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Abbreviations

AMR	Antimicrobial resistance
CI	Confidence interval
ECDC	European Centre for Disease Prevention and Control
ECOFF	Epidemiological cut-off value
EEA	European Economic Area
EQA	External quality assessment
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
Euro-GASP	European Gonococcal Antimicrobial Surveillance Programme
GC	Gonococcal
GRASP	Gonococcal Resistance to Antimicrobials Surveillance Programme
HIV	Human immunodeficiency virus
MDR	Multidrug-resistant
MIC	Minimum inhibitory concentration
MGS	MIC gradient strip test
MSM	Men who have sex with men
NAAT	Nucleic acid amplification test
OR	Odds ratio
PHE	Public Health England
STI	Sexually transmitted infection
UK	United Kingdom
WHO	World Health Organization

Executive summary

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

During 2019, as in previous years, 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 period September–November. Susceptibility testing was performed on all isolates (MIC gradient strip test (mostly Etest) or agar dilution) for the following antimicrobials (where available): ceftriaxone, cefixime, azithromycin, ciprofloxacin, spectinomycin, and gentamicin, 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 2019, 26 EU/EEA Member States participated in Euro-GASP, 19 via decentralised testing. In total, 4 166 isolates were tested; the majority of specimens were from male patients (83.0%), with patient age ranging from under one year to 85 years, with a median age of 30 years. Overall, 28.4% of patients were under 25 years, and males were significantly older than females. The anatomical site of specimen collection was mainly genital (68.1%), followed by rectal (19.6%), and pharyngeal (9.7%). In 2019, for the first time data were captured on samples specifically from blood (0.03%), eye (0.08%), and joint fluid (0.11%) infection sites. Among cases with information on previous diagnosis of gonorrhoea, 24.7% had previously been diagnosed with the infection and 21.8% of the patients were concurrently diagnosed with *Chlamydia trachomatis* infection. Among cases with known sexual orientation and sex (56.6%), 54.4% were heterosexual men or women, and 45.6% were men who have sex with men (MSM). Among all cases, 14.1% were HIV-positive and 84.9% of those were MSM.

In 2019, three isolates with resistance to ceftriaxone (MIC=0.25 mg/L, n=2, and MIC=0.5 mg/L) were detected, in Norway, Portugal and Belgium. All isolates had an azithromycin MIC at or below the azithromycin epidemiological cut-off value (ECOFF) of 1 mg/L (MIC=0.25 mg/L, MIC=1 mg/L and MIC=0.5 mg/L) and all were ciprofloxacin-resistant (MIC>32 mg/L, MIC=4 mg/L and MIC>32 mg/L). The 2019 Euro-GASP results revealed a total of 0.9% of gonococcal isolates with resistance to cefixime (MIC>0.125 mg/L), which has previously displayed stable level of 1.4% to 2.1% from 2014 to 2018 (1.4% in 2018 and 1.9% in 2017) with a stable number of countries reporting any resistant isolates (n=14).

Since January 2019, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical resistance breakpoint for azithromycin of MIC>0.5 mg/L has been replaced with an ECOFF value of MIC>1 mg/L. As observed in 2018, there was again a significant increase in the proportion of isolates above azithromycin ECOFF, with 10.1% observed in 2019 compared to 7.6% in 2018 and 3.7% observed in 2017 ($p<0.01$). In 2019, 24 countries recorded at least one isolate with azithromycin above ECOFF (MICs >1 mg/L) compared to 25 countries in 2018, 21 in 2017 and 20 countries in 2016, respectively. The proportion of isolates showing ciprofloxacin resistance continued the trend of significant increase from 50.3% in 2018 to 57.3% in 2019 ($p<0.01$) compared to 46.5% in 2017.

The decreasing azithromycin susceptibility combined with the continued detection of ceftriaxone resistance is a major concern and threatens the effectiveness of the currently highly effective dual-therapy regimen (ceftriaxone plus azithromycin) and high-dose ceftriaxone monotherapy recently adopted by some European countries. Even though the level of resistance to cefixime has significantly decreased, cefixime resistance needs to be monitored closely, particularly because gonococcal strains with resistance to both cefixime and ceftriaxone continue to spread internationally. The continuation of quality-assured antimicrobial susceptibility surveillance activities, along with the development of alternative gonococcal regimens, is 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 extended-spectrum cephalosporin ceftriaxone is the last remaining option for effective empiric first-line antimicrobial monotherapy and is the main therapeutic agent currently recommended in Europe [1]. Due to a decrease in susceptibility [2-6], the European treatment guideline recommends combination treatment with ceftriaxone plus azithromycin as first-line treatment in an attempt to mitigate the development and/or spread of resistance to these antimicrobials. However, in some circumstances high-dose ceftriaxone monotherapy is also recommended [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 [6].

Since 2009, the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) has been coordinated by ECDC, supported by an international network led by the UK Health Security Agency (UKHSA), formerly Public Health England (United Kingdom), and Örebro University Hospital (Sweden). Euro-GASP has identified decreasing susceptibility to extended-spectrum cephalosporins and treatment failures have been documented [6], prompting the creation of a European response plan to control and manage the threat of multidrug-resistant *N. gonorrhoeae* in the EU/ EEA in 2012 [2]. This response plan was reviewed and updated in 2019 [7], with indicators reviewed in 2020 [8].

1.2 Objectives

The overall aim of Euro-GASP is to strengthen the surveillance of gonococcal antimicrobial susceptibility in EU/EEA countries 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 2019 gonococcal antimicrobial susceptibility sentinel surveillance.

2. Methods

2.1 Participating laboratories and isolate collection

Twenty-six participating laboratories from 26 EU/EEA countries collected *N. gonorrhoeae* isolates from consecutive patients. The official collection window was from September to November 2019 except for the United Kingdom (UK), which collected isolates between July and September 2019 (to coincide with the national Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP)). Twenty-four countries collected outside of the collection window to attempt to reach the minimum 100 isolate target, 13 of which collected throughout the whole year. No new countries joined in 2019, and one country, Luxembourg, was unable to participate due to a lack of available gonococcal cultures.

The Euro-GASP collection criteria and methodology remained the same as in previous years [9]. Ten countries reported more than their target isolates, all isolates reported were included in the analysis. Isolates from seven (26.9%) countries were tested centrally at Public Health England, UK or Örebro University Hospital, Sweden with the remaining 19 (73.1%) countries performing antimicrobial susceptibility testing in their own laboratories. All 26 Euro-GASP laboratories participated in an annual EQA programme [10,11] to ensure comparability of data. Countries that perform decentralised testing have fulfilled established quality criteria prior to commencing their own testing.

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 [9]. The results were interpreted using breakpoints from the European Committee on Antimicrobial Susceptibility Testing (EUCAST): cefixime/ceftriaxone resistance, MIC >0.125 mg/L; azithromycin epidemiological cut-off value (ECOFF), MIC >1 mg/L; and ciprofloxacin resistance, MIC >0.06 mg/L [12]. 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 2019 as a 'snapshot' study year.

2.3 Data collection and analysis

The following data were collected for each isolate, where available: date specimen obtained, specimen site, sex, age, sexual orientation, previous gonorrhoea diagnosis, other sexual transmitted infections (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 The European Surveillance System (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 and 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 v15.1. The Z-test was used to determine the difference between epidemiological and AMR data collected in 2019 versus 2018, and a Mann-Whitney test was used to test 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 and Pearson's $\chi 2$ test was used to measure if these OR differed significantly from 1. For small cell numbers, Fisher's exact test was performed. Using a forward step-wise approach, the most significant and strongest associations for which odds ratios had been calculated in 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 2019, data from a total of 4 166 isolates from 26 countries were available for analysis, representing an increase of 867 isolates (26.3%) compared to 2018. The number of isolates tested from each country varied from two (Cyprus) to 641 (Norway).

3.1 Epidemiological data

Overall, the reporting completeness was 56.4% compared to 62.1% in 2018, 58.2% in 2017 and 61.6% in 2016. The level of completeness was in line with previous years for the majority of variables; lowest completeness, 24.2% for treatment used and highest completeness, 98.0% for sex and 95.7% for age. There was a significant decrease ($p<0.05$) in reporting of all variables with the exception of diagnostic test used, which significantly increased ($p<0.01$) from 75.3% in 2018 to 83.6% in 2019. Further details on reporting completeness for 2019 data can be found in Annex 1.

As in previous years, most gonococci (83.0%) were collected from men, although there has been a significant increase in specimens from females from 14.7% in 2018 to 17.0% in 2019 ($p<0.01$) (Table 1). Information on sexual orientation was available for 56.6% (n=2357) of cases. The proportion of MSM was significantly lower in 2019 compared to 2018 ($p<0.01$), while there was an increase in the proportion of females ($p<0.01$). The main anatomical site of specimen collection was similar to previous years, predominantly genital samples (68.1%). Information on previous diagnosis of gonorrhoea was available for 24.4% of cases (n=1018), of which 24.7% had had a previous infection, which was comparable to the level observed in 2018 (26.9%). Information on other concurrent STIs was available for 33.2% (n=1385) of cases; 21.8% had a concurrent chlamydia infection (not including lymphogranuloma venereum), 7.3% had another STI, and 70.9% had no concurrent STIs. Of 1267 cases (30.4%) with known HIV status, 179 (14.1%) were HIV positive. Of HIV-positive cases with known transmission type (n=156), 97.4% were MSM. Probable country of infection was available for 1 300 (31.2%) cases from 15 different countries; overall, only 10.2% of these cases (n=133) were likely acquired in a country outside of the reporting country.

Table 1. Patient characteristics reported for Euro-GASP gonococcal isolates, 2010–2019

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total number of isolates	1 766	1 902	1 927	1 994	2 151	2 134	2 660	3 248	3 299	4 166
Sex										
Male	1 441 (82.4)	1 505 (82.4)	1 596 (83.7)	1 676 (84.7)	1 821 (85.1)	1 736 (81.8)	2 256 (85.1)^	2 737 (84.5)	2 795 (85.3)	3 389 (83.0)
Female	308 (17.6)	321 (17.6)	310 (16.3)	302 (15.3)	318 (14.9)	385 (18.2)	395 (14.9)	502 (15.5)	483 (14.7)	695 (17.0)
Unknown	17	76	21	16	11	13	9	9	21	82
Age (years)										
<25	599 (34.4)	572 (31.9)	617 (32.9)	554 (28.4)	605 (28.7)	617 (29.5)	720 (27.5)	898 (28.2)	925 (28.4)	1 133 (28.4)
≥25	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)	2 332 (71.6)	2 853 (71.6)
Unknown	26	109	49	41	44	41	38	67	42	180
Sex and sexual orientation										
Females	308 (27.3)	321 (27.1)	310 (28)	302 (25.7)	318 (22.7)	385 (26.4)	395 (22.9)	502 (22.6)	483 (21.3)	695 (29.5)
Heterosexual males	426 (37.7)	423 (35.6)	390 (35.2)	376 (32)	485 (34.7)	419 (28.7)	632 (36.7)	663 (29.9)	595 (26.3)	588 (24.9)
Men who have sex with men	395 (35)	442 (37.3)	408 (36.8)	496 (42.3)	594 (42.5)	657 (45.0)	696 (40.4)^	1 055 (47.5)×	1 186 (52.4)	1 074 (45.6)
Unknown	637*	716	819	820	754	673	937	1 028	1 035	1 809
Site of infection										
Genital	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)	2 155 (70.4)	2 578 (68.1)
Pharyngeal	62 (3.5)	79 (4.4)	92 (5)	122 (6.3)	154 (7.6)	180 (8.7)	165 (6.4)	254 (8.5)	259 (8.5)	368 (9.7)

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Anorectal	191 (11.4)	216 (12.1)	188 (10.2)	255 (13.2)	192 (9.5)	280 (13.5)	366 (14.2)	435 (14.6)	570 (18.6)	743 (19.6)
Other	7 (0.4)	24 (1.3)	35 (1.9)	30 (1.5)	135 (6.6)	103 (5.0)	100 (3.9)	120 (4)	77 (2.5)	97± (2.6)
Unknown	80	117	75	56	121	54	86	273	238	380
Previous gonorrhoea										
Yes	145 (21)	146 (19)	130 (17.2)	142 (17.8)	163 (19.7)	157 (17.5)	171 (17.2)	235 (21.8)	264 (26.9)	251 (24.7)
No	546 (79)	621 (81)	627 (82.8)	654 (82.2)	663 (80.3)	739 (82.5)	824 (82.8)	845 (78.2)	718 (73.1)	767 (75.3)
Unknown	1 075	1 135	1 170	1 198	1 325	1 238	1 665	2 168	2 317	3 148
Concurrent STI										
Concurrent chlamydia infection	172 (22.1)	194 (22.2)	187†† (23.4)	183 (21.8)	170 (20)	153†† (19.0)	203 (23.9)~	243 (23.6)≈	270†† (22.2)	302ᵻ (21.8)
Concurrent other STI (not HIV)	28† (3.6)	43 (4.9)	49ǂ (6.1)	55 (6.5)	41† (4.8)	48†† (6.0)	53 (6.2) ††	67 (6.5)	90†† (7.4)	101 (7.3)
No concurrent STI	579 (74.3)	638 (72.9)	564 (70.6)	603 (71.7)	640 (75.2)	605 (75.1)	593 (69.9)	721 (69.9)	859 (70.7)	982 (70.9)
Unknown	987	1 027	1 127	1 153	1 300	1 328	1 811	2 217	2 084	2 781
HIV status*										
Positive	48 (15.5)	141 (17.6)	104 (13.5)	144 (17.6)	172 (19.3)	132 (15.3)	156 (15.9)	188 (15.4)	224 (15.7)	179 (14.1)
Negative	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)	1 204 (84.3)	1 088 (85.9)
Unknown	556	1 100	1 155	1 175	1 259	1 269	1 681	2 031	1 871	2 899
Probable country of infection										
Same as reporting country	151 (90.4)	700 (95.0)	790 (92.3)	764 (94.1)	552 (94.0)	800 (92.2)	614 (87.0)	795 (88.6)	1 155 (87.6)	1 167 (89.8)
Different from reporting country	16 (9.6)	37 (5.0)	66 (7.7)	48 (5.9)	35 (6.0)	68 (7.8)	92 (13.0)	102 (11.4)	163 (12.4)	133 (10.2)
Unknown	1 599	1 165	1 071	1 182	1 564	1 266	1 954	2 351	1 981	2 866

Percentages calculated from known values.
Cells shaded in blue indicate a significant difference compared to previous year (p<0.05).
** Includes one individual of unknown sex, 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.
ᵻ Includes three individuals with chlamydia and an additionally diagnosed STI.
^ Includes one individual of unknown sex, but with mode of transmission reported as MSM.
~ Includes nine individuals with chlamydia and an additionally diagnosed STI.
ˣ Includes two individuals of unknown sex, but with mode of transmission reported as MSM.
≈Includes 13 individuals with chlamydia and an additionally diagnosed STI.
± Includes one blood, three eye, and four joint fluid samples – included in other site for analysis due to low numbers.
ᵻ Includes three individuals with chlamydia and an additionally diagnosed STI.

The age of the patients ranged from <1 year to 85 years, with a median of 30 years. Males (median age 30 years) were significantly older than females (median age 26 years) (Mann-Whitney p<0.01) (Table 2).

Table 2. Patient age distribution by sex and sexual orientation, 2019

Variable	N†	Age (years)		<25 years N (%)
		Range	Median	
All patients	**3 986**	**0-85**	**30**	**1 133 (28.4)**
Female	689	0-85	26	320 (46.4)
Male*	3 259	0-84	30	803 (24.6)
Male heterosexual	581	14-76	29	179 (30.8)
MSM	1 067	16-78	30	221 (20.7)

† *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, but there was a significant decrease in patients from this service type between 2018 (59.7%) and 2019 (50.3%) ($p<0.01$). This significant change may be an artefact of the decrease in reporting for this variable in 2019, which significantly increased from 24.0% unreported in 2018 to 33.9% unreported in 2019 ($p<0.01$). A 2020 review of clinical service type found no significant associations between AMR and clinical service type that was not also attributable to another variable. For this reason, data on clinical service type will no longer be collected or analysed in future reports.

3.2 Antimicrobial susceptibility and resistance

Resistance to cefixime, ciprofloxacin, and azithromycin (using breakpoints from the EUCAST for cefixime and ciprofloxacin and ECOFF for azithromycin) over time is summarised in Figure 1 and Table 3.

Figure 1. Percentage of resistant *Neisseria gonorrhoeae* by antimicrobial and year, Euro-GASP, 2010–2019

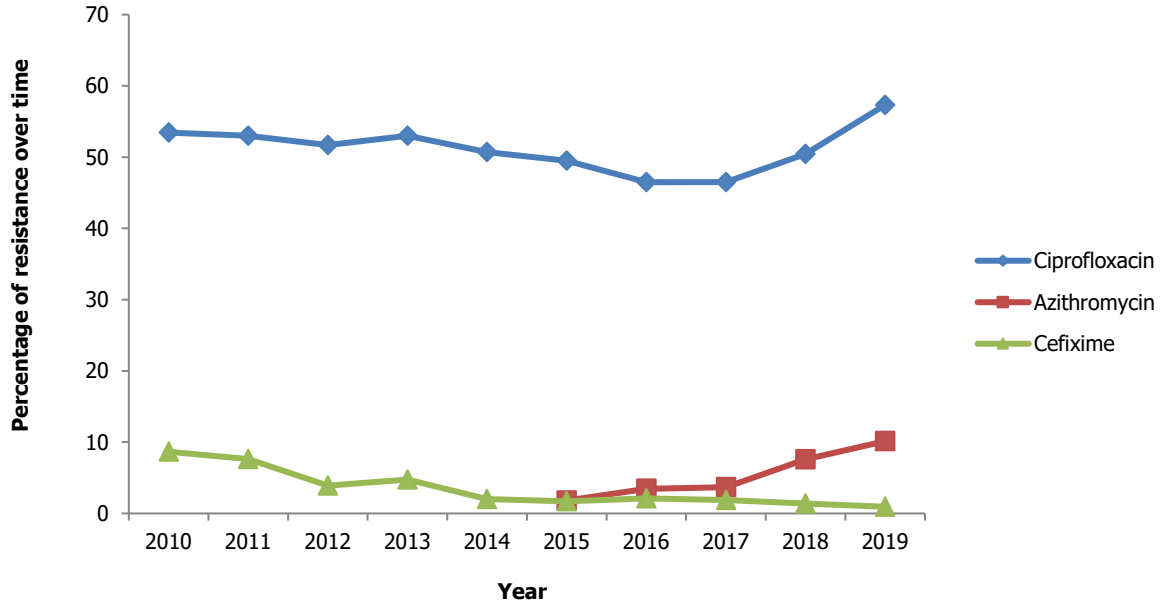


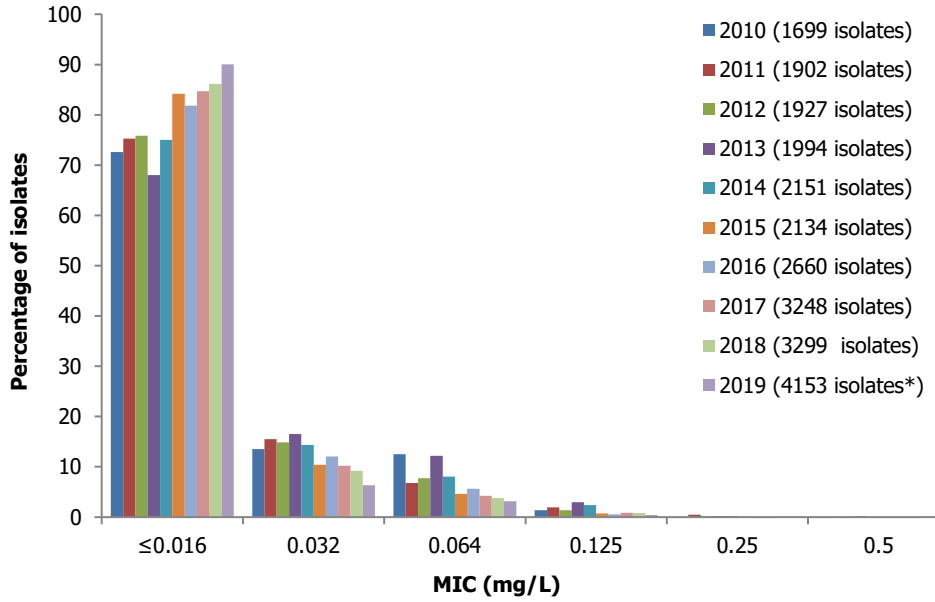
Table 3. Resistance to cefixime, ciprofloxacin and azithromycin (using resistance breakpoints from EUCAST for cefixime and ciprofloxacin and ECOFF for azithromycin) by country, Euro-GASP, 2019

Country	Number of isolates 2019	Number of isolates 2010-2019	Resistance									Method of testing
			Cefixime			Azithromycin			Ciprofloxacin			
			No.	%	% 2010-2019	No.	%	% 2010-2019	No.	%	% 2010-2019	
Austria	434		7	1.6		55	12.9		271	62.4		Decentralised – MGS
Belgium	157		4	2.5		16	10.2		79	50.3		Decentralised – MGS/MIC
Croatia	9		1	11.1		5	55.6		9	100.0		Centralised – MGS
Cyprus	2		1	50.0		0	0.0		2	100.0		Decentralised – MGS
Czech Republic	79		0	0.0		7	8.9		35	44.3		Centralised – MGS
Denmark	118		0	0.0		10	8.5		46	39.0		Decentralised – MGS
Estonia	8		0	0.0		2	25.0		6	75.0		Centralised – MGS
Finland	207		0	0.0		7	3.4		98	47.3		Decentralised – MGS
France	243		3	1.2		21	8.6		136	56.0		Decentralised – MGS
Germany	200		3	1.5		12	6.0		139	69.5		Decentralised – MGS
Greece	98		1	1.0		4	4.1		58	59.2		Decentralised – MGS
Hungary	130		1	0.8		13	10.0		102	78.5		Centralised – MGS/BKP/MIC
Iceland	54		0	0.0		11	20.4		39	72.2		Decentralised – MGS/MIC
Ireland	200		0	0.0		7	3.5		94	47.5		Decentralised – MGS
Italy	100		3	3.0		9	9.0		80	80.0		Decentralised – MGS
Latvia	7		0	0.0		1	14.3		4	57.1		Centralised – MGS
Malta	15		0	0.0		0	0.0		7	46.7		Decentralised – MGS
Netherlands	364		1	0.3		39	10.7		232	63.7		Decentralised – MGS
Norway	641		8	1.2		112	17.6		384	59.9		Decentralised – MGS
Poland	53		0	0.0		10	18.9		34	64.2		Centralised – MGS/BKP/MIC
Portugal	112		2	1.8		13	11.6		54	48.2		Decentralised – MGS
Slovakia	119		0	0.0		17	14.3		61	51.3		Centralised – MGS
Slovenia	178		0	0.0		11	6.2		102	57.3		Decentralised – MGS
Spain	222		2	0.9		14	6.3		120	54.1		Decentralised – MGS
Sweden	200		2	1.0		14	7.0		103	51.5		Decentralised – MGS
United Kingdom	216		0	0.0		11	5.1		92	42.6		Decentralised – MIC/BKP/MGS
Total:	4166											
Cefixime	4166		39	0.9								
Ciprofloxacin	4164								2387	57.3		
Azithromycin	4151					421	10.1					
95% CI				0.7-1.2			9.2-11.1			55.9-58.9		

BKP: Breakpoint; MGS: MIC gradient strip test; MIC: MIC by agar dilution. Proportion with MICs above ECOFF displayed from 2015 to 2019 due to earlier use of breakpoint plates.

Three isolates displayed ceftriaxone resistance in 2019, compared to three isolates in 2018 and zero isolates in both 2017 and 2016 (Figure 2). One resistant isolate was detected in Norway with a ceftriaxone MIC=0.25 mg/L, azithromycin MIC=0.25 mg/L and ciprofloxacin MIC>32 mg/L. This was a pharyngeal isolate from a patient with an unknown country of birth and unknown country of infection and unknown treatment used. The second isolate was detected in Portugal with a ceftriaxone MIC=0.25 mg/L, azithromycin MIC=1 mg/L and ciprofloxacin MIC=4 mg/L. This was a genital isolate from an MSM patient born in Portugal with the probable country of infection recorded as Portugal. This patient was treated with 500 mg ceftriaxone and 1 g azithromycin (regarding treatment outcome see published case report [13]. The third isolate was detected in Belgium with a ceftriaxone MIC=0.5 mg/L, azithromycin MIC=0.5 mg/L and ciprofloxacin MIC>32 mg/L. This was a genital isolate from a patient with unknown country of birth and unknown country of infection and unknown treatment used. All these three isolates were also resistant to cefixime. The MIC distribution for ceftriaxone in 2019 significantly changed compared to 2018, with an increase in highly susceptible strains (MIC≤0.016 mg/L) ($p<0.01$), a decrease in strains with an MIC of 0.032 mg/L ($p<0.01$), and a decrease in strains with an MIC just below the breakpoint (MIC of 0.125 mg/L) ($p=0.05$).

Figure 2. Distribution of MIC for ceftriaxone, Euro-GASP, 2010–2019



** 4 166 isolates were tested in 2019; 13 isolates had an MIC ≤0.125 mg/L. These isolates were excluded from the MIC distribution analysis as they did not fit into one discrete category.*

A total of 39 isolates (0.9%) were cefixime-resistant compared to 46 (1.4%) in 2018 (Figures 1 and 3, Table 3). There has been a significant increase in the number of isolates with a cefixime MIC ≤0.016 mg/L from that recorded in 2018 (81.6% in 2019, 77.0% in 2018, $p<0.01$) and a significant decrease in isolates with cefixime MICs in the 0.064-0.125 mg/L range compared to 2018 ($p<0.01$), as well as in isolates with a cefixime MICs of 0.25 mg/L compared to 2018 ($p=0.05$) (Figure 3). Percentages of cefixime-resistant isolates in 2019 by country are visualised in Map 1.

Map 1. Proportion of gonococcal isolates with cefixime resistance by country, EU/EEA, 2019

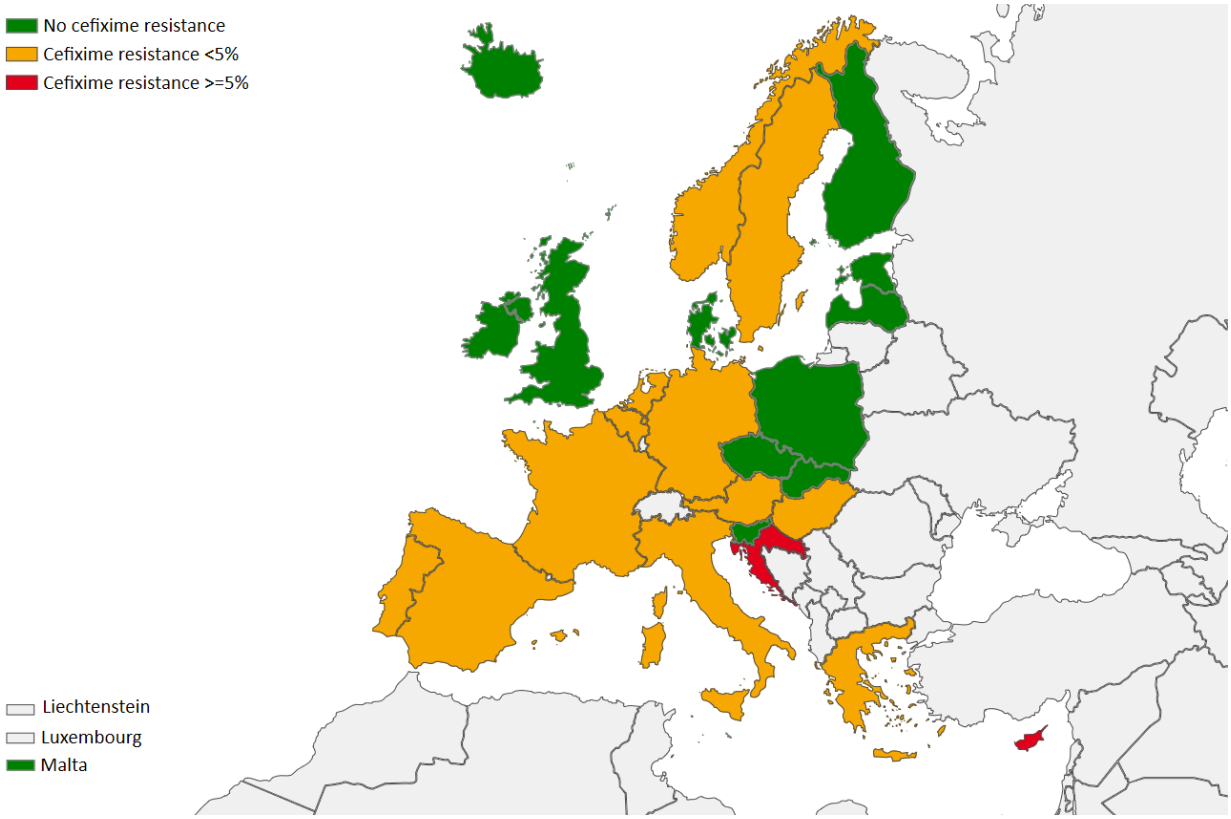
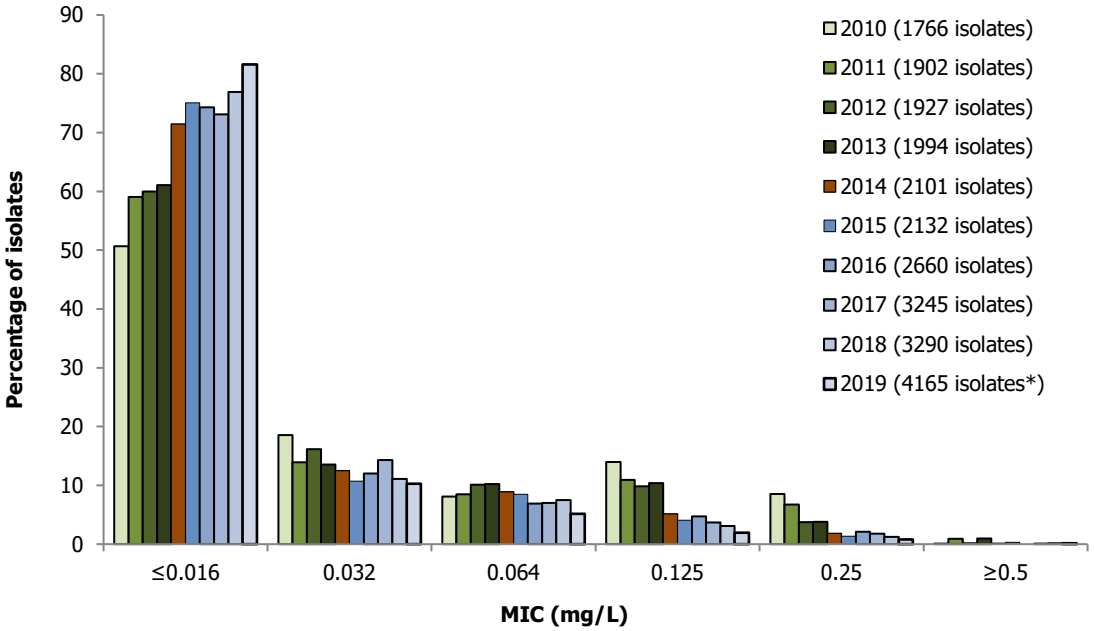


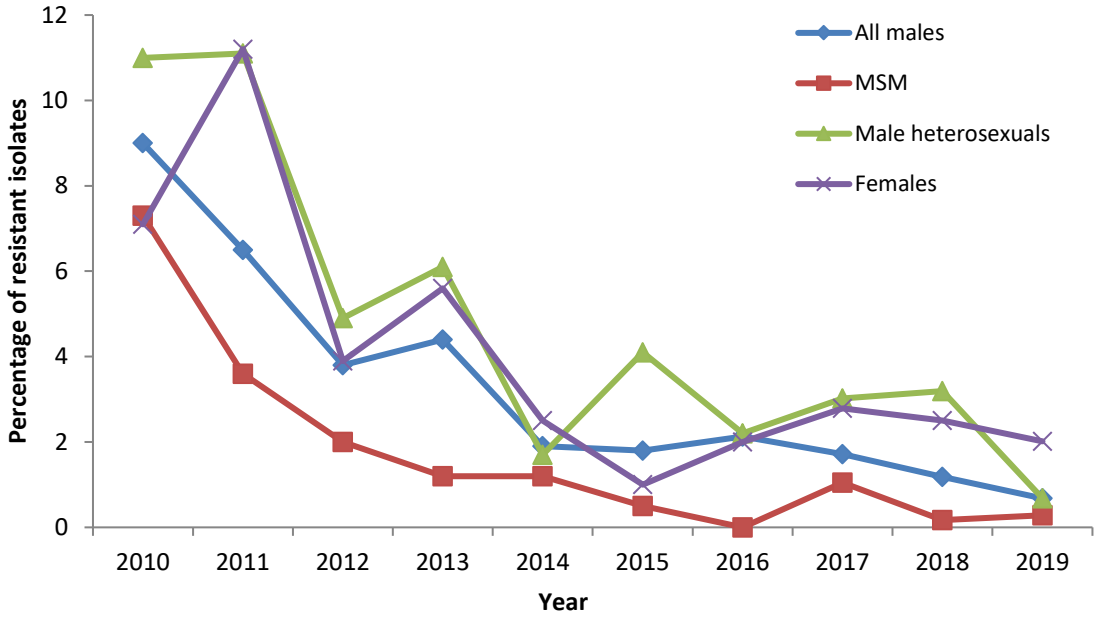
Figure 3. Distribution of MIC for cefixime, Euro-GASP, 2010–2019



** 4 166 isolates were tested in 2019; one isolate had an MIC ≤0.125 MIC. This isolate was excluded from the MIC distribution analysis as it did not fit into one discrete category.*

Cefixime resistance in isolates from female patients was stable (no significant differences) in 2019 compared to 2018 (Figure 4). There was a significant decrease in the proportion of isolates from males with cefixime resistance from 1.2% in 2018 to 0.7% in 2019 (p=0.04). In a change from 2018, when cefixime resistance was significantly associated with heterosexual males cefixime resistance in 2019 was significantly higher in isolates from females than in heterosexual males and MSM (p<0.01, Fisher's exact test). There were no other significant associations identified (Annex 2).

Figure 4. Percentage of isolates with cefixime resistance by sex and male sexual orientation, Euro-GASP, 2010–2019



A total of 421 isolates (10.1%) had an MIC of >1 mg/L (EUCAST ECOFF) to azithromycin which is a significant increase from 2018 (251 isolates, 7.6%) (p<0.01) (Figure 1; Table 3). Fifteen isolates displayed 'high-level azithromycin resistance' with MICs of ≥256 mg/L, compared to five in 2018, eight in 2017, and seven in 2016. These 15 isolates were comprised of six isolates from the UK, three from Ireland, two from Norway, two from Iceland, one from the Netherlands, and one from Denmark. The UK is the only country that has identified high-level azithromycin resistance in an included isolate in each consecutive year for the last three years (2017-2019). All 15 isolates were susceptible to all other antimicrobials tested except for ciprofloxacin, to which two were resistant and one was susceptible to increased exposure (0.06 mg/L).

The MIC distribution for azithromycin in 2019 was different to previous years, with a significant decrease in the number of isolates with an MIC=0.032 mg/L (p=0.04) and isolates with MIC=8 mg/L (p=0.02 mg/L). There were significant increases in isolates with an MIC=0.125 mg/L (p<0.01), MIC=1 mg/L (p<0.01) and MIC=2 mg/L (p<0.01). Seventy-four percent of isolates above the ECOFF had an MIC of 2 mg/L and 46.4% of isolates previously classified as resistant (>0.5 mg/L) had MICs of 1 mg/L. The modal MIC continued to be 0.25 mg/L in 2019 (Figure 5). In 2019, isolates with an azithromycin MIC above the azithromycin ECOFF (>1 mg/L) were highest in males (10.6%) with 8.4% in MSM, closely followed by 8.0% in females and 7.5% in male heterosexuals (Figure 6). Isolates above the azithromycin ECOFF (>1 mg/L) were significantly associated with anorectal (OR 1.4, CI 1.11 to 1.86, p=0.01) and pharyngeal (OR 2.1, CI 1.52 to 2.80, p<0.01) infection sites (Annex 2).

Map 2. Proportion of gonococcal isolates above azithromycin ECOFF (>1 mg/L) by country, EU/EEA, 2019

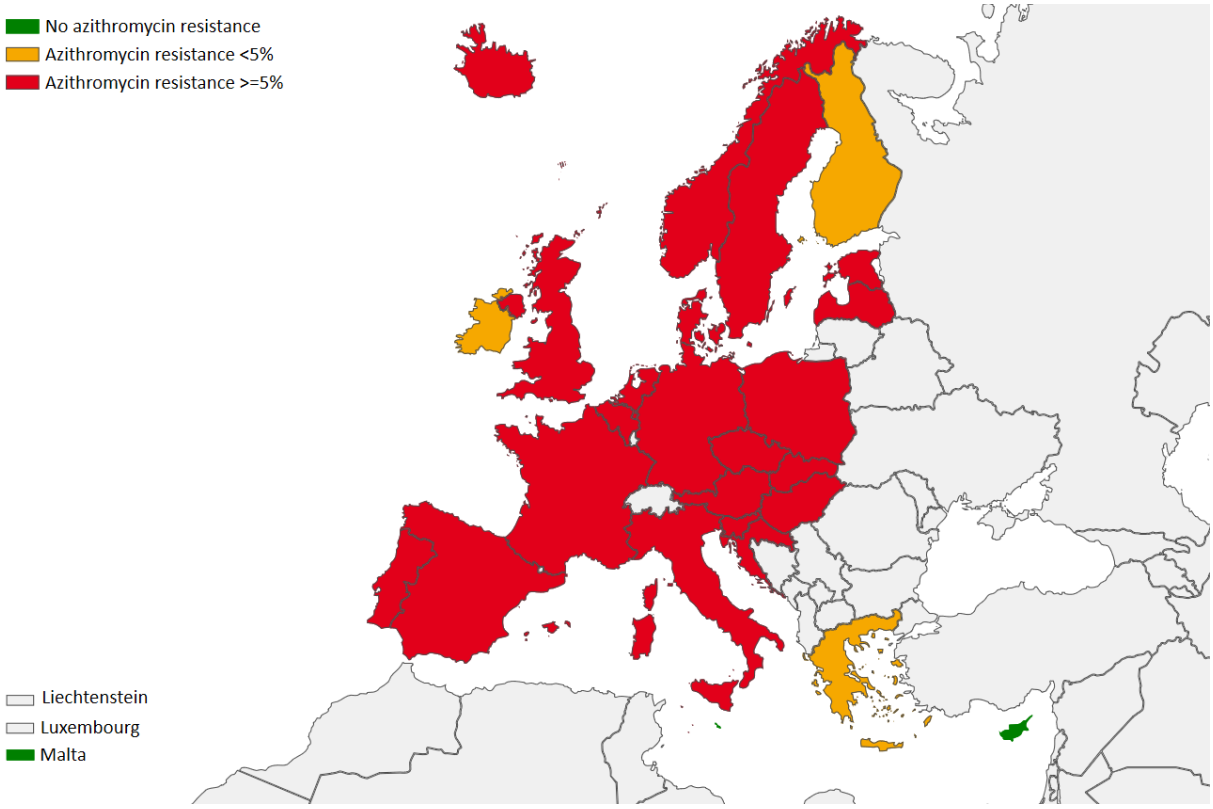
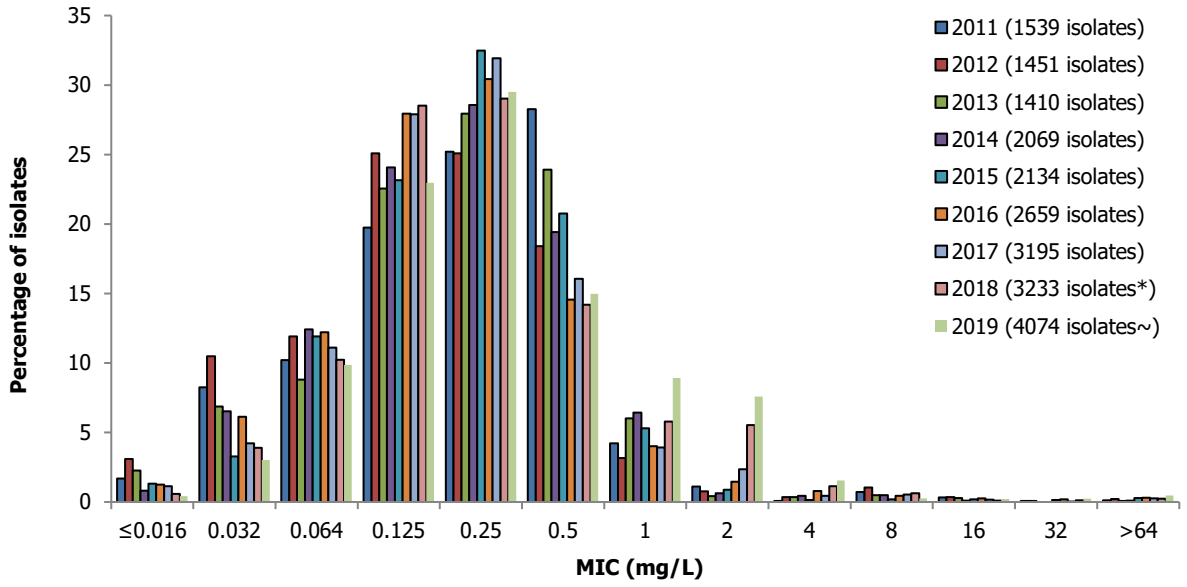
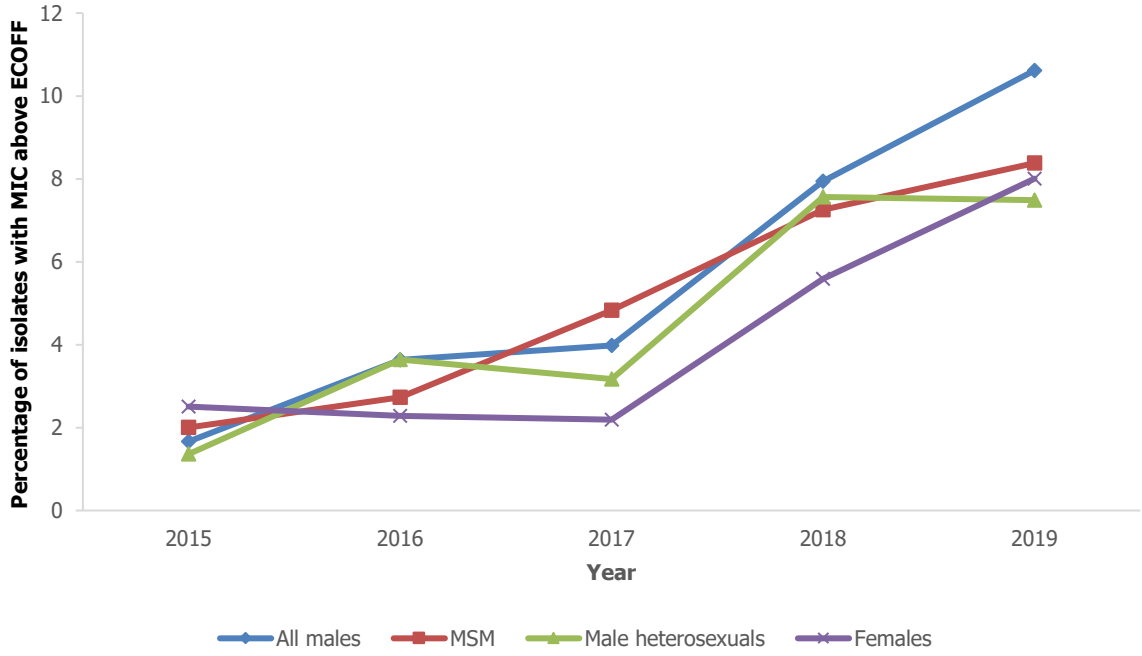


Figure 5. Distribution of MIC for azithromycin in Euro-GASP, 2011–2019



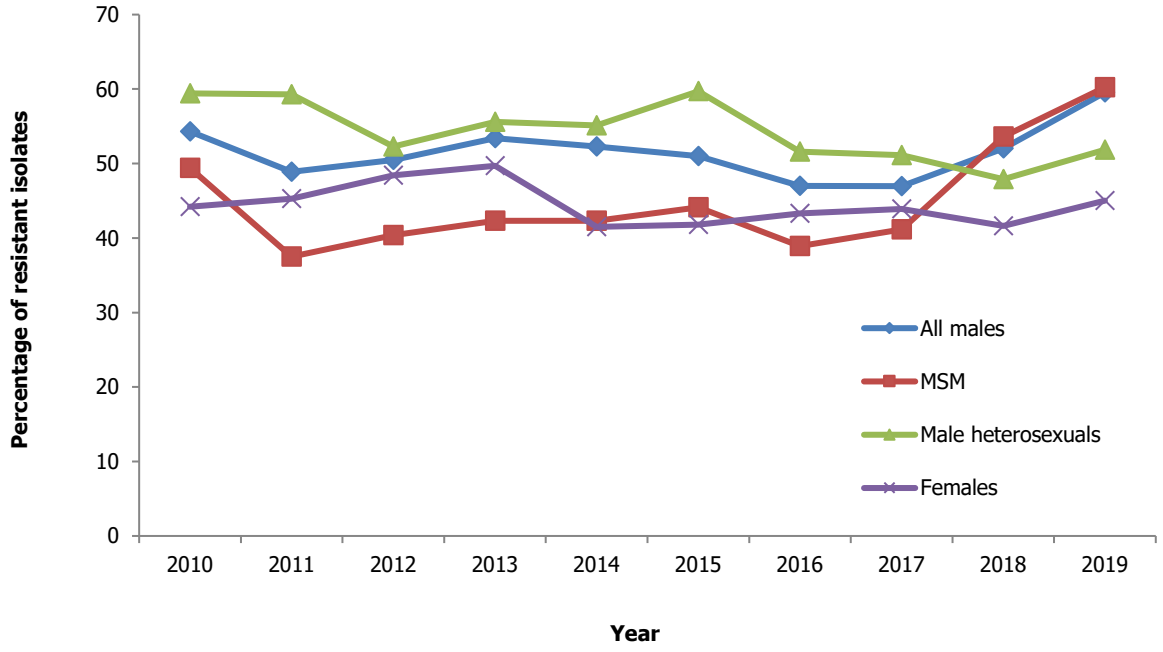
** 3 299 isolates were tested in 2018; 66 isolates had an MIC ≤0.06 mg/L. These isolates were excluded from the MIC distribution analysis as they did not fit into one discrete category.*
~ 4 151 isolates were susceptibility tested with azithromycin in 2019; 77 isolates had an MIC ≤0.06 mg/L. These isolates were excluded from the MIC distribution analysis as they did not fit into one discrete category.

Figure 6. Percentage of isolates with azithromycin MIC above ECOFF (>1 mg/L) by sex and male sexual orientation, Euro-GASP, 2015–2019



Overall, ciprofloxacin resistance levels in 2019 (57.3%; 2 387/4 164) significantly increased (p<0.01) from those observed in 2018 (50.4%), 2017 (46.5%), and 2016 (46.5%) (Figure 1). As observed in 2018, resistance was highest among MSM (60.2%) and lowest in females (45.0%) (Annex 2). Following multivariable analysis, ciprofloxacin resistance remained associated with isolates from MSM (OR 2.79, CI 1.88 to 4.14, p<0.01) and heterosexual males (OR 1.81, CI 1.19 to 2.74, p<0.01) compared to females, the absence of a concurrent chlamydial infection (OR 1.70 CI 1.25 to 2.31, p<0.01), pharyngeal infection sites (OR 2.10, 1.32 to 3.20, p<0.01) and age over 25 years (OR 1.63, 1.21 to 2.19, p<0.01).

Figure 7. Percentage of isolates with ciprofloxacin resistance by sex and male sexual orientation, Euro-GASP, 2010–2019

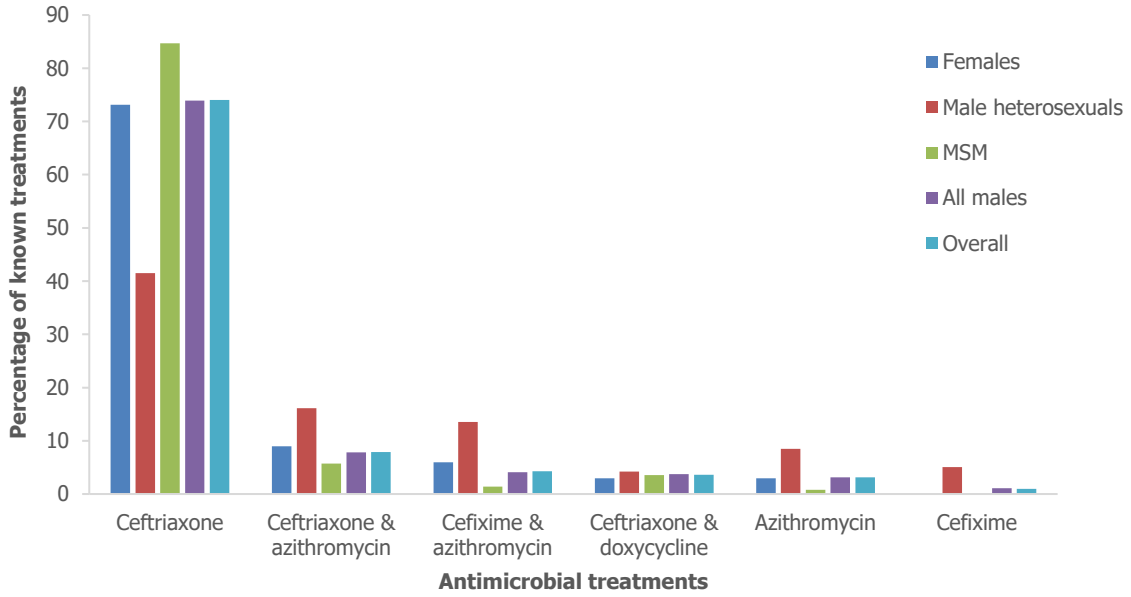


No resistance to spectinomycin (MIC>64 mg/L) was detected in 2019 (2 898 isolates tested) or in any previous year of Euro-GASP. As yet, there are no breakpoints for gentamicin, but overall the MICs of gentamicin continue to be low in all European countries (MIC50 and MIC90 4 mg/L and 8 mg/L respectively), consistent with the MIC50 and MIC90 observed when last tested in 2016. The MIC range in 2019 was similar to when last tested in 2016; 0.25-16 mg/L in 2019, 0.5-16 mg/L in 2016.

3.3 Treatments used

Data on treatment used were known in 1 010 cases, of which 608 were recorded as having no other concurrent STI, the treatment data for these 608 patients is summarised in Figure 8. As in 2018, the most commonly reported treatment for patients with no concurrent STI was ceftriaxone monotherapy (74.0% in 2019, 52% in 2018) followed by ceftriaxone and azithromycin dual therapy (7.9% in 2019) although this was also at a lower level than observed in 2018 (33.7%). Data on the completeness of reporting for treatment type and concurrent STI are presented by country in Table A1 (Annex 1).

Figure 8. Percentage of known treatments used for patients with no other concurrent STI by sex and transmission type for the most frequently used therapies, 2019



Note: Twenty-one different combinations of antimicrobials were recorded in 2019; only treatments with ≥2.5% in any sex/transmission group are shown (differences in concentration of antimicrobials prescribed have been grouped for analysis). Only 982 patients were recorded as having no concurrent STI; of these patients, data for treatment used were available for 61.9% (n=608) patients. The chart presents data for the 608 patients with no concurrent STI and a recorded treatment type. Treatment used was reported by 12 countries, with only 10 also reporting on concurrent STIs (Table A1). Over 50% of the data presented were reported by just two countries: the Netherlands (41.4%) and the UK (26.0%). Slovakia (8.4%), Czechia (7.7%), and Ireland (6.3%) all contributed more than 5% of data each, with Portugal (2.6%), Italy (2.3%), Belgium (1.8%), and Greece (1.3%) all contributing less than 5% each.

4. Conclusions

There was a continuation of a decreasing trend in levels of cefixime resistance within Euro-GASP in 2019: 0.9% compared to 1.4% in 2018 and to the previously stable level of 1.7-2.1% between 2014 and 2017. However, it is concerning that three isolates (0.1%) from three different countries displayed ceftriaxone resistance in 2019. The antibiograms of these isolates do not suggest clonality. In 2018, there was a comparable level of ceftriaxone resistance with three isolates (0.1%) detected compared to none in 2017 and 2016. The countries in which these isolates were detected in 2019 differed from 2018 and none of them were extensively drug-resistant, as all isolates had an MIC at or below the ECOFF for azithromycin. Cefixime-resistant isolates were detected in 14 (53.8%) of the 26 countries reporting in 2019. Cefixime resistance continued to be lowest among MSM (0.3%) with a large decrease in resistance in heterosexual males, which overall has led to a significant decrease in cefixime resistance in males (from 1.2% in 2018 to 0.7% in 2019, p=0.04). Cefixime resistance in females has remained relatively constant at 2% compared to 2.5% in 2018. Although the continuing low levels of cephalosporin resistance is promising, the detection of three ceftriaxone-resistant isolates is concerning as ceftriaxone is the last remaining option for empiric first-line monotherapy. Among patients with no recorded concurrent STI and for whom treatment was reported, 86% were administered ceftriaxone with or without a second antimicrobial which is the same level as observed in both 2018 and 2017. There has been a significant increase in use of ceftriaxone monotherapy from 51.7% in 2018 to 74.0% in 2019 (p<0.01). In 2019 azithromycin with or without a second antimicrobial was used in only 17.4% of patients with no recorded concurrent STI. The observed changes in treatments recorded are likely an artefact of the number of countries reporting these variables, with a decrease from 15 to 12 countries reporting, and the Netherlands and the UK contributing 67.4% of the treatment data in 2019 and only 37.5% in 2018.

The proportion of isolates above the azithromycin ECOFF (>1 mg/L) significantly increased in 2019 (7.6% to 10.1%, p<0.01). This is a continuation of the significant increase observed in 2018 from the previously stable resistance rate of 3.7% in 2017 and 3.6% in 2016. The reported use of azithromycin monotherapy in patients with no concurrent STI has remained constant for the past three years, at 3.1% in 2019, 2.8% in 2018, and 2.9% in 2017. It should be noted that most isolates with an azithromycin >1 mg/L (EUCAST ECOFF) are just above the ECOFF (73.6% had an MIC of 2 mg/L) and 46.4% of isolates previously classified as resistant (>0.5 mg/L) had MICs of 1 mg/L. Minor fluctuations in azithromycin MICs are expected, as susceptibility testing is sensitive to minor differences in agar media composition, pH and CO_2 levels. However, the significant increase in azithromycin MICs is a concern. Ciprofloxacin resistance significantly increased (p<0.01) to 57.3% from 50.4% in 2018. Neither azithromycin nor ciprofloxacin are recommended for monotherapy, unless the isolates are first shown to be susceptible. In 2019, six ciprofloxacin-resistant isolates were recorded as being treated with ciprofloxacin monotherapy and one azithromycin-resistant isolate with azithromycin monotherapy. As in 2018, there was one isolate detected in 2019 with an azithromycin MIC >16 mg/L and both cefixime and ciprofloxacin resistance. In 2018 the isolate came from a Spanish resident with a recorded probable country of infection as Spain. In 2019 the isolate was detected in a Dutch national with an unknown probable country of infection. The ongoing presence of extensively resistant isolates is of concern although it is encouraging that numbers have not increased.

MSM continue to have a lower risk of harbouring AMR isolates [14]; cefixime resistance in 2019 was detected in only 0.3% of MSM compared to 0.7% in heterosexual males.

Given the increase in azithromycin MICs and the continued detection of ceftriaxone resistance, the European response plan to control the threat of multidrug-resistant *N. gonorrhoeae* in Europe [7], 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 which include:

- Strengthening surveillance of gonococcal antimicrobial susceptibility in EU/EEA countries by providing sufficient epidemiological information to inform national treatment guidelines and public health interventions. Overall completeness of variables decreased in 2019, from 62.1% in 2018 to 55.5%, a level similar to 2017 (58.2%). Significant improvements in reporting are urgently required for many variables if statistical analysis of the linked susceptibility and patient data are to be robust.
- Ensuring that appropriate capacity for culture and susceptibility testing in EU/EEA countries is available or further developed. Training in STI diagnostics and antimicrobial susceptibility testing is provided and experts (or related staff) are encouraged to participate, where required, and eventually move towards decentralised testing. Unfortunately, the AMR training scheduled for 2020 had to be postponed due to the COVID-19 pandemic.
- Effectively disseminating results from AMR surveillance in order to increase awareness and inform authorities, professional societies, clinicians and other health care workers and persons at risk about threat of multidrug-resistant (MDR) and extensively drug-resistant *N. gonorrhoeae*. The Euro-GASP AMR surveillance data are freely accessible online via the ECDC ATLAS [15], which is updated annually prior to the publication of the annual surveillance data report. Data from the project are frequently published in peer-reviewed journals and presented at international conferences.

- Introducing strategies to reduce the burden of gonorrhoea, such as implementation of appropriate gonorrhoea management, prevention, control and AMR policies/guidelines, including enhanced focus on high-risk groups, as well as mandatory reporting of gonorrhoea. The use of recommended therapies to treat gonorrhoea is advocated by the Euro-GASP project and, encouragingly, there was a continuation of the use of the highly effective ceftriaxone with or without azithromycin in 86% (75.0% ceftriaxone alone; 7.3% plus azithromycin) of cases with known treatment and no concurrent STI compared to 86% in both 2018 and 2017. Nevertheless, it is of major concern that some patients continue to be treated inappropriately, for example with ciprofloxacin, in particular in those who harboured resistant strains (from six patients treated with ciprofloxacin, four carried a resistant strain).

Even though Euro-GASP detected a decreasing trend in levels of cefixime resistance in 2019, the continued rise in both ciprofloxacin resistance and azithromycin MICs, along with the detection of three ceftriaxone-resistant isolates, are of major concern. Treatment failures have been documented [16,17], along with sustained transmission of high-level azithromycin resistance strains [18] and international spread of gonococcal strains with resistance to ceftriaxone [16,18-23]. Continuous implementation of quality-assured antimicrobial surveillance activities and the recently updated and refined response plan is therefore essential. In addition, the development of alternative therapy regimens is urgently needed to ensure that gonorrhoea remains a treatable infection.

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Annex 1. Percentage completeness of epidemiological variables

Table A1. Completeness of epidemiological variable reporting, 2019

Country	Number of isolates	Sex	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	434	95.4	81.8	17.3	89.9	100.0	0.0	12.7	15.4	70.5	89.2	0.0	0.0	0.0	**44.0**
Belgium	157	98.1	99.4	41.4	95.5	100.0	17.2	40.8	37.6	99.4	22.9	53.5	11.5	34.4	**57.8**
Croatia	9	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	**7.7**
Cyprus	2	100.0	50.0	50.0	50.0	100.0	50.0	0.0	0.0	100.0	100.0	50.0	0.0	0.0	**50.0**
Czech Republic	79	100.0	100.0	91.1	91.1	100.0	91.1	86.1	88.6	91.1	100.0	91.1	91.1	86.1	**92.9**
Denmark	118	100.0	100.0	78.0	100.0	100.0	0.0	100.0	5.1	78.8	100.0	78.8	76.3	64.4	**75.5**
Estonia	8	100.0	100.0	25.0	100.0	100.0	0.0	100.0	100.0	100.0	100.0	0.0	0.0	0.0	**63.5**
Finland	207	100.0	100.0	87.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	95.2	84.5	0.0	**35.9**
France	243	100.0	97.5	39.1	99.6	100.0	0.0	0.0	76.1	78.2	99.2	47.3	65.4	62.1	**66.5**
Germany	200	99.5	99.5	0.0	99.0	100.0	0.0	0.0	0.0	100.0	53.5	0.0	0.0	0.0	**42.4**
Greece	98	100.0	82.7	84.7	100.0	100.0	90.8	73.5	8.2	78.6	100.0	92.9	84.7	0.0	**76.6**
Hungary	130	98.5	97.7	0.0	98.5	98.5	0.0	0.0	0.0	0.0	98.5	0.0	0.0	0.0	**37.8**
Iceland	54	100.0	100.0	51.9	98.1	100.0	0.0	0.0	0.0	94.4	100.0	90.7	0.0	0.0	**56.6**
Ireland	200	100.0	100.0	85.0	99.0	34.0	31.5	45.5	42.0	94.5	96.0	37.0	21.0	36.0	**63.2**
Italy	100	57.0	46.0	27.0	38.0	100.0	21.0	27.0	30.0	32.0	100.0	34.0	18.0	25.0	**42.7**
Latvia	7	100.0	100.0	85.7	100.0	100.0	0.0	100.0	100.0	100.0	100.0	0.0	85.7	0.0	**74.7**
Malta	15	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	**100.0**
Netherlands	364	97.5	100.0	97.5	100.0	100.0	100.0	0.0	100.0	100.0	100.0	100.0	0.0	95.6	**83.9**
Norway	641	99.8	100.0	0.0	95.0	100.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	**30.4**
Poland	53	100.0	94.3	20.8	100.0	100.0	100.0	0.0	0.0	0.0	100.0	0.0	0.0	0.0	**47.3**
Portugal	112	100.0	100.0	26.8	100.0	100.0	25.0	22.3	25.0	100.0	25.9	26.8	25.9	24.1	**54.0**
Slovakia	119	99.2	99.2	57.1	100.0	0.0	52.9	93.3	71.4	99.2	100.0	96.6	58.0	70.6	**76.7**
Slovenia	178	100.0	100.0	34.3	99.4	100.0	0.0	84.8	86.5	98.3	100.0	89.3	0.0	84.3	**75.2**
Spain	222	100.0	99.1	100.0	100.0	100.0	0.0	0.5	0.0	100.0	100.0	79.3	100.0	0.0	**67.6**
Sweden	200	99.0	98.5	96.0	99.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	96.5	0.0	**37.7**
United Kingdom	216	100.0	100.0	73.1	99.5	94.0	99.1	94.9	99.5	100.0	100.0	88.4	50.5	91.2	**91.6**
Grand Total	**4166**	**98.0**	**95.7**	**48.2**	**90.9**	**83.6**	**24.2**	**24.4**	**33.2**	**62.5**	**66.1**	**44.7**	**31.2**	**30.4**	**56.4**

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

Annex 2. Statistical tables

Table A2. Univariate association of cefixime resistance/susceptibility and patient characteristics, Euro-GASP, 2019

	Cefixime resistance N (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection (n=3 786)				
Genital (2 578)	26 (1.0, 0.7-1.5)			0.35*
Anorectal (743)	3 (0.4, 0.1-1.2)			
Pharyngeal (368)	4 (1.1, 0.4-2.8)			
Other (97)	1 (1.0, 0.2-5.6)			
Sexual orientation and sex (n=2 357)				
MSM (1 074)	3 (0.3, 0.1-0.8)			**<0.01***
Male heterosexual (588)	4 (0.7, 0.3-1.7)			
Female (695)	14 (2.0, 1.2-3.4)			
Previous GC (n=1 018)				
Yes (251)	1 (0.4, 0.1-2.2)			0.57*
No (767)	2 (0.3, 0.1-0.9)			
Concurrent chlamydia (n=1 385)				
Yes (302)	3 (1.0, 0.3-2.9)			0.12*
No (1 083)	3 (0.3, 0.1-0.8)			
HIV status (n=1 267)				
Positive (179)	0 (0.0, 0.0-2.1)			1.00*
Negative (1 088)	3 (0.3, 0.1-0.8)			
Age (n=3 986)				
<25 years (1 133)	13 (1.2, 0.7-2.0)	1		0.25
≥25 years (2 853)	22 (0.8, 0.5-1.2)	0.67	0.34-1.33	

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

Table A3. Univariate association of azithromycin MICs above/below ECOFF (>1 mg/L) and patient characteristics, Euro-GASP, 2019

	Azithromycin resistance N (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection (n=3 774)				
Genital (2 571)	231 (9.0, 7.9-10.2)	1		
Anorectal (739)	92 (12.5, 10.3-15.0)	1.44	1.11-1.86	**0.01**
Pharyngeal (367)	62 (16.9, 13.4-21.1)	2.06	1.52-2.80	**<0.01**
Other (97)	10 (10.3, 5.7-17.9)	1.16	0.60-2.27	0.66
Sexual orientation and sex (n=2 349)				
MSM (1 074)	90 (8.4, 6.9-10.2)	1		
Male heterosexual (588)	44 (7.5, 5.6-9.9)	0.88	0.61-1.29	0.52
Female (687)	55 (8.0, 6.2-10.3)	0.95	0.67-1.35	0.78
Previous GC (n=1 013)				
Yes (247)	21 (8.5, 5.6-12.6)	1.13	0.67-1.91	0.64
No (766)	58 (7.6, 5.9-9.7)	1		
Concurrent chlamydia (n=1 385)				
Yes (302)	24 (8.0, 5.4-11.6)	0.82	0.52-1.31	0.41
No (1 083)	103 (9.5, 7.9-11.4)	1		
HIV status (n=1 267)				
Positive (179)	17 (9.5, 6.0-14.7)	1.1	0.62-1.82	0.83
Negative (1 088)	98 (9.0, 7.4-10.9)	1		
Age (n=3 972)				
<25 years (1 128)	101 (9.0, 7.4-10.8)	1		
≥25 years (2 844)	298 (10.5, 9.4-11.7)	1.19	0.94-1.51	0.15

Table A4. Univariate association of ciprofloxacin resistance/susceptibility and patient characteristics, Euro-GASP, 2019

	Ciprofloxacin resistance N (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection (n=3 784)				
Genital (2 577)	1 421 (55.1, 53.2-57.1)	1		
Anorectal (743)	464 (62.5, 58.9-65.9)	1.35	1.14-1.60	**<0.01**
Pharyngeal (367)	233 (63.5, 58.4-68.3)	1.41	1.13-1.77	**<0.01**
Other (97)	59 (60.8, 50.9-69.9)	1.26	0.83-1.91	0.27
Sexual orientation and sex (n=2 355)				
MSM (1 074)	647 (60.2, 57.3-63.1)	1.85	1.53-2.25	**<0.01**
Male heterosexual (588)	305 (51.9, 47.8-55.9)	1.31	1.06-1.64	**0.02**
Female (693)	312 (45.0, 41.4-48.7)	1		
Previous GC (n=1 018)				
Yes (251)	150 (59.8, 53.6-65.6)	1.60	1.20-2.14	**<0.01**
No (767)	369 (48.1, 44.6-51.6)	1		
Concurrent chlamydia (n=1 385)				
Yes (302)	131 (43.4, 37.9-49.0)	1		
No (1 083)	644 (59.5, 56.5-62.4)	1.91	1.48-2.48	**<0.01**
HIV status (n=1 267)				
Positive (179)	106 (59.2, 51.9-66.1)	1.23	0.89-1.69	0.21
Negative (1 088)	590 (54.2, 51.3-57.2)	1		
Age (n=3 984)				
<25 years (1 131)	582 (51.5, 48.5-54.4)	1		
≥25 years (2 853)	1 685 (59.1, 57.2-60.9)	1.36	1.18-1.56	**<0.01**