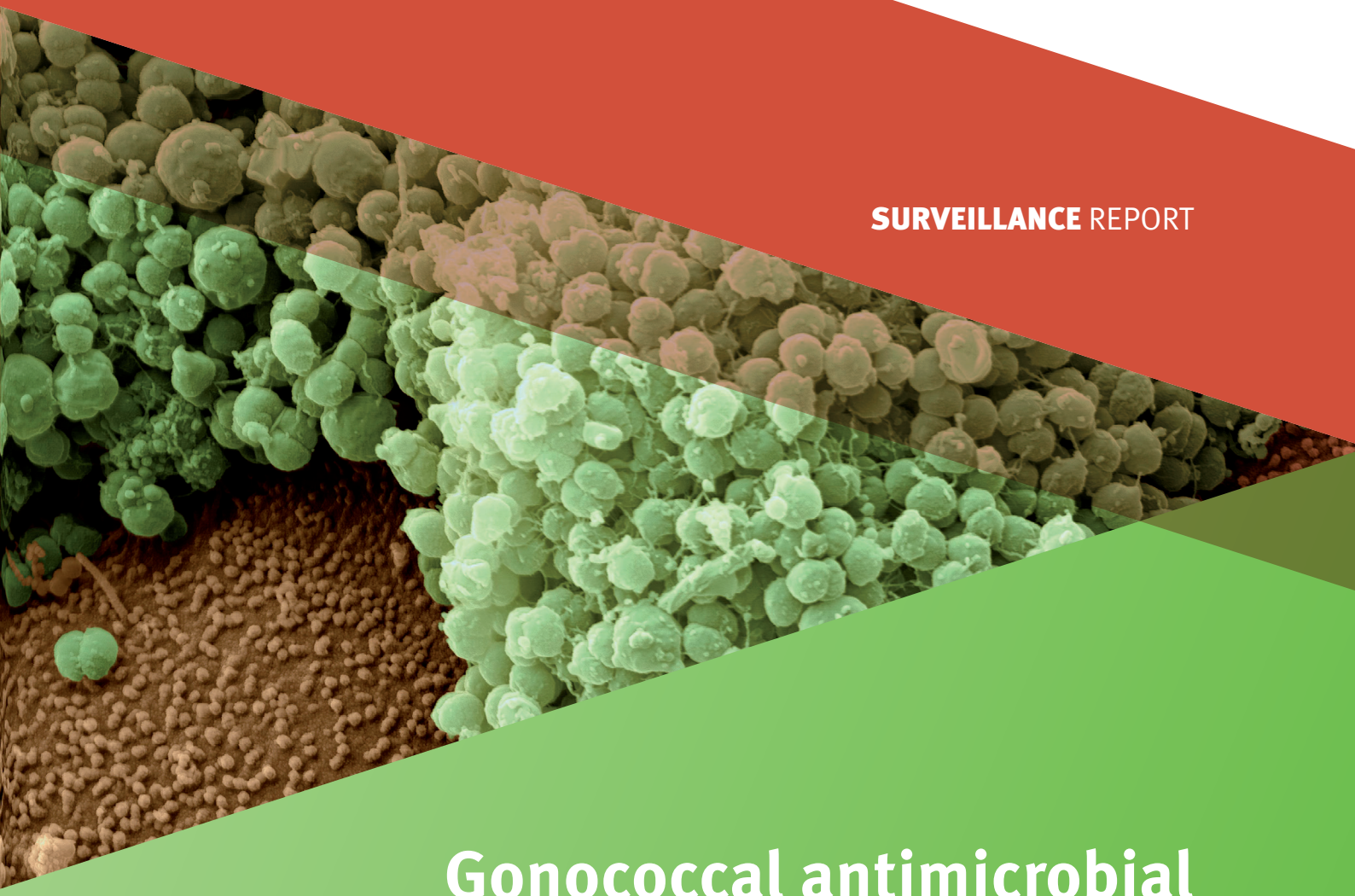

SURVEILLANCE REPORT

Gonococcal antimicrobial susceptibility surveillance in Europe

Results summary

2017

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ECDC SURVEILLANCE REPORT

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This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by Gianfranco Spiteri and Andrew J. Amato-Gauci, and produced by Public Health England, London, United Kingdom, and Örebro University Hospital, Örebro, Sweden.

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Contents

Figures and maps

Tables

Abbreviations

AMR	Antimicrobial resistance
BKP	Breakpoint
CI	Confidence interval
EQA	External quality assessment
EUCAST	European Committee on Antimicrobial Susceptibility Testing
Euro-GASP	European Gonococcal Antimicrobial Surveillance Programme
GC	Gonococcal
GRASP	Gonococcal Resistance to Antimicrobials Surveillance Programme
HLAziR	High level azithromycin resistance
MIC	Minimum inhibitory concentration
MGS	MIC gradient strip test
MSM	Men who have sex with men
NAAT	Nucleic acid amplification test
OR	Odds ratio
PPNG	Penicillinase-producing *Neisseria gonorrhoeae*
STI	Sexually transmitted infection
TESSy	The European Surveillance System

Executive summary

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

During 2017, the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) followed an annual decentralised and centralised testing model, requesting participating laboratories to collect gonococcal isolates during the September–November period. Susceptibility testing was performed on all isolates (MIC gradient strip test–mostly Etest–or agar dilution) for the following antimicrobials: ceftriaxone, cefixime, azithromycin and ciprofloxacin, as well as testing for β-lactamase production for detection of high-level penicillin resistance. Decentralised testing took place on the premise of participating laboratories fulfilling set quality criteria.

In 2017, 27 EU/EEA Member States participated in Euro-GASP, 21 via decentralised testing. In total, 3 248 isolates were tested, the majority of which (84.5%) were collected from male patients. The age of the patients ranged from under one year to 76 years, with a median age of 29 years. Overall, 28.2% of patients were under 25 years, and males were significantly older than females. The anatomical site of specimen collection was mainly genital (72.8%), followed by rectal (14.6%) and pharyngeal (8.5%). Among cases with information on previous diagnosis of gonorrhoea, 21.8% had previously been diagnosed with the disease. Twenty-four percent of the patients were concurrently diagnosed with *Chlamydia trachomatis* infection. Among cases with known sexual orientation and gender (61.5%), 52.5% were heterosexual men or women and 47.5% were men who have sex with men (MSM). Among all cases, 15.4% were HIV positive, and 96.2% of those were MSM.

In 2017, no isolates with resistance to ceftriaxone were detected. The 2017 Euro-GASP results revealed stable cefixime and azithromycin resistance (1.9% and 7.5% respectively) compared with 2016 (2.1% and 7.5%), although the number of countries reporting resistant isolates for both antimicrobials increased. In 2017, 15 countries reported cefixime-resistant isolates, compared with 14 and 9 countries in 2016 and 2015 respectively, and 23 countries reported azithromycin-resistant isolates in 2017, compared with 21 and 18 countries in 2016 and 2015 respectively. The proportion of isolates showing ciprofloxacin resistance remained the same as in 2016: 46.5%.

The absence of ceftriaxone resistance and low level of cefixime resistance is encouraging, and is most probably partly due to the highly effective dual-therapy regimen (ceftriaxone plus azithromycin) or the ceftriaxone high-dose monotherapy used for the treatment of gonorrhoea in the EU/EEA. However, despite the level of resistance to azithromycin (7.5%) being currently stable, the high level of resistance is a concern and threatens the effectiveness of this regimen. Even though the level of resistance to cefixime is stable, cefixime resistance needs to be monitored closely, particularly because gonococcal strains with resistance to both cefixime and ceftriaxone have been spreading internationally in the last years. Novel antimicrobials and/or new dual antimicrobial therapy regimens and continuing surveillance are essential to ensure that gonorrhoea remains treatable.

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 main therapeutic agents currently recommended in Europe [1], extended-spectrum cephalosporins, are the last remaining options for effective empiric first-line antimicrobial monotherapy. Susceptibility to these antimicrobials has decreased in the past [2–4], which is why the current European treatment guideline recommends combination treatment with ceftriaxone plus azithromycin as first-line in an attempt to mitigate the development and/or spread of resistance to these antimicrobials [1]. Surveillance of the susceptibility to these agents is essential in order to ensure effective patient management and monitor current and emerging trends in AMR [3].

Since 2009, the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) has been 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). Euro-GASP has identified decreasing susceptibility to extended-spectrum cephalosporins in the past. This, together with a documentation of treatment failures [3], led to the creation of a European response plan to control and manage the threat of multidrug-resistant *N. gonorrhoeae* in the European Union/European Economic Area (EU/EEA) [4]. This response plan is currently under revision.

1.2 Objectives

The overall aim of Euro-GASP is to strengthen the surveillance of gonococcal antimicrobial susceptibility in EU/EEA Member States in order to provide quality-assured data to inform gonorrhoea treatment guidelines. The objectives are to:

- develop and implement sentinel surveillance of gonococcal 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 the EU/EEA
- link susceptibility data with epidemiological information to better understand the risk factors associated with emerging resistance patterns
- implement an external quality assessment (EQA) scheme for antimicrobial susceptibility testing across the EU/EEA; and
- provide training in gonococcal culture and antimicrobial susceptibility testing to facilitate enhanced gonococcal antimicrobial susceptibility surveillance, using a standardised methodology across the EU/EEA.

This report presents the results from the 2017 gonococcal antimicrobial susceptibility sentinel surveillance.

2 Methods

2.1 Participating laboratories and isolate collection

Twenty-seven participating laboratories from 27 EU/EEA countries collected *N. gonorrhoeae* isolates from consecutive patients. The official collection window was from September–November 2017, except for the United Kingdom (UK), which collected isolates from July–September 2017 to coincide with the national Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP). Twenty countries collected outside of the collection window to reach the minimum 100 isolate target and seven of them collected throughout the whole year. One new country, Finland, joined in 2017.

The Euro-GASP collection criteria and methodology remained the same as in previous years [5]. Fourteen countries reported more than their target isolate number, and all isolates reported were included in the analysis. Isolates from six (22.2%) countries were tested centrally at Public Health England or Örebro University Hospital, Sweden, with the remaining 21 (77.8%) countries performing antimicrobial susceptibility testing in their own laboratories. All Euro-GASP laboratories participated in an annual EQA programme [6] to ensure comparability of data. Countries that perform decentralised testing fulfilled established quality criteria prior to commencing their own testing. Isolates from Estonia and Latvia were tested domestically, even though the laboratories were not assessed for quality because of the low number of collected isolates.

2.2 Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed using MIC gradient strip tests (MGS; mainly Etest) or an agar dilution method (determination of MIC (mg/L) or breakpoint technique) for ceftriaxone, cefixime, azithromycin, and ciprofloxacin. Production of penicillinase resulting in high-level penicillin resistance was tested using nitrocefin, as previously described [5]. The results were interpreted using resistance breakpoints from the European Committee on Antimicrobial Susceptibility Testing (EUCAST): cefixime/ceftriaxone resistance MICs >0.12 mg/L; azithromycin resistance MIC >0.5 mg/L; ciprofloxacin resistance MIC >0.06 mg/L [7].

Gentamicin and spectinomycin were removed from the routine antimicrobial panel in 2014 as these antimicrobials are not in routine use. These are only tested in 'snapshot' studies every three years, with the next 'snapshot' study due in 2019.

2.3 Data collection and analysis

The following data were collected for each isolate, where available: date specimen obtained, specimen site, gender, age, sexual orientation, previous gonorrhoea diagnosis, other STI diagnosed during the current episode, place of residence, clinical service type, HIV status, probable country of infection, diagnostic test and treatment used. All susceptibility and epidemiological data were uploaded to TESSy by Member States and then approved.

To evaluate the reporting completeness of epidemiological data for each country, the number of nil responses and unknowns entered for each variable were subtracted from the total number of isolates received. This number was used to calculate a percentage completeness value (number of responses/total isolates received x 100). An overall response rate for each country was then calculated by taking the average of the percentage completeness for all 13 epidemiological fields.

2.4 Statistical analysis

Statistical analysis was performed using Stata v13.1. The Z-test was used to determine the difference between epidemiological and AMR data collected in 2017 versus 2016 and a Mann-Whitney test was used to determine whether the differences in age distribution were statistically significant. Where datasets contained sufficient numbers, the odds ratios (OR) and 95% confidence intervals (CI) were calculated; Pearson's Chi-square test was used to measure if these odds ratios differed significantly from 1. For small cell numbers, Fisher's exact test was performed. Using a forward stepwise 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

In 2017, a total of 3 248 isolates from 27 countries were tested. This represents an increase of 588 isolates (22.1%) compared with 2016. The number of isolates tested from each country varied from two (Cyprus and Estonia) to 421 (Spain).

3.1 Epidemiological data

Overall, reporting completeness was 58.2% compared with 61.6% in 2016 and in line with previous years for the majority of variables (lowest completeness: 23.6% for probable country of infection; highest completeness: 99.7% for gender) [5]. Gender and age remain the most complete variables, while mode of transmission and HIV status were the only variables where reporting improved in 2017. The completeness of all other variables decreased when compared with 2016. Further details on reporting completeness for 2017 data can be found in Annex 1.

As in previous years, the majority of gonococci (84.5%) were collected from men (Table 1). Information on sexual orientation was available for 68.3% (2 220 cases). The proportion of heterosexual males was significantly lower in 2017 compared with 2016 while on the other hand, there was an increase in the proportion of men who have sex with men (MSM; $p<0.002$). The main anatomical site of specimen collection was similar to previous years (mainly genital samples: 72.8%). However, there was a significant decrease in the proportion of genital samples compared with 2016 (75.5%, $p=0.02$), and a significant increase in the proportion of pharyngeal samples (2016: 6.4%; 2017: 8.5%, $p=0.003$). Information on previous diagnosis of gonorrhoea was available for 33.3% (1 080 cases), 21.8% of which had had a previous infection, which was significantly more than 2016 (17.2%; $p<0.01$).

Information on other concurrent STI was available for 31.7% (1 031) of cases; 23.6% had a concurrent chlamydia infection, 6.5% had another STI, and 69.9% had no concurrent STIs. Of 1 217 cases (37.5%) with known HIV status, 188 (15.4%) were HIV positive. Of these 188 HIV-positive cases, 93.6% were MSM. Probable country of infection was available for 766 cases from 15 different countries; overall, only 13.3% of cases were likely acquired in a country outside of the reporting country.

Table 1. Patient characteristics reported for Euro-GASP gonococcal isolates, 2009–2017

	2009	2010	2011	2012	2013	2014	2015	2016	2017
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total number of isolates	1 366	1 766	1 902	1 927	1 994	2 151	2 134	2 660	3 248
Gender									
Male	1 123 (83.7)	1 441 (82.4)	1 505 (82.4)	1 596 (83.7)	1 676 (84.7)	1 821 (85.1)	1 736 (81.8)	2256 (85.1)^	2 737 (84.5)
Female	219 (16.3)	308 (17.6)	321 (17.6)	310 (16.3)	302 (15.3)	318 (14.9)	385 (18.2)	395 (14.9)	502 (15.5)
Unknown	24	17	76	21	16	11	13	9	9
Age (years)									
<25	422 (32.0)	599 (34.4)	572 (31.9)	617 (32.9)	554 (28.4)	605 (28.7)	617 (29.5)	720 (27.5)	898 (28.2)
≥25	898 (68.0)	1 141 (65.6)	1 221 (68.10)	1 261 (67.1)	1 399 (71.6)	1 501 (71.3)	1 476 (70.5)	1 902 (72.5)	2 283 (71.8)
Unknown	46	26	109	49	41	44	41	38	67
Sexual orientation & gender									
Females	219 (27.9)	308 (27.3)	321 (27.1)	310 (28)	302 (25.7)	318 (22.7)	385 (26.4)	395 (22.9)	502 (22.6)
Heterosexual males	314 (40.1)	426 (37.7)	423 (35.6)	390 (35.2)	376 (32)	485 (34.7)	419 (28.7)	632 (36.7)	663 (29.9)
Men who have sex with men	251 (32)	395 (35)	442 (37.3)	408 (36.8)	496 (42.3)	594 (42.5)	657 (45.0)	696 (40.4)^	1 055 (47.5)
Unknown	582	637*	716	819	820	754	673	937	1 029
Site of infection									
Genital	1 164 (86.5)	1 426 (84.7)	1 466 (82.1)	1 537 (83)	1 531 (79)	1 549 (76.3)	1 517 (72.9)	1 943 (75.5)	2 166 (72.8)
Pharyngeal	34 (2.5)	62 (3.5)	79 (4.4)	92 (5)	122 (6.3)	154 (7.6)	180 (8.7)	165 (6.4)	254 (8.5)
Anorectal	138 (10.3)	191 (11.4)	216 (12.1)	188 (10.2)	255 (13.2)	192 (9.5)	280 (13.5)	366 (14.2)	435 (14.6)
Other	9 (0.7)	7 (0.4)	24 (1.3)	35 (1.9)	30 (1.5)	135 (6.6)	103 (5.0)	100 (3.9)	120 (4)
Unknown	21	80	117	75	56	121	54	86	273
Previous gonorrhoea									
Yes	84 (18.1)	145 (21)	146 (19)	130 (17.2)	142 (17.8)	163 (19.7)	157 (17.5)	171 (17.2)	235 (21.8)
No	379 (81.9)	546 (79)	621 (81)	627 (82.8)	654 (82.2)	663 (80.3)	739 (82.5)	824 (82.8)	845 (78.2)
Unknown	903	1075	1135	1170	1198	1325	1238	1665	2168
Concurrent STI									
Concurrent chlamydia infection	78 (14.3)	172 (22.1)	194 (22.2)	187†† (23.4)	183 (21.8)	170 (20)	153†† (19.0)	203 (23.9)˜	243 (23.6)
Concurrent other STI (not HIV)	35 (6.4)	28† (3.6)	43 (4.9)	49‡ (6.1)	55 (6.5)	41† (4.8)	48†† (6.0)	53 (6.2) ††	67 (6.5)
No concurrent STI	433 (79.3)	579 (74.3)	638 (72.9)	564 (70.6)	603 (71.7)	640 (75.2)	605 (75.1)	593 (69.9)	721 (69.9)
Unknown	820	987	1 027	1 127	1 153	1 300	1 328	1 811	2 217
HIV status*									
Positive	N/D	48 (15.5)	141 (17.6)	104 (13.5)	144 (17.6)	172 (19.3)	132 (15.3)	156 (15.9)	188 (15.4)
Negative	N/D	262 (84.5)	661 (82.4)	668 (86.5)	675 (82.4)	720 (80.7)	733 (84.7)	823 (84.1)	1 029 (84.6)
Unknown	N/D	556	1 100	1 155	1 175	1 259	1 269	1 681	2 031

Percentages calculated from known values.
Cells shaded in blue indicate a significant difference in proportion compared with previous year ($p < 0.05$).
**: includes one individual of unknown gender, but with mode of transmission reported as heterosexual.*
†: includes two individuals with two concurrent STIs
††: includes four individuals with two concurrent STIs
: includes three individuals with two concurrent STIs
‡: includes six individuals with chlamydia and an additionally diagnosed STI
: includes thirteen individuals with chlamydia and an additionally diagnosed STI
^: includes one individual of unknown gender, but with mode of transmission reported as MSM
×: includes two individuals of unknown gender, but with mode of transmission reported as MSM
˜: includes nine individuals with chlamydia and an additionally diagnosed STI.

The age of the patients ranged from <1 year to 76 years, with a median of 29 years. Males (median age 30 years) were significantly older than females (median age 25 years, Mann-Whitney p<0.001; Table 2).

Table 2. Patient age distribution by gender and sexual orientation, 2017

Variable	N†	Age (years)		<25 years
		Range	Median	N (%)
All patients	3181	0-76	29	898 (28.2)
Female	493	0-71	25	226 (45.8)
Male*	2679	0-76	30	672 (25.1)
Male heterosexual	660	14-69	29	210 (31.8)
MSM	1053	15-72	30	222 (21.1)

†: where information was available
**: including all males irrespective of sexual orientation.*

As in previous years, the majority of patients for whom a clinical service type was known had attended a dedicated STI or sexual health clinic. However, there was a significant decrease in patients from this service type between 2016 (59.5%) and 2017 (47.9%) ($p<0.01$). This decrease is largely attributable to the decrease in reporting for this variable in Spain, which recorded 361 isolates from STI clinics in 2016 but only four in 2017 with 409 unknowns. There was a significant change in the number of patients who attended 'other' service types in 2017 compared with 2016; the number decreased from 6.6% to 3.1% ($p<0.01$). A significant increase in patients attending primary care facilities (6.5% in 2016 versus 9.1% in 2017, $p<0.01$) was observed in 2017. At 8.3%, attendance at outpatient clinics remained consistent compared with 2016.

3.2 Antimicrobial susceptibility and resistance

Resistance to cefixime, azithromycin and ciprofloxacin over time is summarised in Figure 1 and Table 3.

Figure 1. Percentage of resistant *Neisseria gonorrhoeae* by antimicrobial and year, Euro-GASP, 2009–2017

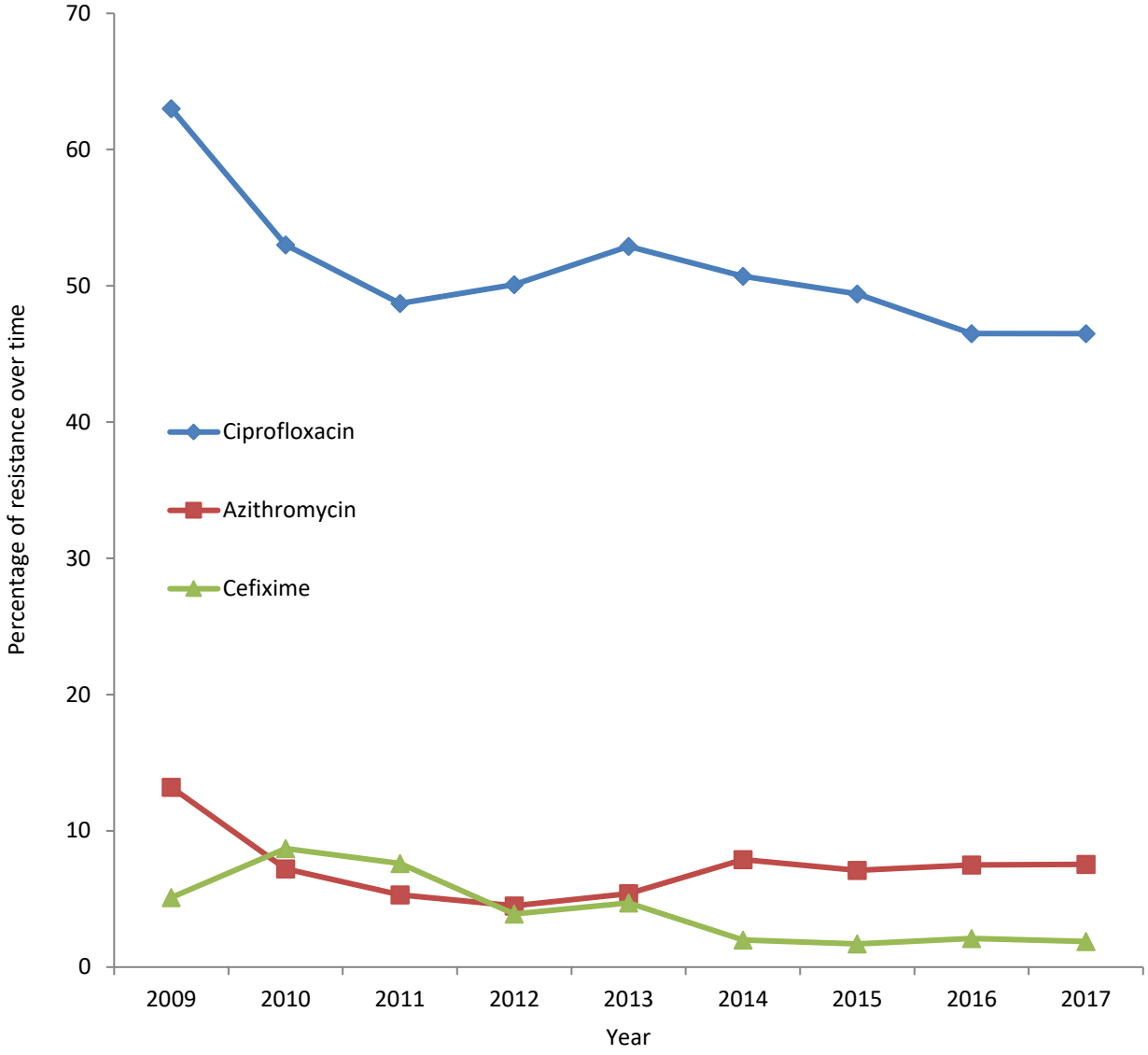


Table 3. Resistance to cefixime, azithromycin and ciprofloxacin by country, Euro-GASP, 2017

Country	Number of isolates 2017	Number of isolates 2009–2017	Resistance									Method of testing
			Cefixime			Azithromycin			Ciprofloxacin			
			No.	%	% 2009–2017	No.	%	% 2009–2017	No.	%	% 2009–2017	
Austria	262		10	3.8		10	3.8		131	50.0		Decentralised – MGS
Belgium	98		2	2.0		12	12.2		46	46.9		Decentralised – MIC
Croatia	6		0	0.0		2	33.3		5	83.3		Centralised – MGS
Cyprus	2		0	0.0		0	0.0		0	0.0		Decentralised – MGS
Czech Republic	104		2	1.9		7	6.7		51	49.0		Centralised – MGS
Denmark	118		1	0.8		15	12.7		33	28.0		Decentralised – MGS
Estonia	2		0	0.0		0	0.0		1	50.0		Decentralised – MGS
Finland	212		0	0.0		8	3.8		89	42.0		Decentralised – BKP
France	110		1	0.9		7	6.4		38	34.5		Decentralised – MGS
Germany	200		2	1.0		9	4.5		122	61.0		Decentralised – MGS
Greece	89		5	5.6		7	7.9		49	55.1		Decentralised – MGS
Hungary	62		4	6.5		5	8.1		29	46.8		Centralised - MGS
Iceland	43		0	0.0		5	11.6		17	42.5		Decentralised – MGS
Ireland	163		0	0.0		16	9.8		84	51.5		Decentralised – MGS
Italy	100		2	2.0		16	16.0		58	58.0		Decentralised – MGS
Latvia	4		0	0.0		0	0.0		1	25.0		Decentralised – MGS
Luxembourg	18		1	5.6		0	0.0		14	77.8		Centralised – MGS
Malta	27		0	0.0		7	25.9		17	63.0		Decentralised – MGS
Netherlands	342		0	0.0		19	5.6		106	31.0		Decentralised – MGS
Norway	107		1	0.9		15	14.0		47	43.9		Decentralised – MGS
Poland	65		0	0.0		8	12.3		50	76.9		Centralised – MGS
Portugal	110		0	0.0		14	12.7		51	46.4		Decentralised – MGS
Slovakia	110		0	0.0		7	6.4		69	62.7		Centralised – MGS
Slovenia	133		2	1.5		3	2.3		56	42.1		Decentralised – MGS
Spain	421		23	5.5		23	5.5		227	53.9		Decentralised – MGS
Sweden	100		2	2.0		3	3.0		35	35.0		Decentralised – MGS
United Kingdom	240		3	1.3		27	11.3		83	34.6		Decentralised-MIC/BKP/MGS
Total:	3248											
Cefixime	3246		61	1.9								
Azithromycin	3245					245	7.5					
Ciprofloxacin	3248								1509	46.5		
95% CI				1.5-2.4			6.7-8.5			44.8-48.2		

N/T: not tested
BKP: breakpoint
MGS: MIC gradient strip test
MIC: MIC by agar dilution.

Cefixime resistance has remained stable at around 2% since 2014 (p=0.59; Figures 1– 2, Table 4). There have been no significant changes in cefixime MIC distribution compared with 2016 (Figure 2). Percentages of cefixime-resistant isolates in 2017 by country are shown in Map 1.

Map 1. Proportion of gonococcal isolates with cefixime resistance by country, EU/EEA, 2017

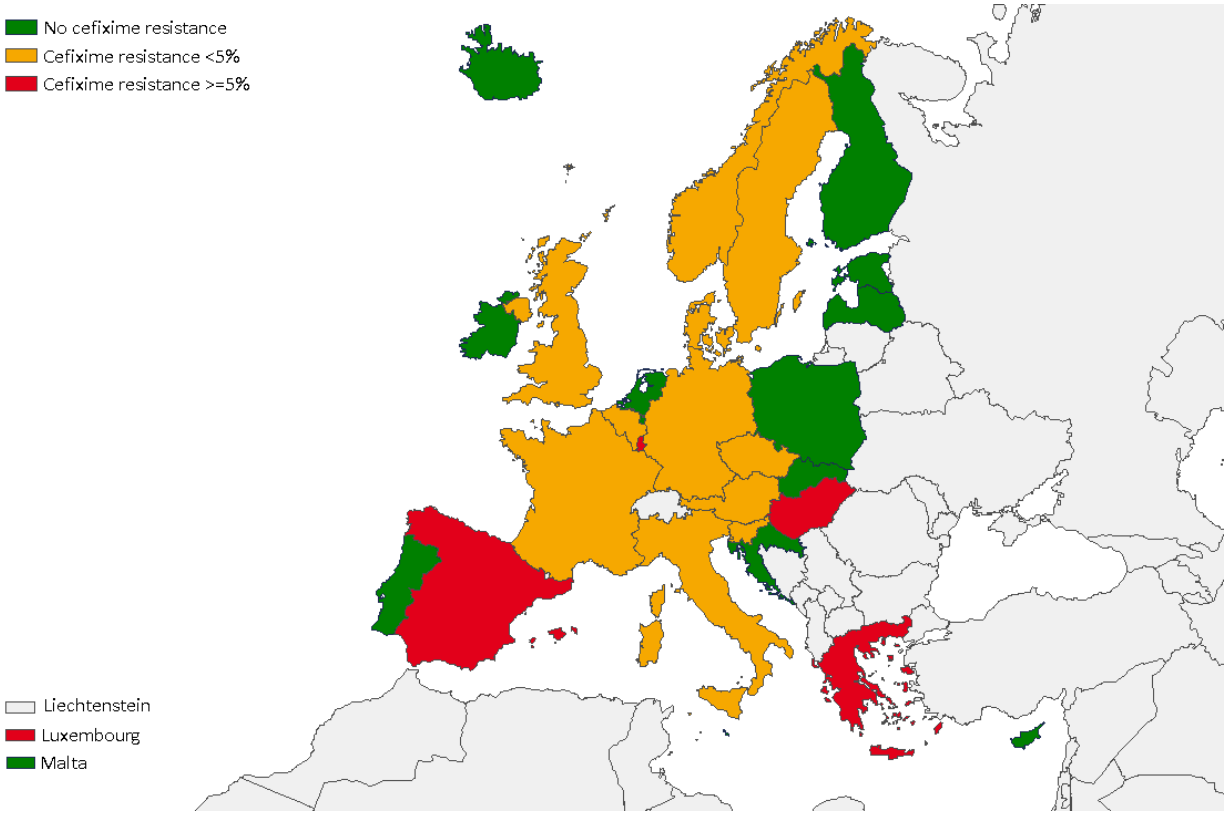
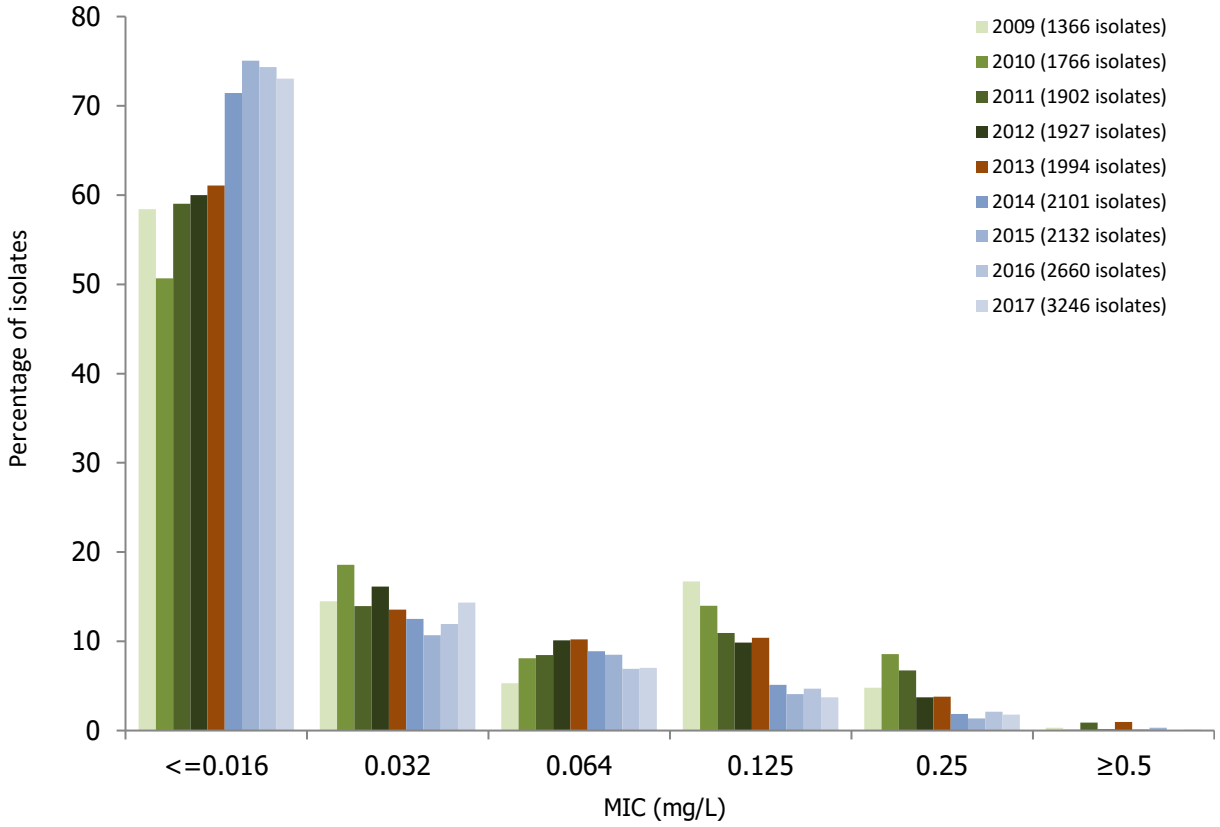


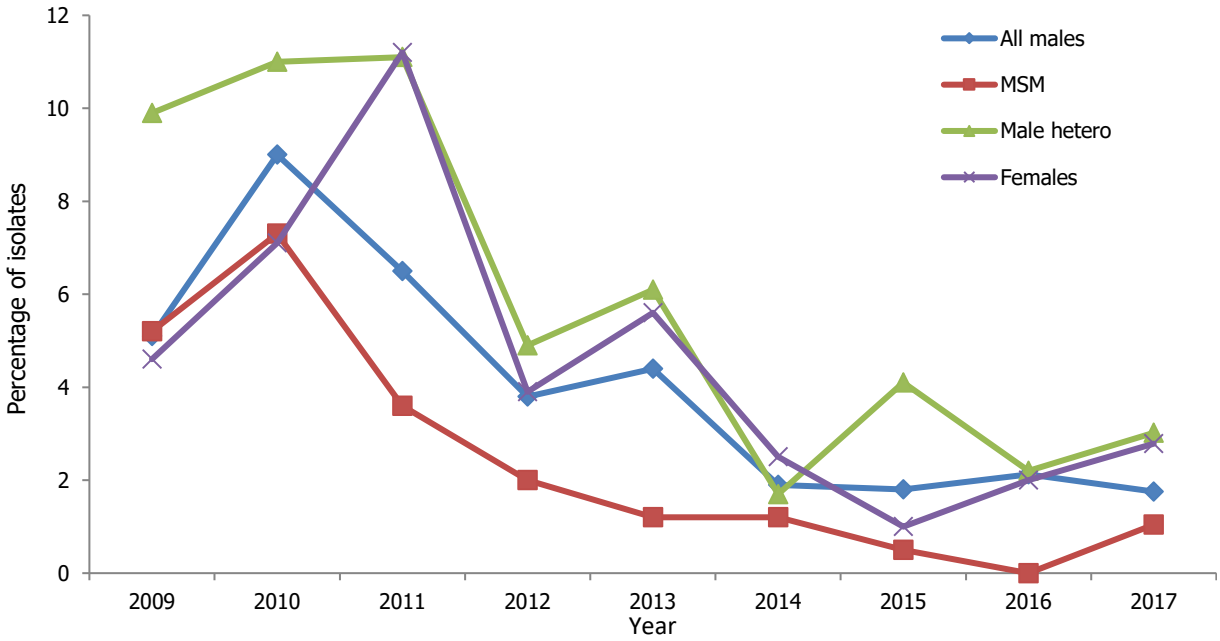
Figure 2. Distribution of MIC for cefixime in Euro-GASP, 2009–2017



Cefixime resistance in isolates from patients by sexual orientation and gender was stable (no significant differences) in 2017 compared with 2016 (Figure 3). Cefixime resistance was significantly associated with isolates from heterosexual males compared to MSM (OR=2.94, CI=1.4–6.2, p=0.003), females compared to males

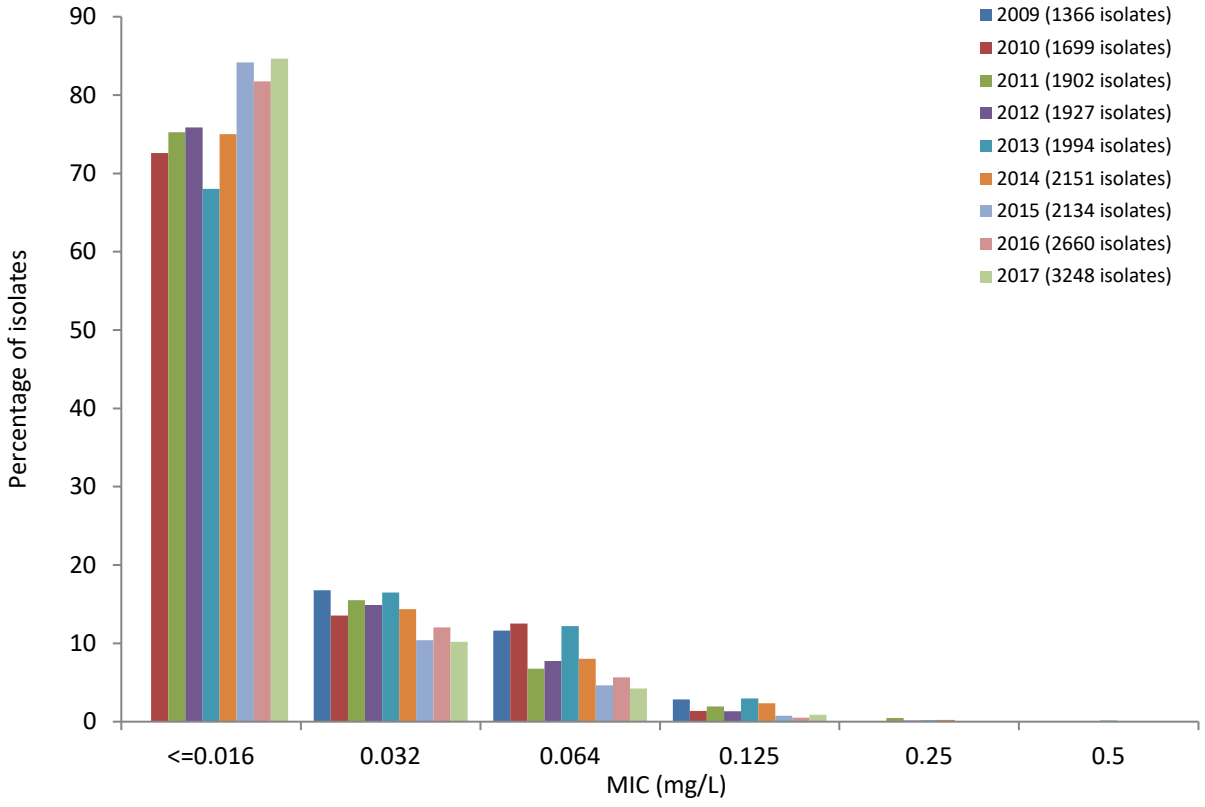
(OR=2.71, CI=1.2–6.0, p=0.01),and genital isolates compared to anorectal isolates (p<0.01, Fisher's exact test; Annex 2). Pharyngeal isolates had significantly higher cefixime MICs (0.125–0.25 mg/L) than anorectal and other isolates.

Figure 3. Percentage of isolates with cefixime resistance by gender and male sexual orientation, Euro-GASP, 2009–2017



No isolates displayed ceftriaxone resistance in 2017 or 2016 compared with one isolate in 2015, five in 2014 and seven in 2013 (Figure 4). The MIC distribution for ceftriaxone in 2017 shows a significantly higher proportion of more susceptible gonococcal isolates (MIC≤0.016 mg/L) compared with 2016 (p<0.003).

Figure 4. Distribution of MIC for ceftriaxone in Euro-GASP, 2009–2017



Azithromycin resistance was observed in 7.5% (245/3 248) of isolates (Figure 1, Table 4). The overall azithromycin resistance has been stable since 2014 at around 7%–8%. As in 2016, seven isolates displayed high-level resistance to azithromycin (MIC≥256 mg/L; HLAziR). These seven isolates were comprised of three isolates from Norway, two from the United Kingdom, one from Finland and one from Portugal and were susceptible to the other antimicrobials tested, except for the Finnish isolate which also displayed ciprofloxacin resistance. The MIC distribution for azithromycin in 2017 was similar to previous years; the majority of resistant isolates had a MIC just above the breakpoint (MIC>0.5 mg/L), and the modal MIC continues to be 0.25 mg/L (Figure 5). In 2017, azithromycin resistance was highest in isolates from MSM (8.3%), followed by heterosexual males (7.2%), and lowest in females (6.8%; Figure 6). Azithromycin resistance was significantly associated with isolates from those under 25 years of age compared to those over 25 years of age (OR=1.45, CI=1.1–1.9, p=0.008; Annex 2). No other significant associations were found.

Map 2. Proportion of gonococcal isolates with azithromycin resistance by country, EU/EEA, 2017

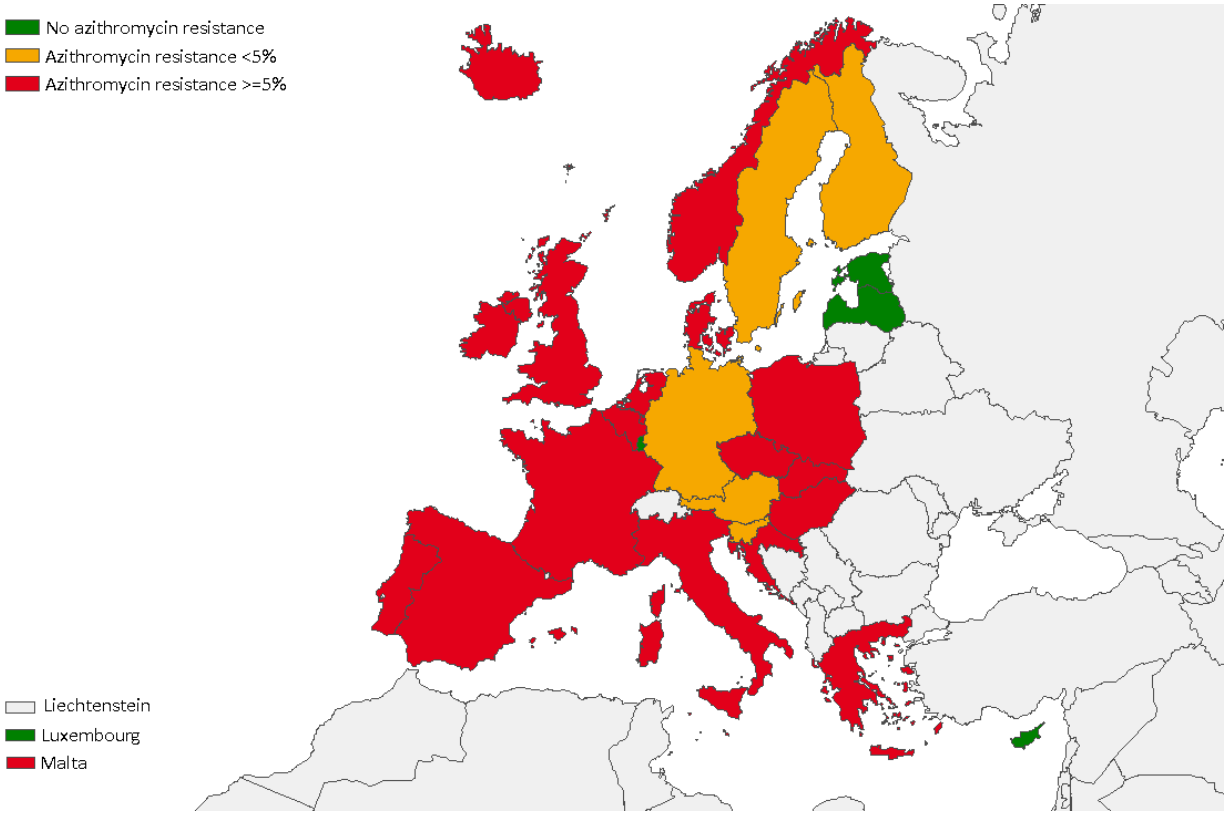


Figure 5. Distribution of MIC for azithromycin in Euro-GASP, 2011–2017

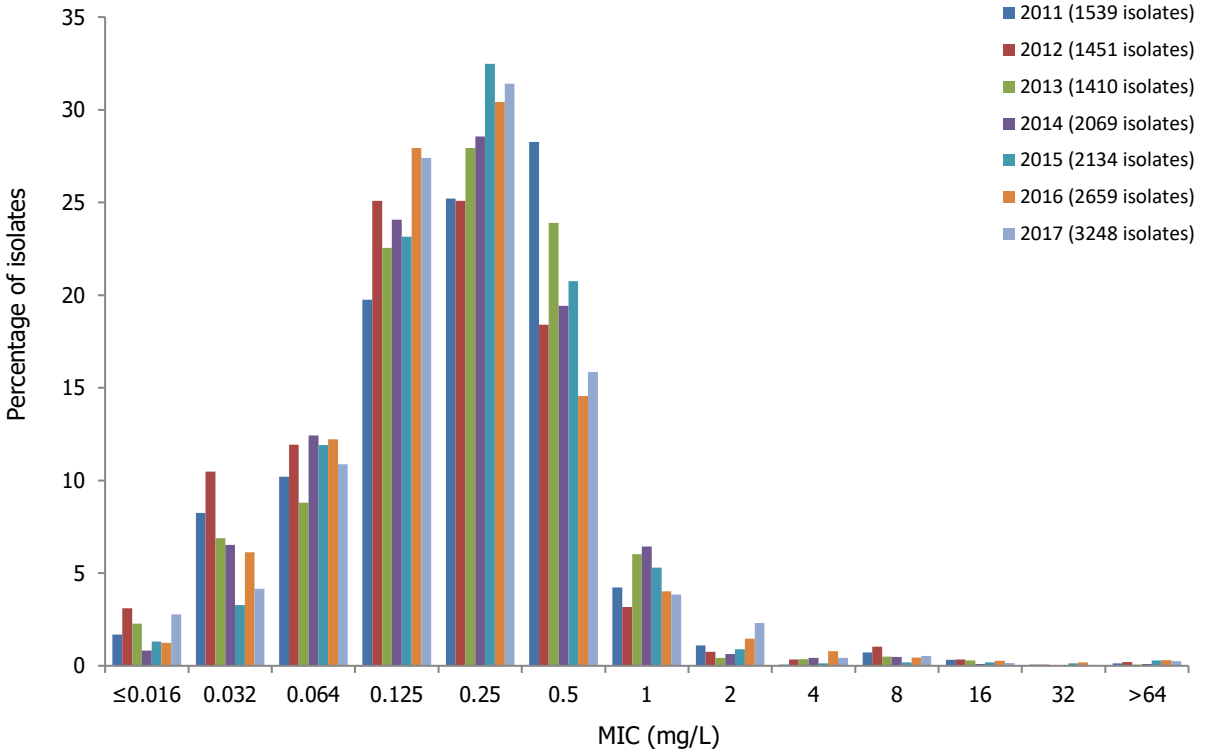


Figure 6. Percentage of isolates with azithromycin resistance by gender and male sexual orientation, Euro-GASP, 2009–2017

Overall, ciprofloxacin resistance levels in 2017 (46.5%, 1 509/3 245) were the same as in 2016 (46.5%; Figure 1). Resistance was highest in heterosexual males (51.1%) and lowest in MSM (41.1%). Following multivariable analysis, ciprofloxacin resistance remained associated with isolates from heterosexual males compared to MSM (OR 1.41, CI 1.01–1.96, p=0.04), those over 25 years old compared to those under 25 years old (OR=1.58,

CI=1.17–2.14, p<0.01) and the absence of a concurrent chlamydial infection (OR 1.79, CI 1.29–2.47, p<0.01; Annex 2). Ciprofloxacin resistance was significantly associated with genital and pharyngeal infection sites compared to anorectal isolates (OR = 1.52, CI=1.23–1.89, p<0.01 and OR=1.44, CI=1.05–1.97, p=0.02 respectively; Annex 2).

3.3 Diagnostic tests and treatments used

Data on the type of diagnostic test are summarised in Table 4. Culture alone was used in 2 191 cases. It was the most common diagnostic test, used in 95.9% of cases overall (2016: 92.7%, 2015: 90.2%). NAAT testing alone was used in 77 cases and microscopy alone in five cases. In the 105 patients that did not have culture specified as their diagnostic test, a NAAT was used to diagnose gonorrhoea in 99 patients; five patients were diagnosed by microscopy, and an unspecified test was used in one patient.

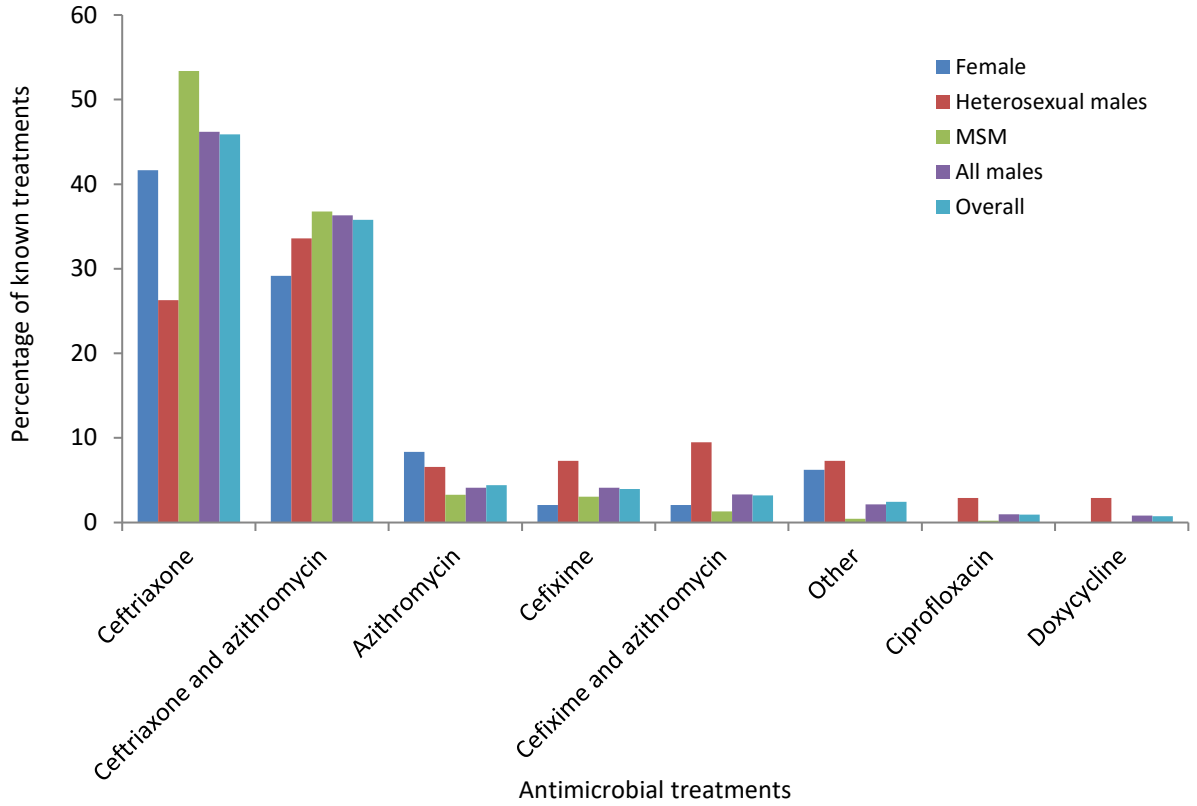
Data on treatment were known in 1 193 cases, of which 654 were recorded as having no other concurrent STI. The treatment data for these patients are summarised in Figure 7.

Table 4. Initial diagnostic tests used for isolates submitted in 2017

	Culture		NAAT		Microscopy	
	Number	%	Number	%	Number	%
Primary diagnostic test only	2 191	87.9	77	3.1	5	0.2
Primary test plus other diagnostic tests	201*	8.1	190†	7.6	141‡	5.7
Total	**2 392**	**95.9**	**267**	**10.7**	**146**	**5.9**

**: includes 31 with microscopy, 80 with NAAT and 90 with both microscopy and NAAT*
†: includes 80 with culture, 20 with microscopy and 90 with culture and microscopy
‡: includes 31 with culture, 20 with NAAT and 90 with culture and NAAT.

Figure 7. Percentage of known treatments used for patients with no other concurrent STI by gender and transmission type for the most frequently used therapies, 2017



Note: Twenty-six different combinations/concentrations of antimicrobials were recorded in 2017; only treatments with ≥2.5% in any gender/transmission group are shown (differences in concentration of antimicrobials prescribed were grouped for analysis). Only 721 patients were recorded as having no concurrent STI; data on treatment were available for 90.8% (n=655) of these patients.

4 Conclusions

Resistance to extended-spectrum cephalosporins has been stable since 2014 (cefixime resistance ranged from 1.8%–2.1% from 2014–2017). Cefixime-resistant isolates were detected in 15 (55.6%) of the 27 countries reporting in 2017. Cefixime resistance continues to be lowest among MSM (1.0%) and highest in male heterosexuals (3.0%) and females (2.8%). No isolates displayed ceftriaxone resistance in 2017 or in 2016, in contrast to the previous three years. The continuing low cephalosporin resistance is promising considering that these are the last remaining options for empiric first-line monotherapy. Among patients for whom treatment was reported, 86% were administered ceftriaxone (with or without azithromycin), so the use of the recommended dual antimicrobial therapy (ceftriaxone plus azithromycin) or ceftriaxone high-dose monotherapy likely contributed to the increased cephalosporin susceptibility.

The overall rate of azithromycin resistance was stable at 7.5% in 2017 and ciprofloxacin resistance was stable at 46.5%. Neither azithromycin nor ciprofloxacin are recommended for monotherapy, unless the isolates are first shown to be susceptible. It should be noted that the majority of resistant isolates are just above the resistance breakpoint (MIC>0.5 mg/L); 51% of resistant isolates had MICs of 1 mg/L. Fluctuations in azithromycin resistance are most probably due to the proximity of isolates to the resistance breakpoint; azithromycin susceptibility testing is also sensitive to minor differences in agar media composition, pH and CO_2 levels.

In previous years, there was a tendency for MSM to have a lower risk of harbouring AMR isolates [8], which was supported by a lower risk of AMR among anorectal isolates. This remains true for cefixime resistance in MSM in 2017. In females, slight increases (non-significant) in azithromycin, cefixime and ciprofloxacin resistance have been observed from 2015–2017, with a significant increase in azithromycin resistance from 2014–2017 (p=0.003).

Although overall resistance levels remained stable for all the antimicrobials in 2017, the European response plan to control the threat of multidrug-resistant *N. gonorrhoeae* in Europe [4], which is currently under revision, should continue to be observed to help identify and report treatment failures and ensure that gonorrhoea remains a treatable infection. Euro-GASP has a major role in fulfilling the objectives of the response plan. Objectives include the following:

- Strengthening the surveillance of gonococcal antimicrobial susceptibility by increasing the number of participating countries and isolates and improving representativeness of Euro-GASP. Finland joined Euro-GASP in 2017 and 27 (87.1%) of the 31 EU/EEA countries now are included in Euro-GASP. Overall completeness of variables remained quite similar to 2016, which needs to be improved for many variables if statistical analysis of the linked susceptibility and patient data is to be robust.
- Country visits to support the inclusion of additional countries and centres and improve isolate numbers, representativeness and reporting of epidemiological data.
- Strengthening capacity for the surveillance of gonococcal antimicrobial susceptibility by developing capacity for culture and susceptibility testing across countries. Training in STI diagnostics and susceptibility testing is provided and experts (or related staff) are encouraged to participate, where required, and eventually move towards decentralised testing.
- Advocating the use of recommended therapies to treat gonorrhoea [1]. Encouragingly, in 2017, 86% received the highly effective ceftriaxone, with or without azithromycin. Nevertheless, it is of major concern that some patients were inappropriately treated, e.g. with ciprofloxacin, in particular in they harboured resistant strains (six resistant strains from 13 patients treated with ciprofloxacin).
- Ensuring that all Euro-GASP laboratories continue to participate in the EQA programme.

Even though Euro-GASP detected stable cefixime, ceftriaxone and azithromycin resistance in 2017, the continued high level of azithromycin resistance and the detection of seven HLAziR isolates (azithromycin MIC≥256 mg/L) are of major concern. Treatment failures have been documented [9–10], along with sustained transmission of HLAziR strains [11] and international spread of gonococcal strains with resistance to ceftriaxone [10, 12–15]. It is therefore essential to continuously implement the response plan. A review of the response plan is currently ongoing and will take into account developments observed in recent years. In addition, the development of novel antimicrobials and/or new dual antimicrobial therapy regimens is urgently needed.

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Annex 1. Percentage completeness of epidemiological variables

Table A-1. Completeness of epidemiological variable reporting, 2017

Country	Number of isolates	Gender	Age	Mode of transmission	Site of infection	Diagnostic test	Treatment	Previous gonorrhoea	Concurrent STI	Place of residence	Clinical service type	Country of birth	Probable country of infection	HIV status	Overall percentage response rate
Austria	262	99.6	99.6	22.5	97.7	100.0	0.0	26.3	10.7	0.0	85.1	13.0	0.0	2.7	42.9
Belgium	98	100.0	94.9	31.6	98.0	0.0	0.0	30.6	0.0	0.0	14.3	27.6	15.3	28.6	33.9
Croatia	6	83.3	66.7	0.0	100.0	100.0	0.0	0.0	33.3	100.0	0.0	100.0	0.0	0.0	44.9
Cyprus	2	100.0	100.0	0.0	100.0	100.0	50.0	100.0	50.0	100.0	100.0	100.0	50.0	0.0	73.1
Czech Republic	104	100.0	100.0	96.2	98.1	100.0	98.1	98.1	100.0	98.1	100.0	0.0	98.1	94.2	90.8
Denmark	118	99.2	100.0	62.7	98.3	100.0	0.0	100.0	0.0	64.4	100.0	65.3	55.9	52.5	69.1
Estonia	2	100.0	100.0	0.0	100.0	100.0	0.0	50.0	100.0	100.0	0.0	0.0	0.0	0.0	50.0
Finland	212	100.0	100.0	86.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	97.6	26.4	0.0	31.6
France	110	100.0	72.7	0.0	70.0	0.0	0.0	0.0	24.5	100.0	100.0	0.0	0.0	0.0	35.9
Germany	200	99.5	99.5	0.0	98.0	100.0	2.0	0.0	0.0	100.0	98.5	0.0	0.0	0.0	46.0
Greece	89	100.0	92.1	88.8	97.8	100.0	85.4	83.1	5.6	87.6	100.0	0.0	86.5	9.0	72.0
Hungary	62	98.4	85.5	0.0	90.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	21.1
Iceland	43	100.0	100.0	7.0	100.0	100.0	2.3	4.7	9.3	90.7	100.0	86.0	90.7	2.3	61.0
Ireland	163	100.0	100.0	99.4	100.0	0.0	99.4	60.1	99.4	98.8	100.0	95.7	12.3	99.4	81.9
Italy	100	100.0	96.0	88.0	100.0	100.0	85.0	88.0	85.0	92.0	100.0	93.0	79.0	83.0	91.5
Latvia	4	100.0	100.0	100.0	100.0	100.0	0.0	100.0	100.0	100.0	100.0	0.0	100.0	0.0	76.9
Luxembourg	18	100.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	100.0	100.0	0.0	0.0	0.0	46.2
Malta	27	96.3	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	99.7
Netherlands	342	99.1	100.0	99.1	100.0	100.0	100.0	0.0	100.0	97.4	100.0	100.0	0.0	95.0	83.9
Norway	107	100.0	100.0	0.0	100.0	100.0	0.0	0.0	0.0	0.0	78.5	0.0	0.0	0.0	36.8
Poland	65	100.0	98.5	0.0	100.0	100.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	38.3
Portugal	110	100.0	100.0	9.1	100.0	100.0	0.0	7.3	8.2	100.0	22.7	8.2	8.2	8.2	44.0
Slovakia	110	100.0	100.0	72.7	99.1	100.0	71.8	100.0	80.0	99.1	100.0	99.1	72.7	78.2	90.2
Slovenia	133	100.0	98.5	85.0	100.0	100.0	76.7	90.2	54.1	97.7	100.0	96.2	54.1	82.7	87.3
Spain	421	100.0	98.8	99.8	100.0	100.0	0.2	0.0	0.0	0.0	2.9	0.0	0.0	0.2	38.6
Sweden	100	100.0	100.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	23.1
United Kingdom	240	100.0	100.0	95.4	98.8	96.3	87.9	94.6	28.8	95	100	46.7	49.6	87.5	83.1
Average completeness	**3248**	**99.7**	**97.9**	**61.6**	**91.6**	**76.8**	**36.7**	**33.3**	**31.7**	**56.3**	**68.4**	**42.1**	**23.6**	**37.5**	**58.2**

Cell shading: green=100%, red=0%, blue=below average.

Annex 2. Statistical tables

Table A-2. Univariate association of cefixime resistance/susceptibility and patient characteristics, Euro-GASP, 2017

	Cefixime resistance N (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection (n=2 975)				
Genital (2166)	54 (2.49, 1.91-3.23)	11.1	1.5-80.7	**<0.01***
Anorectal (435)	1 (0.23, 0.04-1.29)	1.0		
Pharyngeal (254)	5 (1.97, 0.84-4.52)	8.7	1.0-75.8	
Other (120)	1 (0.83, 0.15-4.57)	3.6	0.2-59.0	
Sexual orientation and gender (n=2 218)				
MSM (1 053)	11 (1.04, 0.58-1.86)	1.0		
Male heterosexual (663)	20 (3.02, 1.96-4.61)	2.9	1.4-6.2	**<0.01**
Female (502)	14 (2.79, 1.67-4.62)	2.7	1.2-6.0	**0.01**
Previous GC (n=1 080)				
Yes (235)	1 (0.43, 0.08-2.37)			0.15*
No (845)	17 (2.01, 1.25-3.20)			
Concurrent chlamydia (n=1 031)				
Yes (243)	3 (1.23, 0.42-3.57)			0.37*
No (788)	4 (0.51, 0.20-1.30)			
HIV status (n=1 217)				
Positive (188)	0 (0, 0-2.00)			0.38*
Negative (1 029)	10 (0.97, 0.529-2.78)			
Age (n=3 179)				
<25 years (898)	22 (2.45,1.62-3.68)	1		
≥25 years (2 281)	37 (1.62, 1.18-2.22)	0.7	0.4-1.1	0.12

**: expected value for one cell < 5, so Fisher's exact test performed.*

Table A-3. Univariate association of azithromycin resistance/susceptibility and patient characteristics, Euro-GASP, 2017

	Azithromycin resistance N (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection (n=2 975)				
Genital (2 166)	164 (7.57, 6.53-8.76)	1.0		
Anorectal (435)	32 (7.36, 5.26-10.20)	1.0	0.7-1.4	0.9
Pharyngeal (254)	27 (10.63, 7.41-15.02)	1.5	0.9-2.2	0.1
Other (120)	9 (7.50, 3.10-13.64)	1.0	0.5-2.0	1.0
Sexual orientation and gender (n=2 220)				
MSM (1055)	88 (8.34, 6.82-10.16)	1.0		
Male heterosexual (663)	48 (7.24, 5.50-9.47)	0.9	0.6-1.2	0.4
Female (502)	34 (6.77, 4.88-9.32)	0.8	0.5-1.2	0.3
Previous GC (n=1 080)				
Yes (235)	20 (8.51, 8.64-12.78)	0.8	0.5-1.3	0.4
No (845)	89 (10.53, 5.58-12.78)	1.0		
Concurrent chlamydia (n=1 031)				
Yes (243)	16 (6.58, 4.1-10.42)	0.7	0.4-1.2	0.2
No (788)	72 (9.14, 7.32-11.35)	1.0		
HIV status (n=1 217)				
Positive (188)	16 (8.51, 5.31-13.38)	0.9	0.5-1.6	0.8
Negative (1029)	95 (9.23, 7.61-11.16)	1.0		
Age (n=3 181)				
<25 years (898)	86 (9.58, 7.82-11.68)	1.5	1.1-1.9	**<0.01**
≥25 years (2 283)	155 (6.79, 5.82-7.90)	1.0		

Table A-4. Univariate association of ciprofloxacin resistance/susceptibility and patient characteristics, Euro-GASP, 2017

	Ciprofloxacin resistance N (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection (n=2 972)				
Genital (2 163)	1 055 (48.77, 46.67-50.88)	1.5	1.2-1.9	**<0.01**
Anorectal (435)	167 (38.39, 33.94-43.04)	1.0		
Pharyngeal (254)	120 (47.24, 41.19-53.38)	1.4	1.1-2.0	0.02
Other (120)	53 (44.17, 35.60-53.10)	1.3	0.8-1.9	0.25
Sexual orientation and gender (n=2 219)				
MSM (1 055)	434 (41.14, 38.21-44.13)	1.0		
Male heterosexual (663)	339 (51.13, 47.33-54.92)	1.5	1.2-1.8	**<0.01**
Female (501)	220 (43.91, 39.63-48.29)	1.1	0.9-1.4	0.30
Previous GC (n=1 080)				
Yes (235)	100 (42.55, 42.11-48.81)	0.9	0.7-1.2	0.43
No (845)	384 (45.44, 36.40-48.94)	1.0		
Concurrent chlamydia (n=1 031)				
Yes (243)	83 (34.16, 28.48-40.32)	1.0		
No (788)	365 (46.32, 42.86-49.81)	1.7	1.2-2.3	**<0.01**
HIV status (n=1 217)				
Positive (188)	68 (36.17, 29.64-43.25)	0.8	0.5-1.0	0.08
Negative (1029)	444 (43.15, 40.15-46.19)	1.0		
Age (n=3 178)				
<25 years (898)	355 (39.53, 6.39-42.77)	1.0		
≥25 years (2 280)	1 118 (49.04, 46.99-51.09)	1.5	1.3-1.7	**<0.01**

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