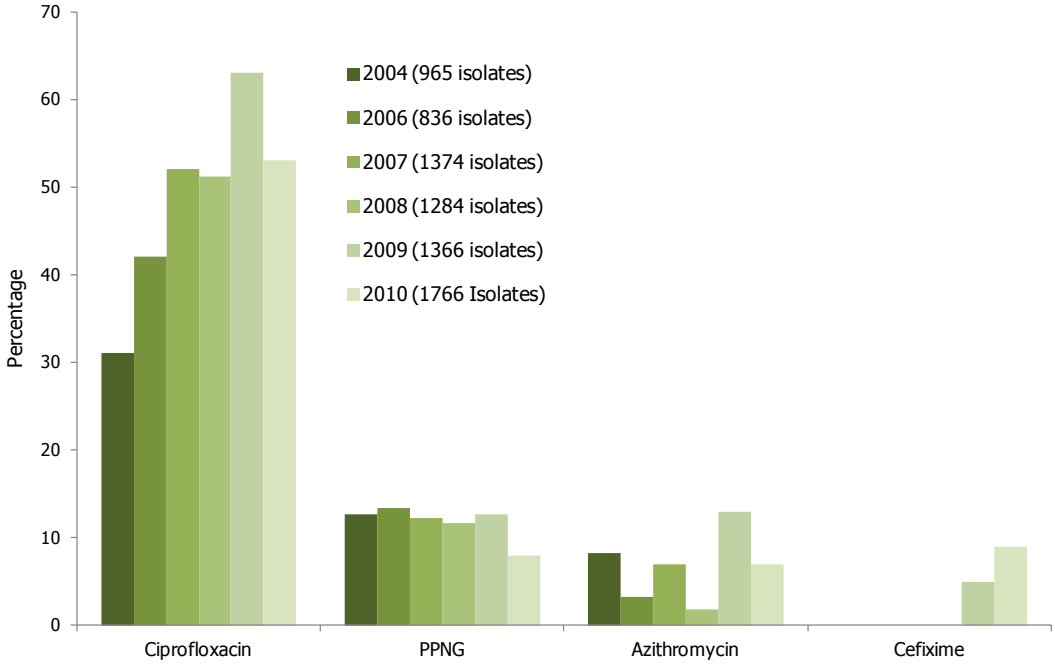
Spectinomycin

No resistance to spectinomycin (>0.64 mg/L) was detected in 2010 (1666 isolates tested). No resistance to spectinomycin was demonstrated in 2008 to 2010, the years when this agent was tested.

Gentamicin

As yet, there are no breakpoints for gentamicin, but the overall MIC distribution continues to be low in all European countries (MIC50 and MIC90 8 mg/L). The MIC range was 0.5–16 mg/L (1500 isolates tested), which is a dilution lower than the previous year. This may be due to the use of E-tests by some laboratories performing decentralised testing. Gentamicin E-tests have previously been found to result in lower MICs when compared to the agar dilution technique [15].

Figure 3: Overall percentage of resistant *Neisseria gonorrhoeae*, 2004–2010



Resistance by patient characteristics was calculated (Table 10), and statistical analysis was performed to explore associations between resistance and patients characteristics (Annex 7). Overall the distribution of resistance is similar across the patient groups and specimen types, other than for the following; there is strong evidence of an association between concurrent chlamydia infection and ciprofloxacin susceptibility (odds ratio no concurrent chlamydia to concurrent chlamydia=0.42, CI 0.295–0.61, p<0.0001) by univariate analysis and also following multivariable analysis to control for age and sexual orientation (odds ratio=0.47, CI 0.32–0.7, p<0.0001). Slight evidence of an association between HIV-positive status and ciprofloxacin susceptibility was observed (odds ratio HIV negative to HIV positive=0.46, CI 0.239–0.871, p=0.015) (Annex 7, table A7.1). The association between age and decreased susceptibility to cefixime has been described above.

Table 10: Resistance to ciprofloxacin, azithromycin, cefixime and penicillin by patient characteristics, 2010

Country	Total	Resistance							
		Ciprofloxacin		Azithromycin		Cefixime†		PPNG	
		No.	%	No.	%	No.	%	No.	%
Age									
<25 years	599	257	42.9	38	6.3	38	6.3	38	6.4
≥25 years	1141	658	57.7	88	7.7	113	10	111	9.8
Transmission									
MSM	395	196	49.6	30	7.6	29	7.3	22	5.6
Heterosexual	606	332	54.8	47	7.8	60	9.9	42	7
Site of infection									
Genital	1426	760	53.3	109	7.6	131	9.2	116	8.1
Pharyngeal	62	38	61.0	3	4.8	7	11.9	4	6.6

Country	Total	Resistance							
		Ciprofloxacin		Azithromycin		Cefixime†		PPNG	
		No.	%	No.	%	No.	%	No.	%
Anorectal	191	92	48.2	11	5.8	11	5.8	13	6.8
Previous GC									
Yes	145	70	48.3	8	5.5	12	8.3	8	5.6
No	546	311	57.0	53	9.7	58	10.6	40	7.4
Concurrent chlamydia									
Yes	172	55	32.0	8	4.7	8	4.7	10	5.9
No	607	319	52.6	48	7.9	50	8.3	31	5.2
HIV status*									
Positive	48	17	35.4	4	8.3	1	2.1	2	4.3
Negative	262	143	54.6	35	13.0	23	8.8	18	6.9
Overall resistance		930	52.7	127	7.2	153	8.7	150	8.6

† Decreased susceptibility

** Data only collected during second collection period.*

4 External quality assessment

4.1 Background

A major objective of the STI microbiology project is to strengthen the surveillance of *N. gonorrhoeae* antimicrobial susceptibility in EU/EEA Member States. An external quality assessment (EQA) scheme for *N. gonorrhoeae* antimicrobial susceptibility was established in 2009 and is offered to participating laboratories in Euro-GASP. An EQA scheme is an essential component of any surveillance programme; ensuring comparability of data and successful performance in EQA will be essential for laboratories participating in decentralised testing as part of AMR surveillance across Europe [16].

The United Kingdom National External Quality Assessment Service (UK-NEQAS) provides a genital pathogens scheme for pathogen identification and antimicrobial susceptibility testing. The scheme contains two pathogens per distribution, distributed three times each year. An additional panel of isolates from the European STI network are incorporated into this scheme so more extensive susceptibility testing EQA can be implemented.

We describe a summary of the 2010 to 2011 EQA scheme, and a full report is available in EPIS-STI [17].

4.2 Antimicrobial susceptibility testing external quality assessment scheme

In October 2010 (QA10-2) and February 2011 (QA11), participating laboratories received the UK-NEQAS genital pathogen EQA for identification and susceptibility testing. The results were reported back to UK-NEQAS. In addition, five gonococcal isolates for susceptibility testing were included in the October 2010 distribution, with one isolate in duplicate; and five in the February 2011 distribution, with one isolate in triplicate to measure intra-laboratory reproducibility. The isolates included in the panel were chosen to cover a range of susceptibilities to therapeutic antimicrobial agents and were selected from a global panel of well-characterised strains. The panels (QA10-2 and QA11) were received by 20 participating laboratories from 18 countries. No EQA results are available from Cyprus, Norway, and Romania.

Susceptibility testing methods

Participating laboratories used their own routine methodology and were requested to test the panel of cultures against the following antimicrobials where possible. The antimicrobials mentioned below are the range of antimicrobials used in the Euro-GASP AMR sentinel surveillance protocol:

- azithromycin
- cefixime
- ceftriaxone
- ciprofloxacin
- gentamicin
- spectinomycin
- beta-lactamase testing

4.3 Results

Results were returned centrally through the European *Neisseria gonorrhoea* antimicrobial resistance external quality assessment programme website http://www.hpa-bioinformatics.org.uk/amr_eqa/home.php. Each laboratory reported details of the testing methodology used and described the breakpoints for determining the category of resistance (resistant, intermediate, or susceptible) for each antimicrobial. The majority of laboratories used the Clinical Laboratory Standards Institute (CLSI) guidelines; other susceptibility criteria used were Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP), European Committee on Antimicrobial Susceptibility Testing (EUCAST), and Swedish Reference Group on Antibiotics (SRGA).

Laboratories reported the results for each strain as the category of resistance and the MIC or zone of inhibition for disc diffusion; after receipt, results were decoded and sent back to the laboratories so that the centres could study their intra-laboratory reproducibility and start working on any identified problems immediately. Centrally, analysis was performed using the category of resistance results to allow for differences in methods and breakpoints used. When all EQA results from participating laboratories were submitted, the consensus was ascertained by establishing the category of resistance that occurred most often. The overall consensus category, percentage

concordance, the modal/range MIC, and mean/range disc zones for each strain in both EQA panels is shown in Table 11.

Resistance categories concordance

The overall concordance of resistance categories for both EQA panels was highest for spectinomycin (100%) and lowest for azithromycin (89%). The agar dilution method and the disc diffusion method gave the highest concordance between the centres, although it should be noted that just three centres used the agar dilution method and six used the disc diffusion method.

The comparison of the overall concordance from previous QA panel distributions (QA2007, QA2008, QA2009) [4] and EQA panels (QA2010-1) [5] (Figure 4) shows that the concordance of resistance categories is very good over the five distributions. It should be noted that the 2007–09 panels contained 30 isolates (10 in triplicate) and the 2010 EQA panel is 10 isolates per year (2010–2011).

Beta-lactamase

The overall concordance for the detection of beta-lactamase production was 97.4%. Of the centres that tested for beta-lactamase production, two centres in each EQA panel did not achieve fully concordant results.

Minimum inhibitory concentration concordance

A high proportion of isolates MIC (agar dilution and E-tests) were within one dilution of the modal MIC (92%), and just 6% within two doubling dilutions. On just twelve occasions (2%), isolate MICs differed from the modal MICs by more than two dilutions; five of which were ciprofloxacin, four were ceftriaxone, and three were cefixime. Overall, the MIC concordance demonstrates the high level of comparability between the participating laboratories and these two methods (agar dilution and E-test).

4.4 Conclusions

There appears to be less variation of breakpoints for azithromycin and gentamicin which may suggest breakpoint harmonisation in the absence of published breakpoints. The overall concordance is high (>90%) for all antimicrobials other than azithromycin (89%). Generally concordance was lower due to strains being close to breakpoints. The overall concordance for the agar dilution and disc method was higher although less centres used these methods when compared with the E-test.

Further participation with the UK-NEQAS genital pathogens scheme EQA should be encouraged to help build confidence, competence and capability in the laboratory isolation and identification of *N. gonorrhoeae*.

Table 11: Consensus results from October 2010 and February 2011 EQA

Strain		Ciprofloxacin consensus	Ceftriaxone consensus	Cefixime consensus	Azithromycin consensus	Spectino-mycin consensus	Genta-micin consensus	Beta-lactamase consensus
	Consensus category	I	S	S	S	S	S	
QA10-11	Modal (range) MIC for E-test* and agar dilution (mg/L)	0.125 (0.064-0.25)	†0.008/0.016 (0.004-0.032)	<0.016 (0.008-0.032)	0.25 (0.064-1)	8 (4-32)	4 (2–4)	NEG
(WHO G)	Mean (range) diameter for disc diffusion (mm)	36 (30-42)	42 (30-52)	41 (37-46)	36 (28-41)	27 (25-32)	20 (19–21)	100%
	% concordance of resistance category	60	100	100	94	100	100	
	Consensus category	R	S	S	S	S	S	
QA10-12	Modal (range) MIC for E-test* and agar dilution (mg/L)	4 (>1->32)	0.008 (0.002-0.032)	<0.016 (0.008-0.032)	0.25 (0.064-0.5)	8 (4-32)	4 (2-8)	POS
(WHO N)	Mean (range) diameter for disc diffusion (mm)	18 (14-25)	48 (40-54)	46 (43-51)	39 (36-42)	31 (22-35)	20 (18-21)	89%
	% concordance of resistance category	100	100	100	100	100	100	
	Consensus category	S	S	S	R	S	S	

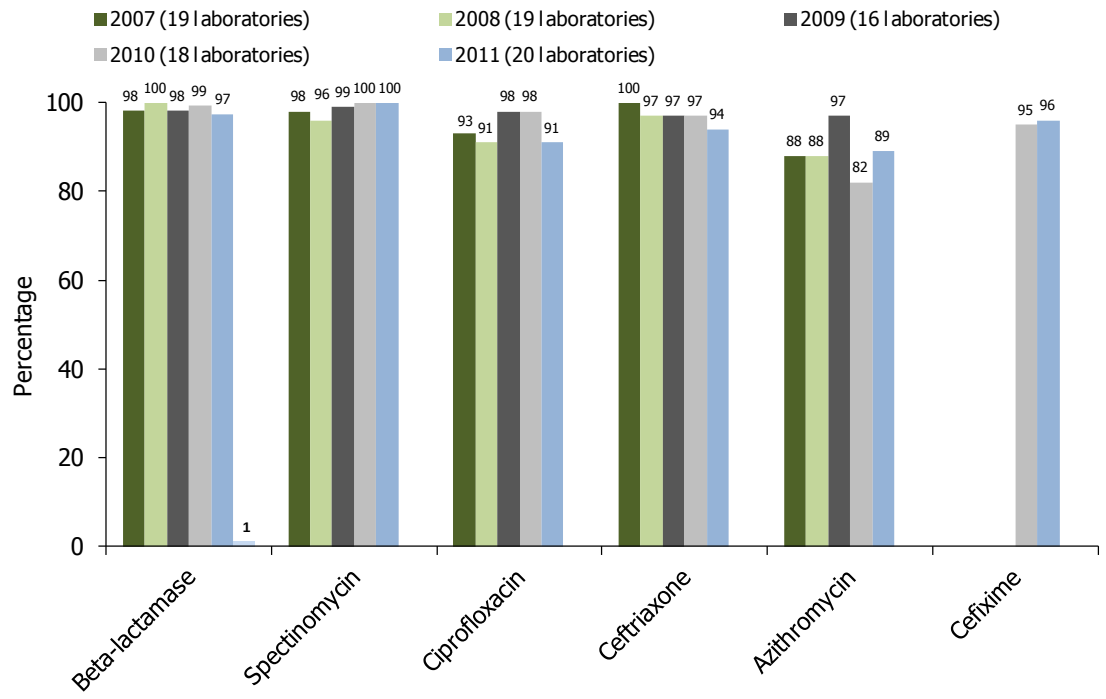
Strain		Ciprofloxacin consensus	Ceftriaxone consensus	Cefixime consensus	Azithromycin consensus	Spectino-mycin consensus	Genta-micin consensus	Beta-lactamase consensus
QA10-13	Modal (range) MIC for E-test* and agar dilution (mg/L)	0.004 (0.002-0.008)	0.008 (0.002-0.032)	0.016 (0.008-0.032)	4 (1-8)	8 (4-32)	4 (2-8)	NEG
QA10-15	Mean (range) diameter for disc diffusion (mm)	49 (32-58)	46 (32-51)	43 (40-48)	26 (22-30)	29 (22-35)	20 (18-21)	100%
(WHO P)	% concordance of resistance category	98	100	100	94	100	100	
	Consensus category	R	S	S/I	S	S	S	
QA10-14**	Modal (range) MIC for E-test* and agar dilution (mg/L)	>32 (>1->32)	†0.125/0.25 (0.064-0.25)	†0.125/0.25 (0.016-0.25)	0.5 (0.125-0.5)	8 (8-32)	4 (4-8)	NEG
(WHO L)	Mean (range) diameter for disc diffusion (mm)	6 (0-11)	40 (39-45)	38 (34-42)	36 (33-40)	29 (28-31)	17 (14-20)	100%
	% concordance of resistance category	100	84	81	87	100	92	
QA11-01	Consensus category	R	S	S	S	S	S	
QA11-03	Modal (range) MIC for E-test* and agar dilution (mg/L)	1 (1–4)	0.008 (0.004–0.125)	0.016 (<0.016–0.032)	0.25 (0.125–1)	8 (2–32)	4 (2–8)	POS
QA11-04	Mean (range) diameter for disc diffusion (mm)	24 (15–31)	47 (43–52)	43 (40–45)	36 (32–40)	29 (25–35)	18 (14–24)	97%
(WHO M)	% concordance of resistance category	92	100	100	76	100	100	
	Consensus category	R	I	S	S	S	S	
QA11-02**	Modal (range) MIC for E-test* and agar dilution (mg/L)	>32 (>1–>32)	0.25 (0.125–0.5)	0.125 (0.064–0.5)	0.25 (0.125–1)	16 (4–16)	4 (2–8)	NEG
(WHO L)	Mean (range) diameter for disc diffusion (mm)	7 (0–16)	41 (35–51)	38 (33–44)	39 (35–43)	31 (29–35)	20 (18–23)	100%
	% concordance of resistance category	100	74	88	72	100	100	
	Consensus category	S	S	S	S	S	S	
QA11-05	Modal (range) MIC for E-test* and agar dilution (mg/L)	0.004 (<0.002–0.032)	<0.002 (<0.002–0.016)	<0.016 (0.002–0.016)	0.125 (0.064–0.25)	8 (8–32)	4 (2–8)	NEG
(WHO F)	Mean (range) diameter for disc diffusion (mm)	40 (26–51)	49 (47–52)	46 (43 -49)	36 (33–41)	26 (23–27)	20 (18–22)	95%
	% concordance of resistance category	90	100	100	100	100	100	

*** Same strain distributed in the two EQA panels*

† No consensus MIC available, but all MICs below value shown.

Number of centres used to calculate disc diffusion mean diameter; ciprofloxacin=6; ceftriaxone=5; azithromycin, cefixime and spectinomycin=4; gentamicin=3

Figure 4: Inter-laboratory concordance



** Testing of cefixime became part of the EQA scheme from 2010. During the ESSTI AMR project cefixime was not part of the antimicrobial panel but is now included in the ECDC Euro-GASP AMR project.*

The QA10-02 andQA11 distributions were joined together for EQA 2011.

5 Conclusions

5.1 Gonococcal antimicrobial resistance

Cefixime remains a recommended therapy for gonorrhoea across Europe [1] and the 9% level of decreased susceptibility identified in 17 countries is of great concern. Most of the isolates displaying decreased susceptibility to cefixime were from men and were heterosexually acquired. However, the patient characteristics of those with isolates displaying decreased susceptibility to cefixime do not differ greatly when compared to the overall population. The exception is for age, where patients with decreased susceptibility to cefixime tend to be older.

Due to the rapid increase and distribution of these isolates it is to be expected that treatment failures will become more likely. The current situation with respect to the emergence of multidrug-resistant gonorrhoea calls for a response plan to support Member States in the control of gonorrhoea. Public health experts and clinicians need to be informed about the current critical situation and should be vigilant for treatment failures. These findings also suggest that the European gonorrhoea treatment guidelines need to be reviewed as a matter of urgency.

Ceftriaxone continues to be an appropriate treatment option as all isolates tested were susceptible. It is obvious that the situation needs to be monitored carefully due to the increasing number of isolates with higher MICs. The loss of both cefixime and ceftriaxone as treatment options for gonorrhoea would be a major public health concern.

Even though the rates of ciprofloxacin and azithromycin resistance have both decreased since 2009, both remain high at 53% and 7%, respectively. This again reiterates the fact that these antimicrobials should not be used for empirical treatment unless the susceptibility profile of the isolates is known in advance of treatment.

Gentamicin and spectinomycin both continue to be an option for gonorrhoea treatment. However the lack of European clinical data for gentamicin and the difficulties in acquiring spectinomycin make these options less than satisfactory.

There was little change in the epidemiological data when compared with 2009, other than with concurrent STI as concurrent chlamydia infection increased significantly from 14% to 22% in 2010, and there was a significant decrease in concurrent infections with other STI (35%–28%) and no concurrent STIs (74%–79%). Overall the distribution of resistance is similar across the patient groups and specimen types, other than an association between concurrent chlamydia infection, age and ciprofloxacin susceptibility, and also between HIV-positive status and ciprofloxacin susceptibility.

5.2 Further developments of Euro-GASP

In 2010, the Euro-GASP has evolved substantially in efforts to increase the timeliness of reporting and to have more frequent testing cycles. This has resulted in a programme that introduced biannual and decentralised testing across several Member States. The development and implementation of the GONOAMR record type in TESSy is also an important component in improving the future timeliness of reporting. An additional four countries (Cyprus, Ireland, Hungary, and Romania) agreed to participate in Euro-GASP and 400 extra strains were tested in 2010. Further participation of additional Member States will be encouraged in the coming years.

Euro-GASP is evolving to collect more timely and useful data, and the programme will be adapted according to the epidemiological situation and needs of the network.

A limitation of this programme is the lack of available epidemiological information for the collected isolates as that limits the analyses and hampers the focus in national control programmes. Improved provision of epidemiological data will give more power to the conclusions and will enable to identify those at risk of acquiring AMR gonorrhoeae.

5.3 Quality assurance

There continues to be common features in the methodology used across Europe, such as the use of GC agar base, making up suspensions equivalent to a 0.5 McFarland standard and adherence to CLSI breakpoints. The overall concordance is high (>90%) for all antimicrobials other than azithromycin (89%). The comparison of the overall concordance with the previous EQA panels shows that the concordance remains high. The inter-laboratory concordance for spectinomycin and ceftriaxone has remained relatively steady over the past five years.

This continuous high level of comparability allows comparison of surveillance data from the members of the STI surveillance network with confidence and gives even more evidence to support decentralised testing as a viable option for Euro-GASP.

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Annex 1. Framework for the European Gonococcal Antimicrobial Surveillance Programme, 2010–2012: reporting protocol and analysis plan

A gonococcal antimicrobial surveillance programme will be implemented from 2010, which allows for more frequent reporting of developments in antimicrobial resistance in Europe.

A1.1 Isolate collection

Numbers

Each country should aim to collect a minimum of 110 gonococcal isolates each year, with the overall aim to retrieve and test a minimum of 100 isolates. For countries where 110 isolates represents less than 10% of the total number of cases of gonorrhoea (Spain, the United Kingdom and the Netherlands), up to a maximum of 200 isolates should be collected.

Selection criteria

Isolates should be selected from consecutive patients and from patients representing different patient groups and geographical regions within the country to reflect the distribution of gonorrhoea cases in that country, if known. Consecutive isolate selection may not be possible if particular patient groups/regions are selected or if isolates with corresponding epidemiological data are selected in place of isolates with no data. Care should be taken to avoid selection bias.

Multiple isolates from a single patient should be considered as a single episode of infection if the isolates were recovered within a period of ≤4 weeks, and only one isolate should be submitted, according to the hierarchy below. Where more than one isolate is collected from a patient, then a hierarchy of desired isolates for collection would be:

Males: pharyngeal; rectal; urethral; other

Females: pharyngeal; cervical; other anogenital (high vaginal swab (HVS)/rectal/urethral); other

Given the current view that cephalosporin resistance emerged through interaction between commensal *Neisseria* species and *N. gonorrhoeae* in the pharynx [18] and the fact that cephalosporins and most other antimicrobials have a lower efficacy in the pharynx, pharyngeal samples (where available) will be selected first as resistance is most likely to develop at this site.

Frequency

The timeliness of testing needs to be improved to allow for more frequent reporting of AMR. It is proposed that this is implemented in phases so laboratories can work to the model of 'best practice', ideally to ultimately achieve biannual decentralised testing.

Submission of isolates for centralised testing

Each participating laboratory will be provided with cryopreservative beads to store gonococcal isolates until collection by courier at intervals (twice yearly minimum for countries collecting the full 110 strains).

Improving timeliness in 2010–2012

The following testing scheme for 2010 to 2012 is proposed and summarised in Table A1.

AMR surveillance, year 2010

This period will introduce biannual centralised testing for all laboratories and also pilot decentralised testing in a subset of laboratories. It is proposed that laboratories collect up to 55 isolates (or 110 for Spain, the UK, and the Netherlands) twice per year in a six-week period starting in Q2 and Q4:

- Q2 – May/June (week 20–25): National samples of isolates will be sent to and tested by the three sentinel laboratories. Centralised testing in the short term will continue to collect longitudinal data on the new antimicrobial panel.
- Q4 – November/December (week 45–50): A pilot project on decentralised testing will be carried out by laboratories fulfilling the EQA criteria (see 2.4 susceptibility testing). All other laboratories will continue with centralised testing. In those laboratories performing decentralised testing, data is required from 50 or 100 isolates.

For laboratories with low collection rates, the collection period can be extended to include the time period preceding the collection start dates (Q1 and Q3) until up to 55 isolates are collected.

AMR surveillance, years 2011–2012 (Table A1)

- It is proposed that decentralised testing will be extended but for laboratories unable to do this, biannual centralised testing will continue.
- The biannual collection period will remain in Q2 (May/June, week 20–25) and Q4 (November/December, week 45–50) in 2011 and 2012.

Table A1. Summary of proposed collection schedules to achieve biannual centralised and decentralised testing and piloting of quarterly testing

Year	Quarter	Isolate collection (centralised testing)	AMR data collection (biannual decentralised testing*)
2010	**Q1** (Jan–Mar)		
	Q2 (Apr–Jun)	55 isolates	Not applicable
	Q3 (Jul–Sep)		
	Q4 (Oct–Dec)	55 isolates	50 isolates
2011	**Q1** (Jan–Mar)		
	Q2 (Apr–Jun)	55 isolates	50 isolates
	Q3 (Jul–Sep)		
	Q4 (Oct–Dec)	55 isolates	50 isolates
2012	**Q1** (Jan–Mar)		
	Q2 (Apr–Jun)	55 isolates	50 isolates

**Only for countries fulfilling the selection criteria described in section 2.4*

A1.2 Data collection

This surveillance system aims to link NG susceptibility data to basic epidemiological data in order to get an overview of risk groups and target prevention measures. All data from the AMR susceptibility testing should be submitted to TESSy. The set of variables are described in Annex 4.

Epidemiological information

A set of variables is collected as part of the enhanced STI surveillance and submitted by the national STI surveillance contact points in each country. To avoid duplication in data collection, it is suggested that the same source of epidemiological information is used for the AMR NG surveillance database if the epidemiological information can be linked to the microbiological information, which is presented in a case-based format.

The method of obtaining epidemiological data could be implemented as follows:

- The microbiology national contact points who submit or test isolates for AMR surveillance will contact the national contact points for STI surveillance and request the collected epidemiological data. This will require a patient identifier – at national level – to link the information. However the patient identifier should not be sent to TESSy; it should be used for internal purposes only.
- If the information submitted by the national contact points for STI surveillance cannot be linked to gonococcal isolates and associated antimicrobial susceptibility data (e.g. if the data for STI surveillance is aggregate, or there is no shared patient identifier between the epidemiological and microbiological data), the national contact points for STI microbiology will enter whatever epidemiological data the laboratory could retrieve, e.g. data submitted with the isolate, or data that was requested from the place of isolate submission.

In both instances the epidemiological and microbiology data will be submitted to TESSy by the national STI contact point (microbiologist, epidemiologist, or data manager).

Please note that the submission of AMR results should not be delayed by incomplete epidemiological data; AMR results should be uploaded as soon as they become available. Incomplete datasets can be replaced by complete data at a later stage. The set of variables for gonococcal AMR surveillance is listed in Annex 4.

Centralised testing

Where centralised testing is carried out, the hub will send results back to the laboratories in the Member States. Epidemiological and AMR data should then be entered in TESSy by the Member States. This could be done by the microbiology or epidemiological focal point as discussed above. As a part of quality control, the hub will check with the TESSy helpdesk whether all tested cases were reported through TESSy so a follow-up can be organised with individual laboratory/epidemiological contacts.

A1.3 Susceptibility testing

While a centralised testing strategy offers the advantage of ensuring stricter comparability of testing methodology and data, this approach is a barrier to the timeliness of reporting surveillance data. As described above, decentralised testing will be trialled in a limited number of pilot laboratories in the 2010 (November) NG strain collection period.

Centralised testing

Testing will initially be centralised and performed at one of the three centres. All isolates will be tested for susceptibility to the following panel of therapeutically relevant antimicrobials:

- azithromycin (breakpoint)
- cefixime (E-test)
- ceftriaxone (E-test)
- ciprofloxacin (breakpoint)
- gentamicin (agar dilution/E-test)
- spectinomycin (breakpoint)

Penicillin and tetracycline will not be tested as they are no longer used to treat gonorrhoea. Further details on the testing methodology can be found in Annex 3.

Decentralised testing

Laboratories from individual countries meeting the criteria described below will perform their own susceptibility testing and enter their results directly into TESSy. Even though susceptibility testing methods may vary, it is important that the breakpoints are harmonised and breakpoints used in Euro-GASP are adhered to (Annex 3). The remaining laboratories will collect and refer isolates for centralised testing as described above. Within this group, some laboratories may be identified who could submit their own data in the future after further training, support, harmonisation, and quality assurance of methods, etc.

Selection criteria for decentralised testing

To ensure the data quality is maintained for decentralised testing, the following criteria will be applied when selecting individual laboratories which use their own methods to test the agreed core antimicrobial panel:

- Laboratories have to perform consistently well in the EQA: no more than 5% of MIC results should differ by more than two doubling dilutions of the modal MICs.
- Laboratories need to demonstrate good comparability: at least 90% concordance between resistance category, and no more than 5% of MIC results should differ by more than two doubling dilutions between the laboratories own national or regional susceptibility testing data and the susceptibility data generated by centralised susceptibility testing.

Procedure for decentralised testing

Laboratories identified as suitable candidates for participating in decentralised testing would be required to:

- submit MIC data and the corresponding resistance category, generated by E-tests, agar dilution method or agar breakpoint method;
- use appropriate control strains (supplied by ECDC) and submit IQC data for quality assurance purposes;
- test a core group of antimicrobials, ideally identical to the core panel tested by the centralised approach (absolute minimum requirement for testing: ceftriaxone and cefixime):
  - ceftriaxone
  - cefixime
  - azithromycin
  - gentamicin
  - ciprofloxacin

  - spectinomycin
  - any other antimicrobial that is used in their country/region for first line therapy for uncomplicated urogenital gonorrhoea.
- submit susceptibility data to TESSy in a timely manner to ensure in timely reporting.

In the short term it is anticipated that data will be submitted from one laboratory per country. If multiple testing sites exist within a country, data should be collected locally and submitted by the (main) national STI laboratory contact.

A1.4 Data analysis

Collated data for each report will be analysed for emerging trends in antimicrobial resistance. It may be necessary to adapt the analysis mechanism to accommodate potential changes, but it is proposed that the following items should be examined and graphically represented in each report:

1. Summary of isolates received and tested for each country (table)
2. Overall incidence of resistance and decreased susceptibility (DS) for each of the following AMR for each testing year (bar graph):

- Cefixime
- Ceftriaxone
- Ciprofloxacin
- Spectinomycin
- Azithromycin
- Gentamicin
- Penicillinase-producing *Neisseria gonorrhoeae* (PPNG)

3. MIC distribution by year for ceftriaxone (bar graph)
4. % ceftriaxone DS isolates by country per year (bar graph)
5. MIC distribution by year for cefixime (bar graph)
6. % ceftriaxone DS isolates by country per year (bar graph)
7. Ciprofloxacin resistance by country by year
8. Summary of epidemiological data received by each country (table)
9. Cefixime DS vs sexual orientation and gender (bar graph/line graph)
10. Cefixime DS vs age group and gender
11. Similar analysis as for #9 and #10 for Ceftriaxone (if examples of DS observed)

Annex 2. Protocol for implementing Euro-GASP at the national level

Each country referring gonococcal isolates or susceptibility data should provide the following information to implement Euro-GASP at the national level. This information is crucial for the interpretation of data, and ensures that laboratory and epidemiological data are linked accurately.

Please complete the form below and return to:

Email: STIHIV@ecdc.europa.eu in copy to michelle.cole@hpa.org.uk

1. Identifying information Name: Laboratory/Institute name: Date form completed:			
2. Sampling strategy. Please provide information on the geographical coverage of isolates submitted (complete, national, regional, local).			
3. Please provide information on regions of the country covered (or place of residence).			
4. Please describe the source of the isolates (STI clinics, DV clinics, GPs, hospitals, etc.).			
5. How are the isolates sampled (consecutive, selective)?			
6. How were the epidemiological data obtained (available with isolate submitted to the laboratory; data were requested from the isolate source, such as the STI clinic/GP surgery; data were requested from the epidemiologist)?			
7. How are the AMR data and epidemiological data linked?			
8. Institute/laboratory/person submitting the GC AMR data to TESSy. Please indicate if you would like the hub to submit the data.			
9. Institute/laboratory/person submitting the epidemiological data to TESSy. Please indicate if you would like the hub to submit the data.			
10. For laboratories performing decentralised testing, please provide the following antimicrobial information:			
	Methodology (E-test/agar dilution/breakpoint)	Agar base (GC, chocolate, DST, etc.)	MIC range (min–max)
Ceftriaxone Cefixime Azithromycin Ciprofloxacin Spectinomycin Gentamicin Beta-lactamase			
11. Please list the control strains tested for each media/reagent batch or for each antimicrobial tested.			

Annex 3. Protocol for gonococcal susceptibility testing

- Isolates are shipped frozen to one of the three testing centres:
  - Health Protection Agency (HPA), London, UK
  - Statens Serum Institut, Copenhagen, Denmark
  - Örebro University Hospital, Örebro, Sweden
- The isolates are stored at −70 °C or in liquid nitrogen.
- Isolates are transferred to non-selective agar (such as GCVIT with 1% Vitox (Oxoid)) and incubated for 18 to 24 hours at 36 °C in 5% CO_2.
- The purity and the identity of the isolates are confirmed by Gram stain, oxidase and the *N. gonorrhoeae* MicroTrak (Trinity Biotech) test. A further sub-culture is grown.
- If there is a high level of contamination, cultures are repeatedly transferred to selective agar.
- Susceptibility testing is performed using the agar dilution breakpoint technique for ciprofloxacin, spectinomycin and azithromycin, and the full agar dilution technique for gentamicin. Suspensions of cultures aged 18 to 24 hours are prepared equivalent to McFarland standard 0.5 (approximately 104 cfu/µl) in saline. Using a multipoint inoculator, suspensions are inoculated onto GC agar plates with 1% Vitox, containing a panel of antimicrobials at the following breakpoint concentrations:

Table A3.1: Concentrations (mg/L) of antimicrobials used for the agar dilution breakpoint technique and the full agar dilution technique

Antimicrobial	Intermediate	Resistant
Azithromycin		0.5
Ciprofloxacin	0.06	0.5
Gentamicin (no breakpoint determined yet)	1, 2, 4, 8, 16	
Spectinomycin		64

- The ceftriaxone and cefixime MICs are determined, using E-tests according to the manufacturer's instructions.
- All isolates are tested for penicillinase production, using the chromogenic reagent nitrocefin.
- E-tests are performed on isolates that are resistant to azithromycin, using the agar dilution breakpoint technique.
- E-tests are performed on isolates are >8 mg/L to gentamicin, using the agar dilution technique.
- The following control strains [19] are tested on the poured agar dilution plates and each batch of E-tests:
  - WHO G (QA07–10)
  - WHO K (QA09–03)
  - WHO M (QA09–09)
  - WHO O (QA09–10)
  - WHO P (QA09–05)
- Bacterial growth is recorded for the agar dilution plates. MIC is recorded from the E-test plates. The category of resistance is determined using the following breakpoints:

Table A3.2: MIC breakpoints for specific antimicrobials

Antimicrobial	MIC breakpoint (mg/L)		
	R ≥	I	S ≤
Azithromycin	1	-	0.5
Cefixime*	0.25		0.125
Ceftriaxone*	0.25		
Ciprofloxacin	1	0.12 – 0.5	0.06
Gentamicin	To be determined		
Spectinomycin	128		64

** Decreased susceptibility*

European Committee on Antimicrobial Susceptibility Testing breakpoints [19] have been used, other than for ciprofloxacin and azithromycin intermediate resistance. The ciprofloxacin resistance breakpoint in this study is more clinically relevant to treatment failure. Azithromycin intermediate resistance has not been recorded as the clinical significance of this is currently unknown.

Isolates that are contaminated in the original vial or are slow to grow are resaved with a pure culture.

Annex 4. Set of variables for gonococcal susceptibility testing

The following table contains the set of basic variables for all diseases as well as the disease-specific and AMR data variables for Euro-GASP.

Variables		
Common set	**Disease specific**	**AMR**
RecordId	**PlaceOfResidence:** NUTS code 0-3	**RecordId**
RecordType	**ClinicalServiceType:** ANC, combined service, dermatology-venereology clinic, hospital emergency dept, family planning clinic, general practitioner gynaecology clinic, infectious disease clinic other primary care, dedicated STI clinic, urology, youth clinics, other, unknown	**RecordType**
RecordTypeVersion	**CountryOfBirth:** ISO-coded value list, UNK	**ParentId**
Status	**ProbableCountryOfInfection:** ISO coded value list, UNK	**Antibiotic:** Ceftriaxone, Cefixime, Azithromycin, Ciprofloxacin, Spectinomycin, Gentamicin
Subject	**Transmission:** Heterosexual contact, MSM/homo or bisexual male, Mother-to-child transmission, Other, Unknown	**TestMethod:** E-test, MIC, Breakpoint
ReportingCountry: ISO coded value list	**SiteOfInfection:** Anorectal Genital Pharyngeal Other Not applicable Unknown	**ResultSign:** < Less than <= Less than or equal = Equal > Greater than ≥ Greater than or equal
DataSource	**PrevGono:** Yes No Unknown	**ResultValue**
DateUsedForStatistics: yyyy-mm-dd	**HIVStatus:** Positive Known HIV positive New HIV diagnosis Negative Unknown	**SIR:** Sensitive Intermediate/decreased susceptibility Resistant Unknown
Gender: Female, male, unknown	**ConcurrentSTI:** Chlamydia Hepatitis B Hepatitis C Genital herpes LGV Syphilis Genital warts Mycoplasma Ureaplasma No concurrent STI Unknown	
Age: Years or unknown	**PenicillinaseActivity:** Yes No Unknown	
	ResultPor: NG-MAST *por* allele number	
	ResultTbpB: NG-MAST *tbpb* allele number	
	ResultSeqType: NG-MAST sequence type number	

During the first collection period in 2010, the following data for each isolate were collected if available: date specimen obtained; specimen site (rectum, cervix, urethra, pharynx, urethra-cervical, high vaginal swab, any other site in full); sex (male, female, unknown); age (in years); sexual orientation (heterosexual, homosexual, bisexual, unknown); previously diagnosed with gonorrhoea (yes, no, unknown); and concurrent STI diagnosed this episode (none, syphilis, chlamydia, herpes, warts, other, unknown).

Annex 5. Description of variables: data source for Euro-GASP

Annex 5 contains the definitions of variables to be used as part of the data source description (includes information on laboratory methods and other aspects related to the surveillance programme).

Variable	Variable description	Coding	Validation rule
Subject mnemonic	Mnemonic of country data source	Coded value list	
Subject name	Name of country data source	Coded value list	
Comment	Short description of the surveillance system for the disease. Important details for the analysis.	Text	
Coverage	Coverage of the surveillance system	NAT = national REG = regional LOC = local UNK = unknown	
Comprehensive	Comprehensive: Reporting is based on cases occurring within the whole population of the geographical area where the surveillance system is set up (national, regional, etc.). Sentinel: Reporting is based on a selected group of physicians/hospitals/laboratories/or other institutions' notifications and/or cases occurring within a selected group of population defined by age group, gender, exposure, or other selection criteria. Other: Reporting is based on a part of the population or group of physicians (or other institutions) which is not specified, for example reporting of some laboratories with no selection criteria.	Comp = comprehensive O = other Sent = sentinel Unk = unknown	
StartSurvSys	Start year for data collection in the surveillance system	YYYY	
InternalQualityControl	WHO-recommended strains used for quality control procedures	G = WHO G K = WHO K M = WHO M O = WHO O P = WHO P OTH = Other control strains used NT = Not tested	

Annex 6. Patient characteristics

Table A6.1: Patient characteristics; all countries and by country, 2010

	All countries		Austria		Belgium		Cyprus		Denmark		France		Germany		Greece		Hungary	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	1766		110		110		12		96		111		109		97		14	
Sex																		
Male	1441	81.6	65	59.1	93	84.5	11	91.7	72	75.0	96	86.5	87	79.8	94	96.9	12	85.7
Female	308	17.4	45	40.9	15	13.6			24	25.0	15	13.5	22	20.2	2	2.1	2	14.3
Unknown	17	1.0			2	1.8	1	8.3	0	0.0	1	0.9		0.0	1	1.0		0.0
Age (years)																		
<25	599	33.9	44	40	19	17.3	2	16.7	29	30.2	50	45.0	51	46.8	13	13.4	9	64.3
≥25	1141	64.6	66	60	90	81.8	9	75.0	67	69.8	57	51.4	58	53.2	75	77.3	5	35.7
Unknown	26	1.5			1	0.9	1	8.3			4	3.6			9	9.3		
Mode of transmission																		
Heterosexual (male and female)	605	34.3	88	80.0	2	1.8			58	60.4			17	15.6	73	75.3	10	71.4
Male heterosexual	426	24.1	43	39.1	2	1.8			35	36.5			13	11.9	71	73.2	8	57.1
MSM	395	22.4	10	9.1	4	3.6			21	21.9			9	8.3	20	20.6	3	21.4
Unknown	766**	43.4	12	10.9	104	94.5	12	100.0	17	17.7	111	100.0	83	76.1	4	4.1	1	7.1
Site of infection																		
Genital	1426	80.7	93	84.5	100	90.9	12	100.0	88	91.7	95	85.6	106	97.2	92	94.8	13	92.9
Pharyngeal	59	3.3	5	4.5	1	0.9			1	1.0	1	0.9	1	0.9			1	7.1
Anorectal	191	10.8	12	10.9	4	3.6			6	6.3	10	9.0	1	0.9	1	1.0		
Other	7	0.4			2	1.8			1	1.0	4	3.6						
Unknown	83	4.7			3	2.7					1	0.9	1	0.9	4	4.1		
Previously diagnosed																		
Yes	145	8.2	24	21.8	2	1.8			10	10.4			16	14.7	15	15.5		
No	546	30.9	3	2.7	10	9.1			86	89.6			4	3.7	74	76.3		
Unknown	1075	60.9	83	75.5	98	89.1	12	100.0			111	100.0	89	81.7	8	8.2	14	100.0
Concurrent STI																		
Concurrent CT	172	9.7	14	12.7							3	2.7	12	11.0				
Concurrent other	98 (*2)	5.5									2	1.8	3	2.8				
No concurrent STI	579	32.8	88	80.0							10	9.0	23	21.1	16	16.5		
Unknown	917	51.9	8	7.3	110	100.0	12	100.0	96	100.0	96	86.5	71	65.1	81	83.5	14	100.0
HIV status*	866		55		55		12		41		57		54		61		14	
Positive	48	5.5							2	4.9	2	3.5	5	9.3	1	1.6		
Negative	262	30.3							25	61.0					11	18.0	1	7.1
Unknown	556	64.2	55	100.0	55	100.0	12	100.0	14	34.1	55	96.5	49	90.7	49	80.3	13	92.9

Table A6.1: Patient characteristics; all countries and by country, 2010 (continued)

	Ireland		Italy		Latvia		Malta		Netherlands		Norway		Portugal		Romania		Slovakia	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	88		105		20		29		215		46		72		9		88	
Sex																		
Male	82	93.2	93	88.6	18	90.0	25	86.2	178	82.8	42	91.3	64	88.9	9	100.0	64	72.7
Female	6	6.8	6	5.7	2	10.0	4	13.8	36	16.7	4	8.7	8	11.1			24	27.3
Unknown			6	5.7					1	0.5								
Age (years)																		
<25	29	33.0	22	21.0	10	50.0	13	44.8	72	33.5	9	19.6	21	29.2	3	33.3	20	22.7
≥25	59	67.0	75	71.4	10	50.0	14	48.3	142	66.0	37	80.4	51	70.8	6	66.7	68	77.3
Unknown			8	7.6			2	6.9	1	0.5								
Mode of transmission																		
Heterosexual (male and female)	12	13.6	40	38.1	17	85.0	20	69.0	83	38.6			15	20.8	9	100.0	54	61.4
Male heterosexual	10	11.4	35	33.3	15	75.0	18	62.1	47	21.9			13	18.1	9	100.0	37	42.0
MSM	27	30.7	56	53.3			6	20.7	131	60.9			14	19.4			4	4.5
Unknown	49	55.7	9	8.6	3	15.0	3	10.3	1	0.5	46	100.0	43	59.7			30	34.1
Site of infection																		
Genital	70	79.5	89	84.8	20	100.0	25	86.2	126	58.6	30	65.2	70	97.2	9	100.0	88	100.0
Pharyngeal	6	6.8	2	1.9			2	6.9	8	3.7	2	4.3						
Anorectal	12	13.6	12	11.4			2	6.9	81	37.7	5	10.9	2	2.8				
Other																		
Unknown			2	1.9							9	19.6						
Previously diagnosed																		
Yes	9	10.2			3	15.0	2	6.9					10	13.9			3	3.4
No	79	89.8			17	85.0	24	82.8					19	26.4	9	100.0	83	94.3
Unknown			105	100.0			3	10.3	215	100.0	46	100.0	43	59.7			2	2.3
Concurrent STI																		
Concurrent CT	21	23.9	1	1.0	6	30.0	1	3.4	59	27.4			5	6.9			5	5.7

	Ireland		Italy		Latvia		Malta		Netherlands		Norway		Portugal		Romania		Slovakia	
Concurrent other	5	5.7			1	5.0	25	86.2	5	2.3							10 (*2)	11.4
No concurrent STI	35	39.8			13	65.0			143	66.5			24	33.3			61	69.3
Unknown	27	30.7	104	99.0			3	10.3	8	3.7	46	100.0	43	59.7	9	100.0	12	13.6
HIV status*	54		50		9		3		100				40		9		69	
Positive			3	6.0					27	27.0			1	2.5				
Negative			40	80.0			3	100.0	68	68.0							60	87.0
Unknown	54	100.0	7	14.0	9	100.0			5	5.0			39	97.5	9	100.0	9	13.0

** Data only collected during the second collection period*

Table A6.1: Patient characteristics; all countries and by country, 2010 (end)

	Slovenia		Spain		Sweden		UK	
	No.	%	No.	%	No.	%	No.	%
	28		101		84		222	
Sex								
Male	28	100.0	90	89.1	50	59.5	169	76.1
Female			11	10.9	30	35.7	52	23.4
Unknown					4	4.8	1	0.5
Age (years)								
<25	10	35.7	39	38.6	37	44.0	97	43.7
≥25	18	64.3	62	61.4	47	56.0	125	56.3
Unknown								
Mode of transmission								
Heterosexual (male and female)	9	32.1					99	44.6
Male heterosexual	9	32.1					61	27.5
MSM	17	60.7					73	32.9
Unknown	2	7.1	101	100.0	84	100.0	50	22.5
Site of infection								
Genital	24	85.7	87	86.1	52	61.9	137	61.7
Pharyngeal	2	7.1	5	5.0	9	10.7	13	5.9
Anorectal	2	7.1	9	8.9	2	2.4	30	13.5
Other								
Unknown					21	25.0	42	18.9
Previously diagnosed								
Yes	3	10.7					48	21.6
No	21	75.0					117	52.7
Unknown	4	14.3	101	100.0	84	100.0	57	25.7
Concurrent STI								
Concurrent CT							45	20.3
Concurrent other	1	3.6					1	0.5
No concurrent STI	22	78.6					119	53.6
Unknown	5	17.9	101	100.0	84	100.0	57	25.7
HIV status*	14		29		29		111	
Positive							7	6.3
Negative							54	48.6
Unknown	14	100.0	29	100.0	29	100.0	50	45.0

** Data only collected during the second collection period*

*** Includes one individual with unknown gender but with known made of transmission; heterosexual*

Table A6.2: Clinical service type, place of residence, country of birth and probable country of infection (variables collected at second collection period)

	Austria (n=55)	Belgium (n=55)	Cyprus (n=12)	Denmark (n=41)	France (n=57)	Germany (n=54)	Greece (n=61)	Hungary (n=14)
Clinical service types								
ANC – antenatal clinic	55 = UNK	55 = UNK	7 = DV	4 = O	1 = DV	54 = UNK	2 = ED	14 = DV
COMB – combined service			2 = URO	20 = OPC	6 = ED		59 = STI	
DV – dermatology-venereology clinic			3= UNK	14 = STI	27 = GP			

	Austria (n=55)	Belgium (n=55)	Cyprus (n=12)	Denmark (n=41)	France (n=57)	Germany (n=54)	Greece (n=61)	Hungary (n=14)
Clinical service types								
ED – Hospital emergency dept				3 = UNK	2 = GYN			
FPC – family planning clinic					4 = O			
GP – general practitioner					10 = STI			
GYN – gynaecology clinic					1 = URO			
ID – infectious disease clinic					6 = UNK			
OPC – other primary care								
STI – dedicated STI clinic								
URO – urology								
YTH – youth clinics								
O – other								
UNK – unknown								
Place of residence								
NUTS level 0-3 (region)	55 = AT	9 = BE1	12 = UNK	41 = UNK	57 = FR	54 = DE	1 = GR	14 = UNK
		37 = BE2					3 = GR12	
		9 = BE3					1 = G13	
							54 = GR30	
							2 = UNK	
Country of birth								
ISO coded value list, UNK	55 = UNK	55 = UNK	11 = CY	33 = DK	57 = UNK	54 = UNK	47 = GR	14 = HU
			1 = UNK	1 = ES			1 = IT	
				1 = GL			1 = RO	
				1 = TR			4 = AL	
				5 = UNK			1 = BD	
							1 = BE	
							1 = BG	
							2 = SY	
							3 = UNK	
Probable country of infection								
ISO coded value list, UNK	55 = UNK	55 = UNK	12 = UNK	1 = CK	19 = FR	54 = UNK	56 = GR	13 = HU
				31 = DK	38 = UNK		1 = TH	1 = BR
				1 = GL			4 = UNK	
				1 = RO				
				3 = TH				
				4 =UNK				

Table A6.2: Clinical service type, place of residence, country of birth and probable country of infection (continued)

	Ireland (n=54)	Italy (n=50)	Latvia (n=9)	Malta (n=3)	Netherlands (n=100)	Norway (n=0)	Portugal (n=40)	Romania (n=9)
Clinical service types								
See first table for codes	11 = GP	28 = DV	9 = O	3 = UNK	100 = STI		13 = STI	6 = DV
	25 = OPC	2 = ID					27 = UNK	3 = OPC
	15 = STI	3 = O						
	1 = UNK	17 = STI						
	2 = YTH							
Place of residence								
NUTS level 0-3 (region)	54 = IE	13 = ITC11	1 = LV003	3 = MT	2 = NL230		9 = PT11	9 = RO321
		1 = ITC16	6 = LV006		2 = NL310		1 = PT15	
		22 = ITC45	2 = LV007		1 = NL325		1 = PT16	

	Ireland (n=54)	Italy (n=50)	Latvia (n=9)	Malta (n=3)	Netherlands (n=100)	Norway (n=0)	Portugal (n=40)	Romania (n=9)
Clinical service types								
		3 = ITC47			80 = NL326		29 = PT17	
		1 = ITD31			1 = NL333			
		1 = ITE43			1 = NL336			
		2 = ITF41			1 = NL414			
		7 = UNK			12 = UNK			
Country of birth								
ISO-coded value list, UNK	54 = UNK	1 = AL	9 = UNK	3 = MT	2 = AN		40 = PT	9 = RO
		1 = BR			2 = BG			
		1 = ER			1 = BR			
		35 = IT			2 = DE			
		1 = MD			1 = DK, EC, EE,			
		3 = RO			ES, FR, GR, HU,			
		8 = UNK			ID, IE, IQ, MA			
					69 = NL			
					1 = RO			
					8 = SR			
					1 = PT			
					2 = PL			
					1 = UK			
Probable country of infection								
ISO coded value list, UNK	54 = UNK	15 = IT	1 = UNK	3 = UNK	100 = UNK		40 = UNK	9 = RO
		1 = MD	8 = LV					
		1 = TH						
		33 UNK						
UNK = unknown								

Table A6.2: Clinical service type, place of residence, country of birth and probable country of infection (end)

	Slovakia (n=69)	Slovenia (n=14)	Spain (n=29)	Sweden (n=29)	UK (n=111)
Clinical Service types					
See first table for codes	27 = DV	14 = DV	13 = STI	29 = UNK	1 = O
	21 = O		16 = UNK		3 = OPC
	2 = OPC				104 = STI
	18 = URO				3 = UNK
	1 = UNK				
Place of residence					
NUTS level 0-3 (region)	48 = SK01	14 = SI	29 = UNK	29 = UNK	111 = UK
	11 = SK021				
	1 = SK022				
	8 = SK023				
	1 = SK041				
Country of birth					
ISO-coded value list, UNK	69 = SK	10 = SI	29 = UNK	29 = UNK	111 = UNK
		4 = UNK			
Probable country of infection					
ISO-coded value list, UNK	69 = UNK	14 = UNK	29 = UNK	29 = UNK	3 = ES
					1 = FR
					1 = PT
					1 = TH
					9 = UNK
					96 = UK

UNK = unknown

Annex 7. Statistical tables

Table A7.1. Patient characteristics vs. ciprofloxacin resistance/susceptibility

Total: 1766	Ciprofloxacin resistant (%, 95% CI)	Ciprofloxacin susceptible (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection n=1679					
Genital (1426)	760 (53.3, 50.7-55.8)	666(46.7, 44.1-49.3)	1	-	-
Anorectal (191)	92 (48.2, 41.2-55.2)	99 (51.8, 44.8-58.8)	0.814	0.602-1.1	0.183
Pharyngeal (62)	38 (61.3, 48.9-72.4)	24 (38.7, 27.6-51.2)	1.4	0.823-2.34	0.217
Previous GC n= 691					
Yes (145)	70 (48.3, 40.3-56.4)	75 (51.7, 43.7-59.7)	0.705	0.488-1.02	0.062
No (546)	311 (57.0, 52.8-61.1)	235 (43.1, 39.0-47.2)	-	-	-
Mode of transmission (total) n=1001:					
MSM (395)	196 (49.6, 44.7-54.4)	199 (50.4, 45.5-55.3)	0.81	0.63-1.05	0.11
Heterosexual (606)	332 (54.8, 50.8-58.7)	274 (45.2, 41.3-49.2)	-	-	-
Concurrent chlamydia n=779					
Yes (172)	55 (32.0, 25.5-39.3)	117 (68.0, 60.7-74.5)	0.424	0.295-0.61	<0.0001
No (607)	319 (52.6, 48.6-56.5)	288 (47.5, 43.5-51.4)	-	-	-
HIV status n=310					
Positive (48)	17 (35.4, 23.4-49.6)	31 (64.6, 50.4-76.6)	0.456	0.239-0.871	0.015
Negative (262)	143 (54.6, 48.5-60.5)	119 (45.4, 39.5-51.5)	-	-	-
Age n=1740					
< 25 years n=599	257 (42.9, 39-46.9)	342 (57.1, 61-61.3)	0.551	0.451-0.675	<0.0001
≥25 years n=1141	658 (57.7, 54.8-60.5)	483 (42.3, 39.5-45.2)	1	-	-

Note: P value obtained from Pearson's chi-squared tests

Baseline variables: Site of infection – genital; previous GC – no; mode of transmission – heterosexual; concurrent chlamydia – no; HIV status – negative; age – ≥25 years

Table A7.2. Patient characteristics vs. azithromycin resistance/susceptibility

Total: 1766	Azithromycin resistant (%, 95% CI)	Azithromycin susceptible (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection n=1679					
Genital (1426)	109 (7.6, 6.4-9.1)	1317 (92.4,90.9-93.6)			N/A
Pharyngeal (62)	3 (4.8, 1.7-13.3)	59 (95.2, 86.7-98.3)			
Anorectal (191)	11 (5.8, 3.3-10.2)	180 (94.2, 91-97.8)			
Previous GC n= 691					
Yes (145)	8 (5.5, 2.8-10.5)	137 (94.5, 89.5-97.2)	0.543	0.252-1.17	0.114
No (546)	53 (9.7, 7.5-12.5)	493 (90.3, 87.5-92.5)	1	-	-
Mode of transmission (total) n=1001:					
MSM (395)	30 (7.6, 5.4-10.6)	365 (92.4, 89.4-94.6)	0.978	0.608-1.57	0.923
Heterosexual (606)	47 (7.8,5.9-10.2)	559 (92.2, 89.8-94.1)	1	-	-
Concurrent chlamydia n=779					
Yes (172)	8 (4.7, 2.4-8.9)	164 (95.3, 91.1-97.6)	0.568	0.263-1.23	0.145
No (607)	48 (7.9, 6.0-10.3)	559 (92.1, 89.7-94.0)	1	-	-
HIV status n=310					
Positive (48)	4 (8.3, 3.3-19.6)	44 (91.7, 80.5-96.7)	0.59	0.199-1.75	0.335
Negative (262)	35 (13.4, 9.8-18)	227 (86.6, 82-90.4)	1	-	-
Age n=1740					
< 25 years n=599	38 (6.3, 4.7-8.6)	561 (93.7, 91.4-95.4)	0.811	0.546-1.2	0.295
≥25 years n=1141	88 (7.7, 6.3-9.4)	1053 (92.3, 90.6-93.7)	1	-	-

Note: P value obtained from Pearson's chi-squared tests

Baseline variables: Site of infection – genital; previous GC – no; mode of transmission – heterosexual; concurrent chlamydia – no; HIV status – negative; age – ≥25 years

N/A = Expected cells less than five – analysis not performed

Table A7.3. Patient characteristics vs. penicillinase activity

Total: 1745	PPNG resistant (%, 95% CI)	PPNG susceptible (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection n=1658					
Genital (1405)	116 (8.1, 6.9-9.8)	1289 (91.7, 90.2-93.1)	1	-	-
Anorectal (191)	13 (6.8, 4.0-11.3)	178 (93.2, 88.7-96.0)	0.812	0.448-1.47	0.491
Pharyngeal (62)	4 (6.6, 2.5-15.5)	58 (93.6, 84.6-97.5)	0.766	0.273-2.15	0.612
Previous GC n= 683					
Yes (143)	8 (5.6, 2.9-10.6)	135 (94.4, 89.4-97.1)	0.741	0.338-1.62	0.451
No (540)	40 (7.4, 5.5-99.3)	500 (92.6, 90.1-94.5)	1	-	-
Mode of transmission (total) n=994:					
MSM (390)	22 (5.6, 3.8-8.4)	368 (94.4, 91.7-96.3)	0.8	0.47-1.36	0.411
Heterosexual (604)	42 (7, 5.2-9.3)	562 (93.1, 90.7-94.8)	1	-	-
Concurrent chlamydia n=770					
Yes (169)	10 (5.9, 3.3-10.6)	159 (94.1, 89.5-96.8)	1.16	0.555-2.41	0.698
No (601)	31 (5.2, 3.7-7.3)	570 (94.8, 92.8-96.3)	1	-	-
HIV status n=309					
Positive (47)	2 (4.3, 1.2-14.3)	45(95.7, 85.7-98.8)			0.558*
Negative (262)	18 (6.9,4.4-10.6)	244 (93.2, 89.4-95.6)			
Age n=1719					
< 25 years n=591	38 (6.4, 4.7-8.7)	553 (93.6, 91.3-95.3)	0.63	0.429-0.924	0.017
≥25 years n=1128	111 (9.8, 8.2-11.7)	1017 (90.2, 88.3-91.8)	1	-	-

Note: P value obtained from Pearson's chi-squared tests

** Expected value for one cell <5 so Fisher's Exact test performed*

Baseline variables: Site of infection – genital; previous GC – no; mode of transmission – heterosexual; concurrent chlamydia – no; HIV status – negative; age – ≥25 years

Table A7.4. Patient characteristics vs. cefixime decreased susceptibility/susceptibility

Total: 1766	Cefixime decreased susceptibility (%, 95% CI)	Cefixime susceptible (%, 95% CI)	Odds Ratio	95% CI	P value
Site of infection n=1679					
Genital (1426)	131 (9.2, 7.8-10.8)	1295 (90.8, 89.2-92.2)	1	-	-
Anorectal (191)	11 (5.8, 3.3-10.0)	180 (94.2, 90.0-96.8)	0.604	0.32-1.14	0.116
Pharyngeal (62)	7 (11.3, 5.6-21.5)	55 (88.7, 78.5-94.4)	1.26	0.561-2.82	0.576
Previous GC n= 691					
Yes (145)	12 (8.3, 4.8-13.9)	133 (91.7, 86.1-95.2)	0.759	0.396-1.46	0.406
No (546)	58 (10.6, 8.3-13.5)	488 (89.4, 86.5-91.7)	1	-	-
Mode of transmission (total) n=1001:					
MSM (395)	29 (7.3, 5.2-10.3)	366 (92.7, 89.7-94.8)	0.72	0.454-1.146	0.165
Heterosexual (606)	60 (9.9, 7.8-12.5)	546 (90.1, 87.5-92.2)	1	-	-
Concurrent chlamydia n=779					
Yes (172)	8 (4.7, 2.4-8.9)	164 (95.4, 91.1-97.6)	0.543	0.252-1.17	0.114
No (607)	50 (8.24, 6.31-10.7)	557 (91.8, 89.3-93.7)	1	-	-
HIV status n=310					
Positive (48)	1 (2.1, 0.37-10.9)	47 (97.9, 89.1-99.6)			P=0.145*
Negative (262)	23 (8.8, 5.9-12.8)	239 (91.2, 87.2-94.1)			
Age n=1740					
< 25 years n=599	38 (6.3, 4.7-8.6)	561 (93.7, 91.4-95.4)	0.62	0.42- 0.903	0.0122
≥25 years n=1141	113 (9.9, 8.3-11.8)	1028 (90.1, 88.23-91.7)	1	-	-

Note: P value obtained from Pearson's chi-squared tests

Baseline variables: Site of infection – genital; previous GC – no; mode of transmission – heterosexual; concurrent chlamydia – no; HIV status – negative; age – ≥25 years