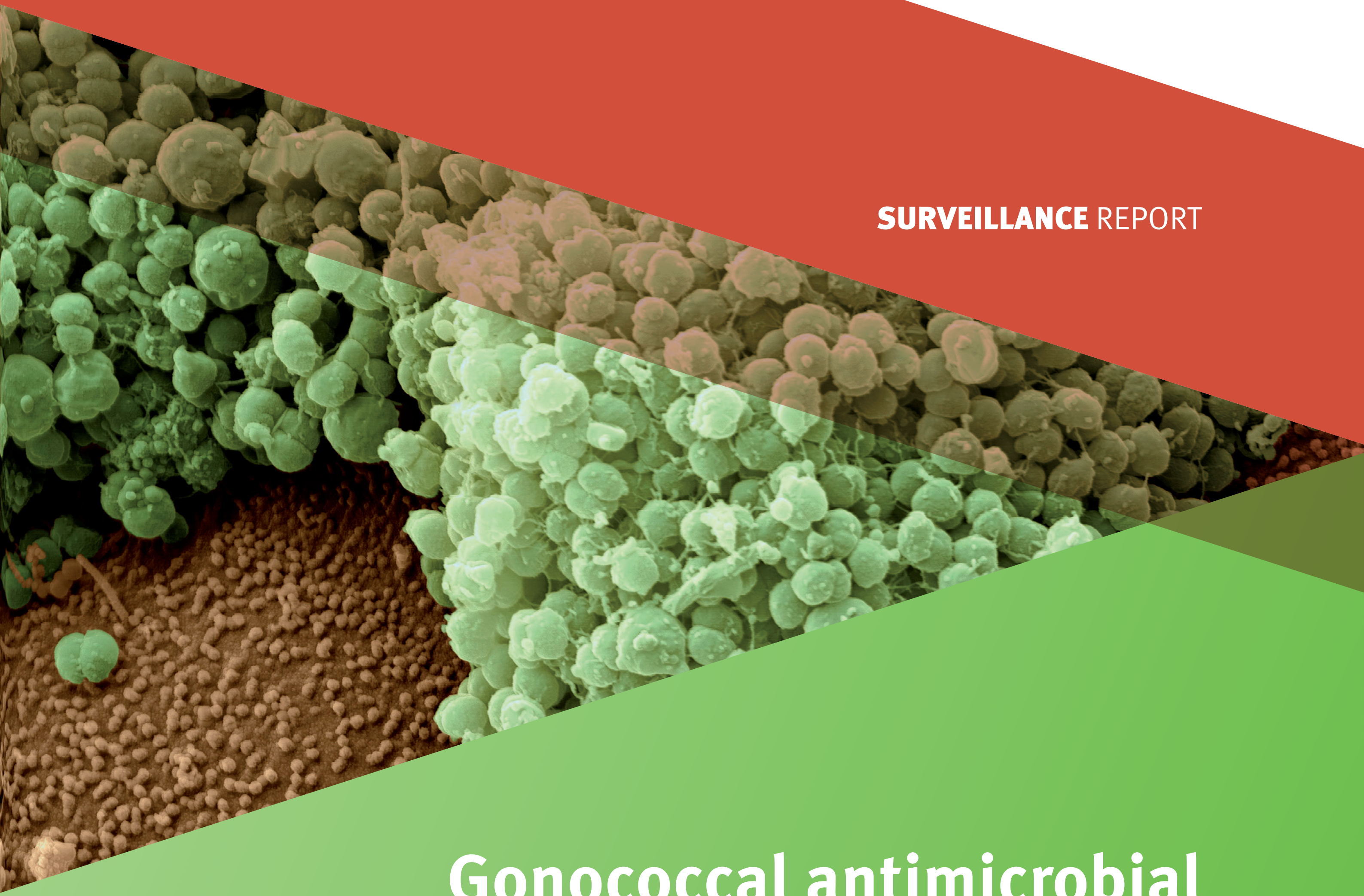
SURVEILLANCE REPORT



Gonococcal antimicrobial susceptibility surveillance in the European Union/ European Economic Area

Summary of results for 2022

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This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by Csaba Ködmön, and produced by Örebro University Hospital, Örebro, Sweden and Health Security Agency, London, United Kingdom.

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Contents

Figures

Tables

Abbreviations

AMR	Antimicrobial resistance
CI	Confidence interval
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
HIV	Human immunodeficiency virus
HLAziR	High-level azithromycin resistance (MIC >256 mg/L)
MDR	Multidrug-resistant
MGS	MIC gradient strip test
MIC	Minimum inhibitory concentration
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
UK	United Kingdom
UKHSA	UK Health Security Agency
WHO	World Health Organization
XDR	Extensively drug-resistant
ÖUH	Örebro University Hospital

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 2022, 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 or agar dilution) for the following antimicrobials (where available): ceftriaxone, cefixime, azithromycin, ciprofloxacin, as well as testing for β-lactamase production for detection of high-level penicillin resistance. Gentamicin and spectinomycin were also tested in 2022 because these are tested every three years. Decentralised testing took place on the premise of participating laboratories fulfilling set quality criteria.

In 2022, 23 EU/EEA countries participated in Euro-GASP, 18 via decentralised testing. In total, 4396 isolates were tested, the majority of specimens were from male patients (80.9%) with patient age ranging from under one year to 75 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 reported for 99.6% of cases, mainly genital (69.0%), followed by rectal (17.8%) and pharyngeal (12.0%). In 2022, data were also captured on samples specifically from blood (0.1%), eye (0.6%) and joint fluid (0.1%) infection sites. Among cases with known sexual orientation and gender reported (56.0%), 54.0% were heterosexual men or women, and 46.0% were men who have sex with men (MSM). Among cases with information on previous diagnosis of gonorrhoea, 27.8% had previously been diagnosed with the infection and among all cases, 8.8% were HIV-positive and 96.0% of those were MSM.

In 2022, two isolates with resistance to ceftriaxone (MIC=0.25 mg/L) were detected, in Austria and Germany, respectively. One was extensively drug-resistant (XDR) and one multidrug-resistant (MDR). Both isolates displayed in addition to resistance to ceftriaxone also resistance to cefixime (MIC of 1 mg/L), had an azithromycin MIC of >256 mg/L and 0.032 mg/L, respectively, and both were ciprofloxacin-resistant (MIC of 8 and 4 mg/L). The 2022 Euro-GASP results revealed a total of 0.3% of gonococcal isolates with resistance to cefixime (MIC>0.125 mg/L), collected from eight countries.

In January 2019, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical resistance breakpoint for azithromycin of MIC>0.5 mg/L was replaced with an epidemiological cut-off (ECOFF) value of MIC>1 mg/L. After a significant increase in the proportion of isolates above azithromycin ECOFF in 2018 (7.6%) and 2019 (10.1%), the proportion remained stable in 2020 at 11.0% to significantly increase again in 2021 (14.2%) and to reach 25.6% in 2022. At least one isolate with azithromycin MIC above ECOFF (MIC>1 mg/L) was recorded in all the 23 participating countries. The proportion of isolates showing resistance to ciprofloxacin substantially increased: 65.9% in 2022 compared to that observed in 2021 (62.8%) and 2020 (57.7%).

Although dual ceftriaxone and azithromycin resistance is exceedingly rare in the EU/EEA, the rapidly decreasing azithromycin susceptibility combined with the continued detection of occasional ceftriaxone resistance is still of concern and threatens the effectiveness of treatment and control of gonorrhoea. Due to this, the European treatment guideline was updated in 2020 to recommend high-dose ceftriaxone plus azithromycin dual therapy or ceftriaxone high-dose monotherapy, which is now most frequently used, as shown in this report. 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 ensure gonorrhoea remains a treatable infection.

1 Introduction

1.1 Background

The emergence and spread of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* are serious threats 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 [1–7]. The 2020 European gonorrhoea treatment guideline recommends combination treatment with high-dose ceftriaxone (1 g) plus azithromycin (2 g) or high-dose ceftriaxone (1 g) monotherapy but only in well controlled settings, see guideline for details [2]. Surveillance of the susceptibility to these agents is essential in order to ensure effective patient management and monitor current and emerging trends in AMR [2–7].

ECDC has co-ordinated epidemiological and microbiological surveillance activities for sexually transmitted infections (STIs) in Europe since 2009. The microbiological components mainly focusing on the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) have been outsourced and are supported by an international network led by Örebro University Hospital (ÖUH) (Sweden) and the UK Health Security Agency (UKHSA) (United Kingdom). Activities have included centralised and decentralised *N. gonorrhoeae* isolate collection and antimicrobial susceptibility testing, establishing of The European Surveillance System (TESSy) reporting for Euro-GASP surveillance data, external quality assessment (EQA) schemes, molecular typing of *N. gonorrhoeae*, laboratory capacity assessment across the European Union/European Economic Area (EU/EEA) and training on STI diagnostic and typing methods.

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 as follows:

- Support ECDC in monitoring the susceptibility of *N. gonorrhoeae* isolates in participating countries by conducting sentinel surveillance for antimicrobial resistance in gonococci.
- Support participating countries in developing technical skills and capacity for high quality antimicrobial susceptibility testing and molecular typing, including whole genome sequencing (WGS).
- Support participating countries in improving the quality of epidemiological data reported through Euro-GASP.
- Through an EQA scheme, assess the accuracy of quantitative *N. gonorrhoeae* antimicrobial susceptibility testing reported by participating laboratories and the comparability of results between laboratories in order to identify any training needed for targeted capacity building.
- Perform analysis of WGS data of *N. gonorrhoeae* strains in order to inform about the geographic and temporal distribution patterns of public health relevant strains of *N. gonorrhoeae* in the EU/EEA, including associations between genotype, antimicrobial resistance and patient characteristics.
- Through an EQA scheme and a bioinformatic ring trial, assess the quality of *N. gonorrhoeae* molecular typing data generated by participating laboratories and the comparability of results between laboratories in order to identify training needs for targeted capacity building.
- Provide training on STI laboratory diagnostics, *N. gonorrhoeae* susceptibility testing and molecular typing, including WGS.

This report presents the results from the 2022 gonococcal antimicrobial susceptibility sentinel surveillance.

2 Methods

2.1 Participating laboratories and isolate collection

Twenty-three participating laboratories from 23 EU/EEA countries collected *N. gonorrhoeae* isolates from consecutive patients (Table 3). Each country aimed to collect 110 gonococcal isolates per year, with the overall aim to retrieve and test 100 isolates per country. For countries where 100 isolates represent less than 10% of the total number of cases (or estimated number of cases) of gonorrhoea (currently Austria, Belgium, Czechia, Denmark, France, Germany, Hungary, Ireland, Italy, the Netherlands, Norway, Portugal, Spain, and Sweden), up to 200 isolates should be collected in order to provide a more representative sample. The official collection window was from 1 September to 30 November 2022; 19 countries collected outside of the collection window to attempt to reach the minimum isolate target, four of which continued into December, two started in August, one added isolates from both August and December, and 12 collected throughout the whole year. Compared to the most recent report in 2020, Bulgaria joined in 2021, and one country, Cyprus, was unable to participate in 2022 due to a lack of available gonococcal cultures.

The Euro-GASP collection criteria and methodology remained the same as in previous years [8,9]. Five countries reported more than their target isolates, all isolates reported were included in the present report. Isolates from five (21.7%) countries were tested centrally at ÖUH, Sweden with the remaining 18 (78.3%) countries performing antimicrobial susceptibility testing in their own laboratories. All 23 Euro-GASP member laboratories were invited to participate in the 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 [8,9]. 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 2022 as a 'snapshot' study year.

2.3 Data collection and analysis

The following data were collected for each isolate, where available: specimen site, gender, age, sexual orientation, previous gonorrhoea diagnosis, HIV status, country of birth, probable country of infection, and treatment used. All antimicrobial susceptibility and epidemiological data were uploaded to TESSy by countries 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 nine epidemiological fields.

2.4 Statistical analysis

Statistical analysis was performed using Stata v17.0. The Z-test was used to determine the difference between epidemiological and AMR data collected in 2022 versus 2020, 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 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 2022, data from a total of 4 396 isolates from 23 countries were available for analysis, which represents an increase by 1 105 isolates (33.6%) compared with 2020 and in line with pre-pandemic isolate numbers (2019; n=4 166). A decrease was seen in 2020 (n=3 291 and 2021; n=3 541) partially due to the decreased number of countries participating and the impact of the COVID-19 pandemic. The number of isolates tested from each country in 2022 varied from eight (Estonia) to 827 (Norway) (Tables 1 and 3).

3.1 Epidemiological data

Overall, the total reporting completeness of all epidemiological data was 53.3%, compared to 56.0% in 2020, 56.4% in 2019, and 62.1% in 2018. In 2022, the completeness of reported data was declining, with highest completeness for gender (99.6%) and for age (99.5%) and lowest for previous gonorrhoea diagnosis (19.8%). There were significant increases in completeness for site of infection (95.5%, p<0.01), treatment used (26.7%, p<0.01) and previous gonorrhoea diagnosis (19.8%, p<0.05), while significant decreases in completeness for mode of transmission (44.0%, p<0.01), country of birth (37.6%, p<0.01) and probable country of infection (24.7%, p<0.01). No significant changes were observed in the remaining variables. Further details on reporting completeness for the 2022 data can be found in Annex 1.

As in previous years, the majority of gonococci (80.9%) were found in men. However there has been a significant decrease in proportion of specimens from males (86.1% in 2021 and 84.4% in 2020) and a significant increase in the proportion of specimens from females: 19.1% in 2022 compared to 13.9% in 2021 and 15.6% (p<0.01) in 2020 (Table 1). Information on gender and sexual orientation was available for 56.0% (n=2 461) of cases. The proportion of heterosexual males was significantly lower in 2022 (20.0%) compared to both 2021 (25.0%) and 2020 (25.1%) (p<0.01) and the proportion of MSM was significantly lower in 2022 (46.0%) compared to 2021 (51.5%) (p<0.01), while there was an increase in the proportion of females (34.0%) compared to both 2021 (23.5%) and 2020 (28.1%) (p<0.01).

The cases were also significantly younger: the proportion aged <25 years increased: 28.4% in 2022 compared to 23.2% in 2021 (p<0.01) and 25.8% in 2020 (p<0.05). The main anatomical site of specimen collection was similar to previous years, predominantly genital samples (69.0%), although there was a significant increase in the proportion of pharyngeal specimens (12.0%) compared to 2021 (9.2%) and 2020 (6.0%) (p<0.01).

Information on previous diagnosis of gonorrhoea was available for 19.8% of cases (n=871), of which 27.8% had had a previous infection, which was comparable to the level observed in 2020 (23.6%) and 2021 (24.0%). Of 1 434 cases (32.6%) with known HIV status, 126 (8.8%) were HIV-positive. Of HIV-positive cases with known transmission route (n=101), 96.0% were MSM. The probable country of infection was available for 1 087 (24.7%) cases from 15 different countries; overall, only 6.6% of these cases (n=72) were likely acquired in a country outside of the reporting country.

Table 1. **Patient characteristics reported for Euro-GASP gonococcal isolates, 2013–2022**

	2013 N (%)	2014 N (%)	2015 N (%)	2016 N (%)	2017 N (%)	2018 N (%)	2019 N (%)	2020 N (%)	2021 N (%)	2022 N (%)
Total number of isolates	1 994	2 151	2 134	2 660	3 248	3 299	4 166	3 291	3 541	4 396
Sex										
Male	1 676 (84.7)	1 821 (85.1)	1 736 (81.8)	2 256 (85.1)[a]	2 737 (84.5)	2 795 (85.3)	3 389 (83.0)	2 762 (84.4)	3 023 (86.1)	3 534 (80.9)
Female	302 (15.3)	318 (14.9)	385 (18.2)	395 (14.9)	502 (15.5)	483 (14.7)	695 (17.0)	509 (15.6)	488 (13.9)	837 (19.1)
Unknown	16	11	13	9	9	21	82	20	30	25
Age (years)										
<25	554 (28.4)	605 (28.7)	617 (29.5)	720 (27.5)	898 (28.2)	925 (28.4)	1 133 (28.4)	844 (25.8)	814 (23.2)	1 244 (28.4)
≥25	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)	2 428 (74.2)	2 690 (76.8)	3 130 (71.6)
Unknown	41	44	41	38	67	42	180	19	37	22
Route of transmission & sex										
Females	302 (25.7)	318 (22.7)	385 (26.4)	395 (22.9)	502 (22.6)	483 (21.3)	695 (29.5)	509 (28.1)	488 (23.5)	837 (34.0)
Heterosexual males	376 (32)	485 (34.7)	419 (28.7)	632 (36.7)	663 (29.9)	595 (26.3)	588 (24.9)	455 (25.1)	519 (25.0)	491 (20.0)
Men who have sex with men	496 (42.3)	594 (42.5)	657 (45.0)	696 (40.4)[a]	1 055 (47.5)[b]	1 186 (52.4)	1 074 (45.6)	847 (46.8)[c]	1 069 (51.5)	1 133 (46.0)
Unknown	820	754	673	937	1028	1035	1809	1480	1465	1935
Site of infection										
Genital	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)	2 175 (71.6)	2 296 (69.9)	2 894 (69.0)
Pharyngeal	122 (6.3)	154 (7.6)	180 (8.7)	165 (6.4)	254 (8.5)	259 (8.5)	368 (9.7)	182 (6.0)	304 (9.2)	503 (12.0)
Anorectal	255 (13.2)	192 (9.5)	280 (13.5)	366 (14.2)	435 (14.6)	570 (18.6)	743 (19.6)	608 (20.0)	642 (19.5)	747 (17.8)
Other	30 (1.5)	135 (6.6)	103 (5.0)	100 (3.9)	120 (4)	77 (2.5)	97 (2.6)[d]	72 (2.4)[e]	45 (1.4)[f]	52 (1.2)[g]
Unknown	56	121	54	86	273	238	380	254	254	200
Previous gonorrhoea										
Yes	142 (17.8)	163 (19.7)	157 (17.5)	171 (17.2)	235 (21.8)	264 (26.9)	251 (24.7)	140 (23.6)	176 (24.0)	242 (27.8)
No	654 (82.2)	663 (80.3)	739 (82.5)	824 (82.8)	845 (78.2)	718 (73.1)	767 (75.3)	452 (76.4)	558 (76.0)	629 (72.2)
Unknown	1 198	1 325	1 238	1 665	2 168	2 317	3 148	2 699	2 807	3 525
HIV status										
Positive	144 (17.6)	172 (19.3)	132 (15.3)	156 (15.9)	188 (15.4)	224 (15.7)	179 (14.1)	124 (12.3)	133 (10.8)	126 (8.8)
Negative	675 (82.4)	720 (80.7)	733 (84.7)	823 (84.1)	1 029 (84.6)	1 204 (84.3)	1 088 (85.9)	887 (87.7)	1 099 (89.2)	1 308 (91.2)
Unknown	1 175	1 259	1 269	1 681	2 031	1 871	2 899	2 280	2 309	2 962
Probable country of infection										
Same as reporting country	764 (94.1)	552 (94.0)	800 (92.2)	614 (87.0)	795 (88.6)	1 155 (87.6)	1 167 (89.8)	1 089 (94.7)	1 169 (94.0)	1 015 (93.4)
Different from reporting country	48 (5.9)	35 (6.0)	68 (7.8)	92 (13.0)	102 (11.4)	163 (12.4)	133 (10.2)	61 (5.3)	75 (6.0)	72 (6.6)
Unknown	1 182	1 564	1 266	1 954	2 351	1 981	2 866	2 141	2 297	3 309

Percentages calculated from known values. Cells shaded in blue indicate a significant difference compared to 2021 ($p<0.05$).
a Includes one individual with mode of transmission reported as MSM, but with gender reported as unknown.
b Includes two individuals with mode of transmission reported as MSM, but with gender reported as unknown.
c Includes one individual with mode of transmission reported as MSM, but with gender reported as other.
d Includes three eye, one blood and four joint fluid samples – included in other site for analysis due to low numbers.
e Includes eight eye and three joint fluid samples.
f Includes eight eye, one blood and four joint fluid samples.
g Includes 25 eye, four blood and four joint fluid samples.

The age of the patients ranged from <1 year to 75 years, with a median of 30 years. Males (median age 31 years) were significantly older than females (median age 24 years) (Mann-Whitney p<0.01) (Table 2).

Table 2. Patient age distribution by route of transmission and sex, 2022#

Variable	N†	Age (years)		<25 years N (%)
		Range	Median	
All patients	4 374	0-75	30	1 244 (28.4)
Female	836	0-73	24	435 (52.0)
Male*	3 522	0-75	31	808 (22.9)
Heterosexual males	488	15-73	30	139 (28.5)
Men who have sex with men	1 131	16-74	31	193 (17.1)

 # Cases with missing information on sex or age are not included in this table.
† Where information was available.
** Including all males, irrespective of sexual orientation.*

3.2 Antimicrobial susceptibility and resistance

Resistance to cefixime, ciprofloxacin and azithromycin (using clinical 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, 2013–2022

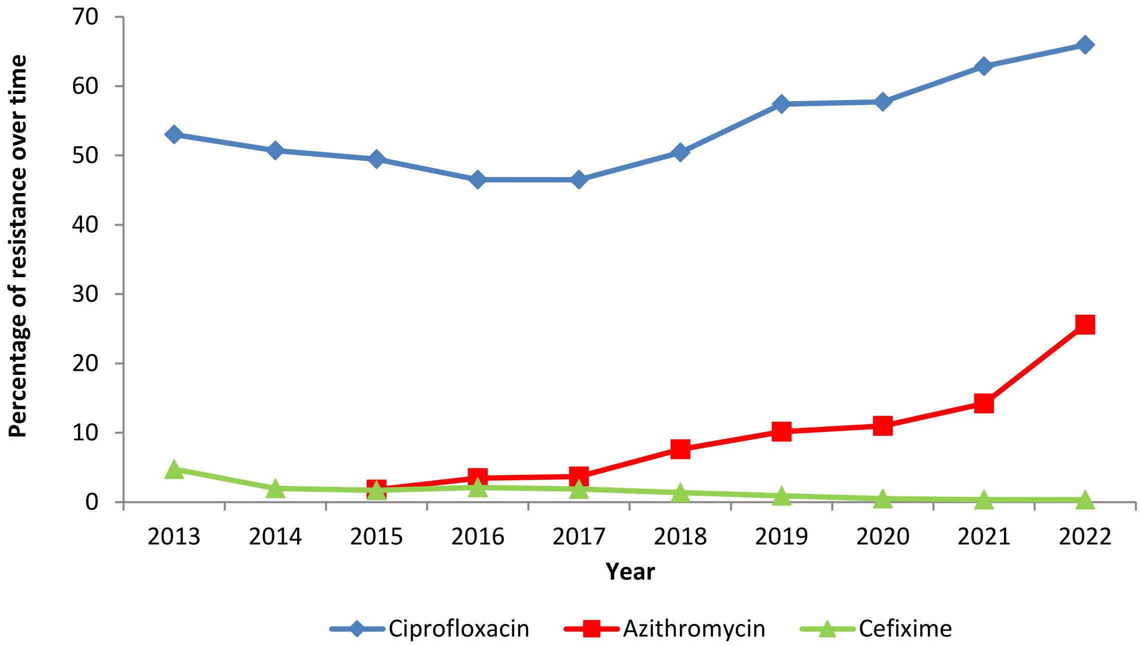


Table 3. Resistance to cefixime, ciprofloxacin and azithromycin (using resistance breakpoints from EUCAST for cefixime and ciprofloxacin and ECOFF for azithromycin) by country, Euro-GASP, 2022

Country	Number of isolates 2022	Number of isolates 2009-2022	Cefixime resistance			Azithromycin resistance			Ciprofloxacin resistance			Method of testing
			No.	%	% 2013-2022	No.	%	% 2015-2022	No.	%	% 2013-2022	
Austria	377		3	0.8		105	27.9		290	76.9		Decentralised – MGS
Belgium	200		1	0.5		86	43.0		113	56.5		Decentralised – MGS/MIC
Bulgaria	12		0	0		2	16.7		4	33.3		Centralised – MGS
Czech Republic	111		0	0		24	21.6		66	59.5		Centralised – MGS
Denmark	135		0	0		3	2.2		44	32.6		Decentralised – MGS
Estonia	8		0	0		1	16.7		6	75.0		Decentralised – MGS
Finland	91		0	0		12	13.2		48	52.7		Decentralised – MIC
France	220		0	0		27	12.3		149	67.7		Decentralised – MGS
Germany	200		1	0.5		49	24.5		128	64.0		Decentralised – MGS
Greece	100		0	0		25	25.0		66	66.0		Decentralised – MGS
Hungary	122		2	1.6		18	14.8		94	77.0		Centralised – MGS
Iceland	63		1	1.6		22	34.9		36	57.1		Decentralised – MGS/MIC
Ireland	294		1	0.3		138	46.9		175	59.5		Decentralised – MGS
Italy	100		0	0		22	22.0		84	84.0		Decentralised – MGS
Malta	61		0	0		8	13.1		52	85.2		Decentralised – MGS
Netherlands	572		0	0		201	35.1		364	63.6		Decentralised – MGS
Norway	827		2	0.2		174	21.0		495	59.9		Decentralised – MGS
Poland	15		0	0		6	40.0		10	66.7		Centralised – MGS
Portugal	110		0	0		65	59.1		75	68.2		Decentralised – MGS
Slovakia	80		0	0		13	16.3		58	72.5		Centralised – MGS
Slovenia	285		0	0		32	11.2		249	87.4		Decentralised – MGS
Spain	213		0	0		6	2.8		161	75.6		Decentralised – MGS
Sweden	200		4	2.0		86	43.0		132	66.0		Decentralised – MGS
Total:	4396											
Cefixime	4396		15	0.3								
Azithromycin	4394					1125	25.6					
Ciprofloxacin	4396								2899	65.9		
95% CI				0.2-0.6			24.3-26.9			64.5-67.3		

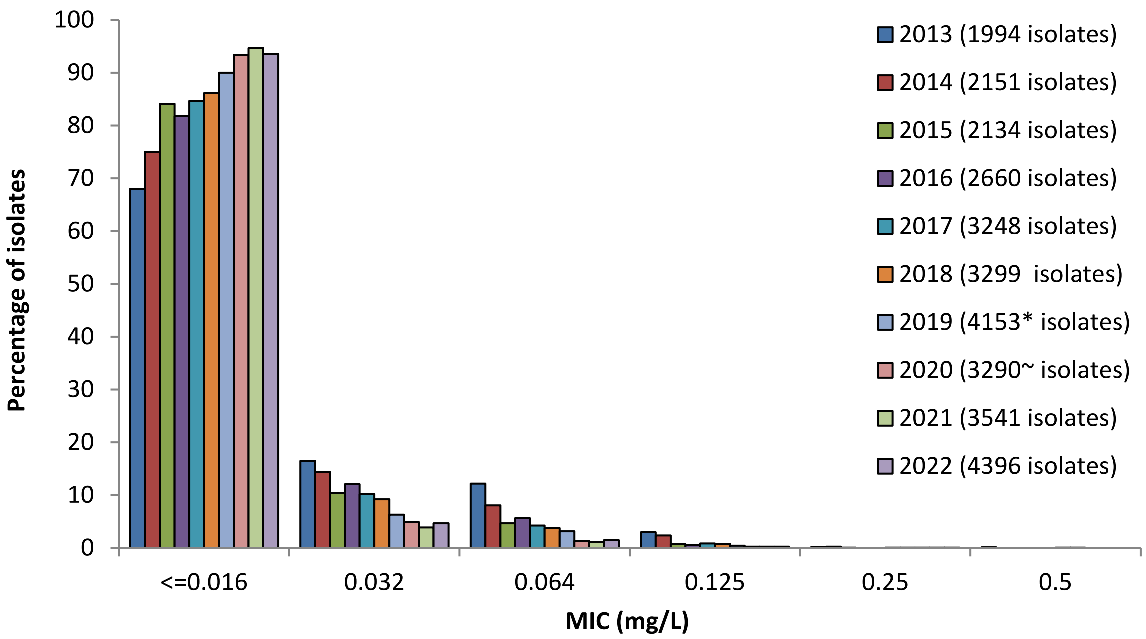
MGS: MIC gradient strip test; MIC: MIC by agar dilution. Proportion with azithromycin MICs above ECOFF displayed from 2015 to 2022 due to earlier use of breakpoint plates.

3.2.1 Ceftriaxone

Two isolates displayed ceftriaxone resistance in 2022 in comparison with one isolate each in 2021 and 2020, three isolates each in 2019, and 2018 and zero in both 2017 and 2016 (Figure 2). The ceftriaxone resistant isolates (both with MIC=0.25 mg/L) were detected in Austria and Germany, respectively. The isolate from Austria was a genital isolate from a heterosexual male patient displaying cefixime MIC=1 mg/L, azithromycin MIC>256 mg/L and ciprofloxacin MIC=8 mg/L, with infection likely in Cambodia and a possible treatment failure with ceftriaxone plus azithromycin dual therapy [16]. The isolate from Germany displayed cefixime MIC=1 mg/L, azithromycin MIC=0.032 mg/L and ciprofloxacin MIC=4 mg/L but was otherwise missing epidemiological data.

The MIC distribution for ceftriaxone has been stable over the past three years. However, the increase in the proportion of highly susceptible isolates (MIC≤0.016 mg/L) seen from 2013 and onwards has in 2022 ceased and a small decrease was seen relative to 2021. The decrease in the proportion of isolates with an MIC of 0.032 mg/L and 0.064 mg/L seen up to 2019 ceased to a stable level from 2020 and onwards. In addition, the proportion of samples with MICs just below the breakpoint (MIC of 0.125 mg/L) has remained consistent since 2019.

Figure 2. **Distribution of MIC for ceftriaxone in Euro-GASP, 2013–2022**

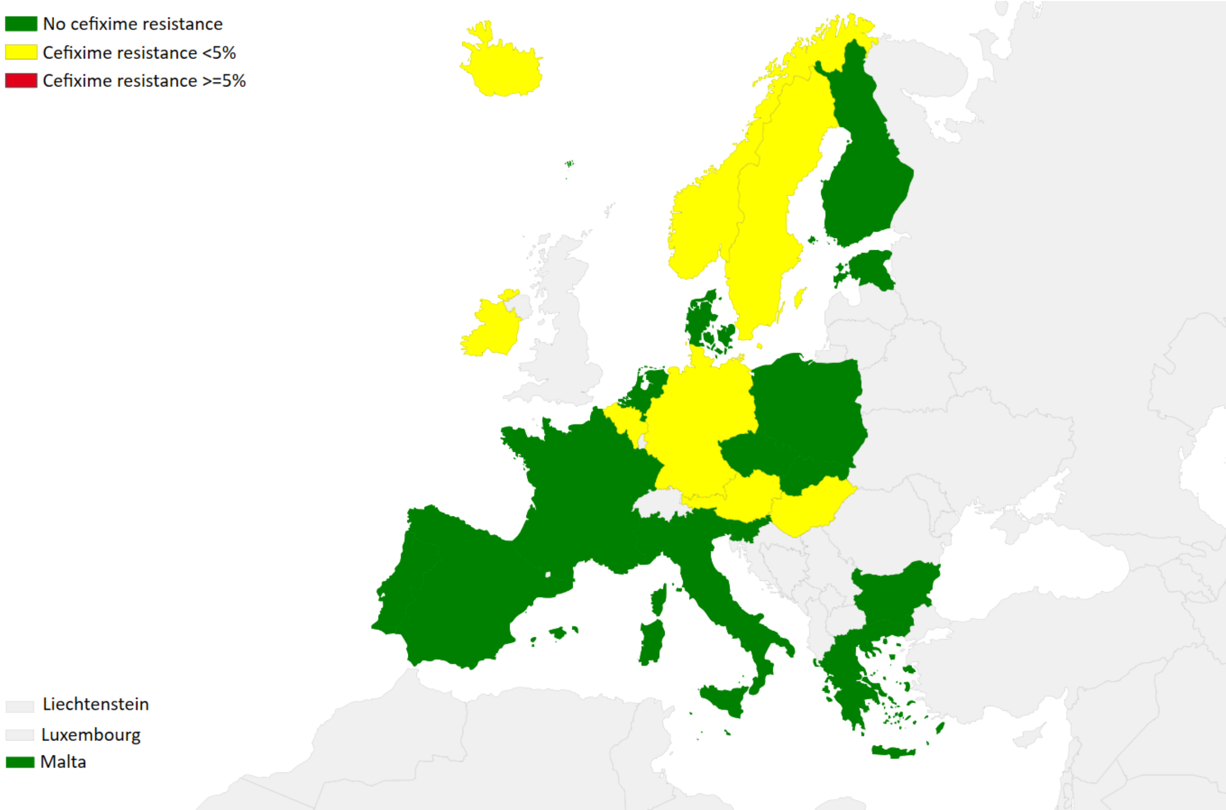


*Note: * 4 166 isolates were tested in 2019; 13 isolates were reported with an MIC of ≤0.125 mg/L and these were excluded from the MIC distribution analysis as they did not have an exact MIC reported.*
~ 3 291 isolates were tested in 2020; one had an MIC ≤0.032 mg/L and was excluded from the MIC distribution analysis as it did not fit into one discrete MIC category.

3.2.2 Cefixime

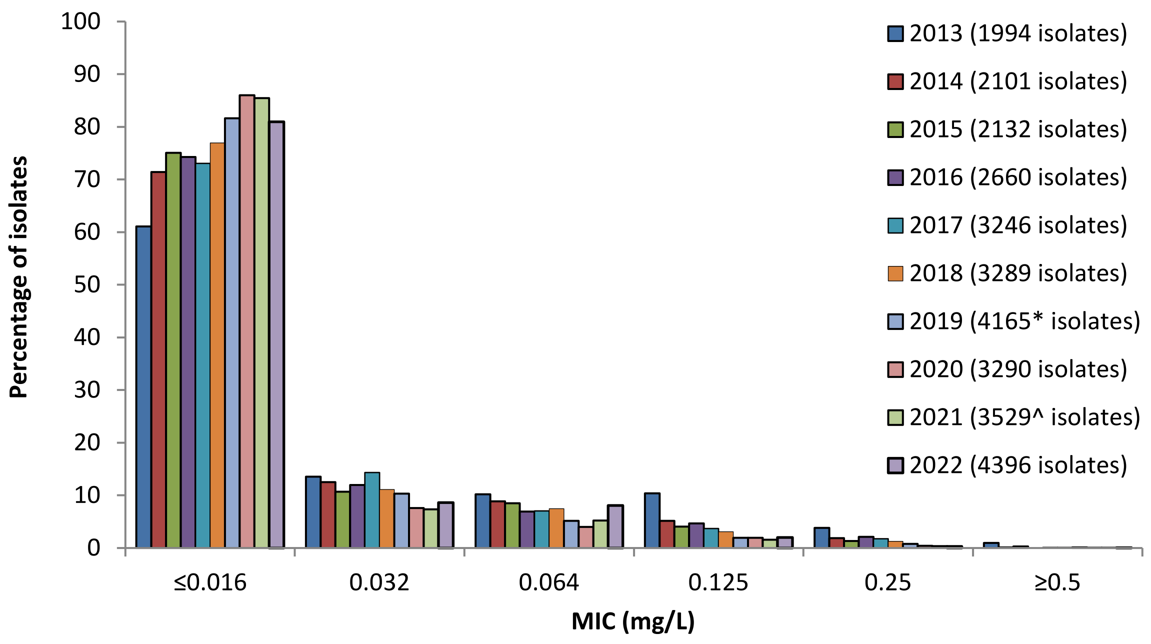
A total of 15 isolates (0.3%) from eight countries were cefixime-resistant in 2022; this level of resistance has been consistent since 2020 (Figures 1 and 3, Table 3). Within the susceptible population, there has been a significant decrease in the proportion of isolates with a cefixime MIC ≤0.016 mg/L after the peak in 2020 (86.0% in 2020, 85.4% in 2021, and 81.0% in 2022, p<0.01). In addition, significant increases in isolates with MICs in the 0.032-0.064 mg/L range were seen, increase in isolates with MIC of 0.032 mg/L in 2022 (8.6%) compared to 2021 (7.3%) (p=0.05), increase in isolates with MIC of 0.064 mg/L in 2022 (8.1%) compared to both 2021 (5.2%) and 2020 (4.0%) (p<0.01) (Figure 3). Percentages of cefixime-resistant isolates in 2022 by country are visualised in Map 1.

Map 1. Proportion of gonococcal isolates with cefixime resistance by country, EU/EEA, 2022*



** Bulgaria, Estonia and Poland reported less than 20 cases in 2022.*

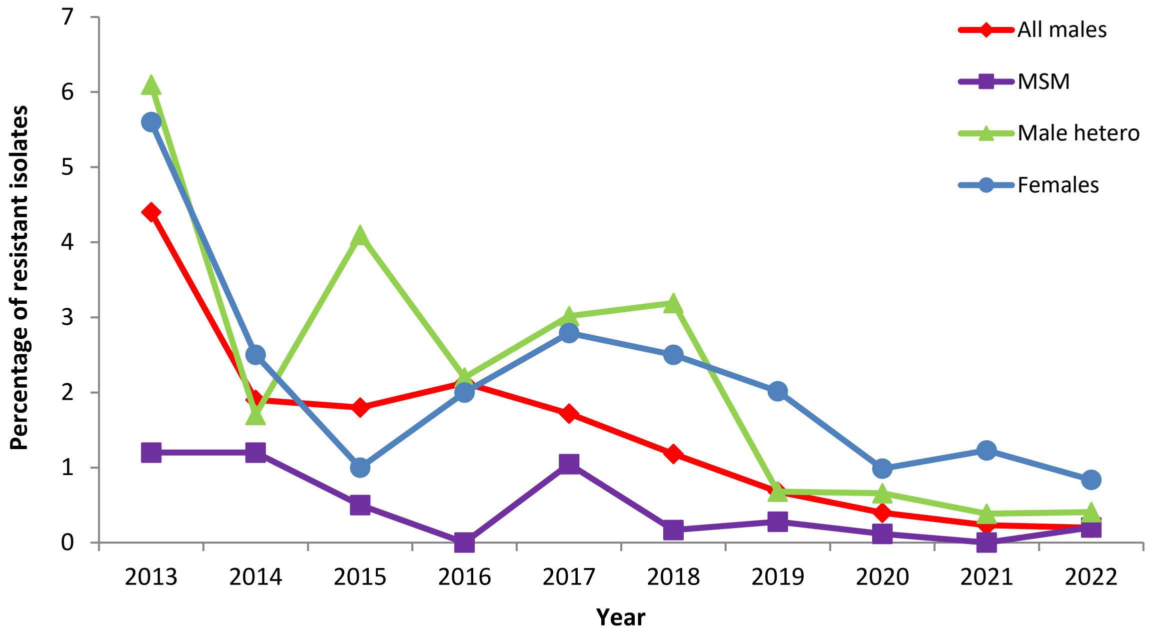
Figure 3. Distribution of MIC for cefixime in Euro-GASP, 2013–2022



** 4 166 isolates were tested in 2019; one isolate had an MIC ≤0.125 MIC and was excluded from the MIC distribution analysis as it did not fit into one discrete MIC category.*
^ 3 531 isolates were tested in 2021; two isolates had an MIC ≤0.023 MIC and were excluded from the MIC distribution analysis as they did not fit into one discrete MIC category.

Cefixime resistance in isolates from both male and female patients was stable (no significant differences) in 2022 compared to both 2021 and 2020 (Figure 4). As in previous years, cefixime resistance was significantly higher in isolates from females compared to heterosexual males and MSM (p=0.05, Fisher's exact test). There were no other significant associations identified in 2022 (Annex 2).

Figure 4. Percentage of isolates with cefixime resistance by gender and male sexual orientation, Euro-GASP, 2013–2022



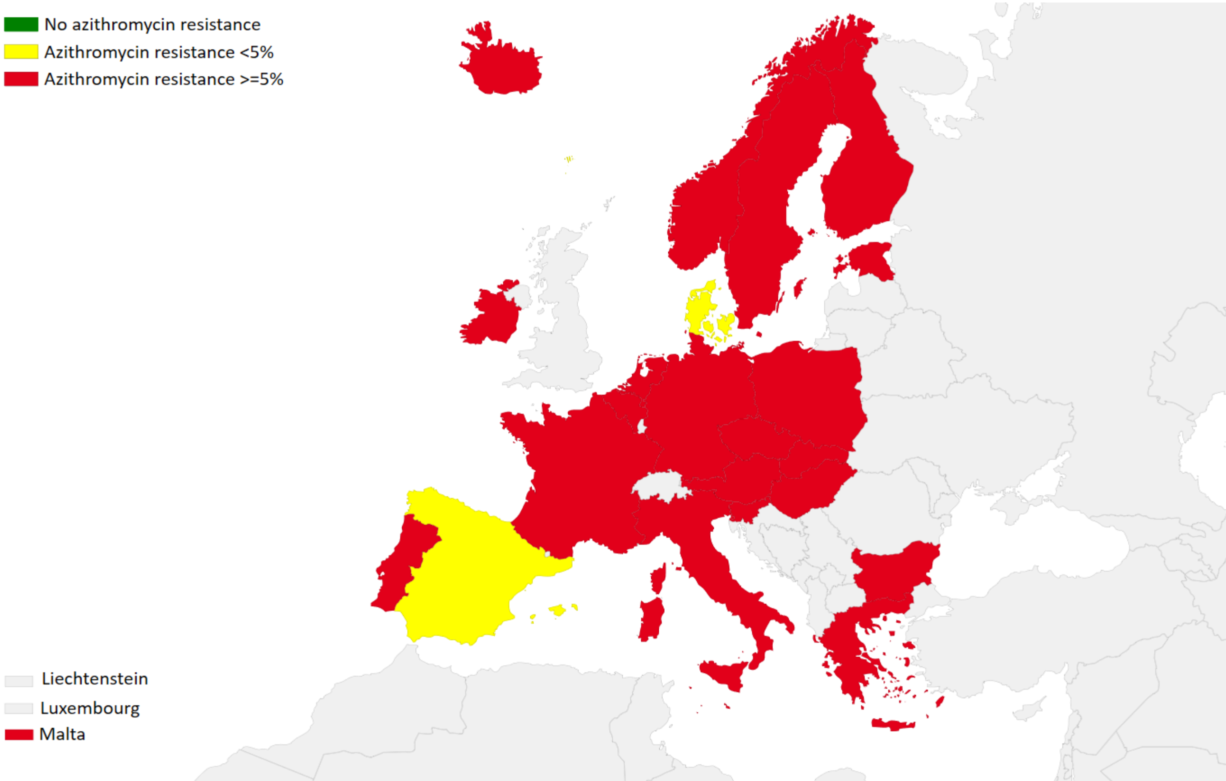
3.2.3 Azithromycin

A total of 1125 isolates (25.6%) had an MIC above ECOFF (>1 mg/L) for azithromycin in 2022, which is a significant increase compared to 2021 (504 isolates, 14.2%) and 2020 (362 isolates, 11.0%), p<0.01 (Figure 1; Table 3). Isolates with an azithromycin MIC above the ECOFF were collected in all 23 countries, 13 isolates displayed 'high-level azithromycin resistance' with MICs of ≥256 mg/L compared to 19 in 2021, 15 in 2020, 15 in 2019, five in 2018, eight in 2017 and seven in 2016. These 13 isolates comprised four isolates from Norway, three from Sweden, three from Austria, two from Finland, and one from Greece. During the collection period in each year, Norway has identified at least one 'high-level azithromycin resistant' isolate in each consecutive year for the last four years (2019 to 2022). Of the 13 high-level azithromycin-resistant isolates, one was also resistant to ceftriaxone (MIC=0.25 mg/L), cefixime (MIC=1 mg/L) and ciprofloxacin [16].

The MIC distribution for azithromycin has shown the same pattern since 2020 with a significant decrease in the proportion of isolates with an MIC of 0.064 mg/L (2022, 5.2%, 2021, 7.6% (p>0.01), 2020, 8.4% (p<0.01)), MIC of 0.125 mg/L (2022, 12.3%, 2021, 18.4% (p>0.01), 2020, 23.4% (p<0.01)) and MIC of 0.25 mg/L (2022, 20.0%, 2021, 23.0% (p>0.01), 2020, 26.8% (p<0.01)). An increase has been seen in the proportion of isolates with MIC of 0.5 mg/L compared to both 2021 and 2020 (p<0.01) and for isolates with MIC of 1 mg/L there has been a significant decrease compared to 2021 (p<0.05) but a significant increase compared to 2020 (p<0.01). Isolates with MICs of both 2 and 4 mg/L have significantly increased compared to both 2021 and 2020 (p<0.01) together with an increase of isolates with MICs of 8 and 16 mg/L in 2022 (p<0.05). Seventy-eight percent of isolates above the ECOFF had an MIC of 2 mg/L and 13.8% an MIC of 4 mg/L. The modal MICs were 2 mg/L in 2022 followed by the modal MIC from previous years 0.25 mg/L (Figure 5).

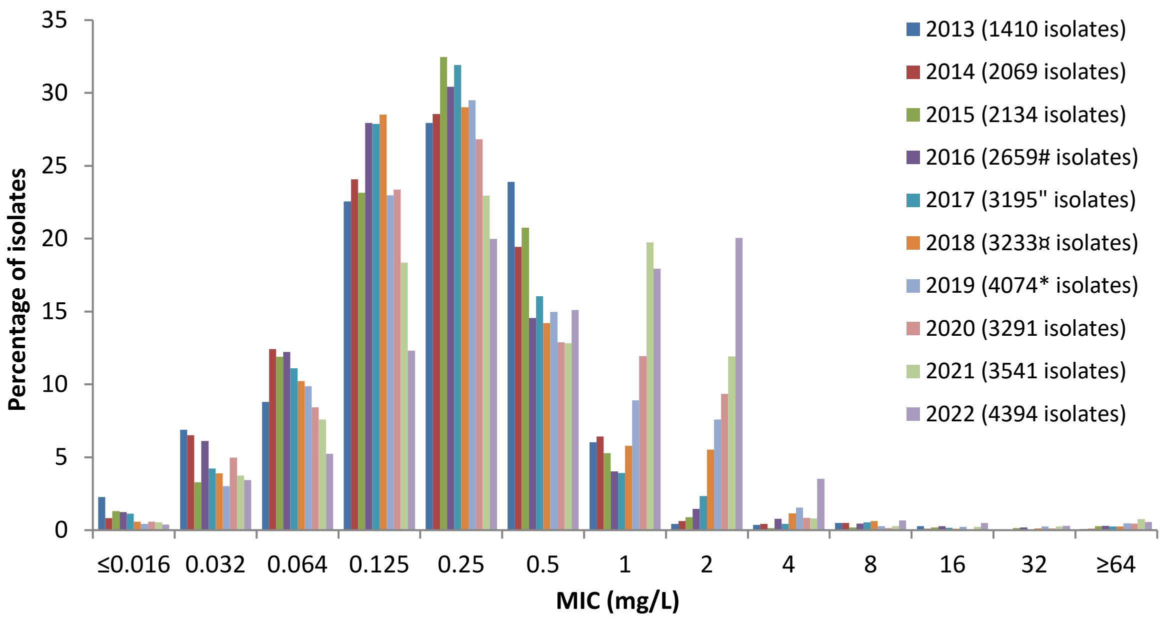
In 2022, as in previous years since 2019, isolates with an azithromycin MIC above the azithromycin ECOFF (>1 mg/L) were highest in males (28.6%). Significant increases were seen in both males and females irrespective of sexual orientation, males (28.6% in 2022, 15.0% in 2021 and 11.6% in 2020, p<0.01), females (20.4% in 2022, 9.0% in 2021 and 8.1% in 2020, p<0.01), MSM (37.2% in 2022, 17.5% in 2021 and 15.0% in 2020 p<0.01) and male heterosexuals (13.6% in 2022, 9.4% in 2021 (p<0.05) and 6.2% in 2020, p<0.01) (Figure 6). Following multivariant analysis, azithromycin MICs above the ECOFF (>1 mg/L) only remained significantly associated with isolates from MSM patients (OR 2.23, CI 1.38-3.59, p<0.01) compared to male heterosexuals.

Map 2. Proportion of gonococcal isolates with azithromycin MICs above ECOFF (>1 mg/L) by country, EU/EEA, 2022*



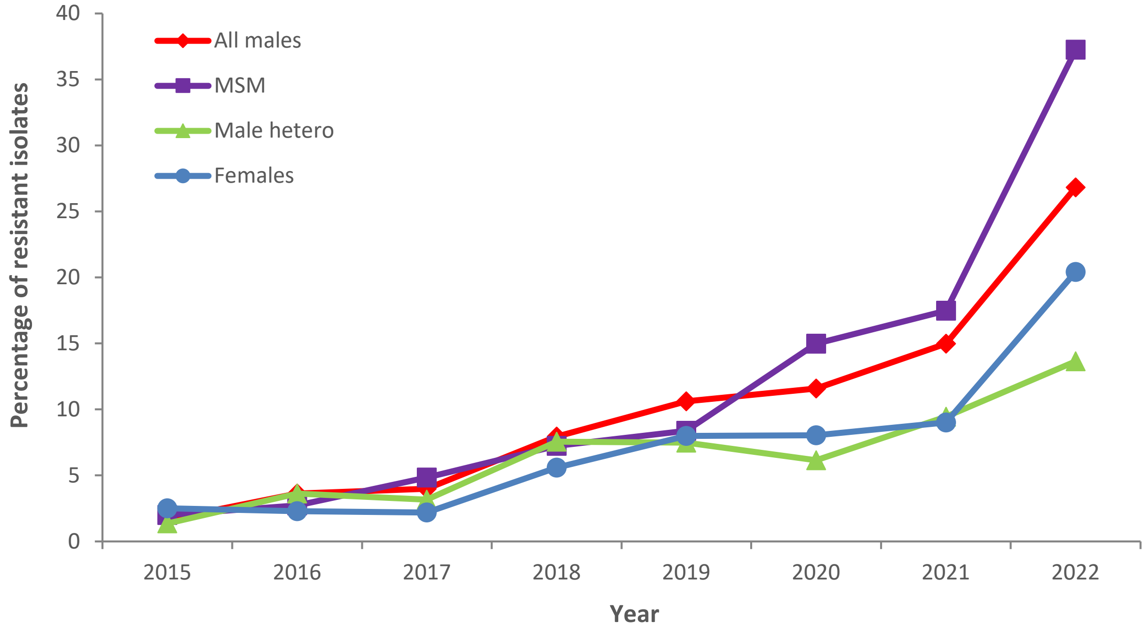
** Bulgaria, Estonia and Poland reported less than 20 cases in 2022.*

Figure 5. Distribution of MIC for azithromycin in Euro-GASP, 2013–2022



 # 2 811 isolates were susceptibility tested with azithromycin in 2016; 24 isolates had an MIC≤0.032 mg/L.
" 3 250 isolates were susceptibility tested with azithromycin in 2017; 52 isolates had an MIC≤0.06 mg/L.
¤ 3 301 isolates were susceptibility tested with azithromycin in 2018; 66 isolates had an MIC≤0.06 mg/L.
~ 4 151 isolates were susceptibility tested with azithromycin in 2019; one isolate had an MIC>32 mg/L, and 77 isolates had an MIC≤0.06 mg/L.
All above mentioned isolates were excluded from the MIC distribution analysis as they did not fit into one discrete MIC category.

Figure 6. Percentage of isolates with azithromycin MICs above ECOFF (>1 mg/L) by gender and male sexual orientation, Euro-GASP, 2015–2022



3.2.4 Ciprofloxacin

Briefly, ciprofloxacin resistance levels have steadily increased during the last years. In 2022 65.9% of the isolates were resistant (MIC>0.064) compared to 62.8% in 2021, 57.7% in 2020, 57.3% in 2019 and 50.4% in 2018 ($p<0.01$) (Figure 1).

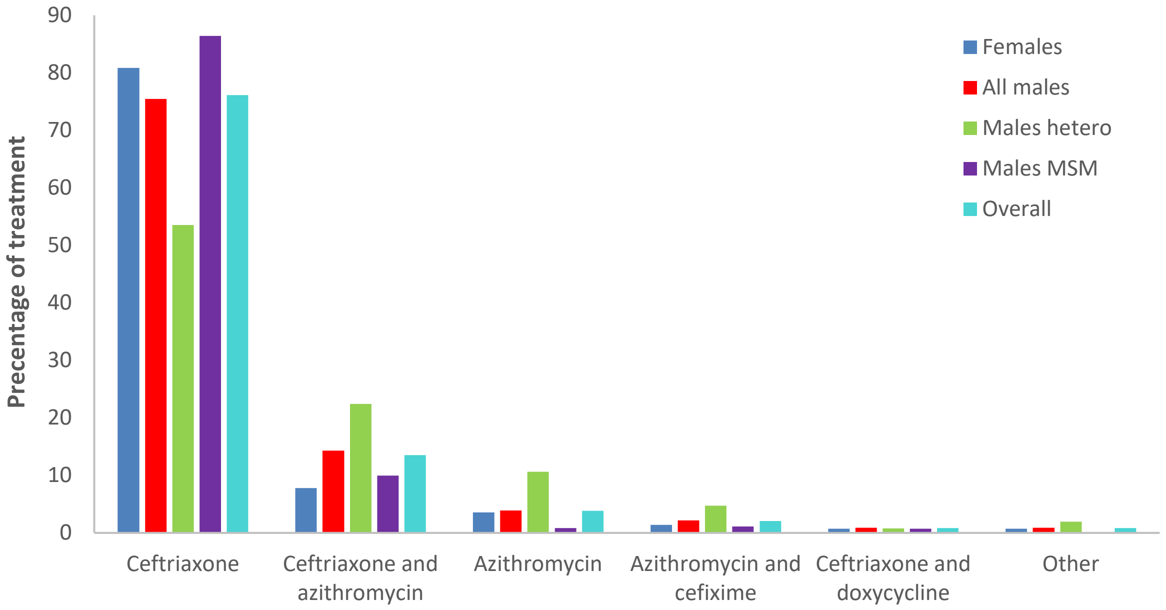
3.2.5 Spectinomycin and gentamicin

No resistance to spectinomycin (MIC>64 mg/L) was detected in 2022 (n=3111) or in any previous year of Euro-GASP. As yet, there are no breakpoints for gentamicin, but overall the MICs of gentamicin (n=2173) continue to be low in Euro-GASP (MIC50 and MIC90 4 mg/L and 8 mg/L respectively), consistent with the MIC50 and MIC90 observed when last tested (in 2019). In addition, the MIC range in 2022 was similar to when last tested (2019): 0.25-32 mg/L in 2022, 0.25-16 mg/L in 2019.

3.3 Treatments used

Data on treatment used were recorded for 1175 (26.7%) cases, of which 1167 (26.5%) also had reported gender and sexual orientation. Data regarding concurrent STI, which might have been treated at the same visit are missing. The treatment data for the most common treatments or combination of treatments in the 1 167 patients are summarised in Figure 7. As in previous years, the most commonly reported treatment for patients was ceftriaxone monotherapy (76.1% in 2022, 66.4% in 2021 70.1% in 2020, 74.0% in 2019, 52% in 2018) followed by ceftriaxone and azithromycin dual therapy (13.5%) although this was at a lower level than observed in 2021 (18.8%) but higher than in 2020 (10.4%) and 2019 (7.9%). The third and fourth most common treatments were azithromycin monotherapy (3.9%) and azithromycin together with cefixime (2.1%). Nineteen different combinations of antimicrobials and dose regimens were reported in 2022 from 12 different countries. Data on the completeness of reporting for treatment type are presented by country in Table A1 (Annex 1).

Figure 7. Percentage of known treatments used for patients by gender and transmission type for the most frequently used therapies, 2022



Nineteen different combinations of antimicrobials and dose regimens were recorded in 2022 (grouped for analysis). Differences in concentration of antimicrobials prescribed have been grouped for analysis in Figure 7.

4 Conclusions

Trends in susceptibility for the antimicrobials tested in Euro-GASP were similar to recent years [8,9,13–15]. Encouragingly, ceftriaxone susceptibility continued to be high in 2022, although it is of concern that two isolates (0.05%), from Austria and Germany, respectively, displayed ceftriaxone resistance in 2022. In 2021 and 2020, there was one ceftriaxone resistant isolate (0.03%) from Spain and another from Belgium, compared to three isolates each in 2019 and 2018 (0.1%) and none in 2017 and 2016. The isolates identified in 2022 were either multi-drug (MDR) or extensively-drug resistant (XDR), as they also displayed resistance to cefixime, ciprofloxacin and one of the two also 'high-level azithromycin resistance'.

A continuing decreasing or possible stabilising trend in levels of cefixime resistance within Euro-GASP was observed in 2022, 0.3% compared to 0.3% in 2021, 0.5% in 2020, 0.9% in 2019, 1.4% in 2018 compared to the previously stable level of 1.7 to 2.1% in 2014 to 2017. Cefixime-resistant isolates were detected in eight (34.8%) of the 23 countries reporting in 2022, which is comparable to 9/24 (37.5%) counties reporting resistant isolates in 2021, 6/23 (26.1%) countries in 2020, but a substantial decrease from the 14/26 (53.8%) counties reporting resistant isolates in 2019. Cefixime resistance continued to be lowest among males (0.2%) and especially in MSM (0.2%), and highest among females (0.8%).

Although the continuing low levels of cephalosporin resistance is promising, the detection of two ceftriaxone-resistant isolates is concerning, as ceftriaxone is the last remaining option for empiric first-line monotherapy. Among patients for whom treatment was reported, 76.1% were administered ceftriaxone alone and 14.4% were administered ceftriaxone with a second antimicrobial (azithromycin or doxycycline). However, there are substantial limitations to the interpretation of data on the treatment used given the low completeness of this variable, i.e. only <27% of cases had treatment reported with only 12 countries reporting on this variable, and the Netherlands contributed 48.5% of the data alone.

The most pronounced change in 2022 was the increase in the proportion of isolates above the azithromycin ECOFF (>1 mg/L), which in 2022 represented 25.6% of the reporting isolates, and these isolates were present in all participating countries. The reported use of azithromycin monotherapy remained constant compared to previous years, 3.9% in 2022, and predominantly administered to heterosexual males. It should be noted that the majority of isolates with an azithromycin MIC of >1 mg/L were just above the ECOFF (>1 mg/L), 78.3% had an MIC of 2 mg/L, but the isolates with MIC of 4 mg/L also significantly increased in 2022 (13.8%). Ciprofloxacin resistance significantly increased in 2022, to 65.9% from 62.8% in 2021 and 57.7% in 2020. Neither azithromycin nor ciprofloxacin are recommended for monotherapy, unless the isolates are first shown to be susceptible. In 2022, six patients were recorded as being treated with ciprofloxacin monotherapy whereof three harboured ciprofloxacin-resistant isolates and 45 patients with azithromycin monotherapy, of which seven carried azithromycin-resistant isolates.

Regarding XDR isolates, in 2022 there was one ceftriaxone-resistant isolate that was additionally resistant to cefixime and ciprofloxacin and displayed 'high-level azithromycin resistance' (MIC >256 mg/L), and this isolate was cultured from a genital sample from an Austrian heterosexual male patient, further described in Pleininger et al. [16]. Furthermore, one isolate with resistance to cefixime, azithromycin, and ciprofloxacin was isolated in Sweden, with Sweden as probably country of infection. The ongoing presence of XDR isolates is of concern, although it is encouraging that the numbers of XDR isolates have not increased. In addition, one MDR isolate from Germany was observed, displaying resistance to ceftriaxone, cefixime and ciprofloxacin but susceptible to azithromycin.

From 2020 and onwards, MSM have had the highest levels of resistance to azithromycin (37.2%), with significant increases observed (from 15.0% and 17.5% in 2020 and 2021, respectively, $p<0.01$). Despite the overall decrease in cefixime resistance and that MSM displays the lowest incidence of cefixime resistance, it was the only group increasing in 2022, to 0.2% compared to 0.1% in 2020 and 0% in 2021. However, it should also be taken into account that the overall completeness of the mode of transmission data was 44.0%.

The significant increase of samples from females was also notable in 2022: 19.1% of all isolates in 2022 were collected in females, compared to 13.9% in 2021 and 15.6% in 2020 ($p<0.01$). The patients were also significantly younger, with the proportion of cases under 25 years increased to 28.4% in 2022, from 23.2% in 2021 ($p<0.01$) and 25.8% in 2020 ($p<0.05$). The proportion of pharyngeal isolates among patients significantly increased in 2022: 12.0% compared to 9.2% in 2021 and 6.0% in 2020 ($p<0.01$). These results reflect the representativeness of Euro-GASP that mirrors the epidemiology of gonococcal infection in the EU/EEA and observations notified through the EpiPulse and Early Warning and Response platforms coordinated by ECDC; for further information, see Nerlander et al [17].

Given the continuously increasing incidence of gonococcal isolates with azithromycin MICs above the ECOFF and the continued detection of ceftriaxone resistance, the European response plan to control the threat of MDR and XDR N. gonorrhoeae in Europe [18], with indicators reviewed in 2020 [19,20], should continue to be implemented 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 was 53.3% in 2022 compared to 56.0% in 2020 and 56.4% in 2019. Significant improvements in reporting are urgently required for many variables if statistical analysis of the linked antimicrobial susceptibility and patient data is to be robust.
- Ensuring that appropriate capacity for culture and antimicrobial 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. A Euro-GASP STI and AMR training is planned in 2024.
- Effectively disseminate 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 the threat of MDR and XDR 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.
- Introduce 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 high-dose (1 g) with or without azithromycin in 89.6% (76.1% ceftriaxone alone; 13.5% plus azithromycin). Nevertheless, it is of major concern that some patients continue to be inappropriately treated, e.g. with azithromycin or ciprofloxacin monotherapy, in particular in those who harboured resistant strains.

The overall coverage of included countries in the Euro-GASP programme within the EU/EEA is good, however seven countries are missing (Cyprus, Croatia, Latvia, Liechtenstein, Lithuania, Luxembourg, and Romania) and three countries (Bulgaria, Estonia and Poland) submitted less than 20 isolates in 2022. The work continues to encourage countries to participate to increase the overall coverage of isolates as well as encourage countries to improve the reporting of epidemiological data is ongoing. The lack of reporting, especially some epidemiological data, limits the preciseness of some estimates when the sample size for specific sub-groups in the present report is quite low and thus those estimates are less precise.

Even though Euro-GASP detected a stable low trend in levels of cefixime resistance in 2022, the continually increasing azithromycin MICs along with the detection of two ceftriaxone-resistant isolates are of concern. Ceftriaxone treatment failures have been documented [21,22], together with sustained transmission of 'high-level azithromycin-resistant' (MIC ≥256 mg/L) strains [21] and international spread of gonococcal strains with resistance to ceftriaxone and/or azithromycin have been detected [4,16,21–28]. Therefore, continuous implementation of quality-assured antimicrobial surveillance activities and the recently updated and refined response plan, is essential. Collection of susceptibility data for tetracycline will also be included in 2023 due to the high level of relevance to monitor the impact of usages of doxycycline post exposure prophylaxis (doxy-PEP) in the EU/EEA. Euro-GASP recently published tetracycline resistance data for gonococcal isolates from 19 EU/EEA countries in 2022, which showed a high-level of tetracycline resistance [29]. Finally, the development of alternative therapy regimens is urgently needed to ensure gonorrhoea remains a treatable infection.

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Annex 1. Percentage completeness of epidemiological variables

Table A1. Completeness of epidemiological variable reporting, 2022

Country	Number of isolates	Gender	Age	Mode of transmission	Site of infection	Treatment	Previous gonorrhoea	Country of birth	Probable country of infection	HIV status	Overall Percentage response rate
Austria	377	100	100	0	93.1	0	13.8	12.2	0	0	**35.5**
Belgium	200	100	99.5	40.5	97.0	41.5	41.5	49.5	14.5	35.5	**57.7**
Cyprus	12	100	83.3	91.7	100	83.3	83.3	100	83.3	83.3	**89.8**
Czech Republic	111	100	100	75.7	79.3	79.3	55.9	0	75.7	69.4	**70.6**
Denmark	135	100	100	74.8	99.3	46.7	0.7	76.3	74.8	20.0	**65.8**
Estonia	8	100	100	25.0	100	0	100	0	0	12.5	**48.6**
Finland	91	100	100	60.4	0	0	0	97.8	42.9	0	**44.6**
France	220	100	100	19.1	100	0	0	30.0	22.7	59.5	**47.9**
Germany	200	94.0	96.0	12.0	89.5	15.5	12.5	9.5	12.5	4.5	**38.4**
Greece	100	99.0	95.0	77.0	89.0	87.0	72.0	85.0	84.0	4.0	**76.9**
Hungary	122	100	100	0	98.4	0	0	0	0	0	**33.2**
Iceland	63	100	100	52.4	100	0	0	96.8	0	0	**49.9**
Ireland	294	99.7	99.3	65.0	98.3	19.7	26.5	37.4	25.2	50.7	**58.0**
Italy	100	100	98.0	75.0	99.0	78.0	91.0	89.0	66.0	68.0	**84.9**
Malta	61	100	100	96.7	100	100	95.1	100	100	80.3	**96.9**
Netherlands	572	100	100	99.0	100	100	0	99.7	0	94.2	**77.0**
Norway	827	99.8	100	0	98.4	0	0	0	0	0	**33.1**
Poland	15	100	100	80.0	100	0	0	0	100	0	**53.3**
Portugal	110	100	100	10.9	100	0	3.6	5.5	0	0	**35.6**
Slovakia	80	100	100	52.5	100	53.8	98.8	97.5	53.8	71.3	**80.8**
Slovenia	285	100	100	37.9	100	0	87.0	56.1	0	84.9	**62.9**
Spain	213	100	99.1	77.5	100	0.5	0	0	100	0	**53.0**
Sweden	200	100	100	97.5	100	0	0	0	96.5	0	**54.9**
Average completeness	**4396**	**99.6**	**99.5**	**44.0**	**95.5**	**26.7**	**19.8**	**37.6**	**24.7**	**32.6**	**53.3**

Cell shading; green =100%, red =0%, light red =below average, white =above average but not 100%

Annex 2. Statistical tables

Table A2. Univariate association of cefixime resistance/susceptibility and patient characteristics, Euro-GASP, 2022

	Cefixime resistance N (%, 95% CI)	P value
Site of infection (n=4196)		
Genital (2894)	10 (0.46, 0.3-1.0)	0.44*
Anorectal (747)	1 (0.1, 0.0-0.8)	
Pharyngeal (503)	3 (0.6, 0.2-1.7)	
Other (52)	0 (0.0, 0.0-6.9)	
Route of transmission and sex (n=2461)		
MSM (1133)	1 (0.1, 0.0-0.5)	**0.03***
Male heterosexual (491)	2 (0.4, 0.1-1.5)	
Female (837)	7 (0.8, 0.4-1.7)	
Previous GC (n=871)		
Yes (242)	0 (0.0, 0.0-1.6)	1.00*
No (629)	1 (0.4, 0.0-0.9)	
HIV status (n=1434)		
Positive (126)	0 (0.0, 0.0-3.0)	#
Negative (1308)	0 (0.0, 0.0-0.3)	
Age (n=4374)		
<25 years (1244)	6 (0.5, 0.3-1.4)	
≥25 years (3130)	8 (0.3, 0.2-0.8)	0.23

** Expected value for at least one cell < 5, so Fisher's Exact test performed.*
 # Not possible to test as both variables are zero.

Table A3. Univariate association of azithromycin MICs above/below ECOFF (>1 mg/L) and patient characteristics, Euro-GASP, 2022

	Azithromycin resistance N (%, 95% CI)	Odds ratio	95% CI	P value
Site of infection (n=4194)				
Genital (2892)	664 (23.0, 9.7-12.3)	Reference		
Anorectal (747)	234 (31.3, 12.1-17.7)	1.53	1.28-1.83	**<0.01**
Pharyngeal (503)	164 (32.6, 5.9-14.4)	1.62	1.32-2.00	**<0.01**
Other (52)	14 (26.9, 5.7-20.4)	1.24	0.67-2.30	0.50
Route of transmission and sex (n=2 461)				
MSM (1 133)	422 (37.3, 34.5-40.1)	3.76	2.80-5.03	**<0.01**
Male heterosexual (491)	67 (13.7, 4.3-8.8)	Reference		
Female (837)	171 (20.4, 10.9-17.0)	1.62	1.19-2.21	**<0.01**
Previous GC (n=869)				
Yes (242)	66 (27.3, 22.1-33.2)	1.45	1.03-2.05	**0.03**
No (627)	129 (20.5, 17.6-23.9)	Reference		
HIV status (n=1434)				
Positive (126)	39 (31.0, 23.5-39.5)	1.21	0.82-1.80	0.34
Negative (1308)	353 (27.0, 24.7-29.5)	Reference		
Age (n=4372)				
<25 years (1 244)	294 (23.6, 21.4-26.1)	Reference		
≥25 years (3 128)	828 (26.5, 24.9-28.0)	1.16	1.00-1.36	0.05

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