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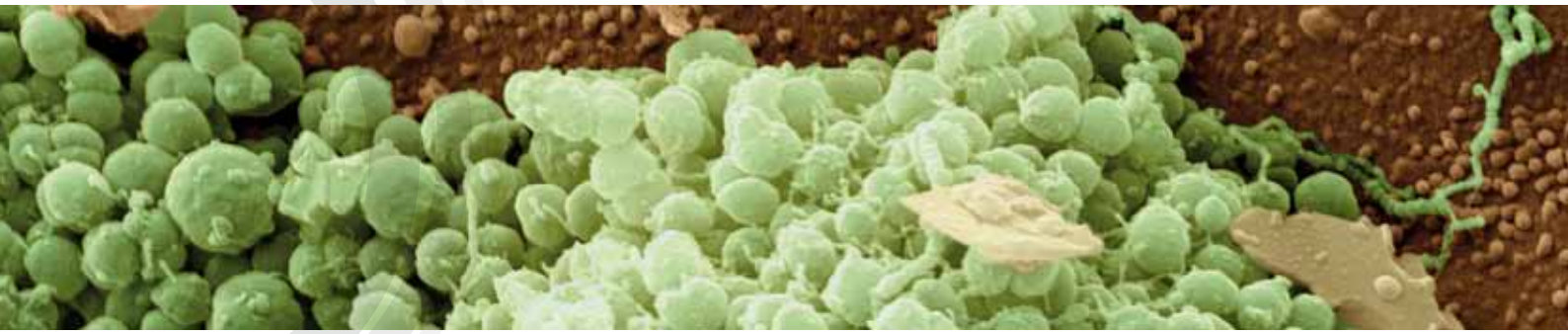

Gonococcal antimicrobial susceptibility surveillance in Europe

2013

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Erratum

The following corrections were made on 14 July 2015: Page 12, Table 7. The value for cefixime resistance (United Kingdom) has been corrected to 0.8, the list of countries has been rearranged, and the document has been repaginated.

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Abbreviations

AMR	Antimicrobial resistance
CI	Confidence interval
CT	*Chlamydia trachomatis*
DV	Dermatovenerology
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EQA	External quality assessment
ESSTI	European Surveillance of Sexually Transmitted Infections Project
EU	European Union
Euro-GASP	European Gonococcal Antimicrobial Surveillance Programme
GC	Gonococcal
GONOAMR	Gonococcal antimicrobial resistance
GP	General practitioner
GRASP	Gonococcal Resistance to Antimicrobials Surveillance Programme
GUM	Genitourinary medicine
HIV	Human immunodeficiency virus
MIC	Minimum inhibitory concentration
MSM	Men who have sex with men
OR	Odds ratio
PHE	Public Health England
PPNG	Penicillinase-producing *Neisseria gonorrhoeae*
STI	Sexually transmitted infection
TESSy	The European Surveillance System
UK-NEQAS	United Kingdom National External Quality Assessment Service
WHO	World Health Organization

Executive summary

The surveillance of *Neisseria gonorrhoeae* antimicrobial susceptibility in the European Union/European Economic Area (EU/EEA) has been co-ordinated by the European Centre for Disease Prevention and Control (ECDC) since 2009. This surveillance is essential for detecting emerging and increasing antimicrobial resistance and making quality-assured data available to inform treatment guidelines.

During 2013, the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) followed the biannual decentralised and centralised testing model used in previous years, requesting participating laboratories to collect gonococcal isolates during two periods (April/May and October/November). For centralised testing, susceptibility testing was performed on all isolates centrally by Etest or agar dilution for the following antimicrobials: cefixime, ceftriaxone, ciprofloxacin, azithromycin, spectinomycin and gentamicin. Testing was decentralised to participating laboratories if they fulfilled set criteria.

In 2013, 21 EU/EEA Member States participated in Euro-GASP, 13 via decentralised testing. A total of 1 994 isolates were collected and tested. The majority of gonococci (85%) were collected from male patient samples. The age of the patients ranged from less than one year to 85 years, with a median of 29 years. Overall, 28% of patients were under 25 years. Males were significantly older than women. The site of specimen was mainly genital (79%), followed by rectal (13%) and pharyngeal (6%). Among cases with information on previous diagnosis of gonorrhoea, 18% had previously been diagnosed with the disease. Twenty-two per cent of the patients were concurrently diagnosed with chlamydia infection. Among cases with known sexual preference, 58% stated that they were heterosexual and 42% were men who have sex with men (MSM). Eighteen per cent of all cases were HIV-positive and 90% of those were MSM.

In 2013, a slightly higher proportion of tested isolates showed cefixime resistance: 4.7%, compared with 3.9% in 2012. Isolates with this phenotype were detected in 13 countries, one less than in 2012. In 2013, patients who acquired a strain displaying cefixime resistance were more likely to be females or heterosexual males. Seven isolates were detected with ceftriaxone resistance (minimum inhibitory concentration (MIC)>0.125 mg/L), compared to three in 2012. Rates of ciprofloxacin resistance are very high and have been increasing since 2011 (48.7% in 2011, 50.1% in 2012, 52.9% in 2013) and the level of azithromycin resistance slightly increased (4.5% in 2012, 5.4% in 2013). One isolate displayed high-level resistance to azithromycin (MIC≥256 mg/L). The MIC distribution of gentamicin continues to offer hope that gentamicin could be considered for therapy in the future.

Twenty-one countries participated in the gonococcal antimicrobial resistance external quality assessment (EQA) scheme. The EQA has continued to show high comparability between participants, which in turn raises confidence in the quality and comparability of the gonococcal antimicrobial susceptibility testing in Euro-GASP, particularly for decentralised testing.

The increasing cefixime and ceftriaxone resistance in Europe is of concern and highlights the importance of implementing the European response plan to control the threat of multidrug-resistant *N. gonorrhoeae* in Europe. In addition, novel antimicrobials and/or new dual antimicrobial therapy regimens are essential to ensuring that gonorrhoea remains a treatable infection.

1 Introduction

1.1 Background

The emergence and spread of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* is a serious threat to the treatment and control of gonorrhoea. The therapeutic agents currently recommended in Europe [1], extended-spectrum cephalosporins (ideally given together with azithromycin), are the last remaining options for effective first-line and alternative antimicrobial monotherapy [2]. Surveillance of the susceptibility of these agents is therefore essential in order to ensure efficient patient management and monitor currently emerging resistance [3].

In the European Union, surveillance of *N. gonorrhoeae* antimicrobial susceptibility is coordinated by the European Centre for Disease Prevention and Control (ECDC), supported by an international network led by Public Health England (United Kingdom) and also including Örebro University Hospital (Sweden).

The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) has identified decreasing susceptibility to extended-spectrum cephalosporins and treatment failures have been documented [3], prompting the creation of a European response plan to control and manage the threat of multidrug-resistant *N. gonorrhoeae* in Europe [4].

In 2012, Euro-GASP ran a sentinel surveillance programme in 20 EU countries. The major findings were [5]:

- Four per cent of tested isolates were resistant to cefixime, using a cut-off of minimum inhibitory concentration (MIC)>0.125 mg/L. This represented a 3.7% decrease over 2011.
- Three isolates resistant to ceftriaxone, using a cut-off of MIC>0.125 mg/L, were detected in Euro-GASP compared to 10 in the previous year.
- Rates of ciprofloxacin and azithromycin resistance decreased but remained very high for ciprofloxacin resistance and azithromycin resistance remained close to the 5% level (50% and 4.5%, respectively).
- The MIC distribution (*in vitro* susceptibility) of gentamicin suggests that this antimicrobial might be used for therapy in the future.

1.2 Objectives

With 3.9% of isolates (tested in Euro-GASP 2012) displaying resistance to cefixime, and with documented treatment failures, the need to monitor *N. gonorrhoeae* AMR in the EU/EEA Member States is clear.

The overall aim of this project is to strengthen the surveillance of gonococcal antimicrobial susceptibility in the EU/EEA Member States. The objectives are as follows:

- Develop and implement sentinel surveillance of gonococcal antimicrobial susceptibility to a range of therapeutically relevant antimicrobials.
- Improve the timeliness of surveillance to allow more frequent monitoring of developments in gonococcal antimicrobial susceptibility across Europe.
- Link susceptibility data with epidemiological information to better understand the risk factors associated with emerging resistance patterns.
- Implement an EQA scheme for antimicrobial susceptibility testing across Europe.
- Provide training in gonococcal culture and antimicrobial susceptibility testing to facilitate enhanced gonococcal antimicrobial susceptibility surveillance, using a standardised methodology across Europe.

This report presents the results from the 2013 gonococcal antimicrobial susceptibility sentinel surveillance and a summary of the 2014 EQA scheme.

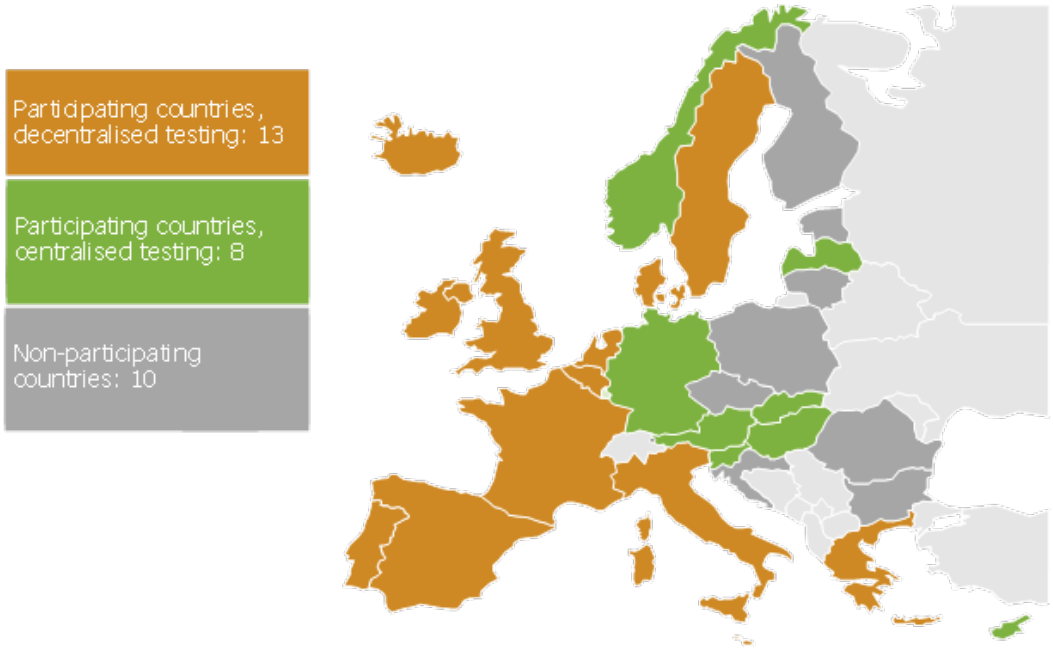
2 Methods

In 2013, Euro-GASP followed a biannual testing approach. Participating laboratories were requested to collect gonococcal isolates during two periods: April/May and October/November. The centralised and decentralised testing model continued to be used: for decentralised testing, participating laboratories fulfilling set quality criteria performed susceptibility testing themselves. Countries were then asked to upload their results to the European Surveillance System (TESSy). All other participating countries followed the centralised testing model, where susceptibility testing was performed at Public Health England (London) using the same methodology (see 2.4). Full details on the framework for Euro-GASP and the criteria for decentralised testing can be found in Annex 1.

2.1 Participating laboratories

In 2013, nominated contact points for STI surveillance from twenty-one EU/EEA countries participated in Euro-GASP (Map 1) which was one country more (Iceland) than in 2012.

Map 1. EU/EEA Member States participating in Euro-GASP, 2013



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 the national level (Annex 2). This information is critical in interpreting data and ensuring accurate linkage of laboratory and epidemiological data.

2.3 Isolate collection

Each country was asked to contribute 100 isolates each year (110 from centralised-testing model countries with the aim of retrieving and testing 100 isolates). Countries where 100 isolates represent less than 10% of the total number of gonorrhoea cases (the Netherlands, Spain and the United Kingdom), were requested to collect 200 isolates. The aim was for laboratories to collect half of the isolates in April/May and the remainder in October/November. 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.

When multiple sites were infected in one patient, laboratories were requested to only collect one isolate in the following order of preference:

- Males: pharyngeal, rectal, urethral, other
- Females: pharyngeal, cervical, other anogenital (high vaginal swab/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 Public Health England, London for susceptibility testing.

2.4 Antimicrobial susceptibility testing

Centralised susceptibility testing

Centralised susceptibility testing was performed using either an agar dilution breakpoint technique that allows for isolates to be categorised as susceptible or resistant (including intermediate resistance, where applicable), or Etests to determine the MIC and monitor drift in susceptibility.

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

The following methods were used to determine susceptibility:

- Breakpoint (azithromycin, ciprofloxacin and spectinomycin)
- Etest (cefixime, ceftriaxone and gentamicin)
- Agar dilution (gentamicin)
- Penicillinase production by nitrocefin.

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 standard breakpoints (Annex 3). For 2013, the Netherlands and Iceland did not test for penicillinase production. Belgium, Greece, Ireland, Malta, the Netherlands and the United Kingdom did not test for susceptibility to gentamicin.

2.5 Data collection and analysis

The following data for each isolate were collected, where available: date specimen obtained, specimen site, gender, age, sexual orientation, previously diagnosed with gonorrhoea, and concurrent STI diagnosed this episode, 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.

To aid the clinical service type analysis, the 14 coded variables were merged into six groups (Table 1).

Data generated by centralised testing were sent to the national contacts; complemented with epidemiological data (where available); uploaded to TESSy by each Member State and then approved. Data from centres performing decentralised testing were uploaded to TESSy in the same manner. Percentages shown are for known data. Where available, graphs display data between 2004 and 2013 (note that no data collection was organised in 2005).

Table 1. 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

Statistical analysis

Statistical analysis was performed using Stata v11.2. The Z-test was used to determine if the difference between epidemiological and AMR data collected in 2013 versus 2012 and whether the differences in age distribution were statistically significant. A univariate analysis was performed to investigate associations between patient characteristics and antimicrobial resistance. The odds ratios (OR) and 95% confidence intervals (CI) were calculated, where datasets contained sufficient numbers. For small cell numbers, Fisher's exact test was performed. Using a forward step-wise approach, the most significant and strongest associations from the univariate analysis were added to a multivariable logistic regression model sequentially. Statistical significance for all tests was assumed when $p<0.05$.

3 Results

3.1 Isolate and patient data

Information on the source of the data as described by the 'Protocol implementing Euro-GASP at the national level' (Annex 2) and/or the data source variable in TESSy is described in Table 2.

Table 2. Characteristics of national protocols for implementing Euro-GASP, 2013

Country	Coverage	Specimen source	Comprehensiveness	Sampling method
Austria	Regional/capital area	STI clinics, DV clinics, GPs, hospitals	Sentinel	Consecutively but from a select population
Belgium	National	GPs, hospitals, STI clinics, gynaecologists	Comprehensive	Consecutively
Cyprus	Regional	DV and urology clinic	Unknown	Selectively
Denmark	National	STI clinics, DV clinics, GPs, hospitals	Comprehensive	Consecutively
France	National	GPs, STI clinics and hospitals	Sentinel	Consecutively
Germany	National	Medical practices, out-patients, hospital laboratories, public health departments, STI ambulances and Federal armed forces.	Other	Consecutively
Greece	National	STI clinics and general hospitals	Other	Consecutively
Hungary	Regional/capital area	STI clinics	Sentinel	Selectively
Iceland	National	STI clinics, DV clinics, GPs, hospitals, private practitioners	Comprehensive	Consecutively
Ireland	Local	STI clinic and GPs	Other	Consecutively and some selective isolates
Italy	Regional	STI clinics, hospitals, university/hospital microbiology units, DV clinics	Comprehensive	Consecutively
Latvia	National	STI clinics/in-patients	Other	Consecutively
Malta	National	STI clinic. GPs and hospitals	Comprehensive	Selectively
Netherlands	Regional/Amsterdam	STI clinic	Sentinel	Consecutively
Norway	National	STI clinics, GPs	Unknown	Consecutively
Portugal	National	STI clinics, DV clinics, GPs, hospitals, urology and gynaecology clinics	Sentinel	Consecutively
Slovakia	Regional	DV, urology and gynaecology practices	Comprehensive	Consecutively
Slovenia	Regional	DV and STI clinics	Other	Consecutively
Spain	National	STI clinics and hospitals	Sentinel	Consecutively
Sweden	National	STI clinics	Comprehensive	Consecutively
United Kingdom	National†	GUM/STI clinics, GPs and out-patients	Sentinel	Consecutively

DV: Dermatology-venereology, GUM: Genitourinary medicine, GP: General practitioner

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 population group defined by age, 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 by some laboratories with no selection criteria.

† National except for Northern Ireland.

A total of 1 994 isolates were tested during 2013: 864 during the first collection period and 1 130 during the second collection period. This represents an increase of 67 isolates (3.5%) from 2012. The number of isolates tested from each country varied from nine (Cyprus) to 240 (United Kingdom) (Table 3). The coverage (number of isolates tested compared to the number of reported cases as part of the enhanced epidemiological surveillance of STI in 2013 [5]) ranged from <1% (United Kingdom) to 95% (Portugal). Cyprus and Slovenia had coverage of over 100% as the number of isolates received exceeded the number of reported cases. The Netherlands, Spain and the United Kingdom had less than 5% coverage, which would have been achieved for Spain and the Netherlands if 200 isolates had been submitted. Greece, Hungary and Latvia reported on less than the required 100 isolates, although there were sufficient numbers of cases reported to achieve the aim of 100 isolates. It would not have been possible for Cyprus, Iceland, Malta or Slovenia to achieve 100 isolates as the number of reported cases was less than 100. To monitor the progress of Euro-GASP, the percentage of isolates tested from 2009 to 2013 is also displayed in Table 3.

Table 3. Number of *N. gonorrhoeae* isolates tested in Euro-GASP, sampled from gonorrhoea patients reported in 2013 and percentage of isolates tested 2009–2013, EU/EEA

Country	Number of isolates tested 2013	Number of cases reported 2013 [6]	% isolates tested*				
			2013	2012	2011	2010	2009
Austria	109	1148**	9	27	23	32	77
Belgium	110	1011**	11	12	13	15	15
Cyprus	9	2	450	50	91	52	N/A
Denmark	110	817	13	17	25	20	20
France	112	1349**	8	12	18	24	32
Germany	101	NR	NR	NR	NR	NR	NR
Greece	75	219	34	29	26	31	67
Hungary	88	1526**	6	5	1	1	NP
Iceland	5	19	26	NP	NP	NP	NP
Ireland	103	1264	8	7	8	14	NP
Italy	100	NR	NR	35	24	42	48
Latvia	38	554	7	6	5	6	3
Malta	31	61	51	55	28	62	92
Netherlands	139	4171**	3	4	6	8	5
Norway	112	506	22	25	21	11	54
Portugal	110	116	95	92	91	81	75
Romania	NP	NP	NP	NP	5	2	NP
Slovakia	110	374	29	38	58	70	13
Slovenia	73	62	118	104	76	64	80
Spain	119	3314	4	3	4	5	5
Sweden	100	1111	9	10	11	10	18
United Kingdom	240	32377	1	1	1	1	1
Total	**1994**	**50001**	4	4	**5**	**6**	**6**

** Percentages above 100% suggest under-reporting of cases in epidemiological surveillance*
*** Sentinel data*
NR = not reported; NP = not participating

As in the previous years, the majority of gonococci (85%, n=1 676) were collected from men. Gender was reported as unknown for 16 cases (Table 4). The age of the patients ranged from <1 year to 85 years, with a median of 29 years, an interquartile range of 24 to 38 years and 28% (554) of patients under 25 years (Table 5). Males were significantly older than females (p<0.01), with the highest and lowest percentage of <25-year-olds in the female (52%) and MSM patient groups (18%) respectively (Table 5). There was a significant reduction in the proportion of all patients under 25 years (p<0.01), and in male patients under 25 years (p<0.01) compared to the previous year's data.

Site of specimen was mainly genital (79%, n=1 531), followed by rectal (13%, n=255), pharyngeal (6.3%, n=122) and other (1.5%, n=30); site of infection was reported as unknown for 56 cases.

Information on previous diagnosis of gonorrhoea was available for 40% (796) of cases, 18% (142) of which had had a previous infection. Information on concurrent STI was available for 42% (841) of cases; 22% (183) of patients had a concurrent chlamydia infection, 6.5% (55) had another STI, and 72% (603) did not have any other STIs. When HIV status was known (819), 18% (144) were HIV-positive, 90% (130) of whom were MSM.

Table 4. Patient characteristics 2009–2013

	2009 N (%)	2010 N (%)	2011 N (%)	2012 N (%)	2013 N (%)
Total number of isolates	1 366	1 766	1 902	1 927	1 994
Gender					
Male	1123 (83.7)	1441 (82.4)	1505 (82.4)	1596 (83.7)	1676 (84.7)
Female	219 (16.3)	308 (17.6)	321 (17.6)	310 (16.3)	302 (15.3)
Unknown	24	17	76	21	16
Age (years)					
<25	422 (32.0)	599 (34.4)	572 (31.9)	617 (32.9)	554 (28.4) ǂǂ
≥25	898 (68.0)	1141 (65.6)	1221 (68.10)	1261 (67.1)	1399 (71.6)
Unknown	46	26	109	49	41
Sexual orientation & gender					
Heterosexual males	314 (40.1)	426 (37.7)	423 (35.6)	390 (35.2)	376 (32)
Men who have sex with men	251 (32)	395 (35)	442 (37.3)	408 (36.8)	496 (42.3) ǂǂ
Females	219 (27.9)	308 (27.3)	321(27.1)	310 (28)	302 (25.7)
Unknown	582	637**	716	819	820
Site of infection					
Genital	1164 (86.5)	1426 (84.7)	1466 (82.1)	1537 (83)	1531 (79) ǂǂ
Pharyngeal	34 (2.5)	62 (3.5)	79 (4.4)	92 (5)	122 (6.3)
Anorectal	138 (10.3)	191 (11.4)	216 (12.1)	188 (10.2)	255 (13.2) ǂǂ
Other	9 (0.7)	7 (0.4)	24 (1.3)	35 (1.9)	30 (1.5)
Unknown	21	80	117	75	56
Previously diagnosed					
Yes	84 (18.1)	145 (21)	146 (19)	130 (17.2)	142 (17.8)
No	379 (81.9)	546 (79)	621 (81)	627 (82.8)	654 (82.2)
Unknown	903	1075	1135	1170	1198
Concurrent STI					
Concurrent chlamydia infection	78 (14.3)	172 (22.1)	194 (22.2)	187†† (23.4)	183 (21.8)
Concurrent other STI (not HIV)	35 (6.4)	28† (3.6)	43 (4.9)	49ǂ (6.1)	55 (6.5)
No concurrent STI	433 (79.3)	579 (74.3)	638 (72.9)	564 (70.6)	603 (71.7)
Unknown	820	987	1027	1127	1153
HIV status*					
Positive	N/D	48 (15.5)	141 (17.6)	104 (13.5)	144 (17.6) ǂǂ
Negative	N/D	262 (84.5)	661 (82.4)	668 (86.5)	675 (82.4) ǂǂ
Unknown	N/D	556	1100	1155	1175

N/D: no data
Percentages calculated from known values
** Data from 866 patients in 2010*
*** Includes one individual with unknown gender, but with mode of transmission reported as heterosexual*
† Includes two individuals with two concurrent STIs
†† Includes four individuals with two concurrent STIs
ǂ Includes six individuals with chlamydia and an additionally diagnosed STI
ǂǂ Significant difference compared to previous year (p < 0.05).

Information on sexual orientation and gender was available for 58.9% (1174) of the cases. In these cases, 57.7% (678) of the *N. gonorrhoeae* infections were reported as heterosexually acquired (25.7% females and 32% males) and 42.3% (496) were from MSM. Eighty-three additional males with unknown mode of transmission had *N. gonorrhoeae* isolated from the pharynx or anogenital region.

There was little change in the epidemiological data compared with 2012 (Table 4); however, there was a significant increase in anorectal isolates (p<0.01), isolates from MSM (p=0.01) and HIV-positive patients (p=0.04). Significant decreases were identified in the number of genital isolates (p<0.01) and isolates from HIV-negative patients (p<0.01). Between 2011 and 2013, isolates from females decreased from 18% to 15%, with concomitant increases in the number of isolates from males (82% to 85%) since 2010. Between 2009 and 2013, increasing percentages of isolates from MSM (32% to 42%) were received along with a reduction in isolates from male heterosexuals (40% to 32%). The proportion of genital isolates continues to decrease (87% to 79%) while the number of pharyngeal (2.5% to 6.3%) and anorectal isolates (10% to 13%) continues to increase.

Table 5. Patient age distribution by gender and sexual orientation, 2013

Variable	N†	Age (years)			
		Range	Mode	Median	<25 (%)
All patients	1953	0 - 85	25	29	554 (28.4)
Male	1645	2 - 85	25	30	396 (24.1)
Female	301	0 - 73	21	24	157 (52.2)
Male heterosexual	373	16 - 71	21/27	29	106 (28.4)
MSM	490	15 - 64	28	31	88 (18.0)

† Where information was available

As in previous years, the majority of patients with known clinical service type attended a dedicated STI or sexual health clinic (56%) and there was no difference compared to 2012 (Table 6).

Table 6. Clinical service type attendance

Grouping	2010 N=866 n (%)	2011 N=1902 n (%)	2012 N=1927 n (%)	2013 N=1994 n (%)
STI and sexual health clinics	444 (51.3)	1079 (56.7)	1076 (55.8)	1123 (56.3)
Antenatal	0	0	2 (0.1)	0
Out-patient clinic	36 (4.2)	128 (6.7)	148 (7.7)	122 (6.1)
Other	42 (4.9)	60 (3.2)	47 (2.4)	75 (3.8)
Primary care	88 (10.2)	277 (14.6)	203 (10.5)	215 (10.8)
Unknown	256 (29.6)	358 (18.8)	451 (23.4)	459 (23.0)

Note: grouping of clinical service type as described in Table 1.

Information on country of birth was supplied by 14 countries. In total, 12 of these countries (Belgium, Cyprus, Denmark, Germany, Greece, Ireland, Italy, Malta, the Netherlands, Slovenia, Slovakia and the United Kingdom) reported patients who had acquired gonorrhoea in their country of residence but had a different country of birth, with the Netherlands having the largest number of nationalities (n=30). Of the 1 029 cases with known country of birth, 83% (n=856) had been diagnosed and reported with gonorrhoea in their country of birth, which was similar to 2012 (81%). In cases where country of birth and reporting differed, the most common countries of birth (with >5 patients) were Brazil (15 patients), Albania and Italy (12 patients each), Turkey (9 patients), Spain and Romania (7 patients) and Greece (6 patients). Probable country of infection data were supplied by 17 countries, one more than 2012, with 12 countries reporting patients acquiring gonorrhoea outside the reporting country. The majority of cases (94%; 764/812) most probably acquired gonorrhoea in the country reporting the case. Those countries most commonly reported as probable countries of infection (with ≥4 patients) and differing from the reporting country were France with six patients (all male, four MSM and one heterosexual, with an anorectal infection), Thailand with five patients (five males, two heterosexual and one MSM) and Spain with four patients (two heterosexual men; one female and one MSM).

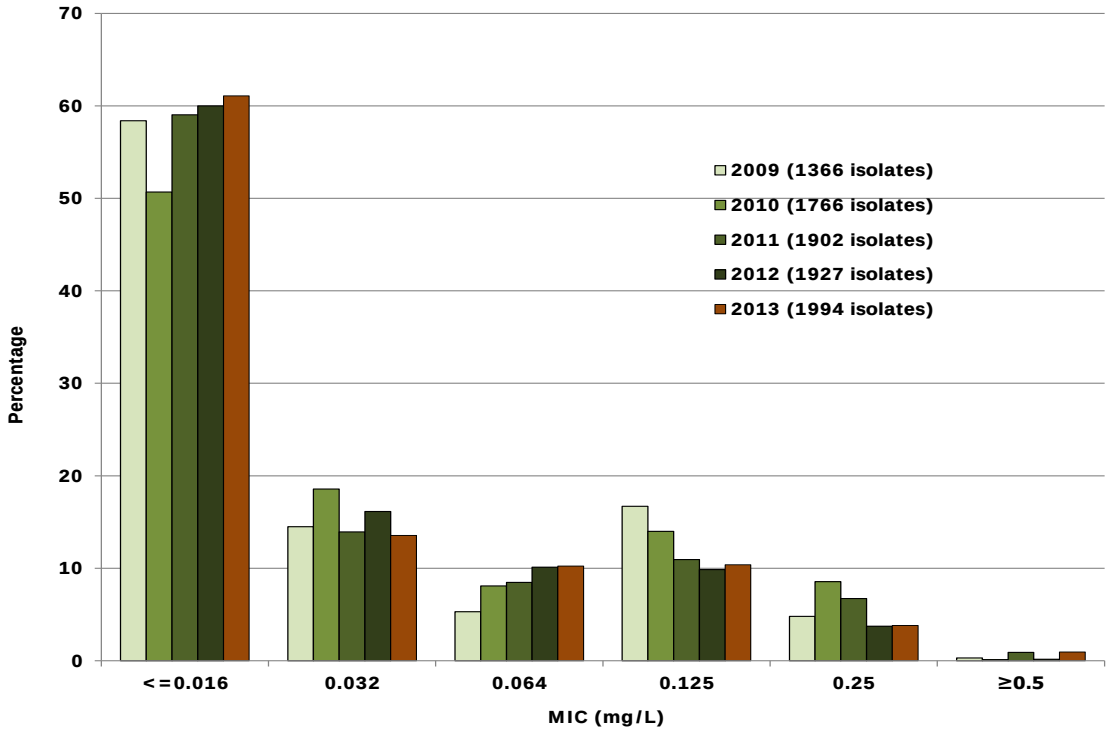
Further country-specific data are presented in Annex 6 which includes a breakdown by clinical service type, country of birth, place of residence and probable country of infection.

3.2 Antimicrobial susceptibility and resistance

Ceftriaxone and cefixime

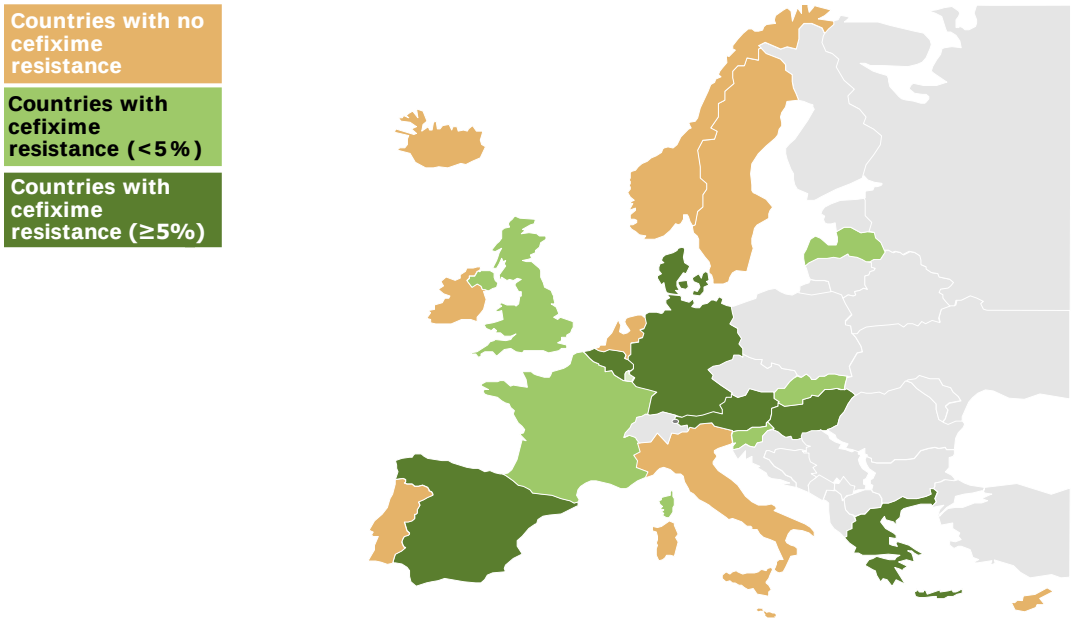
Cefixime resistance (MIC>0.125 mg/L) was observed in 4.7% (n=93) of isolates (Figure 1). Despite not being a significant increase (p=0.23), it is still more than in 2012 (3.9%), even though the trend has been decreasing since 2010 (8.7%). The number of most susceptible isolates (MIC ≤0.016 mg/L) slightly increased from 2012 (60%, n=1 156) to 2013 (63%, n=1 218). The number of isolates displaying a MIC of ≥0.5 mg/L increased from three isolates in 2012 to 19 isolates in 2013, which is greater than the previous high of 17 isolates with a MIC of ≥0.5 mg/L in 2011.

Figure 1. Distribution of MIC for cefixime in Euro-GASP, 2009–2013



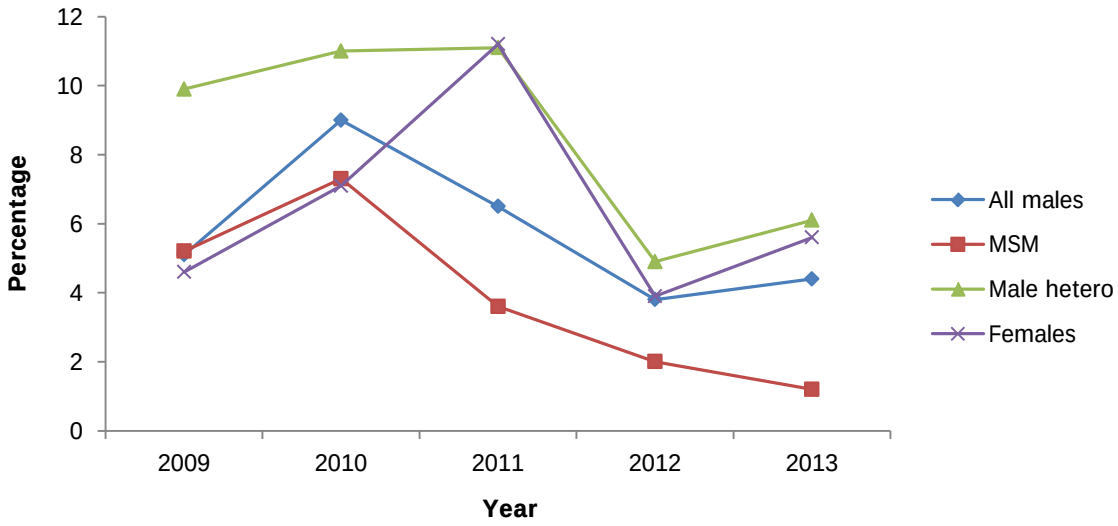
In 2013, cefixime resistance was detected in 13 countries (Table 7), compared to 14 in 2012. Since 2012, there has been a slight increase in the United Kingdom (0–0.8%), and 2013 saw an increase in Belgium from 0.9% to 6.4%. Cefixime resistance was no longer detected in Ireland and Italy. Compared to 2012, six countries (Austria, Denmark, Germany, Greece, Hungary and Spain) continued to have ≥5% resistance in 2013, and France, Latvia, Slovakia and Slovenia continued to have <5% cefixime resistance. Map 2 displays the widespread geographical distribution of isolates with cefixime resistance.

Map 2. Proportion of isolates with cefixime resistance in Europe, 2013



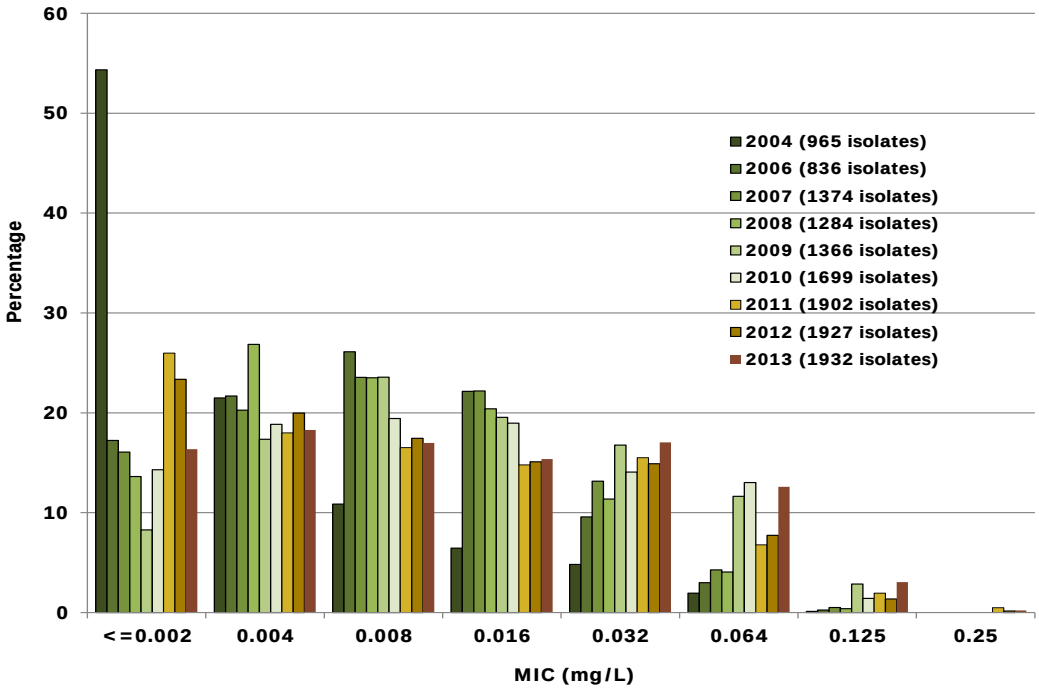
Cefixime resistance among MSM has declined since 2010. Among females and heterosexual males, cefixime resistance has declined since 2010, but between 2012 and 2013 it began to increase again, to 6.1% and 5.6% respectively (Figure 2).

Figure 2. Percentage of isolates with cefixime resistance by gender and male sexual orientation, Euro-GASP, 2009–2013



Seven isolates displayed ceftriaxone resistance (MIC>0.125 mg/L) in 2013 compared to three in 2012 and ten in 2011 (Figure 3). Six isolates were from Spain and one from Germany. All were from men and were genital isolates. All displayed the classical ST1407 profile of cefixime and ciprofloxacin resistance. In 2013, the MIC distribution for ceftriaxone showed a decreased proportion of highly susceptible gonococcal isolates (MIC≤0.002 mg/L) compared to 2011 and 2012, along with an increased proportion of isolates with higher MICs (0.064 mg/L and 0.125 mg/L) (Figure 3).

Figure 3. Distribution of MIC for ceftriaxone in Euro-GASP, 2004–2013



Note: 2013 MIC distribution data do not include 33 isolates from Ireland and 29 isolates from Malta as Etests with the lowest concentration of 0.016 mg/L were used.

Table 7. Resistance to cefixime, ciprofloxacin, azithromycin and penicillin G by country, Euro-GASP, 2013

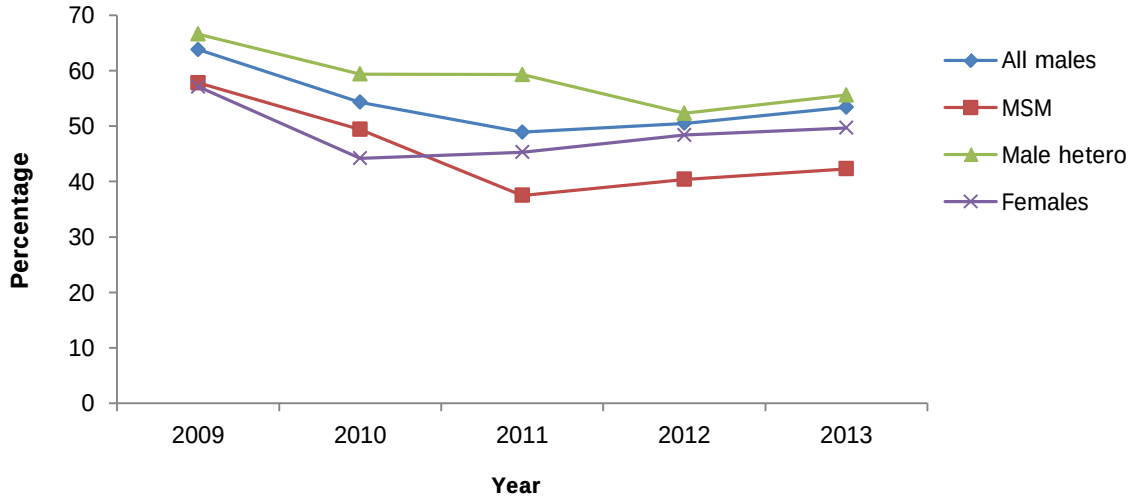
Country	Antimicrobial												Method of testing
	Cefixime			Ciprofloxacin			Azithromycin			Penicillinase-producing *Neisseria gonorrhoeae* (PPNG)			
	No. resistant	No. tested	%	No. resistant	No. tested	%	No. resistant	No. tested	%	No. resistant	No. tested	%	
Austria	7	109	6.4	78	109	71.6	6	109	5.5	28	109	25.7	Centralised
Belgium	7	110	6.4	62	110	56.4	2	110	1.8	17	110	15.5	Decentralised – MIC
Cyprus	0	9	0.0	8	9	88.9	3	9	33.3	1	9	11.1	Centralised
Denmark	13	110	11.8	64	110	58.2	10	110	9.1	9	110	8.2	Decentralised – Etest
France	4	112	3.6	50	112	44.6	0	112	0.0	19	58	32.8	Decentralised – Etest
Germany	13	101	12.9	64	101	63.4	4	101	4.0	17	101	16.8	Centralised
Greece	11	75	14.7	54	75	72.0	15	66	22.7	2	75	2.7	Decentralised – Etest
Hungary	6	88	6.8	60	88	68.2	2	88	2.3	6	88	6.8	Centralised
Iceland	0	5	0.0	2	5	40.0	0	5	0.0		Not done		Decentralised – Etest
Ireland	0	103	0.0	27	103	26.2	3	103	2.9	5	103	4.9	Decentralised – Etest
Italy	0	100	0.0	63	100	63.0	1	100	1.0	9	100	9.0	Decentralised – Etest
Latvia	1	38	2.6	10	38	26.3	6	38	15.8	5	38	13.2	Centralised
Malta	0	31	0.0	11	31	35.5	0	31	0.0	2	31	6.4	Decentralised – Etest
Netherlands	0	139	0.0	48	139	34.5	2	139	1.4		Not done		Decentralised – Etest
Norway	5	112	4.5	89	112	79.5	12	112	10.7	32	112	28.6	Centralised
Portugal	0	110	0.0	52	110	47.3	20	110	18.2	7	110	6.4	Decentralised – Etest
Slovakia	5	110	4.5	52	110	47.3	2	110	1.8	4	110	3.6	Centralised
Slovenia	1	73	1.4	46	73	63.0	0	73	0.0	10	73	13.7	Centralised
Spain	18	119	15.1	78	119	65.5	10	119	8.4	15	119	12.6	Decentralised – MIC
Sweden	0	100	0.0	60	100	60.0	9	100	9.0	18	100	18.0	Decentralised – Etest
UK	2	240	0.8	77	240	32.1	1	240	0.4	25	240	10.4	Decentralised – MIC
Total	93	1994	4.7	1055	1994	52.9	108	1985	5.4	231	1796	12.9	
95% CI			3.8–5.7			50.7– 55.1			4.5–6.5			11.4–14.5	
Median			2.6			58.2			2.9			11.1	

CI: confidence interval of the percentage %

Ciprofloxacin

In 2013, resistance (MIC>0.06 mg/L) ranged from 26% (Ireland and Latvia) to 89% (Cyprus) (same low and high-prevalence countries as previous year); the mean was 53% (Table 7). Overall resistance levels were similar to 2012 (50%), continuing the gradually increasing trend since 2011. Resistance is highest in heterosexual males (56%) and lowest in MSM (42%) (Figure 4).

Figure 4. Percentage of isolates with ciprofloxacin resistance by gender and male sexual orientation, Euro-GASP, 2009–13

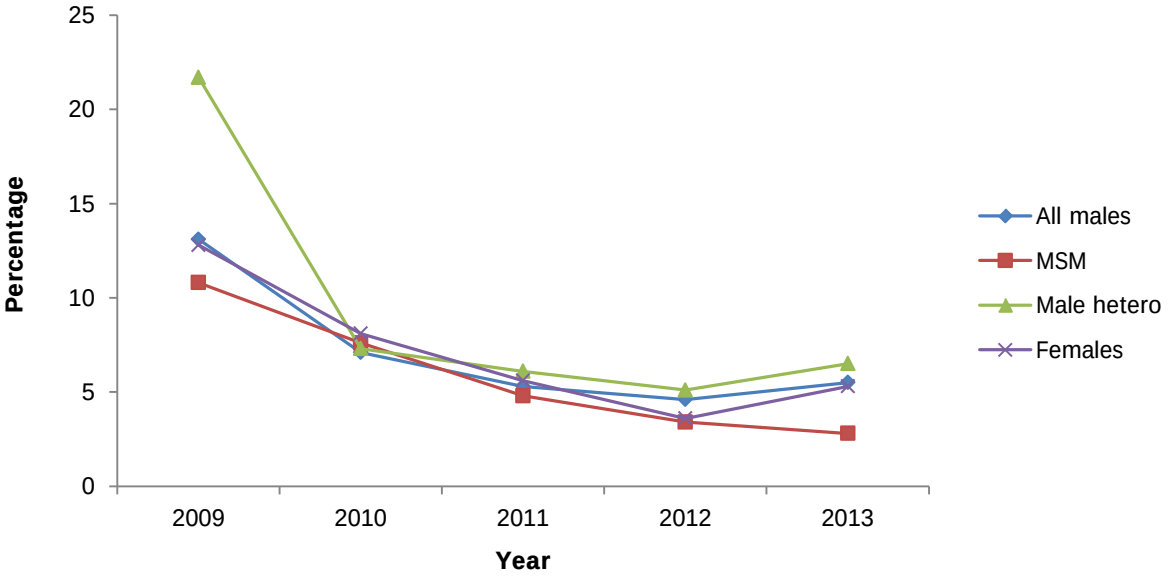


Azithromycin

In 2013, resistance (MIC>0.5 mg/L) ranged from 0% (France, Iceland, Malta and Slovenia) (note: France and Malta 0% also in 2012) to 33% in Cyprus (note: only nine isolates), and 23% in Greece, with a mean of 5.4% which is an increase from 4.5% in 2012 (Table 7). Resistance levels increased for the first time since 2009. Just one isolate displayed high-level resistance to azithromycin (MIC≥256 mg/L) and this was from a heterosexual male in Ireland. Isolates displaying this high-level resistance to azithromycin were detected in 2006 (n=1), 2007 (n=4), 2011 (n=2) and 2012 (n=3).

The overall trend in azithromycin resistance was the same in both genders, heterosexual males and MSM (Figure 5). The highest resistance in 2013 (6.5%) was observed in heterosexual males, the lowest (2.8%) in MSM (Figure 5).

Figure 5. Percentage of isolates with azithromycin resistance by gender and male sexual orientation, Euro-GASP, 2009–13



The overall percentages of *N. gonorrhoeae* isolates resistant to ciprofloxacin, azithromycin, cefixime and producing β-lactamase from 2004 to 2013 are summarised in Figure 6.

Penicillin G

High-level plasmid-mediated resistance to penicillin G (penicillinase-producing *N. gonorrhoeae* (PPNG)) ranged from 2.7% (Greece) to 33% (France), with a mean of 13% (Table 7). High-level resistance to penicillin G continues to remain fairly constant at 8.0–13% (Figure 6).

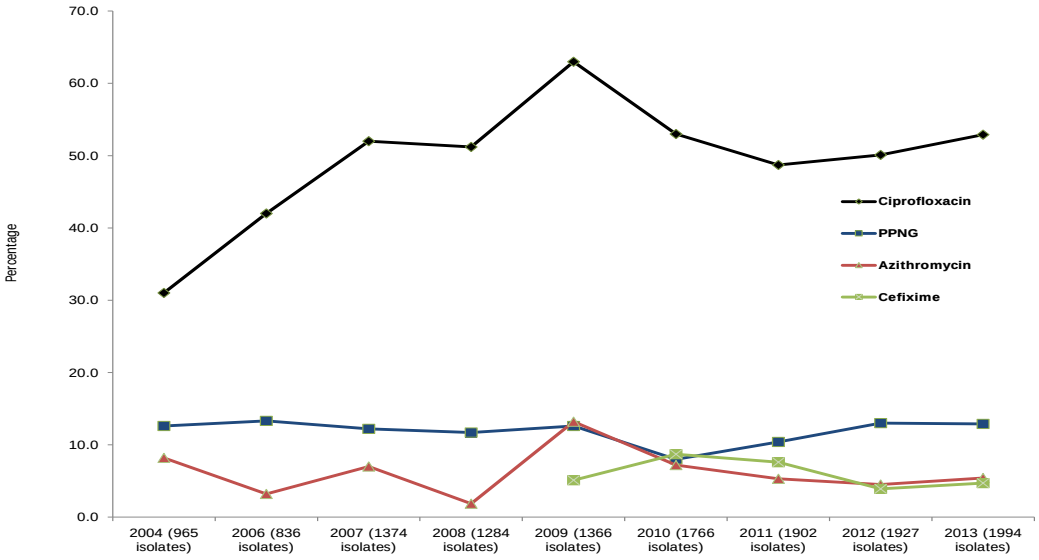
Spectinomycin

No resistance to spectinomycin (MIC>64 mg/L) was detected in 2013 (1 989 isolates tested). No resistance to spectinomycin has been detected since 2008, when this agent started being tested.

Gentamicin

Gentamicin data was available for 1 291 isolates, with no data reported from Belgium, Greece, Iceland, Ireland, Malta, the Netherlands and the United Kingdom. As yet, there are no breakpoints for gentamicin, but overall, the MICs of gentamicin continue to be low in all European countries (MIC50 and MIC90 8 mg/L and 12 mg/L respectively), with similar MIC50 and MIC90 to previous years. The MIC range in 2013 was the same as in the previous year (1–16 mg/L).

Figure 6. Overall percentage of resistant *N. gonorrhoeae* by antimicrobial and year, Euro-GASP, 2004–2013



PPNG: penicillinase-producing N. gonorrhoeae

Associations between patient characteristics and resistance

Table 8 shows resistance by patient characteristics. Further statistical analysis of the associations is available in Annex 7. Overall, the distribution of resistance is similar across patient groups and specimen types, other than for the following:

- Ciprofloxacin: by univariate analysis, the same associations as in 2012 were observed between ciprofloxacin resistance and age (≥25 years, OR 1.36, CI 1.12-1.66, p<0.01), being a heterosexual male compared to MSM (OR 1.7, CI 1.3-2.24, p<0.01), being female compared to MSM (OR 1.34, CI 1.01-1.79, p=0.04) and the absence of a concurrent chlamydial infection (OR 1.44, 1.03-2.02, p=0.03) (Table A7.1, Annex 7). Following multivariable analysis, ciprofloxacin resistance remained associated with heterosexual males and the absence of a concurrent chlamydial infection (odds ratio for heterosexual male compared to MSM: OR 1.57, CI 1.13–2.18, p=0.01 and odds ratio for no concurrent chlamydia infection: OR 1.57, CI 1.09-2.24, p=0.02). Similar to 2012, isolates from the anorectal and pharyngeal sites were less likely to harbour ciprofloxacin resistance than isolates from genital sites (anorectal OR 0.56, CI 0.43-0.73, p=<0.01; pharyngeal OR 0.63, CI 0.44-0.92, p=0.015) (Table A7.1, Annex 7).
- Azithromycin: univariate analysis revealed an association between azithromycin resistance and being a heterosexual male compared to MSM (OR 2.39, CI 1.21-4.69, p=0.01) (Table A7.2, Annex 7) which was not observed in 2012. Using Fisher's exact test there was a significant difference (p<0.01) between the site of infection and azithromycin resistance which was not observed in 2012; genital and pharyngeal sites harboured isolates with more resistance than anorectal sites (Table A7.2, Annex 7).
- PPNG: univariate analysis revealed an association between PPNG and being female compared to MSM (OR 1.68, CI 1.04-2.72, p=0.03) (Table A7.3, Annex 7). This association was observed in 2012; however, the association between PPNG and being a heterosexual male was no longer significant in 2013.
- Cefixime: in the univariate analysis, cefixime resistance was associated with being a heterosexual male (OR 5.32, CI 2.12-13.3, p<0.01) or female (OR 4.87, CI 1.89-12.6, p<0.01) compared to MSM. The association

with being a heterosexual male was also observed in 2012, but the association with female gender was not observed in 2012. Using Fisher's exact test there was a significant difference ($p<0.01$) between the site of infection and cefixime resistance which was not observed in 2012; genital sites harboured isolates with more resistance than pharyngeal and anorectal sites (Table A7.4, Annex 7).

- It should be noted that the completeness of the sexual orientation variable is poor (52%), and it is possible that MSM are under-reported overall.

Table 8. Resistance to ciprofloxacin, azithromycin, cefixime and penicillin G by patient characteristics, Euro-GASP, 2013

Country	Ciprofloxacin			Azithromycin			Cefixime			PPNG		
	Tested	Resistant	%	Tested	Resistant	%	Tested	Resistant	%	Tested	Resistant	%
Sexual orientation & gender												
Male	1676	895	53.4	1667	92	5.5	1676	74	4.4	1503	187	12.4
Female	302	150	49.7	302	16	5.3	302	17	5.6	277	41	14.8
MSM	496	210	42.3	494	14	2.8	496	6	1.2	385	36	9.4
Heterosexual male	376	209	55.6	369	24	6.5	376	23	6.1	364	42	11.5
Age												
<25 years	554	262	47.3	553	35	6.3	554	22	4.0	499	54	10.8
≥25 years	1399	769	55.0	1391	72	5.2	1399	68	4.9	1256	175	13.9
Site of infection												
Genital	1531	852	55.6	1522	95	6.2	1531	85	5.6	1426	190	13.3
Anorectal	255	105	41.2	255	3	1.2	255	3	1.2	176	19	10.8
Pharyngeal	122	54	44.3	122	7	5.7	122	1	0.8	109	7	6.4
Other	30	12	40.0	30	0	0.0	30	1	3.3	29	4	13.8
Previous gonorrhoea infection												
Yes	142	65	45.8	142	9	6.3	142	5	3.5	142	9	6.3
No	654	325	49.7	645	29	4.5	654	34	5.2	653	56	8.6
Concurrent chlamydia												
Yes	183	69	37.7	183	3	1.6	183	3	1.6	132	19	14.4
No	658	307	46.7	658	20	3.0	658	13	2.0	546	62	11.4
HIV status												
Positive	144	64	44.4	144	3	2.1	144	2	1.4	90	9	10.0
Negative	675	314	46.5	675	20	3.0	675	21	3.1	591	53	9.0
Overall resistance	1994	1055	52.9	1985	108	5.4	1994	93	4.7	1796	231	12.9

3.3 Completeness of data

Overall completeness of variables remained similar to the 2012 data (Table 9). Completeness of data remained high for 'gender', 'age' and 'site of infection' (over 97%). Since 2012, there has been a slight improvement in the completeness of reporting for mode of transmission, concurrent STI and HIV status.

Table 9. Completeness of reporting, Euro-GASP, 2013

Variables	2010 (n=1766)		2011 (n=1902)		2012 (n=1927)		2013 (n=1994)	
	No	%	No	%	No	%	No	%
Gender	1749	99.0	1826	96.0	1906	98.9	1978	99.2
Age	1740	98.5	1793	94.3	1878	97.5	1953	97.9
Mode of transmission	1001	56.7	1061	55.8	987	51.2	1044	52.4
Site of infection	1683	95.3	1785	93.8	1852	96.1	1938	97.2
Previous gonorrhoea	691	39.1	767	40.3	757	39.3	796	39.9
Concurrent STI	779	44.1	875	46.0	800	41.5	841	42.2
Place of residence*	720	83.1	1437	75.6	1541	80.0	1436	72.0
Clinical service type*	610	70.4	1544	81.2	1476	76.6	1535	77.0
Country of birth*	392	45.3	861	45.3	988	51.3	1029	51.6
Probable country of infection*	263	30.4	737	38.8	856	44.4	812	40.7
HIV status*	310	35.8	802	42.2	772	40.0	819	41.1

** Inclusion from 2010 second collection period only*

4 Conclusions

A slight increase in cefixime resistance was observed in 2013 across the EU/EEA (from 3.9% in 2012 to 4.7% in 2013), with cefixime-resistant isolates detected in 13 of the 21 countries. Even though there was a slight increase in the number of highly susceptible isolates (MIC≤0.016 mg/L) in 2013 (63%) compared to 2012 (60%), the proportion of isolates displaying a MIC of ≥0.5 mg/L increased from three isolates in 2012 to 19 isolates in 2013, which is greater than the previous high of 17 isolates with a MIC of ≥0.5 mg/L in 2011. Cefixime resistance continues to be lowest among MSM (1.2%) and highest in heterosexual males (6.1%) and females (5.6%). Seven isolates displayed ceftriaxone resistance (MIC>0.125 mg/L) in 2013, compared to three in 2012 and ten in 2011.

Rates of ciprofloxacin resistance have continued to increase gradually since 2011 (53% in 2013). Azithromycin resistance increased for the first time since 2008, to 5.4%. However, none of those antimicrobials are recommended for monotherapy, unless the isolates are first shown to be susceptible. There continues to be no resistance to spectinomycin in Euro-GASP, but it is feared that resistance might rapidly emerge if use of spectinomycin becomes more frequent, although this antimicrobial can be difficult to acquire in many European countries.

The MIC distribution of gentamicin has not changed over the years and gentamicin may therefore be a potential future therapeutic option. However, this is based on in-vitro data only and appropriately designed and quality-assured clinical trials using gentamicin as monotherapy are needed. As gentamicin is not yet recommended for the treatment of gonorrhoea, it will no longer be tested annually in Euro-GASP. Spectinomycin will also not be tested as this antimicrobial is difficult to acquire and is therefore used infrequently across Europe.

As in previous years, there is a continuing tendency for MSM to have a lower risk of harbouring resistant isolates. This is supported by a lower risk of resistance among anorectal isolates. The lower levels of resistance among isolates from MSM could be related to better diagnosis among MSM, particularly more use of molecular tests in extra genital sites, leading to more appropriate treatment with third generation cephalosporins (i.e. ceftriaxone). This has possibly led to disruption in the transmission of strains resistant to azithromycin, ciprofloxacin and/or ceftriaxone [7].

Implementation of the European response plan to control the threat of multidrug-resistant *N. gonorrhoeae* in Europe [4] should continue in order to help identify and report treatment failures and strengthen AMR surveillance to ensure that gonorrhoea remains a treatable infection. Euro-GASP has a major role in fulfilling the objectives of the response plan which include:

- Strengthening the surveillance of gonococcal antimicrobial susceptibility by increasing the number of participating countries and isolates, improving representativeness of the programme and collecting more epidemiological variables. A review of the representativeness of Euro-GASP to identify areas for improvement is underway – for example the difference in sampling methods across countries is a limitation. Iceland joined Euro-GASP in 2013 and several additional countries are scheduled to join in 2014. Even though there has been a slight decrease since 2009 in the percentage of isolates tested in Euro-GASP compared to the European epidemiological surveillance data (2009: 6%; 2013: 4%) the total number of gonorrhoea cases reported from the countries participating in Euro-GASP increased between 2012 (44632) and 2013 (50001) [5]. Even though the overall completeness of variables remained similar to 2012, the fact that information on place of residence and probable country of infection was less complete is disappointing.
- Continuing country visits to promote the inclusion of additional centres and improve isolate numbers.
- Strengthening capacity for the surveillance of gonococcal antimicrobial susceptibility and developing capacity for culture and susceptibility testing across countries. Training in STI diagnostics and susceptibility testing is provided annually and experts (or related staff) are encouraged to participate, where required, and eventually move towards decentralised testing.
- Ensuring that all Euro-GASP laboratories participate in the EQA programme. Even though participation in the EQA is high (see section 4), all Euro-GASP countries need to ensure full implementation.

Isolate numbers from countries that previously supplied low numbers are increasing annually (Cyprus, Greece, Hungary, Ireland, Malta and Slovenia). More isolates are required from Spain and the Netherlands to achieve 5% coverage. The number of gonorrhoea diagnoses from the United Kingdom (32 377) is too large to achieve 5% coverage (1 619 isolates) in Euro-GASP. The review of the representativeness of Euro-GASP should identify whether the weighting of data from low coverage countries is statistically feasible.

Even though there has been a slight improvement in the completeness of patient variable reporting since 2012, improvements still need to be made if robust statistical analysis is to be performed on the linked susceptibility and patient data.

Euro-GASP detected a non-significant increase in cefixime and ceftriaxone resistance in 2013, along with isolates containing higher cefixime MICs (≥0.5 mg/L) plus one isolate with a very high MIC of azithromycin (≥256 mg/L). These factors are a major concern and the risk of treatment failures remains high. Therefore, continuous implementation of the response plan is essential, along with the development of novel antimicrobials and/or new dual antimicrobial therapy regimens.

5 External quality assessment – 2014

5.1 Background

A priority of any surveillance programme featuring decentralised testing is ensuring the concordance and comparability of the data generated, in this case, antimicrobial susceptibility data. An external quality assessment (EQA) scheme facilitates the monitoring of the data across and within different testing centres.

An EQA scheme for *N. gonorrhoeae* has been available for laboratories participating in the European Sexually Transmitted Infections (STI) surveillance network since 2009.

In 2014, a panel of *N. gonorrhoeae* was distributed by the United Kingdom National External Quality Assessment Service (UK-NEQAS) for the European gonococcal antimicrobial resistance quality assessment programme (GC AMR EQA). Successful performance in the EQA scheme was essential for participation in decentralised susceptibility testing across Europe (Annex 1).

The EQA distribution dataset for 2014 is summarised. A full report is available upon request from ECDC [8].

5.2 Antimicrobial susceptibility testing external quality assessment scheme

In January 2014, 21 participating laboratories from 20 countries received ten gonococcal isolates (QA14) for susceptibility testing from UK-NEQAS. In order to measure intra-laboratory reproducibility, one of these ten isolates was supplied in triplicate (1958/1962/1965), two were supplied in duplicate (1960/1963 and 1961/1964), and the remaining three isolates were supplied singularly. This resulted in six different strains. The isolates included in the panel were selected by PHE to represent a range of susceptibility profiles to therapeutic antimicrobial agents and were selected from a global panel of well characterised and recently isolated clinical strains.

Susceptibility testing methods

Participating laboratories tested the European GC AMR EQA panel of isolates using their own routine methodology for the following list of therapeutic antimicrobials where possible:

- Azithromycin
- Cefixime
- Ceftriaxone
- Ciprofloxacin
- Gentamicin
- Spectinomycin
- Beta-lactamase testing.

Results for the EQA were submitted directly to UK-NEQAS for the production of an individual laboratory report. The results were then forwarded to PHE for further analysis.

Laboratories described details of the methodology and the local breakpoints used for determining the category of susceptibility (resistant, intermediate or susceptible) for each antimicrobial tested. Results were reported as the category of susceptibility and the MIC for the Etest and agar dilution methods, or the zone of inhibition for the disc diffusion method for each isolate. To allow for differences in local methods and breakpoints used, blind testing results were analysed only using the susceptibility categories. For the purposes of this report, consensus susceptibility categories for the panel isolates tested were calculated once all participating laboratories had reported results (‘consensus’ was assigned to the category reported most often, irrespective of breakpoint criteria used).

5.3 Results

The table below details the consensus category, the modal (range) MIC for Etests and agar dilution (mg/L) and the percentage concordance of the resistance category.

Table 10. Consensus results for QA14 EQA panel

Strain	Azithromycin consensus	Cefixime consensus	Ceftriaxone consensus	Ciprofloxacin consensus	Gentamicin consensus	Spectinomycin consensus	Beta-lactamase consensus
1958/1962/1965 (WHO K) (cefR, ciproR)	S 0.25 (0.125-0.5) 75.4	R 0.25 (0.064-0.5) 86.9	S 0.125 (0.032-0.25) 90.5	R >32 (0.004-64) 98.4	N/A 4 (1-8) N/A	S 16 (4-32) 100	NEG 95%
1960/1963 (WHO P) (AzR)	R 4 (1-4) 100	S S0.016 (≤0.016-0.032) 100	S 0.008 (<0.002-0.032) 100	S 0.004 (<0.004-0.008) 100	N/A 4 (2-8) N/A	S 16 (4-32) 100	NEG 95%
1961/1964 (WHO O) (SpecR, PPNG)	S 0.25 (0.125-1) 65.8	0.016 (≤0.016-0.064) 100	S 0.016 (≤0.016-0.064) 100	0.016 (0.004-0.16) 100	N/A 4 (2-8) N/A	R >1024 (16>1024) 92.9	POS 100%
1956 (H134160540) (cipR, Phadebact negative strain)	S 0.25 (0.125-1) 68.4	S 0.125 (0.016-0.25) 81	S 0.064 (0.012-0.064) 100	R >32 (2->132) 100	NA 4 (1-8) N/A	S 16 (1-32) 100	NEG 100%
1957 (RB12000689) (PPNG – with low penicillin MIC of 1-2mg/L)	S 0.25 (0.125-1) 84.2	S S0.016 (≤0.016-0.032) 100	S 0.004 (<0.002-0.023) 100	S 0.0042 (0.002-0.008) 100	N/A 4 (2-8) N/A	S 16 (4-32) 100	POS 100%
1959 (WHO F) (Fully susceptible)	S 0.064/0.125 (0.064-0.5) 94.7	S ≤0.016 (≤0.016-0.16) 100	S S0.002 (<0.001-0.016)) 100	S 0.004 (<0.002-S0.032) 100	N/A 4 (1-8) N/A	S 16 (4-32) 100	NEG 100%

Note: No consensus category of susceptibility was assigned to gentamicin as there were no published breakpoint guidelines for this antimicrobial at the time.
Disc diffusion zones not shown as only 1–2 laboratories performed this technique.

5.3.1. Susceptibility category concordance

Of the laboratories that returned results, one (92630) had an issue with the retrieval of strain 1960 and therefore returned an incomplete set of results. Three laboratories did not submit complete susceptibility category results (92784:1962/1965 cefixime and azithromycin; 92631: 1963 spectinomycin; 92628: 1965 ciprofloxacin; 93994: 1957 ciprofloxacin; 92631: 1963 spectinomycin).

Overall consensus results and MIC/disc diameter ranges were determined (Table 10). The highest levels of susceptibility category concordance were seen with ciprofloxacin (as in previous years) – 99.7% concordance (Table 11). The lowest level was seen in azithromycin, with an overall concordance of 81.4%, which is due to four of the six strains having a MIC on a breakpoint. None of the antimicrobials tested by Etest gave 100% concordance, although in four out of the five antimicrobials tested the concordance was above 96%.The agar dilution and disc diffusion methods both showed higher levels of concordance than Etest; however, there were very few laboratories performing these techniques (in most cases just two or three laboratories) (Table A1.1 – A1.6).

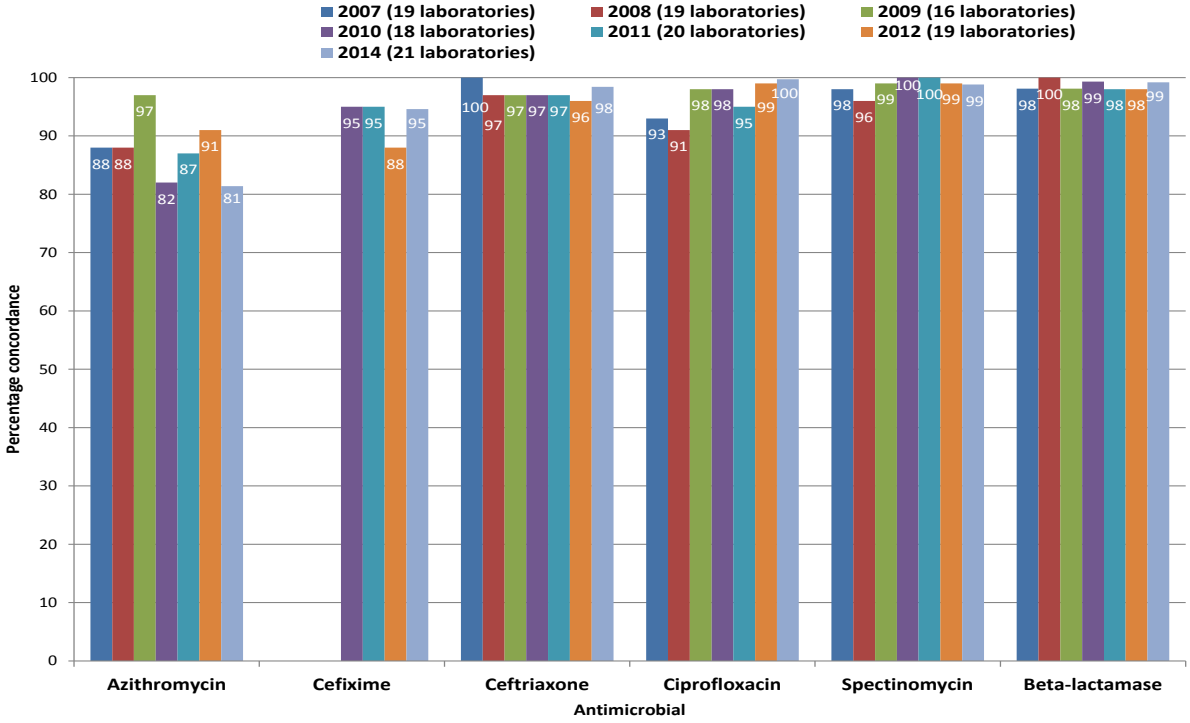
Table 11. Overall concordance (%) of susceptibility categories for *N. gonorrhoeae*, EQA panel QA14, 2014

	All	Etest	Agar dilution	Disc diffusion
Azithromycin	81.4	74.8	100.0	NA
Cefixime	94.6	96.1	91.7	NA
Ceftriaxone	98.4	99.0	95.8	NA
Ciprofloxacin	99.7	99.6	100.0	100.0
Spectinomycin	98.8	98.3	100.0	100.0

NA = Results from one laboratory only

When comparing susceptibility category concordance with previous EQA distributions from both ESSTI (QA2007, QA2008 and QA2009) and ECDC Euro—GASP (QA2010-12), levels appear relatively stable for most antimicrobials tested. Only cefixime shows a 7% increase to reach previous levels (Figure 1), while azithromycin concordance has decreased by 10% in this distribution, continuing the concordance fluctuation which has been occurring since 2008. Beta-lactamase result concordance remained high at 99%.

Figure 7. Interlaboratory concordance of susceptibility categories for *N. gonorrhoeae*, EQA panel QA14, 2014



5.3.2. Beta-lactamase concordance

One laboratory did not test for the production of beta-lactamase in the EQA panel of strains. One centre incorrectly identified the set of triplicate isolates. Overall, the concordance of beta-lactamase results, 99.2% in 2014, has remained stable since the previous EQA distribution (QA12).

5.3.3. Minimum inhibitory concentration concordance

Overall, 93.6% of the MIC results submitted were within one doubling dilution of the modal MIC recorded for all antimicrobials tested, showing an increase in concordance from the previous EQA panel distribution (89.7%) [9]. In total, 5.3% were within two doubling dilutions of the modal MIC and a further 1.2% differed from the modal MIC by more than two doubling dilutions. The highest MIC concordances were seen for ciprofloxacin (96.4%) and cefixime (97.5%) whilst the lowest were for ceftriaxone (87.9%). The overall MIC concordance remains very high, demonstrating comparability between different testing methods.

5.4 Conclusions

As noted in previous EQA distributions, there is a commonality of agar base and testing methodology used for antimicrobial susceptibility testing of *N. gonorrhoeae* across Europe. Despite the use of different methods and breakpoint guidelines, the majority of susceptibility categories reported were concordant and reported MICs were within one doubling dilution of each other.

Overall, the laboratories participating in EQA scheme QA14 performed very well and showed high levels of competence in testing *N. gonorrhoeae* strains of unknown phenotype. Both inter- and intra-laboratory concordance was high in most cases, demonstrating comparability between different testing methodologies and justifying confidence in decentralised testing. Analysis of the individual results submitted by the participating laboratories highlighted no centres in need of further guidance to bring them into line with the recommended target (95% of MICs within two dilutions of the modal MICs). More laboratories are now using EUCAST breakpoints which is a positive move as a recent revision of the EU case definition now includes definitions of antimicrobial resistance and EUCAST clinical breakpoints which should be adhered to.

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Annex 1. Framework for the European Gonococcal Antimicrobial Surveillance Programme, 2013 reporting protocol and analysis plan

A1.1 Isolate collection

Numbers

Each country should aim to collect a minimum of 110 gonococcal isolates each year, with the overall aim of retrieving and testing a minimum of 100 isolates. For countries where 110 isolates are less than 10% of the total number of gonorrhoea cases (Spain, the United Kingdom and the Netherlands), up to 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, a hierarchy of desired isolates for collection would be:

Males: pharyngeal; rectal; urethral; other

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

Given the current view that cephalosporin resistance emerged through interaction between commensal Neisseria species and *N. gonorrhoeae* in the pharynx, 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).

Isolate collection schedule

- The biannual collection period will continue to be during the second quarter (April/May) and the fourth quarter (October/November) in 2013.
- 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 have been collected.

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.

Epidemiological data could be obtained using the following methods:

- 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 requested from the place where the isolate was submitted.)

In both instances the epidemiological and microbiological 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 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 Antimicrobial 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 that could submit their own data in the future after further training, support, harmonisation, and quality assurance of methods.

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 internal quality control 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 within the proposed timeframe to ensure 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:

- Summary of isolates received and tested for each country (table)
- Overall incidence of resistance for each of the following AMR for each testing year (bar graph):
  - Cefixime
  - Ceftriaxone
  - Ciprofloxacin
  - Spectinomycin
  - Azithromycin
  - Gentamicin
  - Penicillinase-producing *Neisseria gonorrhoeae*
- MIC distribution by year for ceftriaxone (bar graph)
- Percentage ceftriaxone resistant isolates by country per year (bar graph)
- MIC distribution by year for cefixime (bar graph)
- Percentage ceftriaxone resistant isolates by country per year (bar graph)
- Ciprofloxacin resistance by country by year
- Summary of epidemiological data received by each country (table)
- Cefixime (and ceftriaxone if relevant) resistance versus sexual orientation and gender (bar graph/line graph)
- Cefixime (and ceftriaxone if relevant) resistance versus age group and gender

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.

<table>
<tr><td colspan="4">1. Identifying information
Name:
Laboratory/Institute name:
Date form completed:</td></tr>
<tr><td colspan="4">2. Sampling strategy. Please provide information on the geographical coverage of isolates submitted (complete, national, regional, local).</td></tr>
<tr><td colspan="4">3. Please provide information on regions of the country covered (or place of residence).</td></tr>
<tr><td colspan="4">4. Please describe the source of the isolates (STI clinics, DV clinics, GPs, hospitals, etc.).</td></tr>
<tr><td colspan="4">5. How are the isolates sampled (consecutively, selectively)?</td></tr>
<tr><td colspan="4">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)?</td></tr>
<tr><td colspan="4">7. How are the AMR data and epidemiological data linked?</td></tr>
<tr><td colspan="4">8. Institute/laboratory/person submitting the GC AMR data to TESSy. Please indicate if you would like the hub to submit the data.</td></tr>
<tr><td colspan="4">9. Institute/laboratory/person submitting the epidemiological data to TESSy. Please indicate if you would like the hub to submit the data.</td></tr>
<tr><td colspan="4">10. For laboratories performing decentralised testing, please provide the following antimicrobial information:</td></tr>
<tr><td></td><td>Methodology (Etest/agar dilution/breakpoint)</td><td>Agar base (GC, chocolate, DST, etc.)</td><td>MIC range (min–max)</td></tr>
<tr><td>Ceftriaxone
Cefixime
Azithromycin
Ciprofloxacin
Spectinomycin
Gentamicin
Beta-lactamase</td><td></td><td></td><td></td></tr>
<tr><td colspan="4">11. Please list the control strains tested for each media/reagent batch or for each antimicrobial tested.</td></tr>
</table>

Annex 3. Protocol for centralised gonococcal antimicrobial susceptibility testing

- Isolates are shipped frozen to one of the two testing centres:
  - Public Health England, London, United Kingdom
  - 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 Maldi-TOF or the Phadebact (Launch Diagnostics) 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 or Etest for gentamicin. Suspensions of cultures aged 18 to 24 hours are prepared equivalent to McFarland standard 0.5 (approximately 10^4 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

** Resistant according to EUCAST breakpoints but recorded as 'Intermediate' in TESSy*
The ceftriaxone and cefixime MICs are determined using Etests according to the manufacturer's instructions.

- All isolates are tested for penicillinase production, using the chromogenic reagent nitrocefin.
- Etests are performed on isolates that are resistant to azithromycin, using the agar dilution breakpoint technique.
- Etests are performed on all isolates with MIC>8 mg/L of gentamicin, using the agar dilution technique.
- The following control strains are tested on the poured agar dilution plates and each batch of Etests:
  - 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 Etest plates. European Committee on Antimicrobial Susceptibility Testing breakpoints [9] are used (Table A3.2).

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		0.125
Ciprofloxacin	1	0.12 – 0.5**	0.06
Gentamicin	To be determined		
Spectinomycin	128		64

** Reported as I or R in the European Surveillance System.*

*** Resistant according to EUCAST breakpoints but recorded as 'Intermediate' in TESSy. All isolates ≥0.06 mg/L will be categorised as resistant in the final report.*

The EUCAST azithromycin intermediate resistance is not 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 antimicrobial 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**
Record Id	**Place of residence:** NUTS code 0–3	**Record Id**
Record type	**Clinical service type:** ANC, combined service, dermatology-venereology clinic, hospital emergency department, family planning clinic, general practitioner, gynaecology clinic, infectious disease clinic, other primary care, dedicated STI clinic, urology, youth clinics, other, unknown.	**Record type**
Record type version	**Country of birth:** ISO-coded value list, UNK	**Parent Id**
Status	**Probable country of infection:** ISO coded value list, UNK	**Antibiotic:** Ceftriaxone, Cefixime, Azithromycin, Ciprofloxacin, Spectinomycin, Gentamicin, Penicillinase
Subject	**Transmission:** Heterosexual contact MSM/homosexual or bisexual male Mother-to-child transmission Other, unknown.	**Test method:** E-test, MIC, Breakpoint, Penicillinase
Reporting country: ISO coded value list	**Site of infection:** Anorectal Genital Pharyngeal Other Not applicable Unknown	**Result sign:** < Less than <= Less than or equal = Equal > Greater than ≥ Greater than or equal
Data source	**Prev Gono:** Yes No Unknown	**Result value**
Date used for statistics: yyyy-mm-dd	**HIV status:** Positive Known HIV positive New HIV diagnosis Negative Unknown	**SIR:** Sensitive Intermediate/decreased susceptibility Resistant Unknown
Gender: Female, male, unknown	**Concurrent STI:** Chlamydia Hepatitis B Hepatitis C Genital herpes LGV Syphilis Genital warts Mycoplasma Ureaplasma No concurrent STI Unknown	
Age: Years or unknown	**Result por:** NG-MAST *por* allele number	
	Result TbpB: NG-MAST *tbpb* allele number	
	Result Seq Type: NG-MAST sequence type number	

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	
Star tSurv Sys	Start year for data collection in the surveillance system	YYYY	
Internal quality control	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. Summary of patient characteristics

Table A6.1. Patient characteristics for cases reported to Euro-GASP; overall and by country, 2013

	All countries		Austria		Belgium		Cyprus		Denmark		France		Germany		Greece		Hungary	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	1994		109		110		9		110		112		101		75		88	
Sexual orientation & gender																		
MSM	496	42.3	6	8.6	22	39.3	0	0.0	30	30.3	0	0.0	9	30.0	19	28.8	0	0.0
Male heterosexual	376	32.0	32	45.7	24	42.8	1	25.0	34	34.3	0	0.0	9	30.0	47	71.2	3	18.8
Female	302	25.7	32	45.7	10	17.9	3	75.0	35	35.4	18	100.0	12	40.0	0	0.0	13	81.2
Unknown	820		39		54		5		11		94		71		9		72	
Gender																		
All males	1676	84.7	77	70.6	97	90.7	6	66.7	75	68.2	93	83.8	87	87.9	75	100.0	71	84.5
Female	302	15.3	32	29.4	10	9.3	3	33.3	35	31.8	18	16.2	12	12.1	0	0.0	13	15.5
Unknown	16		0		3		0		0		1		2		0		4	
Age (years)																		
<25	554	28.4	31	28.4	29	28.2	2	22.2	41	37.3	44	39.6	27	27.3	13	18.1	13	17.3
≥25	1399	71.6	78	71.6	74	71.8	7	77.8	69	62.7	67	60.4	72	73.7	59	81.9	62	82.7
Unknown	41		0		7		0		0				2		3		13	
Site of infection																		
Genital	1531	79.0	97	89.0	81	77.1	9	100.0	97	88.2	100	89.3	91	92.9	74	100.0	60	93.8
Anorectal	255	13.2	8	7.3	8	7.6	0	0.0	9	8.2	11	9.8	3	3.1	0	0.0	0	0.0
Pharyngeal	122	6.3	3	2.8	0	0.0	0	0.0	3	2.7	0	0.0	2	2.0	0	0.0	3	4.7
Other	30	1.6	1	0.9	16	15.3	0	0.0	1	0.9	1	0.9	2	2.0	0	0.0	1	1.6
Unknown	56		0		5		0		0		0		3		1		24	
Previously diagnosed																		
No	654	82.2	4	22.0	35	83.3	2	100.0	102	92.7	0	0.0	10	58.8	54	80.6	0	0.0
Yes	142	17.8	15	78.0	7	16.7	0	0.0	8	7.3	0	0.0	7	41.2	13	19.4	0	0.0
Unknown	1198		90		68		7		0		112		84		8		88	
Concurrent STI																		
Concurrent CT	183	21.9	21	28.8	10	31.3	0	0.0	0	0.0	16	36.4	5	18.5	0	0.0	0	0.0
Concurrent other	55	5.9	3	4.1	7	21.9	0	0.0	0	0.0	3	6.8	1	3.7	3	18.75	0	0.0
No concurrent STI	603	72.2	49	67.1	15	46.9	0	0.0	0	0.0	25	56.8	21	77.8	13	81.25	0	0.0
Unknown	1153		36		78		9		110		68		74		59		88	
HIV status																		
Positive	144	17.6	4	13.3	18	54.6	0	0.0	5	6.7	4	100.0	2	9.5	2	11.8	0	0.0
Negative	675	82.4	26	86.7	15	45.5	0	0.0	70	93.3	0	0.0	19	90.5	15	88.2	0	0.0
Unknown	1175		79		77		9		35		108		80		58		88	

Table A6.1. Patient characteristics for cases reported to Euro-GASP; overall and by country, 2013 (continued)

	Iceland		Ireland		Italy		Latvia		Malta		Netherlands		Norway		Portugal		Slovakia	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	5		103		100		38		31		139		112		110		110	
Sexual orientation & gender																		
MSM	0	0	68	74.7	61	62.2	0	0.0	13	44.8	111	79.9	0	0.0	7	16.7	10	12.4
Male heterosexual	0	0	13	14.3	32	32.7	28	73.7	11	37.9	12	8.6	0	0.0	21	50.0	39	48.2
Female	0	0	10	11.0	5	5.1	10	26.3	5	17.2	16	11.5	13	100.0	14	33.3	32	39.5
Unknown	5		12		2		0		2		0		99		68		29	
Gender																		
Male	5	100	93	90.3	93	94.9	28	73.7	26	83.9	123	88.5	96	88.1	96	87.3	78	70.9
Female	0	0	10	9.7	5	5.1	10	26.3	5	16.1	16	11.5	13	11.9	14	12.7	32	29.1
Unknown	0		0		2		0		0		0		3		0		0	
Age (years)																		
<25	0	0	30	29.1	16	16.5	12	31.6	11	35.5	36	25.9	33	29.5	44	40.0	32	29.4
≥25	5	100	73	70.9	81	83.5	26	68.4	20	64.5	103	74.1	79	70.5	66	60.0	77	70.6
Unknown	0		0		3		0		0		0		0		0		1	
Site of infection																		
Genital	5	100	47	45.3	88	88.0	38	100.0	21	70.0	49	35.3	87	85.3	106	96.4	108	98.2
Anorectal	0	0	23	22.3	11	11.0	0	0.0	8	26.7	77	55.4	9	8.8	0	0.0	1	0.9
Pharyngeal	0	0	33	32.0	1	1.0	0	0.0	1	3.3	13	9.4	5	4.9	2	1.8	1	0.9
Other	0	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0	2	1.8	0	0.0
Unknown	0		0		0		0		1		0		10		0		0	
Previously diagnosed																		
No	1	100	84	82.4	78	87.4	0	0.0	22	78.6	0	0.0	0	0.0	22	68.8	100	91.7
Yes	0	0	18	17.6	11	12.4	1	100.0	6	21.4	0	0.0	0	0.0	10	31.2	9	8.3
Unknown	4		1		11		37		3		139		112		78		1	
Concurrent STI																		
Concurrent CT	0	0	13	12.7	7	8.0	6	15.8	7	28	42	30.2	0	0.0	3	9.7	10	10.4
Concurrent other	0	0	0	0.0	2	2.3	3	8	1	4	12	8.6	0	0.0	0	0.0	9	9.4
No concurrent STI	1	100	89	87.3	79	89.8	29	76.3	17	68	85	61.2	0	0.0	28	90.3	77	80.2
Unknown	4		1		12		0		6		0		112		79		14	
HIV status																		
Positive	0	0	4	3.9	18	18.9	1	100.0	1	3.6	51	37.8	0	0.0	1	3.4	2	2.1
Negative	0	0	98	96.1	77	81.1	0	0.0	27	96.4	84	62.2	0	0.0	28	96.6	94	97.9
Unknown	5		1		5		37		3		4		112		81		14	

Table A6.1. Patient characteristics for cases reported to Euro-GASP; overall and by country, 2013 (end)

	Slovenia		Spain		Sweden		UK	
	No.	%	No.	%	No.	%	No.	%
	73		119		100		240	
Sexual orientation & gender								
MSM	25	36.8	0	0	0	0.0	115	66.1
Male heterosexual	37	54.4	0	0	0	0.0	33	19.0
Female	6	8.8	9	100	33	100.0	26	14.9
Unknown	5		110		67		66	
Gender								
Male	67	91.8	110	92.4	67	67.0	213	89.1
Female	6	8.2	9	7.6	33	33.0	26	10.9
Unknown	0		0		0		1	
Age (years)								
<25	10	14.9	30	25.9	27	27.0	73	30.7
≥25	57	85.1	86	74.1	73	73.0	165	69.3
Unknown	6		3		0		2	
Site of infection								
Genital	52	73.2	117	98.3	62	68.9	142	59.2
Anorectal	4	5.6	2	1.7	10	11.1	71	29.6
Pharyngeal	15	21.1	0	0.0	18	20.0	22	9.2
Other	0	0.0	0	0.0	0	0.0	5	2.1
Unknown	2		0		10		0	
Previously diagnosed								
No	54	91.5	0	0.0	0	0.0	86	72.9
Yes	5	8.5	0	0.0	0	0.0	32	27.1
Unknown	14		119		100		122	
Concurrent STI								
Concurrent CT	8	15.1	0	0.0	0	0.0	35	46.1
Concurrent other	7	13.2	0	0.0	0	0.0	4	5.3
No concurrent STI	38	71.7	0	0.0	0	0.0	37	48.6
Unknown	20		119		100		164	
HIV status								
Positive	6	10.7	0	0.0	0	0.0	25	25.8
Negative	50	89.3	0	0.0	0	0.0	72	74.2
Unknown	17		119		100		143	

** For males only; all females classified as acquiring gonorrhoea via heterosexual transmission*

Table A6.2. Clinical service type, place of residence, country of birth and probable country of infection for cases reported to Euro-GASP, by country, 2013

	Austria (n= 109)	Belgium (n=110)	Cyprus (n=9)	Denmark (n=110)	France (n=112)	Germany (n=101)	Greece (n=75)	Hungary (n=88)
Clinical service types								
ANC – antenatal clinic	0	0	0	0	0	0	0	0
COMB – combined service	0	0	0	0	0	0	8	0
DV – dermatology-venereology clinic	30	0	4	0	2	13	0	9
ED – Hospital emergency dept	0	0	0	0	2	1	0	0
FPC – family planning clinic	0	0	0	0	0	0	0	0
GP – general practitioner	46	0	0	46	75	8	0	0
GYN – gynaecology clinic	0	0	3	0	5	6	0	0
ID – infectious disease clinic	0	0	0	0	2	6	0	0
OPC – other primary care	0	0	0	0	4	15	0	0
STI – dedicated STI clinic	24	15	0	60	14	3	67	0
URO – urology	0	0	2	0	0	34	0	0
YTH – youth clinics	0	0	0	0	0	0	0	0
O – other	9	0	0	4	4	13	0	0
UNK – unknown	0	95	0	0	4	2	0	79
Place of residence								
NUTS level 0-3 (region)	AT13=83	UNK=110	CY000=9	DK011=24	FR=112	DE=28	EL=28	UNK=88
	AT21=2			DK012=9		DE125=8	EL124=1	
	AT221=10			DK013=4		DE126=5	EL254=1	
	AT32=1			DK021=2		DE21H=5	EL30=3	
	AT33=8			DK022=5		DE224=1	EL300=42	
	AT332=5			DK031=16		DE254=3		
				DK032=19		DE256=1		
				DK041=3		DE3=5		
				DK042=12		DE6=7		
				DK05=6		DEA1=1		
				UNK=10		DEA23=1		
						DEA24=5		
						DEA4=1		
						DEA41=5		
						DEA46=1		
						DED2=22		
						DED2D=1		
						UNK=1		
Country of birth								
ISO coded value list	UNK=109	BE=48	CY=7	AF=1	UNK=112	DE=20	AL=10	HU=20
		MA=1	EL=2	DK=96		IT=2	BD=1	UNK=68
		NL=1		GL=1		TR=4	EL=57	
		PT=1		IS=1		UNK=75	GE=1	
		RW=1		MA=1			NG=1	
		TR=2		PL=1, RO=1			RO=1	
		UNK=56		SG=1, SY=1			RW=1, UA=1	
				VN=1, UNK=5			UNK=2	
Probable country of infection								
ISO coded value list	UNK=109	BE=20	CY=7	DE=1, DK=84	FR=31	DE=17	EL=66	HU=18
		FR=2	UNK=2	EG=1, ES=1	UNK=81	TR=1	UNK=9	KH=1
		TH=1		GL=1, MA=1		UNK=83		UNK=69
		UNK=87		NZ=1, TH=1				
				UNK=19				

UNK: unknown

Table A6.2. Clinical service type, place of residence, country of birth and probable country of infection for cases reported to Euro-GASP, by country, 2013 (continued)

	Iceland (n=5)	Ireland (n=103)	Italy (n=100)	Latvia (n=38)	Malta (n=31)	Netherlands (n=139)	Norway (n=112)	Portugal (n=110)
Clinical service types								
See first table for codes	DV=4, OPC=1	GP=13, STI=90	DV=9, O=23, STI=68	COMB=38	ED=1, GP=1, GYN=1, STI=28	STI=139	UNK=112	GP=1, O=12, STI=29, YTH=1, UNK=67
Place of residence								
NUTS level 0-3 (region)	IS=1	IE=103	ITC11=12	LV005=1	MT001=31	NL113=1	UNK=112	PT112=4
	UNK=4		ITC42=1	LV006=23		NL122=1		PT113=2
			ITC45=21	LV007=11		NL211=1		PT114=9
			ITF33=1	LV008=2		NL230=6		PT116=1
			ITF41=1	LV009=1		NL310=6		PT150=6
			ITH42=1			NL322=1		PT162=1
			ITH55=6			NL324=5		PT163=2
			ITI18=1			NL325=2		PT165=2
			ITI21=3			NL326=98		PT16B=2
			ITI43=3			NL327=2		PT171=72
			UNK=50			NL331=1		PT172=8
						NL333=1		PT185=1
						NL336=2		
						NL337=2		
						NL339=2		
						NL411=1		
						UNK=7		
Country of birth								
ISO-coded value list	UNK=5	BR=9	AL=2	UNK=38	ES=1	AT=1, ANHH=1	UNK=112	PT=110
		ES=2	BR=1		IT=2	AU=1, BR=2		
		FR=1	EG=1		MT=21	CA=1, CH=1		
		HU=1	EL=1		SO=2	CL=1, CU=1		
		IE=51	HR=1		UK=2	CW=1, CZ=1		
		IT=2	IE=1		UNK=3	DE=3, EL=2		
		LT=2	IT=82			ES=1, ET=2		
		PK=2	MA=2			FR=2, ID=1		
		PL=4	RO=4			IL=1, IQ=1		
		RO=1	RU=1			IT=4, LV=1		
		TH=1	TN=2			MX=1, NL=95		
		UK=2	UNK=2			RU=2, SO=1		
		UNK=23				SR=4, TR=2		
		VE=1				UG=1, US=1		
		ZA=1				ZA=1, ZW=1		
						UNK=1		
Probable country of infection								
ISO coded value list.	TH=1	IE=62, NL=1	ES=1	ES=1	FR=1	UNK=139	UNK=112	PT=110
	UNK=4	PK=1, RO=1	IT=45	LV=37	MT=26			
		TH=1, UK=1	UNK=54		TH=1			
		UNK=36			UNK=3			

UNK: unknown

Table A6.2. Clinical service type, place of residence, country of birth and probable country of infection for cases reported to Euro-GASP, by country, 2013 (end)

	Slovakia (n=110)	Slovenia (n=73)	Spain (n=119)	Sweden (n=100)	United Kingdom (n=240)
Clinical Service types					
See first table for codes	DV=48, GP=3, GYN=24, O=1, URO=34	DV=53, O=8, STI=11, URO=1	COM=119	UNK=112	GP=2, O=1, STI=237
Place of residence					
NUTS level 0-3 (region)	RU=1	ID=1	ES111=4	UNK=100	UKD3=5, UKD4=1
	SK01=41	MX=1	ES112=1		UKD7=4, UKE32=4
	SK021=36	SI=65	ES113=4		UKE42=3, UKF1=2
	SK022=4	UNK=6	ES114=3		UKF14=3, UKF2=1
	SK023=25		ES120=27		UKG13=1, UKG2=1
	SK032=1		ES30=1		UKG31=10, UKH12=1
	SK041=2		ES300=40		UKH21=2, UKH23=1
			ES411=1		UKH25=1, UKI=51
			ES417=1		UKI1=47, UKJ11=1
			ES419=6		UKJ13=1, UKJ2=1
			ES422=1		UKJ21=2, UKJ22=1
			ES511=1		UKJ23=1, UKK11=3
			ES521=9		UKK13=1, UKK2=1
			ES523=9		UKM2=4, UKM21=1
			ES611=8		UKM22=2, UKM3=12
			ES617=3		UKM5=1
					UNK=70
Country of birth					
ISO-coded value list. UNK	HR=1	CA=1	UNK=119	UNK=100	BG=1, BR=3
	RU=1	RS=2			CA=2, CL=1
	SK=105	SI=62			CM=1,CZ=1
	TR=1	UNK=8			DK=1, EL=1
	UNK=2				ES=3, FI=1
					FR=1, GM=1
					HU=2, IE=1
					IN=1, IT=2
					JM=1, LK=1
					NG=2, PK=1
					PT=1, SD=1
					SL=1, SO=1
					UK=82, YE=1
					UNK=125
Probable country of infection					
ISO-coded value list.	CH=1, CZ=1	AT=2, DE=2	ES=119	UNK=100	AU=1, BR=1
	HU=1, ID=1	ES=1, RS=1			FR=3, IE=1
	RU=1, SK=66	SI=53, UA=1			IN=1, IT=2
	UK=1, UNK=38	UK=1, UNK=12			NO=1, PT=1
					SD=1, UK=3
					UNK=225

UNK = unknown

Annex 7. Statistical tables

Table A7.1. Univariate association of ciprofloxacin resistance/susceptibility and patient characteristics, Euro-GASP, 2013

	Ciprofloxacin resistance (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection n= (1938)				
Genital (1531)	852 (55.7, 53.2 – 58.1)			
Anorectal (255)	105 (41.2, 35.3 – 47.3)	0.56	0.43 – 0.73	<0.0001
Pharyngeal (122)	54 (44.3, 35.8 – 53.1)	0.63	0.44 – 0.92	0.015
Other (30)	12 (40, 24.6 – 57.7)	0.53	0.25 – 1.11	0.0878
Sexual orientation & gender (n=1174)				
MSM (496)	210 (42.3, 38.1 – 46.7)			
Male heterosexual (376)	209 (55.6, 50.5 – 60.5)	1.70	1.30 – 2.24	0.0001
Female (302)	150 (49.7, 44.1 – 55.3)	1.34	1.01 – 1.79	0.0437
Previous GC (n=796)				
Yes (142)	65 (45.8, 37.8 - 54)	0.86	0.59 – 1.23	0.3974
No (654)	325 (49.7, 45.9 – 53.5)			
Concurrent chlamydia (n=841)				
Yes (183)	69 (37.7			
No (658)	307 (46.7	1.44	1.03 – 2.02	0.0313
HIV status (n=819)				
Positive (144)	64 (44.4, 36.6 – 52.6)			
Negative (675)	314 (46.5, 42.8 – 50.3)	1.09	0.76 – 1.56	0.6506
Age (n=1953)				
<25 years (554)	262 (47.3, 43.2 – 51.5)			
≥25 years (1399)	769 (55, 52.4 – 57.6)	1.36	1.12 – 1.66	0.0022

Table A7.2. Univariate association of azithromycin resistance/susceptibility and patient characteristics, Euro-GASP, 2013

	Azithromycin resistance (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection (n=1929)				
Genital (1522)	95 (6.3, 5.1 – 7.6)			
Anorectal (255)	3 (1.2, 0.4 – 3.4)			
Pharyngeal (122)	7 (5.7, 2.8 – 11.4)			
Other (30)	0		0.002*	
Sexual orientation & gender (n=1165)				
MSM (494)	14 (2.8, 1.7 – 4.7)			
Male heterosexual (369)	24 (6.5, 4.4 – 9.5)	2.39	1.21 – 4.69	0.0094
Female (302)	16 (5.3, 3.3 – 8.4)	1.92	0.92 – 4.00	0.077
Previous GC (n=787)				
Yes (142)	9 (6.3, 3.4 – 11.6)	1.44	0.66 – 3.11	0.3543
No (645)	29 (4.5, 3.2 – 6.4)			
Concurrent chlamydia (n=841)				
Yes (183)	3 (1.6, 0.6 – 4.7)			
No (658)	20 (3, 2.0 – 4.7)			0.443*
HIV status (n=819)				
Positive (144)	3 (2.1, 0.7 – 6.0)			
Negative (675)	20 (3, 1.9 – 4.5)			0.782*
Age (n=1944)				
<25 years (553)	35 (6.3, 4.6 – 8.7)			
≥25 years (1391)	72 (5.2, 4.1 – 6.5)	0.81	0.53 – 1.23	0.3147

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

Table A7.3. Univariate association of penicillinase activity and patient characteristics, Euro-GASP, 2013

	Penicillinase activity (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection (n=1740)				
Genital (1426)	190 (13.3, 11.7 – 15.2)			
Anorectal (179)	19 (10.8, 7.0 – 16.2)			
Pharyngeal (109)	7 (6.4, 3.2 – 12.7)			
Other (29)	4 (13.8, 5.5 – 30.6)			0.156
Sexual orientation & gender (n=1026)				
MSM (385)	36 (9.4, 6.8 – 12.7)			
Male heterosexual (364)	42 (11.5, 8.7 – 15.2)	1.27	0.79 – 2.03	0.3275
Female (277)	41 (14.8, 11.1 – 19.5)	1.68	1.04 – 2.72	0.0311
Previous GC n=795				
Yes (142)	9 (6.3, 3.4 – 11.6)	0.72	0.35 – 1.50	0.3781
No (653)	56 (8.6, 6.7 – 11)			
Concurrent chlamydia (n=678)				
Yes (132)	19 (14.4, 9.4 – 21.4)			
No (546)	62 (11.4, 9.0 – 14.3)	0.76	0.44 - 1.33	0.3344
HIV status (n=681)				
Positive (90)	9 (10, 5.4 – 17.9)			
Negative (591)	53 (9, 6.9 – 11.5)	0.89	0.42 – 1.87	0.7513
Age (n=1755)				
<25 years (499)	54 (10.8, 8.4 – 13.9)			
≥25 years (1256)	175 (13.9, 12.1 – 15.0)	1.33	0.96 – 1.85	0.080

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

Table A7.4. Univariate association of cefixime resistance/susceptibility and patient characteristics, Euro-GASP, 2013

	Cefixime resistance (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection (n=1938)				
Genital (1531)	85 (5.6, 4.5 – 6.8)			
Anorectal (255)	3 (1.2, 0.4 – 3.4)			
Pharyngeal (122)	1 (0.8, 0.1 – 4.5)			
Other (30)	1 (3.3, 0.6 – 16.7)		0.001*	
Sexual orientation & gender (n=1174)				
MSM (496)	6 (1.2, 0.6 – 2.6)			
Male heterosexual (376)	23 (6.1, 4.1 – 9.0)	5.32	2.12 – 13.3	0.0001
Female (302)	17 (5.6, 3.5 – 8.8)	4.87	1.89 – 12.6	0.0003
Previous GC (n=796)				
Yes (142)	5 (3.5, 1.5 – 8.0)	0.67	0.26 – 1.73	0.4015
No (654)	34 (5.2, 3.7 – 7.2)			
Concurrent chlamydia (n=841)				
Yes (183)	3 (1.6, 0.6 – 4.7)			
No (658)	13 (2.0, 1.2 – 3.4)			1*
HIV status (n=819)				
Positive (144)	2 (1.4, 0.4 – 4.9)			
Negative (675)	21 (3.1, 2 – 4.7)			0.403*
Age (n=1953)				
<25 years (554)	22 (4.0, 2.6 – 5.9)			
≥25 years (1399)	68 (4.9, 3.9 – 6.1)	1.24	0.76 – 2.02	0.3982

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

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