

**SURVEILLANCE** REPORT



# Gonococcal antimicrobial susceptibility surveillance in Europe

Results summary

# 2018

**ECDC** TECHNICAL DOCUMENT

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## Abbreviations

|           |  |
|-----------|--|
| AMR       | Antimicrobial resistance                                       |
| BKP       | Breakpoint   |
| 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   |
| GRASP     | Gonococcal Resistance to Antimicrobials Surveillance Programme |
| HIV       | Human immunodeficiency virus                                   |
| HLAzIR    | High-level azithromycin resistance                             |
| 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  |
| PPNG      | Penicillinase-producing <i>Neisseria gonorrhoeae</i>           |
| STI       | Sexually transmitted infection                                 |
| TESSy     | The European Surveillance System at ECDC                       |
| UK        | United Kingdom   |
| WHO       | World Health Organization                                      |
| XDR       | Extensively drug resistant                                     |

## Executive summary

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

During 2018, 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: ceftriaxone, cefixime, azithromycin, and ciprofloxacin, as well as testing for  $\beta$ -lactamase production for the detection of high-level penicillin resistance. Decentralised testing took place at participating laboratories that met a defined set of quality criteria.

In 2018, 27 EU/EEA Member States participated in Euro-GASP, 19 via decentralised testing. In total, 3 299 isolates were tested, the majority of which (85.3%) were collected from male patients. The age of the patients ranged from under one year to 86 years, with a median age of 30 years. Overall, 28.0% of patients were under 25 years, and males were significantly older than females. The anatomical site of specimen collection was mainly genital (70.4%), followed by rectal (18.6%) and pharyngeal (8.5%). Among cases with information on previous diagnosis of gonorrhoea, 26.9% had previously been diagnosed with the infection. Twenty-two percent of the patients were concurrently diagnosed with *Chlamydia trachomatis* infection. Among cases with known sexual orientation and gender (68.6%), 47.6% were heterosexual men or women, and 52.4% were men who have sex with men (MSM). Among all cases, 15.7% were HIV positive, and 92.4% of those were MSM.

In 2018, three isolates with resistance to ceftriaxone (two MIC=0.25 mg/L, one MIC=0.5 mg/L) were detected, one in Germany and two in Spain. One of the three ceftriaxone-resistant isolates had an azithromycin MIC over the epidemiological cut-off (MIC=16 mg/L) with susceptibility to increased exposure of ciprofloxacin (MIC=0.064 mg/L). The other two isolates had azithromycin MICs below the ECOFF (MIC=0.5 mg/L and 0.25 mg/L), both of which were resistant to ciprofloxacin (MIC $\geq$ 32 mg/L). The 2018 Euro-GASP results revealed stable cefixime resistance (MIC>0.125 mg/L) at 1.4% compared to 2017 (1.9%), with a stable number of countries reporting any resistant isolates (n=12). There was a significant increase in the number of isolates with azithromycin MICs above 0.5 mg/L (i.e. the previously recommended EUCAST azithromycin resistance breakpoint); 7.5% of the isolates observed in 2016 and 2017 showed azithromycin MICs above 0.5 mg/L, compared to 13.3% in 2018 (p<0.0002). Since January 2019, the EUCAST clinical resistance breakpoint for azithromycin of MIC>0.5 mg/L has been replaced with an ECOFF of MIC>1 mg/L. Using also the EUCAST ECOFF, a significant increase in the proportion of isolates above this ECOFF was observed: from 3.7% in 2017 to 7.6% in 2018 (p<0.0002). In 2018, 24 countries reported isolates with azithromycin MICs >0.5mg/L, compared to 23 countries in 2017, and 21 and 18 countries in 2016 and 2015, respectively. The proportion of isolates showing ciprofloxacin resistance significantly increased from 46.5% in 2017 to 50.3% in 2018 (p<0.01).

The decreasing azithromycin susceptibility combined with the appearance of ceftriaxone resistance is a major concern and threatens the effectiveness of the currently highly effective dual-therapy regimen (ceftriaxone plus azithromycin). Even though the level of resistance to cefixime is stable, cefixime resistance needs to be monitored closely, particularly because gonococcal strains with resistance to both cefixime and ceftriaxone 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* is a serious threat to the treatment and control of gonorrhoea. The main therapeutic agents currently recommended in Europe [1], extended-spectrum cephalosporins, are the last remaining options for effective empiric first-line antimicrobial monotherapy. Susceptibility to these antimicrobials has decreased in the past [2-6], which is why the current European treatment guideline recommends combination treatment with ceftriaxone plus azithromycin as first-line in an attempt to mitigate the development and/or spread of resistance to these antimicrobials [1]. Surveillance of the susceptibility to these agents is essential in order to ensure effective patient management and monitor current and emerging trends in AMR [3].

Since 2009, the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) is coordinated by the European Centre for Disease Prevention and Control (ECDC), supported by an international network led by Public Health England (United Kingdom) and Örebro University Hospital (Sweden). Euro-GASP has identified decreasing susceptibility to extended-spectrum cephalosporins, and treatment failures have been documented [3], prompting the creation of a European response plan to control and manage the threat of multidrug-resistant *N. gonorrhoeae* in the European Union (EU)/European Economic Area (EEA) [4]. This response plan was reviewed and updated in 2019 [7].

## 1.2 Objectives

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

- 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 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 EU/EEA.
- Provide training in gonococcal culture and antimicrobial susceptibility testing to facilitate enhanced gonococcal antimicrobial susceptibility surveillance, using a standardised methodology across EU/EEA.

This report presents the results from the 2018 gonococcal antimicrobial susceptibility sentinel surveillance.

## 2 Methods

### 2.1 Participating laboratories and isolate collection

Twenty-seven participating laboratories from 27 EU/EEA countries collected *N. gonorrhoeae* isolates from consecutive patients. The official collection window was from September to November 2018, except for the United Kingdom (UK), which collected isolates between July and September 2018 to coincide with the national Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP). Twenty-four countries collected isolates outside of the collection window to attempt to reach the minimum 100 isolate target. Eight of these countries collected isolates throughout the whole year. No new countries joined Euro-GASP in 2018.

The Euro-GASP collection criteria and methodology remained the same as in previous years [8]. Eight countries reported more than their target isolate number, and all isolates reported were included in the analysis. Isolates from eight (29.6%) countries were tested centrally at Public Health England, UK, or Örebro University Hospital, Sweden, with the remaining 19 (70.4%) countries performing antimicrobial susceptibility testing in their own laboratories. Twenty-six Euro-GASP laboratories participated in an annual EQA programme [9, 10] to ensure comparability of data. The one laboratory that did not participate was tested centrally. Countries that perform decentralised testing have fulfilled established quality criteria prior to commencing their own testing. Isolates from Luxembourg were not tested centrally, even though the country it was not assessed for decentralised testing, due to low isolate numbers (one isolate in 2018).

### 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]. 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 [11]. Due to the absence of a clinical resistance breakpoint for azithromycin in the 2019 EUCAST guidelines, also the previously recommended EUCAST breakpoint of azithromycin resistance (MIC >0.5 mg/L) was used for comparison to historical data in this report.

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

### 2.3 Data collection and analysis

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

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

### 2.4 Statistical analysis

Statistical analysis was performed using Stata v15.1. The Z-test was used to determine the difference between epidemiological and AMR data collected in 2018 versus 2017, 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 2018, a total of 3 299 isolates from 27 countries were tested. This represents an increase of 51 isolates (1.6%) compared with 2017. The number of isolates tested from each country varied from one (Luxembourg) to 402 (Netherlands).

### 3.1 Epidemiological data

Overall, reporting completeness was 62.1% compared to 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: 29.8% for previous gonorrhoea; highest completeness: 99.4% for gender and 98.7% for age) [8]. Treatment and previous gonorrhoea were the only variables where reporting decreased in 2018 (significant decrease for previous gonorrhoea  $p=0.0002$ ), whereas the completeness of all other variables increased when compared to 2017 (significantly for gender  $p=0.03$ ; age  $p=0.01$ ; concurrent STI  $p<0.0002$ ; place of residence  $p<0.0002$ ; clinical service type  $p<0.0002$ ; country of birth  $p<0.0002$ ; probable country of infection  $p<0.0002$  and HIV status  $p<0.0002$ ). Further details on reporting completeness for 2018 data can be found in Annex 1.

As in previous years, the majority of gonococci (85.3%) were collected from men (Table 1). Information on sexual orientation was available for 68.6% ( $n=2264$ ) of cases. The proportion of heterosexual males was significantly lower in 2018 compared to 2017 ( $p=0.008$ ); at the same time there was an increase in the proportion of men who have sex with men (MSM) ( $p=0.001$ ). The main anatomical site of specimen collection was similar to previous years, predominantly genital samples (70.4%). There was a significant decrease, however, in the proportion of genital samples compared to 2017 (72.8%,  $p=0.04$ ); a significant increase was recorded in the proportion of anorectal samples (2017: 14.6%; 2018: 18.6%,  $p<0.002$ ). Information on previous diagnosis of gonorrhoea was available for 29.8% of cases ( $n=982$ ) of which 26.9% had had a previous infection, which was significantly more than 2017 (21.8%;  $p=0.007$ ). Information on other concurrent STIs was available for 36.8% ( $n=1215$ ) of cases; 22.2% had a concurrent chlamydia infection, 7.4% had another STI, and 70.7% had no concurrent STIs. Of 1 428 cases (43.3%) with known HIV status, 224 (15.7%) were HIV positive. Of these 224 HIV-positive cases, 92.4% were MSM. Probable country of infection was available for 1 318 (40.0%) cases from 17 different countries; overall, only 11.2% of these cases ( $n=148$ ) were likely acquired in a country outside of the reporting country.

**Table 1. Patient characteristics reported for Euro-GASP gonococcal isolates, 2009–2018**

|  | 2009        | 2010                  | 2011         | 2012                     | 2013        | 2014                  | 2015                     | 2016                     | 2017                     | 2018                     |
|--|-------------|-----------------------|--------------|--------------------------|-------------|-----------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|  | N (%)       | N (%)                 | N (%)        | N (%)                    | N (%)       | N (%)                 | N (%)                    | N (%)                    | N (%)                    | N (%)                    |
| <b>Total number of isolates</b>        | 1366        | 1766                  | 1902         | 1927                     | 1994        | 2151                  | 2134                     | 2660                     | 3248                     | 3299                     |
| <b>Gender</b>                          |             |                       |              |                          |             |                       |                          |                          |                          |                          |
| Male                                   | 1123 (83.7) | 1441 (82.4)           | 1505 (82.4)  | 1596 (83.7)              | 1676 (84.7) | 1821 (85.1)           | 1736 (81.8)              | 2256 (85.1) <sup>^</sup> | 2737 (84.5)              | 2795 (85.3)              |
| Female                                 | 219 (16.3)  | 308 (17.6)            | 321 (17.6)   | 310 (16.3)               | 302 (15.3)  | 318 (14.9)            | 385 (18.2)               | 395 (14.9)               | 502 (15.5)               | 483 (14.7)               |
| Unknown                                | 24          | 17                    | 76           | 21                       | 16          | 11                    | 13                       | 9                        | 9                        | 21                       |
| <b>Age (years)</b>                     |             |                       |              |                          |             |                       |                          |                          |                          |                          |
| <25                                    | 422 (32.0)  | 599 (34.4)            | 572 (31.9)   | 617 (32.9)               | 554 (28.4)  | 605 (28.7)            | 617 (29.5)               | 720 (27.5)               | 898 (28.2)               | 925 (28.4)               |
| ≥25                                    | 898 (68.0)  | 1141 (65.6)           | 1221 (68.10) | 1261 (67.1)              | 1399 (71.6) | 1501 (71.3)           | 1476 (70.5)              | 1902 (72.5)              | 2283 (71.8)              | 2332 (71.6)              |
| Unknown                                | 46          | 26                    | 109          | 49                       | 41          | 44                    | 41                       | 38                       | 67                       | 42                       |
| <b>Sexual orientation &amp; gender</b> |             |                       |              |                          |             |                       |                          |                          |                          |                          |
| Females                                | 219 (27.9)  | 308 (27.3)            | 321 (27.1)   | 310 (28)                 | 302 (25.7)  | 318 (22.7)            | 385 (26.4)               | 395 (22.9)               | 502 (22.6)               | 483 (21.3)               |
| Heterosexual males                     | 314 (40.1)  | 426 (37.7)            | 423 (35.6)   | 390 (35.2)               | 376 (32)    | 485 (34.7)            | 419 (28.7)               | 632 (36.7)               | 663 (29.9)               | 595 (26.3)               |
| Men who have sex with men              | 251 (32)    | 395 (35)              | 442 (37.3)   | 408 (36.8)               | 496 (42.3)  | 594 (42.5)            | 657 (45.0)               | 696 (40.4) <sup>^</sup>  | 1055 (47.5) <sup>x</sup> | 1186 (52.4)              |
| Unknown                                | 582         | 637 <sup>*</sup>      | 716          | 819                      | 820         | 754                   | 673                      | 937                      | 1028                     | 1035                     |
| <b>Site of infection</b>               |             |                       |              |                          |             |                       |                          |                          |                          |                          |
| Genital                                | 1164 (86.5) | 1426 (84.7)           | 1466 (82.1)  | 1537 (83)                | 1531 (79)   | 1549 (76.3)           | 1517 (72.9)              | 1943 (75.5)              | 2166 (72.8)              | 2155 (70.4)              |
| Pharyngeal                             | 34 (2.5)    | 62 (3.5)              | 79 (4.4)     | 92 (5)                   | 122 (6.3)   | 154 (7.6)             | 180 (8.7)                | 165 (6.4)                | 254 (8.5)                | 259 (8.5)                |
| Anorectal                              | 138 (10.3)  | 191 (11.4)            | 216 (12.1)   | 188 (10.2)               | 255 (13.2)  | 192 (9.5)             | 280 (13.5)               | 366 (14.2)               | 435 (14.6)               | 570 (18.6)               |
| Other                                  | 9 (0.7)     | 7 (0.4)               | 24 (1.3)     | 35 (1.9)                 | 30 (1.5)    | 135 (6.6)             | 103 (5.0)                | 100 (3.9)                | 120 (4)                  | 77 (2.5)                 |
| Unknown                                | 21          | 80                    | 117          | 75                       | 56          | 121                   | 54                       | 86                       | 273                      | 238                      |
| <b>Previous gonorrhoea</b>             |             |                       |              |                          |             |                       |                          |                          |                          |                          |
| Yes                                    | 84 (18.1)   | 145 (21)              | 146 (19)     | 130 (17.2)               | 142 (17.8)  | 163 (19.7)            | 157 (17.5)               | 171 (17.2)               | 235 (21.8)               | 264 (26.9)               |
| No                                     | 379 (81.9)  | 546 (79)              | 621 (81)     | 627 (82.8)               | 654 (82.2)  | 663 (80.3)            | 739 (82.5)               | 824 (82.8)               | 845 (78.2)               | 718 (73.1)               |
| Unknown                                | 903         | 1075                  | 1135         | 1170                     | 1198        | 1325                  | 1238                     | 1665                     | 2168                     | 2317                     |
| <b>Concurrent STI</b>                  |             |                       |              |                          |             |                       |                          |                          |                          |                          |
| Concurrent chlamydia infection         | 78 (14.3)   | 172 (22.1)            | 194 (22.2)   | 187 <sup>††</sup> (23.4) | 183 (21.8)  | 170 (20)              | 153 <sup>††</sup> (19.0) | 203 (23.9) <sup>~</sup>  | 243 (23.6) <sup>°</sup>  | 270 <sup>††</sup> (22.2) |
| Concurrent other STI (not HIV)         | 35 (6.4)    | 28 <sup>†</sup> (3.6) | 43 (4.9)     | 49 <sup>†</sup> (6.1)    | 55 (6.5)    | 41 <sup>†</sup> (4.8) | 48 <sup>††</sup> (6.0)   | 53 (6.2) <sup>††</sup>   | 67 (6.5)                 | 90 <sup>††</sup> (7.4)   |
| No concurrent STI                      | 433 (79.3)  | 579 (74.3)            | 638 (72.9)   | 564 (70.6)               | 603 (71.7)  | 640 (75.2)            | 605 (75.1)               | 593 (69.9)               | 721 (69.9)               | 859 (70.7)               |
| Unknown                                | 820         | 987                   | 1027         | 1127                     | 1153        | 1300                  | 1328                     | 1811                     | 2217                     | 2084                     |
| <b>HIV status*</b>                     |             |                       |              |                          |             |                       |                          |                          |                          |                          |
| Positive                               | N/D         | 48 (15.5)             | 141 (17.6)   | 104 (13.5)               | 144 (17.6)  | 172 (19.3)            | 132 (15.3)               | 156 (15.9)               | 188 (15.4)               | 224 (15.7)               |
| Negative                               | N/D         | 262 (84.5)            | 661 (82.4)   | 668 (86.5)               | 675 (82.4)  | 720 (80.7)            | 733 (84.7)               | 823 (84.1)               | 1029 (84.6)              | 1204 (84.3)              |
| Unknown                                | N/D         | 556                   | 1100         | 1155                     | 1175        | 1259                  | 1269                     | 1681                     | 2031                     | 1871                     |
| <b>Probable country of infection</b>   |             |                       |              |                          |             |                       |                          |                          |                          |                          |
| Same as reporting country              | N/D         | 151 (90.4)            | 700 (95.0)   | 790 (92.3)               | 764 (94.1)  | 552 (94.0)            | 800 (92.2)               | 614 (87.0)               | 795 (88.6)               | 1155 (87.6)              |
| Different from reporting country       | N/D         | 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)               |
| Unknown                                | N/D         | 1599                  | 1165         | 1071                     | 1182        | 1564                  | 1266                     | 1954                     | 2351                     | 1981                     |

Percentages calculated from known values.

Cells shaded in blue indicate a significant difference in proportion compared to previous year ( $p < 0.05$ )

\* Includes one individual of unknown gender, but with mode of transmission reported as heterosexual.

<sup>†</sup> Includes two individuals with two concurrent STIs

<sup>††</sup> Includes four individuals with two concurrent STIs

<sup>°</sup> Includes three individuals with two concurrent STIs

<sup>‡</sup> Includes six individuals with chlamydia and an additionally diagnosed STI.

<sup>°°</sup> Includes thirteen individuals with chlamydia and an additionally diagnosed STI.

<sup>^</sup> Includes one individual of unknown gender, but with mode of transmission reported as MSM.

<sup>x</sup> Includes two individuals of unknown gender, but with mode of transmission reported as MSM

<sup>~</sup> Includes nine individuals with chlamydia and an additionally diagnosed STI

The age of the patients ranged from <1 year to 86 years, with a median of 30 years. Males (median age 31 years) were significantly older than females (median age 24 years) (Mann-Whitney  $p < 0.001$ ) (Table 2).

**Table 2. Patient age distribution by gender and sexual orientation, 2018**

| Variable          | N†   | Age (years) |        | <25 years N (%) |
|-------------------|------|-------------|--------|-----------------|
|                   |      | Range       | Median |                 |
| All patients      | 3299 | 0-86        | 30     | 925 (28.0)      |
| Female            | 482  | 0-67        | 24     | 254 (52.7)      |
| Male*             | 2795 | 10-86       | 31     | 670 (24.0)      |
| Male heterosexual | 590  | 15-68       | 29     | 182 (30.8)      |
| MSM               | 1177 | 16-69       | 31     | 238 (20.2)      |

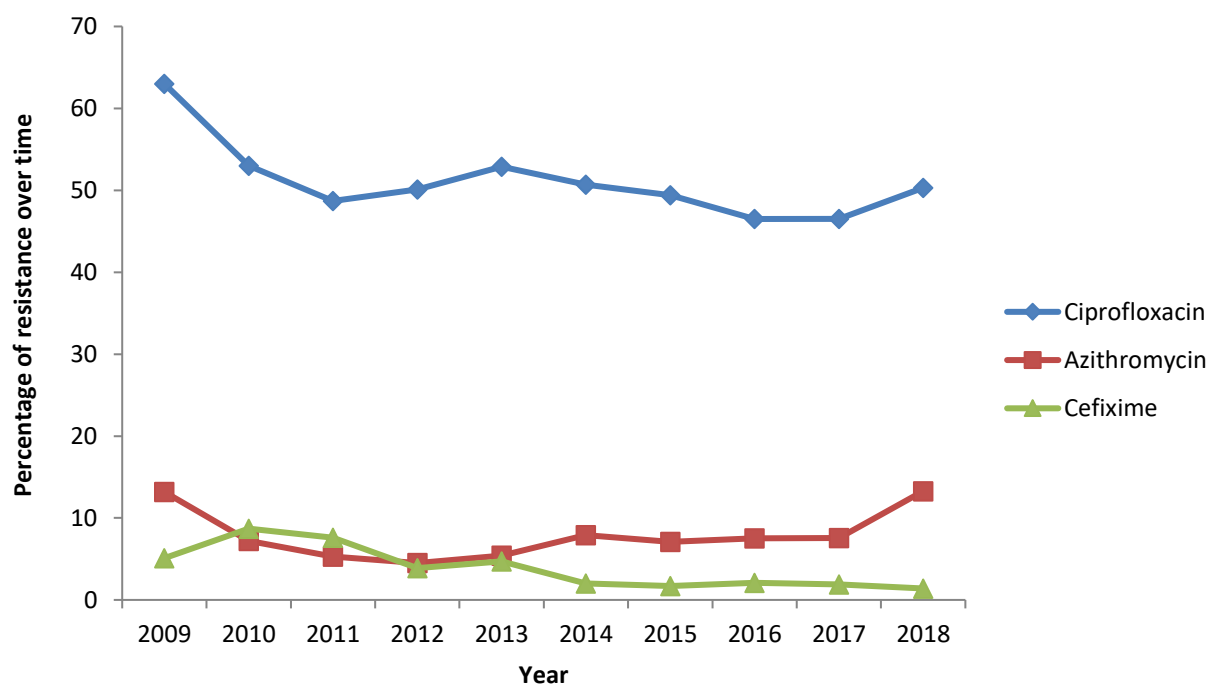
† Where information was available.

\* 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. There was a significant increase in patients from this service type between 2017 (47.9%) and 2018 (59.7%) ( $p < 0.01$ ). This increase is largely attributable to the increase in reporting for this variable in Spain which recorded 189 isolates from STI clinics in 2018 compared to 2017 when only four isolates from STI clinics were reported, with 409 unknowns. There was a significant decrease in the number of patients attending primary care facilities, 3.2% in 2018 vs 9.1% in 2017 and 6.5% in 2016 ( $p < 0.002$ ). This decrease is largely attributable to a change in clinic type in Germany which recorded 100 patients attending primary care facilities in 2017 and zero in 2019. There was a significant increase in the number of patients who attended 'other' service types in 2018 compared to 2017, with an increase from 3.1% to 4.5% ( $p = 0.03$ ). Attendance at outpatient clinics remained consistent compared to 2017 at 8.5%.

### 3.2 Antimicrobial susceptibility and resistance

Resistance to cefixime, ciprofloxacin and azithromycin (using the previously recommended EUCAST azithromycin  $>0.5$  mg/L breakpoint) over time is summarised in Figure 1 and Table 3.

**Figure 1. Percentage of resistant *Neisseria gonorrhoeae* by antimicrobial and year, Euro-GASP, 2009–2018**

Azithromycin data is presented using the historical EUCAST  $>0.5$  mg/L resistance breakpoint in figure one and table three.

**Table 3. Resistance to cefixime, ciprofloxacin and azithromycin (using the previously recommended EUCAST azithromycin resistance breakpoint), by country, Euro-GASP, 2018**

| Country        | Number of isolates 2018 | Number of isolates 2009-2018 | Resistance |      |              |     |               |             | Method of testing |      |   |                     |
|----------------|-------------------------|------------------------------|------------|------|--------------|-----|---------------|-------------|-------------------|------|---|---------------------|
|                |                         |                              | Cefixime   |      | Azithromycin |     | Ciprofloxacin |             |                   |      |   |                     |
|                |                         |                              | No.        | %    | % 2009-2018  | No. | %             | % 2009-2018 |                   | No.  | % | % 2009-2018         |
| Austria        | 267                     |                              | 9          | 3.4  |              | 38  | 14.2          |             | 151               | 56.6 |   | Decentralised – MGS |
| Belgium        | 180                     |                              | 5          | 2.9  |              | 26  | 14.4          |             | 80                | 44.4 |   | Decentralised – MIC |
| Croatia        | 10                      |                              | 0          | 0.0  |              | 6   | 60.0          |             | 8                 | 80.0 |   | Centralised – MGS   |
| Cyprus         | 5                       |                              | 1          | 20.0 |              | 1   | 20.0          |             | 3                 | 60.0 |   | Decentralised – MGS |
| Czech Republic | 95                      |                              | 1          | 1.1  |              | 20  | 21.1          |             | 47                | 49.5 |   | Centralised – MGS   |
| Denmark        | 114                     |                              | 0          | 0.0  |              | 9   | 7.9           |             | 47                | 41.2 |   | Decentralised – MGS |
| Estonia        | 7                       |                              | 0          | 0.0  |              | 0   | 0.0           |             | 3                 | 42.9 |   | Centralised – MGS   |
| Finland        | 168                     |                              | 0          | 0.0  |              | 19  | 11.3          |             | 86                | 51.2 |   | Decentralised – BKP |
| France         | 109                     |                              | 0          | 0.0  |              | 16  | 14.7          |             | 69                | 63.3 |   | Decentralised – MGS |
| Germany        | 201                     |                              | 2          | 1.0  |              | 28  | 13.9          |             | 123               | 61.2 |   | Decentralised – MGS |
| Greece         | 83                      |                              | 5          | 6.0  |              | 1   | 1.2           |             | 47                | 56.6 |   | Decentralised – MGS |
| Hungary        | 89                      |                              | 2          | 2.2  |              | 12  | 13.5          |             | 35                | 39.3 |   | Centralised – MGS   |
| Iceland        | 45                      |                              | 0          | 0.0  |              | 8   | 17.8          |             | 22                | 48.9 |   | Decentralised – MGS |
| Ireland        | 200                     |                              | 0          | 0.0  |              | 16  | 8.0           |             | 119               | 60.1 |   | Decentralised – MGS |
| Italy          | 100                     |                              | 5          | 5.0  |              | 36  | 36.0          |             | 55                | 55.0 |   | Decentralised – MGS |
| Latvia         | 5                       |                              | 0          | 0.0  |              | 0   | 0.0           |             | 3                 | 60.0 |   | Centralised – MGS   |
| Luxembourg     | 1                       |                              | 0          | 0.0  |              | 0   | 0.0           |             | 0                 | 0.0  |   | Decentralised – MGS |
| Malta          | 25                      |                              | 0          | 0.0  |              | 5   | 20.0          |             | 19                | 76.0 |   | Decentralised – MGS |
| Netherlands    | 402                     |                              | 0          | 0.0  |              | 43  | 10.7          |             | 169               | 42.0 |   | Decentralised – MGS |
| Norway         | 126                     |                              | 0          | 0.0  |              | 31  | 24.6          |             | 70                | 55.6 |   | Centralised – MGS   |
| Poland         | 73                      |                              | 1          | 1.4  |              | 6   | 8.2           |             | 37                | 50.7 |   | Centralised – MGS   |
| Portugal       | 122                     |                              | 0          | 0.0  |              | 21  | 17.2          |             | 40                | 32.8 |   | Decentralised – MGS |
| Slovakia       | 77                      |                              | 0          | 0.0  |              | 5   | 6.5           |             | 27                | 35.1 |   | Centralised – MGS   |
| Slovenia       | 155                     |                              | 0          | 0.0  |              | 12  | 7.7           |             | 86                | 55.5 |   | Decentralised – MGS |

**Table 3. Resistance to cefixime, ciprofloxacin and azithromycin (using the previously recommended EUCAST azithromycin resistance breakpoint), by country, Euro-GASP, 2018 (continued)**

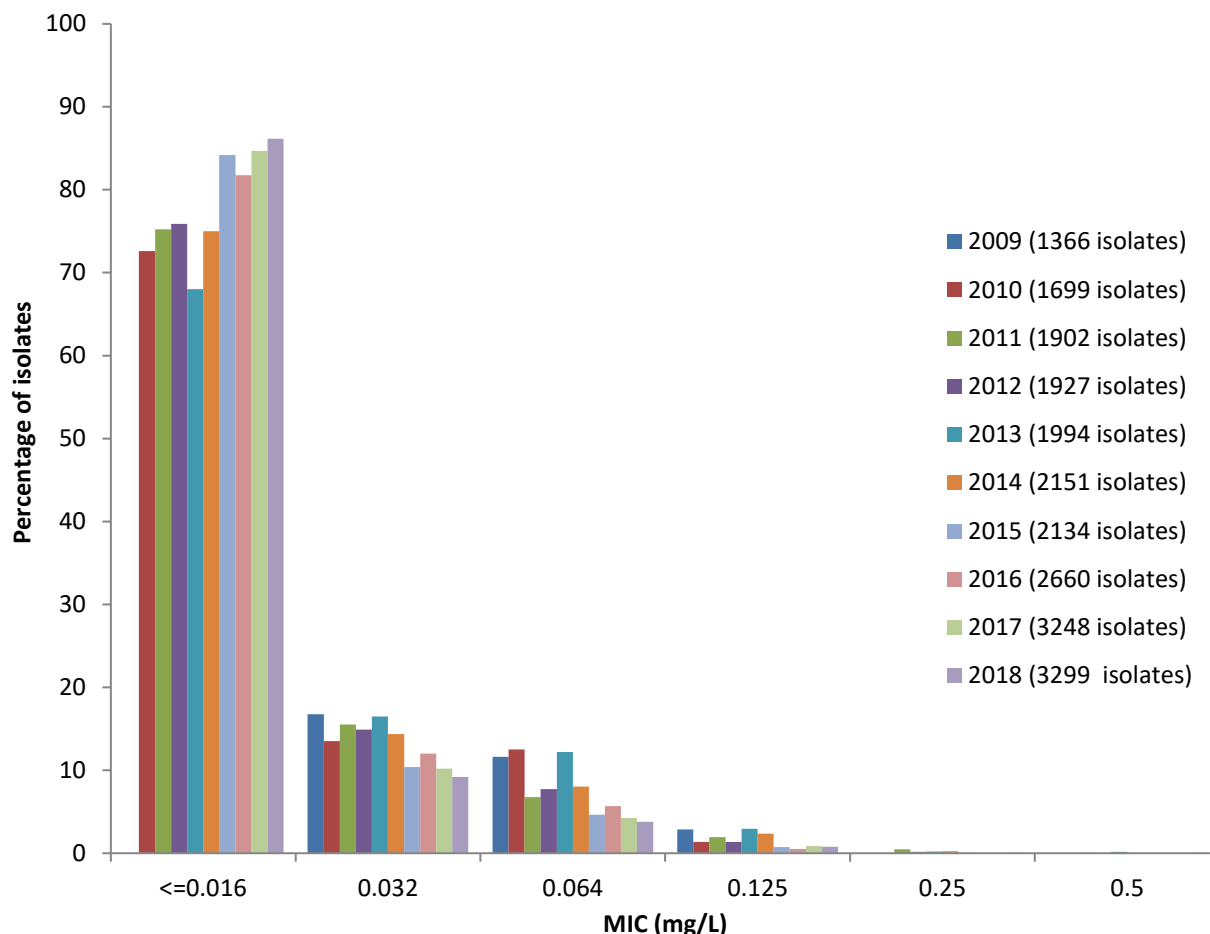
| Country              | Number of isolates 2018 | Number of isolates 2009-2018 | Resistance |         |              |     |               |             | Method of testing |           |   |                             |
|----------------------|-------------------------|------------------------------|------------|---------|--------------|-----|---------------|-------------|-------------------|-----------|---|-----------------------------|
|                      |                         |                              | Cefixime   |         | Azithromycin |     | Ciprofloxacin |             |                   |           |   |                             |
|                      |                         |                              | No.        | %       | % 2009-2018  | No. | %             | % 2009-2018 |                   | No.       | % | % 2009-2018                 |
| Spain                | 189                     |                              | 9          | 4.8     |              | 33  | 17.5          |             | 96                | 50.8      |   | Decentralised – MGS         |
| Sweden               | 200                     |                              | 3          | 1.5     |              | 17  | 8.5           |             | 120               | 60.0      |   | Decentralised – MGS         |
| United Kingdom       | 251                     |                              | 3          | 1.2     |              | 29  | 11.6          |             | 98                | 39.0      |   | Decentralised – MIC/BKP/MGS |
| <b>Total:</b>        | 3299                    |                              |            |         |              |     |               |             |                   |           |   |                             |
| <b>Cefixime</b>      | 3289                    |                              | 46         | 1.4     |              |     |               |             |                   |           |   |                             |
| <b>Ciprofloxacin</b> | 3297                    |                              |            |         |              |     |               |             | 1660              | 50.3      |   |                             |
| <b>Azithromycin</b>  | 3299                    |                              |            |         |              | 438 | 13.3          |             |                   |           |   |                             |
| <b>95% CI</b>        |                         |                              |            | 1.0-1.9 |              |     | 12.2-14.5     |             |                   | 46.0-49.4 |   |                             |

*N/T: not tested; BKP: Breakpoint; MGS: MIC gradient strip test; MIC: MIC by agar dilution*

Three isolates displayed ceftriaxone resistance in 2018 compared to zero in 2017 and 2016 (Figure 2). One resistant isolate was detected in Germany, with a ceftriaxone MIC=0.25 mg/L, azithromycin MIC=0.5 mg/L and

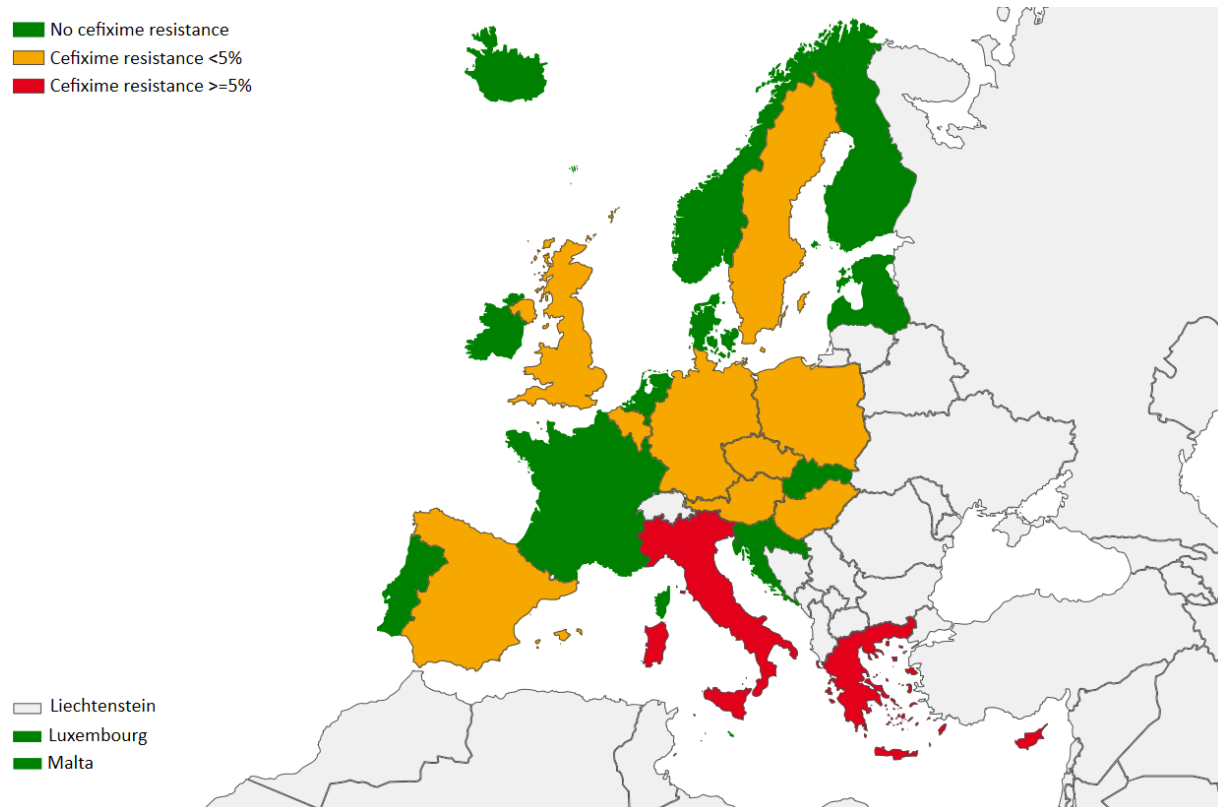
ciprofloxacin MIC=32 mg/L. Both country of birth and probable country of infection were unknown for this patient. Two resistant isolates were detected in Spain, one was extensively-drug resistant (XDR), with a ceftriaxone MIC=0.25 mg/L, azithromycin MIC=16 mg/L and ciprofloxacin MIC=0.064 mg/L; the other Spanish isolate had a ceftriaxone MIC=0.5 mg/L, azithromycin MIC=0.25 mg/L and ciprofloxacin MIC $\geq$ 32 mg/L. The countries of birth for both patients in Spain were unknown; the probable country of infection was recorded as Spain. The MIC distribution for ceftriaxone in 2018 showed no significant changes compared to 2017.

**Figure 2. Distribution of MIC for ceftriaxone in Euro-GASP, 2009–2018**

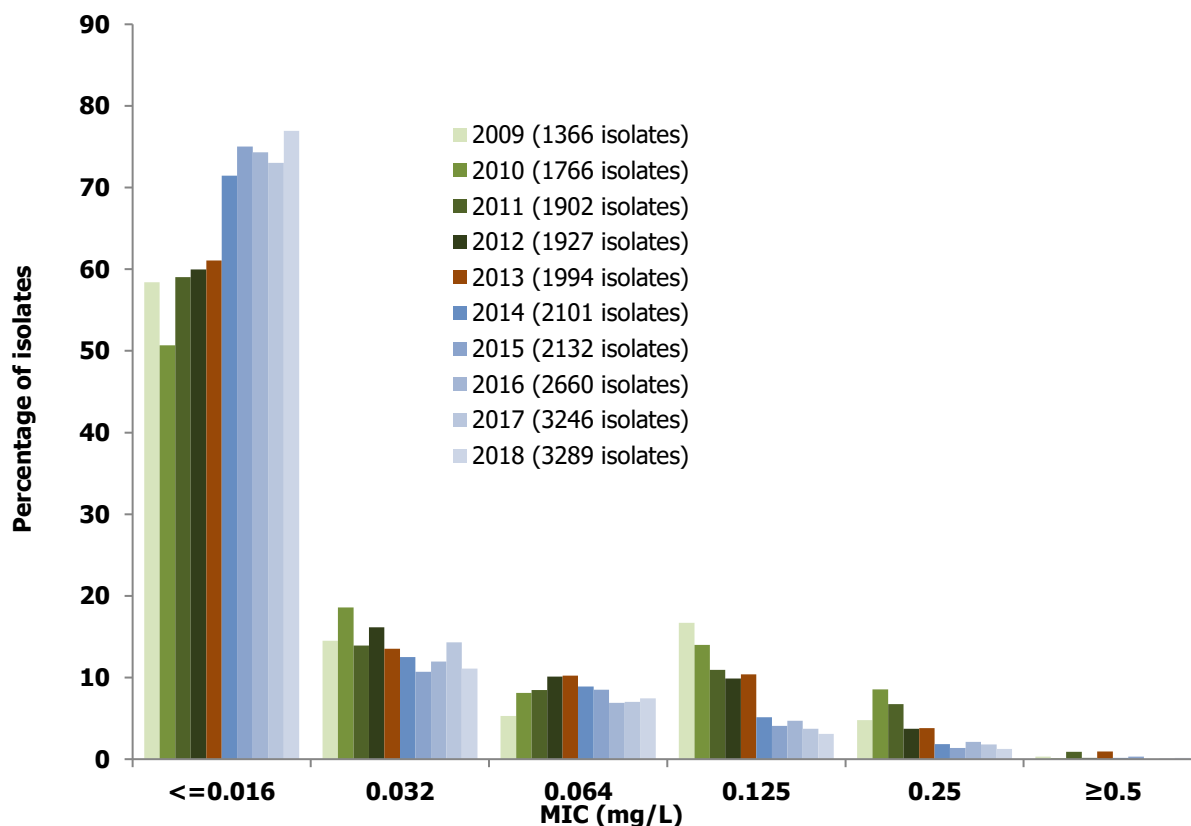


Cefixime resistance has remained stable at around 2% since 2014 ( $p=0.09$  (Figures 1 and 3, Table 4)). There has been a significant increase in the number of isolates with a cefixime MIC  $\leq 0.016$  mg/L (77.0% in 2018 vs 73.0% in 2017,  $p<0.002$ ) and a significant decrease in isolates with a cefixime MIC 0.032 mg/L compared to 2017 (11.1% in 2018 vs 14.3% in 2017,  $p<0.002$ ) (Figure 3). There has been an increase in the number of isolates with a cefixime MIC  $\geq 0.5$  mg/L, from three in 2017 to five in 2018 – although these numbers are too low to test for statistical significance. Percentages of cefixime-resistant isolates in 2018 by country are shown in Map 1.

**Map 1. Proportion of gonococcal isolates with cefixime resistance by country, EU/EEA, 2018**



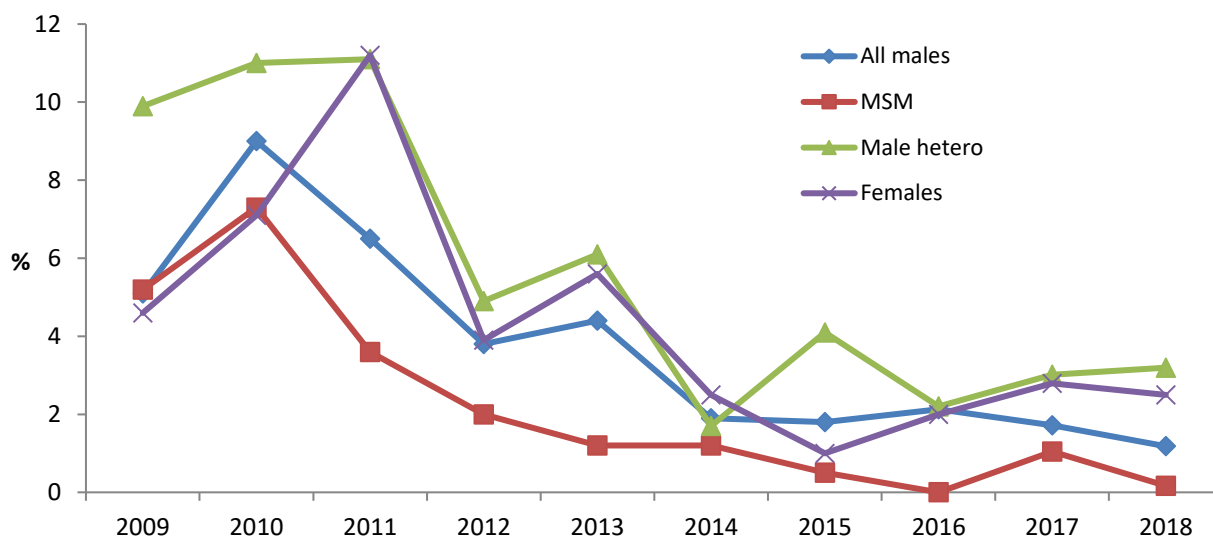
**Figure 3. Distribution of MIC for cefixime in Euro-GASP, 2009–2018**



Cefixime resistance in isolates from patients by sexual orientation and gender was stable (no significant differences) in 2018 compared to 2017 (Figure 4). Cefixime resistance was significantly higher in isolates from heterosexual males and females compared to MSM ( $p < 0.01$ , Fisher’s exact test). There was a higher proportion of

genital isolates with cefixime resistance compared to other anatomical sites ( $p=0.02$ , Fisher's exact test) (Annex 2).

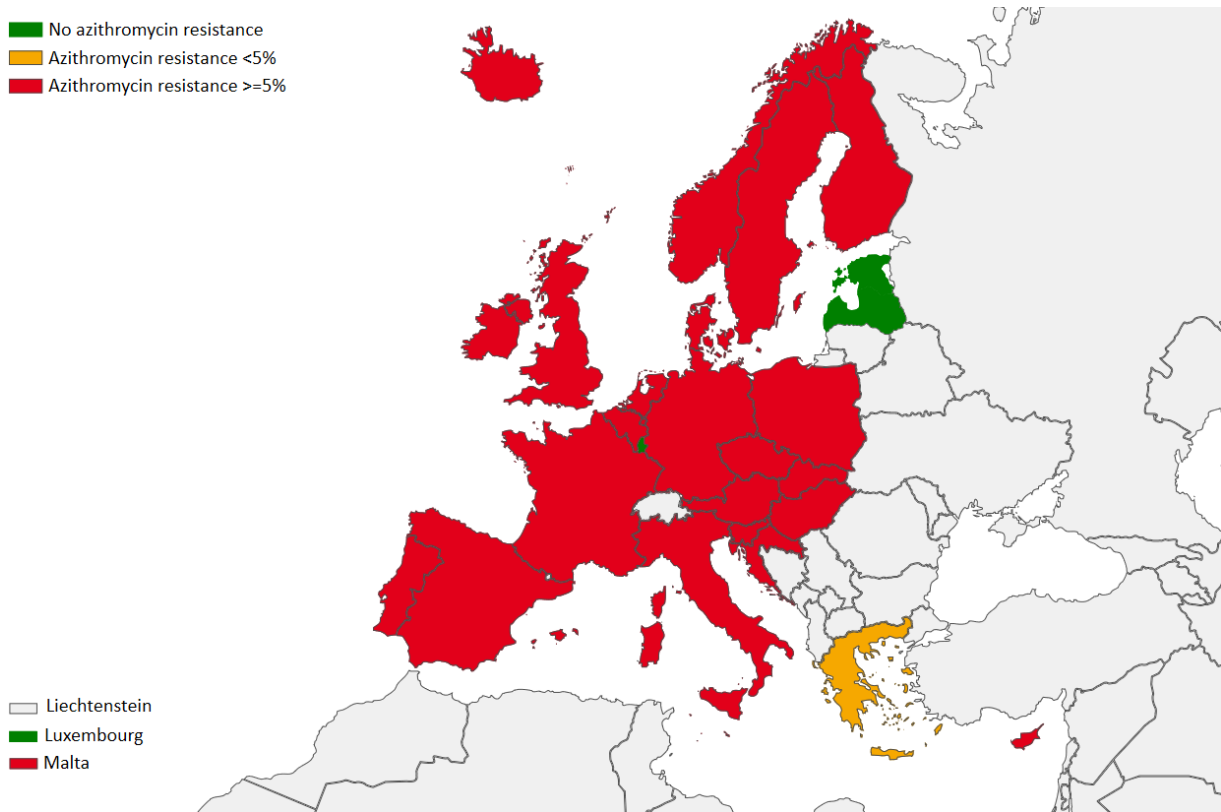
**Figure 4. Percentage of isolates with cefixime resistance by gender and male sexual orientation, Euro-GASP, 2009–2018**



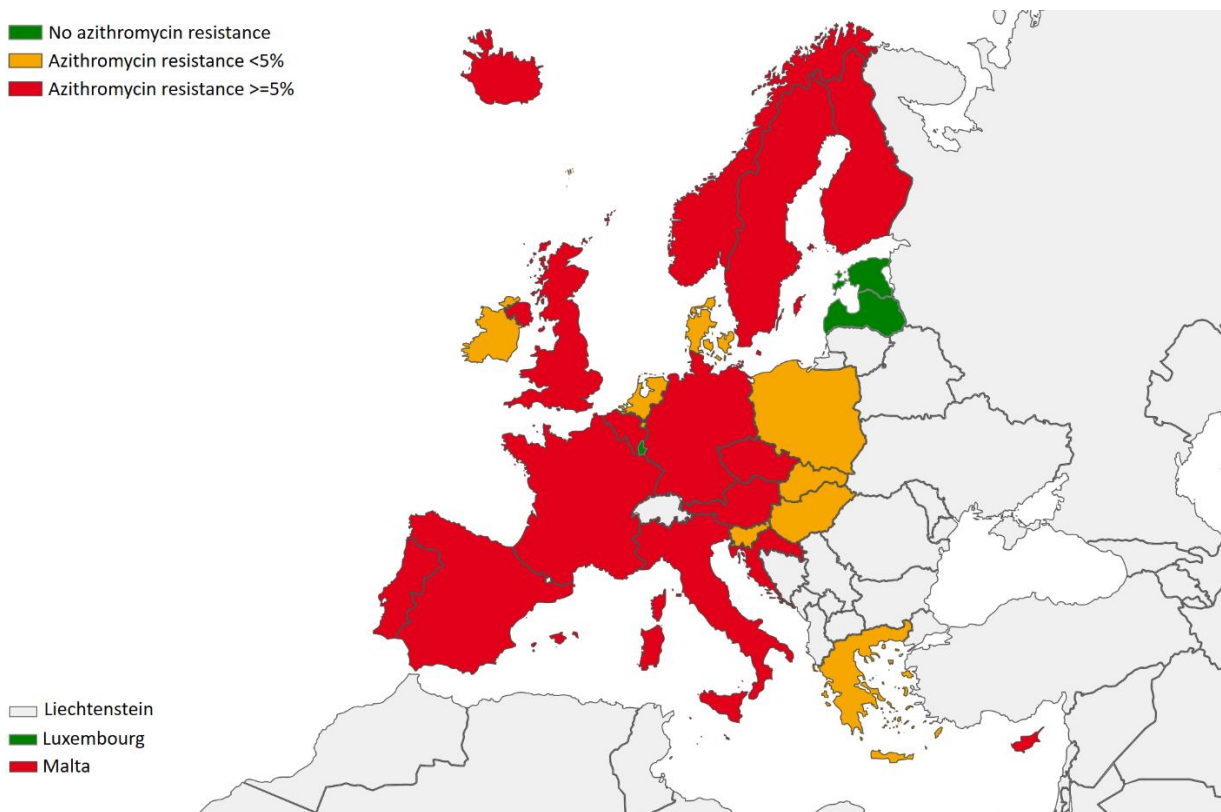
A total of 251 isolates (7.6%) had an MIC of  $>1$  mg/L (EUCAST ECOFF) to azithromycin. Using the previously recommended EUCAST clinical resistance breakpoint of  $>0.5$  mg/L, there was a large increase to 13.3% from the previously stable 7%–8% observed from 2014 to 2017 ( $p<0.0002$ ) (Figure 1; Table 4). Five isolates displayed 'high-level azithromycin resistance' with MICs of  $\geq 256$  mg/L, compared to seven in 2017 and seven in 2016. These five isolates were comprised of one isolate from Cyprus, one from Ireland, one from Italy, one from the Netherlands and one from the United Kingdom. The United Kingdom is the only country that has identified a 'high-level azithromycin resistant' isolate in each consecutive year (2016–2018). All five isolates were susceptible to the other antimicrobials tested, except for ciprofloxacin to which three were resistant and one was susceptible to increased exposure (0.06 mg/L). The MIC distribution for azithromycin in 2018 was different to previous years, with a significant decrease in the number of 'highly susceptible' isolates with an MIC  $\leq 0.016$  mg/L ( $p<0.002$ ) and isolates with MIC=0.25 mg/L ( $p=0.04$ ). Seventy one percent of isolates above the ECOFF had an MIC of 2 mg/L, and 42.7% 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 2018 (Figure 5). In 2018, isolates with an azithromycin MIC  $>0.5$  mg/L (previously recommended EUCAST resistance breakpoint) were highest in male heterosexuals (13.6%), followed by MSM (12.3%), and lowest in females (9.7%) (Figure 6). No significant associations between patient demographics and azithromycin MICs of  $>0.5$  mg/L and  $>1$  mg/L (ECOFF) were identified (Annex 2).



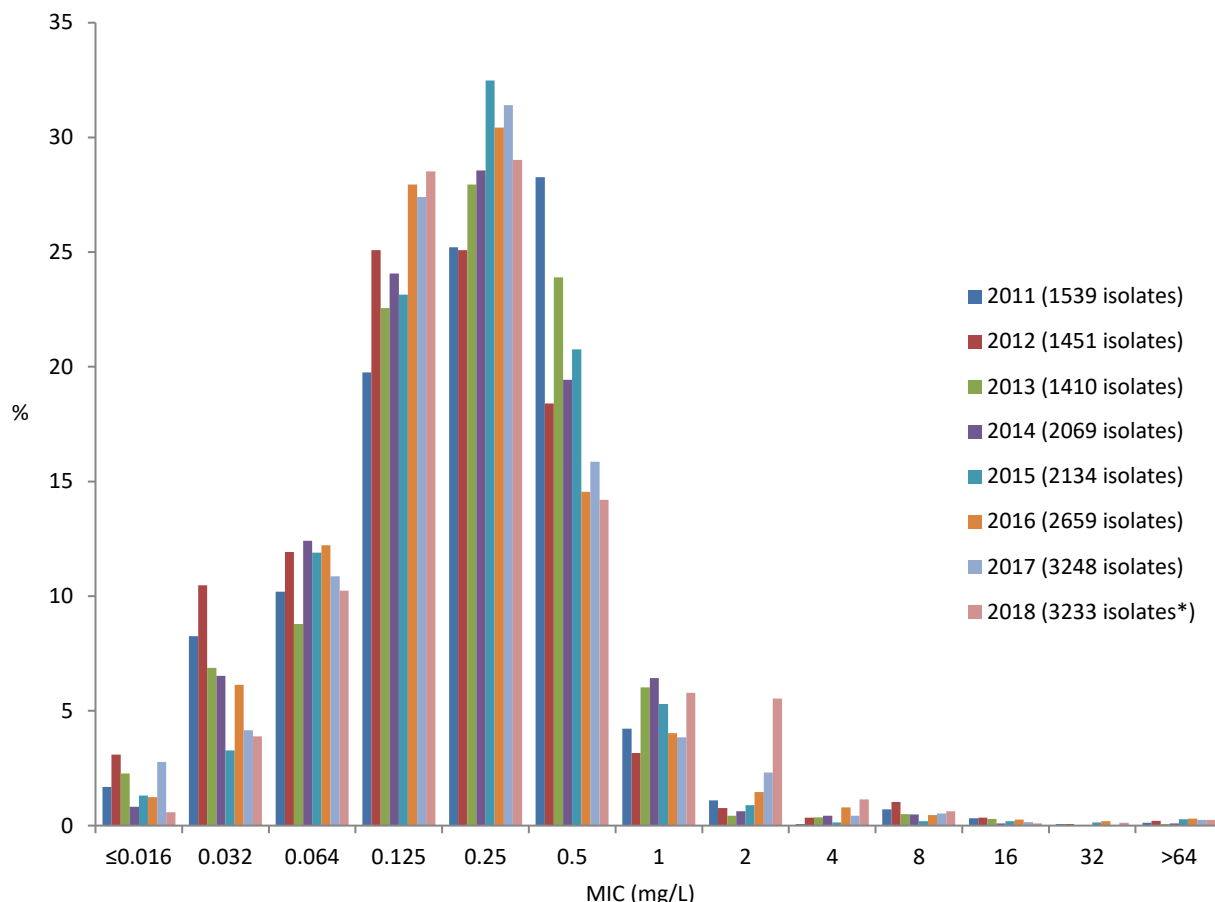
**Map 2. Proportion of gonococcal isolates with azithromycin MICs >0.5 mg/L (previously recommended EUCAST resistance breakpoint) by country, EU/EEA, 2018**



**Map 3. Proportion of gonococcal isolates above azithromycin ECOFF (>1 mg/L) by country, EU/EEA, 2018**

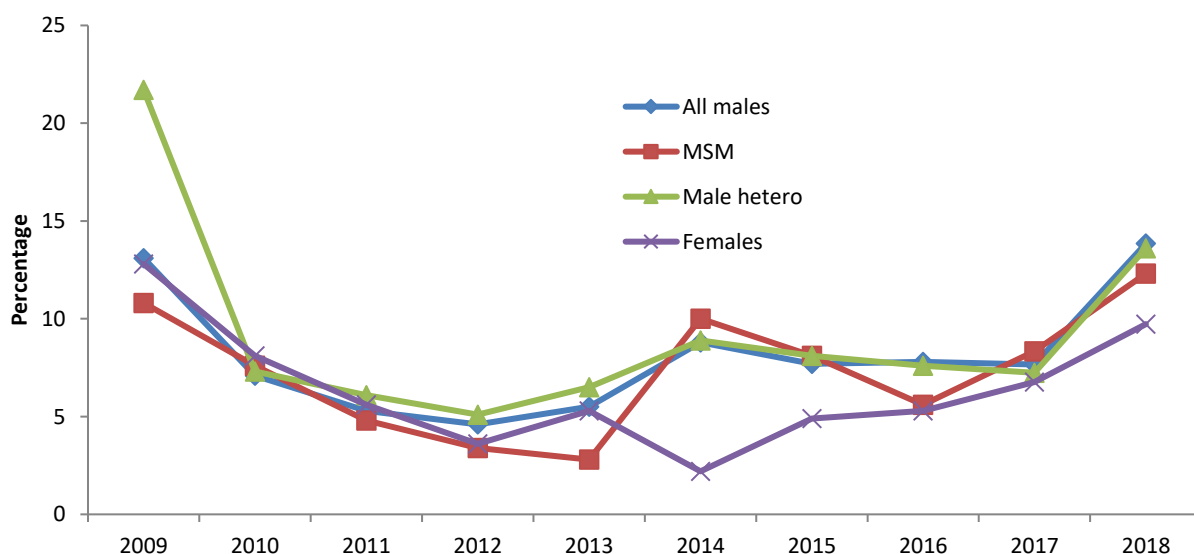


**Figure 5. Distribution of MIC for azithromycin in Euro-GASP, 2011–2018**

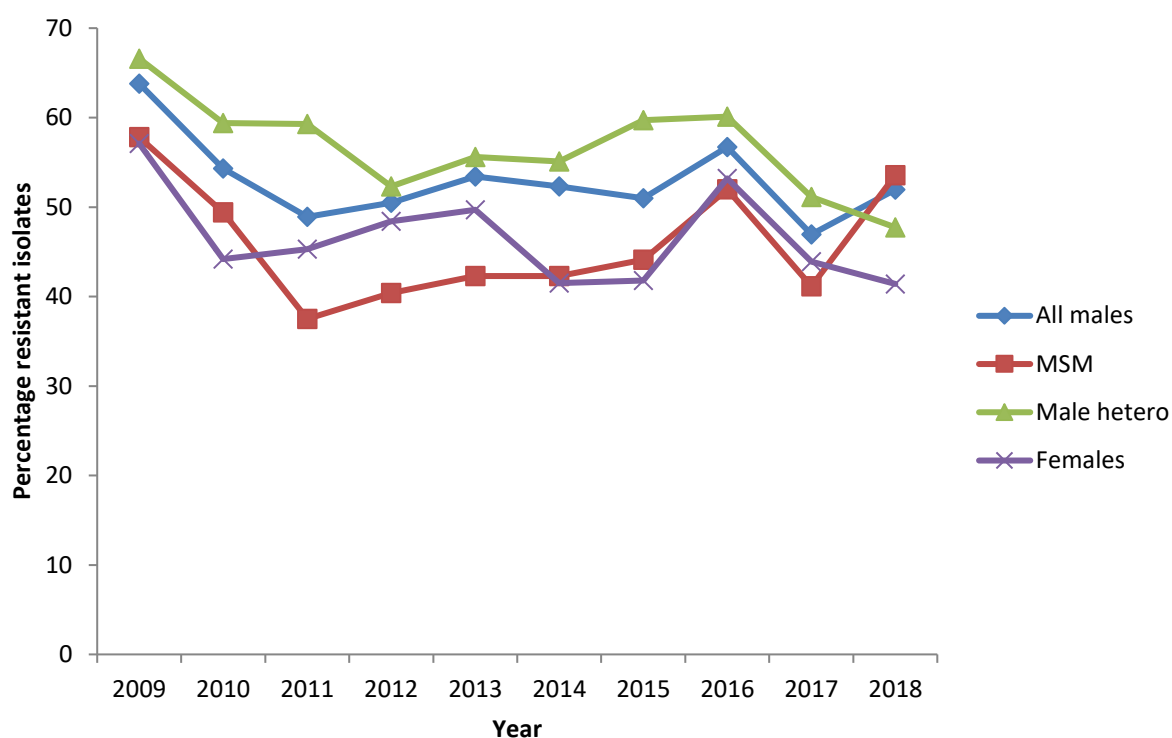


\* 3 299 isolates were susceptibility tested with azithromycin in 2018; 66 isolates had an MIC  $\leq 0.06$  mg/L. These isolates were excluded from the MIC distribution analysis as they did not fit into one discrete category.

**Figure 6. Percentage of isolates with azithromycin MIC >0.5 mg/L (previously recommended EUCAST resistance breakpoint), by gender and male sexual orientation, Euro-GASP, 2009–2018**



Overall, ciprofloxacin resistance levels in 2018 (50.3%; 1660/3297) significantly increased ( $p < 0.01$ ) from those observed in 2017 (46.5%) and 2016 (46.5%) (Figure 1). In a change from 2017, resistance was highest among MSM (53.5%) and lowest in females (41.4%). Following multivariable analysis, ciprofloxacin resistance remained associated with isolates from MSM compared to male heterosexuals (OR 1.26, CI 1.03–1.54,  $p = 0.02$ ) and the absence of a concurrent chlamydial infection (OR 1.4, CI 1.07–1.85,  $p = 0.01$ ) (Annex 2).

**Figure 7. Percentage of isolates with ciprofloxacin resistance by gender and male sexual orientation, Euro-GASP, 2009–2018**

### 3.3 Diagnostic tests and treatments used

Data on the type of diagnostic test are summarised in Table 5. Culture alone was used in 2016 cases; this was the most common diagnostic test (95.1% of all cases), which is comparable to 2017 (95.9%), 2016 (92.7%) and 2015 (90.2%). To identify *N. gonorrhoeae*, NAAT testing alone was used in 85 cases and microscopy alone in 15 cases.

**Table 4. Initial diagnostic tests used for isolates submitted in 2018**

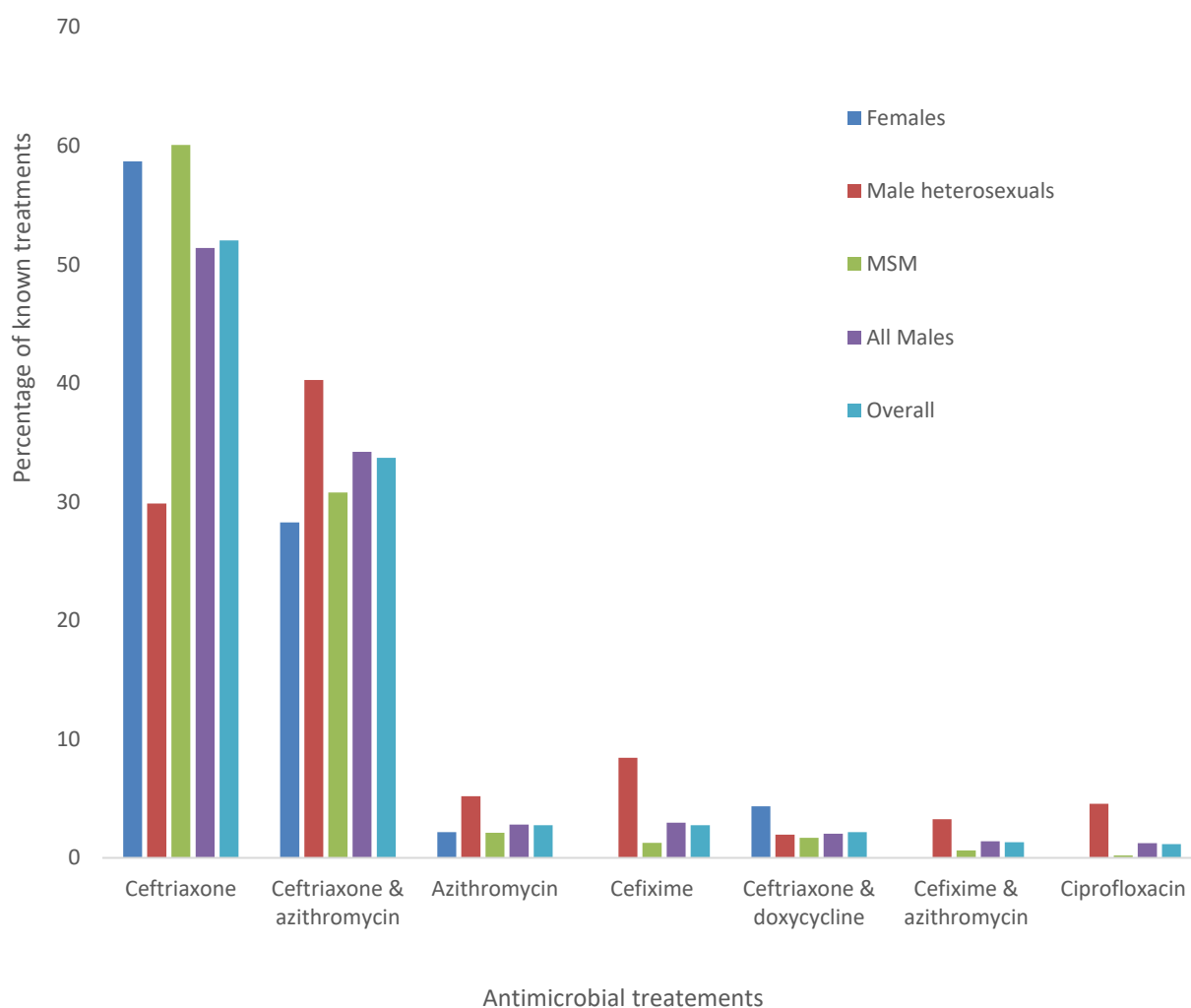
|  | Culture     |             | NAAT       |             | Microscopy |            |
|--|-------------|-------------|------------|-------------|------------|------------|
|  | No.         | %           | No.        | %           | No.        | %          |
| Primary diagnostic test only             | 2016        | 81.2        | 85         | 3.4         | 15         | 0.6        |
| Primary test plus other diagnostic tests | 346*        | 13.9        | 318†       | 12.8        | 140‡       | 5.6        |
| <b>Total</b>                             | <b>2362</b> | <b>95.1</b> | <b>403</b> | <b>16.2</b> | <b>155</b> | <b>6.2</b> |

\* Includes 50 tests with microscopy, 178 with NAAT and 118 with both microscopy and NAAT

† Includes 178 tests with culture, 22 with microscopy and 118 with culture and microscopy

‡ Includes 50 tests with culture, 22 with NAAT and 118 with culture and NAAT

**Figure 8. Percentage of known treatments used for patients with no other concurrent STI by gender and transmission type for the most frequently used therapies, 2018**



*Note: Thirty-eight different combinations/concentrations of antimicrobials were recorded in 2018, only treatments with  $\geq 2.5\%$  in any gender/ transmission group are shown (differences in concentration of antimicrobials prescribed have been grouped for analysis). Only 859 patients were recorded as having no concurrent STI, of these patients, data for treatment used were available for 80.1% ( $n=688$ ) patients. The chart presents data for the 688 patients with no concurrent STI and a recorded treatment type.*

Data on used type of treatment were known in 1 264 cases, of which 688 were recorded as having no other concurrent STI (Figure 8). As in 2017, the most common treatment was azithromycin alone (52%), followed by ceftriaxone and azithromycin (33.7%). Data on countries reporting treatment type and concurrent STI is presented in Table A1 (Annex 1).

## 4 Conclusions

Overall, resistance to extended-spectrum cephalosporins has been stable since 2014 (cefixime resistance ranged from 1.4% to 2.1% between 2014 and 2018). Three isolates displayed ceftriaxone resistance in 2018 (0.1%), compared to none in 2017 and 2016. These ceftriaxone-resistant isolates were detected in two different countries, and their antibiograms do not suggest clonality. One of the isolates was extensively drug resistant, with an azithromycin MIC=16 mg/L and ciprofloxacin resistance. Cefixime-resistant isolates were detected in 12 (44.4%) of the 27 countries reporting in 2018. Cefixime resistance continues to be lowest among MSM (0.2%) and highest in male heterosexuals (3.2%) and females (2.5%). Although the continuing low levels of cephalosporin resistance is promising, the detection of three ceftriaxone-resistant isolates is concerning because cephalosporins are the last remaining options 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 azithromycin, which is the same level as in 2017. The increased use of the recommended dual antimicrobial therapy (ceftriaxone plus azithromycin) or ceftriaxone high-dose monotherapy is promising and is likely to have contributed to the overall low-level of cephalosporin resistance.

The proportion of isolates above the azithromycin ECOFF (>1 mg/L) and above the previously recommended EUCAST azithromycin resistance breakpoint (>0.5 mg/L) significantly increased in 2018 (3.7% to 7.6% ECOFF; 7.5% to 13.3% >0.5 mg/L breakpoint,  $p<0.0002$ ). This is a large change from the previously stable resistance rate despite the reported use of azithromycin monotherapy remaining the same in 2017 (2.9%) and 2018 (2.8%). It should be noted that the majority of isolates with an azithromycin MIC >1 mg/L (EUCAST ECOFF) are just above the ECOFF (71.3% had an MIC of 2 mg/L), and 42.7% of isolates previously classified as resistant (>0.5 mg/L) had MICs of 1 mg/L. Minor fluctuations in azithromycin MICs are expected because susceptibility testing is sensitive to minor differences in agar media composition, pH and CO<sub>2</sub> levels. However, the increase in azithromycin MICs is of concern. Ciprofloxacin resistance significantly increased ( $p<0.01$ ) to 50.3% (46.5% in 2017). Neither azithromycin nor ciprofloxacin are recommended for monotherapy unless the isolates are first shown to be susceptible. The detection of an isolate in Spain with an azithromycin MIC >16 mg/L and both ceftriaxone and ciprofloxacin resistance is very concerning. This isolate came from a Spanish resident and the recorded probable country of infection was Spain. These findings deviate from other reported extensively resistant isolates which are largely connected to travel to south-east Asia.

MSM continue to have a lower risk of harbouring AMR isolates [12]; cefixime resistance in 2018 was detected in only 0.2% of MSM, compared to 3.2% in heterosexual males.

Given the increase in azithromycin MICs and the appearance of ceftriaxone resistance, the recently reviewed European response plan to control the threat of multidrug-resistant *N. gonorrhoeae* in Europe [4] should continue to be observed to identify and report treatment failures and ensure that gonorrhoea remains a treatable infection.

Euro-GASP has a major role in meeting the objectives of the response plan which include:

- Strengthening surveillance of gonococcal antimicrobial susceptibility in the EU/EEA Member States by providing sufficient epidemiological information to inform national treatment guidelines and public health interventions. Overall completeness of variables has increased from 58.2% in 2017 to 62.1% in 2018. Improvements in reporting are still required for many variables if statistical analysis of the linked susceptibility and patient data is to be robust.
- Ensure that appropriate capacity for culture and susceptibility testing in EU/EEA Member States is available or developed further. In addition, training in STI diagnostics and antimicrobial susceptibility testing should be provided and experts (and other staff related to the field) are encouraged to participate, where required, with the goal to eventually move towards decentralised testing.
- Effectively disseminate results from AMR surveillance in order to increase awareness and inform authorities, professional societies, clinicians and other healthcare workers and persons at risk about the threat of multidrug-resistant (MDR) and XDR *N. gonorrhoeae*. The Euro-GASP AMR surveillance data are freely accessible online via the ECDC surveillance atlas of infectious diseases [13]. Data are updated annually prior to the publication of the annual surveillance 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 the implementation of appropriate gonorrhoea management, prevention, control. Strategic measures should also include AMR policies/guidelines, including an enhanced focus on high-risk groups, as well as mandatory reporting of gonorrhoea. Recommended therapies to treat gonorrhoea are supported by the Euro-GASP project. It is encouraging to see that the highly effective ceftriaxone, with or without azithromycin, was used in 86% (52% ceftriaxone alone; 34% plus azithromycin) of cases with known treatment and no concurrent STI. The same percentage was recorded in 2017. It is, however, of major concern that some patients continue to be inappropriately treated, for example with ciprofloxacin. This is particularly worrisome if patients harbour resistant strains: four resistant strains from 13 patients were treated with ciprofloxacin.

Even though Euro-GASP detected stable levels of cefixime resistance in 2018, the increase in ciprofloxacin resistance, azithromycin MICs and the detection of three ceftriaxone resistant isolates are of major concern. Treatment failures have been documented [14, 15], along with sustained transmission of HLAziR strains [16] and the international spread of gonococcal strains with resistance to ceftriaxone [15-21]. It is therefore essential to continuously conduct quality-assured antimicrobial surveillance. In this context, adherence to the recently updated and refined response plan is 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 A 1. Completeness of epidemiological variable reporting, 2018**

| Country                     | Number of isolates | Gender      | Age         | Mode of transmission | Site of infection | Diagnostic test | Treatment   | Previous gonorrhoea | Concurrent STI | Place of residence | Clinical service type | Country of birth | Probable country of infection | HIV status  | Overall Percentage response rate |
|-----------------------------|--------------------|-------------|-------------|----------------------|-------------------|-----------------|-------------|---------------------|----------------|--------------------|-----------------------|------------------|-------------------------------|-------------|----------------------------------|
| Austria                     | 267                | 100.0       | 100.0       | 18.7                 | 98.9              | 100.0           | 0.0         | 21.0                | 9.4            | 71.9               | 91.8                  | 15.0             | 0.0                           | 4.5         | 48.5                             |
| Belgium                     | 180                | 98.9        | 95.0        | 36.1                 | 90.6              | 0.0             | 0.0         | 38.9                | 0.0            | 0.0                | 23.3                  | 31.1             | 20.6                          | 35.6        | 36.2                             |
| Croatia                     | 10                 | 70.0        | 70.0        | 0.0                  | 100.0             | 100.0           | 0.0         | 0.0                 | 30.0           | 100.0              | 0.0                   | 100.0            | 0.0                           | 0.0         | 43.8                             |
| Cyprus                      | 5                  | 100.0       | 100.0       | 0.0                  | 100.0             | 100.0           | 20.0        | 0.0                 | 0.0            | 100.0              | 100.0                 | 80.0             | 0.0                           | 0.0         | 53.8                             |
| Czech Republic              | 95                 | 100.0       | 100.0       | 86.3                 | 95.8              | 100.0           | 85.3        | 85.3                | 80.0           | 87.4               | 100.0                 | 95.8             | 87.4                          | 83.2        | 91.3                             |
| Denmark                     | 114                | 100.0       | 100.0       | 79.8                 | 93.9              | 100.0           | 0.0         | 0.0                 | 0.0            | 83.3               | 100.0                 | 0.0              | 79.8                          | 64.0        | 61.6                             |
| Estonia                     | 7                  | 100.0       | 100.0       | 57.1                 | 100.0             | 100.0           | 0.0         | 0.0                 | 100.0          | 100.0              | 100.0                 | 0.0              | 0.0                           | 0.0         | 58.2                             |
| Finland                     | 168                | 100.0       | 100.0       | 91.7                 | 0.0               | 0.0             | 0.0         | 0.0                 | 0.0            | 0.0                | 0.0                   | 97.6             | 88.7                          | 0.0         | 36.8                             |
| France                      | 109                | 100.0       | 99.1        | 34.9                 | 99.1              | 100.0           | 0.0         | 0.0                 | 45.9           | 71.6               | 100.0                 | 38.5             | 42.2                          | 56.9        | 60.6                             |
| Germany                     | 201                | 99.0        | 98.5        | 0.0                  | 96.0              | 100.0           | 0.0         | 0.0                 | 0.0            | 100.0              | 60.2                  | 0.0              | 0.0                           | 0.0         | 42.6                             |
| Greece                      | 83                 | 98.8        | 90.4        | 88.0                 | 95.2              | 100.0           | 89.2        | 89.2                | 10.8           | 84.3               | 100.0                 | 0.0              | 86.7                          | 13.3        | 72.8                             |
| Hungary                     | 89                 | 97.8        | 96.6        | 0.0                  | 96.6              | 0.0             | 0.0         | 0.0                 | 0.0            | 0.0                | 97.8                  | 1.1              | 1.1                           | 0.0         | 30.1                             |
| Iceland                     | 45                 | 100.0       | 100.0       | 66.7                 | 93.3              | 100.0           | 0.0         | 0.0                 | 95.6           | 88.9               | 97.8                  | 91.1             | 0.0                           | 100.0       | 71.8                             |
| Ireland                     | 200                | 100.0       | 100.0       | 96.0                 | 99.0              | 88.0            | 87.5        | 80.0                | 92.0           | 98.5               | 98.5                  | 84.5             | 18.5                          | 86.5        | 86.8                             |
| Italy                       | 100                | 97.0        | 93.0        | 76.0                 | 98.0              | 100.0           | 75.0        | 72.0                | 71.0           | 86.0               | 100.0                 | 88.0             | 61.0                          | 69.0        | 83.5                             |
| Latvia                      | 5                  | 100.0       | 100.0       | 80.0                 | 100.0             | 100.0           | 0.0         | 100.0               | 100.0          | 100.0              | 100.0                 | 0.0              | 80.0                          | 0.0         | 73.8                             |
| Luxembourg                  | 1                  | 100.0       | 100.0       | 0.0                  | 100.0             | 100.0           | 0.0         | 100.0               | 0.0            | 100.0              | 100.0                 | 0.0              | 0.0                           | 0.0         | 53.8                             |
| Malta                       | 25                 | 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                 | 402                | 99.3        | 100.0       | 99.3                 | 100.0             | 100.0           | 100.0       | 0.0                 | 100.0          | 99.3               | 100.0                 | 99.8             | 0.0                           | 94.5        | 84.0                             |
| Norway                      | 126                | 100.0       | 100.0       | 0.0                  | 97.6              | 0.0             | 0.0         | 0.0                 | 0.0            | 0.0                | 54.8                  | 0.0              | 0.0                           | 0.0         | 27.1                             |
| Poland                      | 73                 | 100.0       | 100.0       | 0.0                  | 100.0             | 100.0           | 89.0        | 0.0                 | 0.0            | 0.0                | 100.0                 | 0.0              | 0.0                           | 0.0         | 45.3                             |
| Portugal                    | 122                | 100.0       | 100.0       | 15.6                 | 100.0             | 100.0           | 3.3         | 4.9                 | 9.8            | 76.2               | 12.3                  | 12.3             | 12.3                          | 12.3        | 43.0                             |
| Slovakia                    | 77                 | 100.0       | 100.0       | 64.9                 | 100.0             | 100.0           | 57.1        | 97.4                | 80.5           | 98.7               | 100.0                 | 96.1             | 57.1                          | 81.8        | 87.2                             |
| Slovenia                    | 155                | 100.0       | 100.0       | 89.0                 | 98.1              | 100.0           | 64.5        | 88.4                | 96.1           | 97.4               | 100.0                 | 97.4             | 89.0                          | 93.5        | 93.3                             |
| Spain                       | 189                | 100.0       | 98.4        | 98.4                 | 100.0             | 100.0           | 0.0         | 3.2                 | 0.5            | 100.0              | 100.0                 | 0.0              | 100.0                         | 0.5         | 61.6                             |
| Sweden                      | 200                | 100.0       | 100.0       | 94.5                 | 100.0             | 0.0             | 0.0         | 0.0                 | 0.0            | 0.0                | 0.0                   | 0.0              | 97.0                          | 0.0         | 37.8                             |
| United Kingdom              | 251                | 98.01       | 98.01       | 86.85                | 96.02             | 88.84           | 86.85       | 85.26               | 36.25          | 75.3               | 98.01                 | 70.92            | 52.59                         | 84.06       | 81.3                             |
| <b>Average completeness</b> | <b>3299</b>        | <b>99.4</b> | <b>98.7</b> | <b>63.1</b>          | <b>92.8</b>       | <b>75.3</b>     | <b>38.3</b> | <b>29.8</b>         | <b>36.8</b>    | <b>66.4</b>        | <b>76</b>             | <b>47</b>        | <b>40</b>                     | <b>43.3</b> | <b>62.1</b>                      |

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

## Annex 2. Statistical tables

**Table A 2. Univariate association of cefixime resistance/susceptibility and patient characteristics, Euro-GASP, 2018**

|   | Cefixime resistance<br>N (%), 95% CI | Odds ratio | 95% CI    | P value          |
|---|--------------------------------------|------------|-----------|------------------|
| <b>Site of infection (n=3057)</b>             |                                      |            |           |                  |
| Genital (2152)                                | 40 (1.9, 1.4-2.5)                    |            |           | <b>0.02*</b>     |
| Anorectal (569)                               | 2 (0.4, 0.1-1.3)                     |            |           |                  |
| Pharyngeal (259)                              | 2 (0.8, 0.2-2.8)                     |            |           |                  |
| Other (77)                                    | 2 (2.6, 0.7-9.0)                     |            |           |                  |
| <b>Sexual orientation and gender (n=2260)</b> |                                      |            |           |                  |
| MSM (1185)                                    | 2 (0.2, 0.0-0.6)                     |            |           | <b>&lt;0.01*</b> |
| Male heterosexual (595)                       | 19 (3.2, 2.1-4.9)                    |            |           |                  |
| Female (480)                                  | 12 (2.5, 1.4-4.3)                    |            |           |                  |
| <b>Previous GC (n=981)</b>                    |                                      |            |           |                  |
| Yes (263)                                     | 2 (0.8, 0.2-2.7)                     |            |           | 0.26*            |
| No (718)                                      | 14 (2.0, 1.2-3.2)                    |            |           |                  |
| <b>Concurrent chlamydia (n=1213)</b>          |                                      |            |           |                  |
| Yes (269)                                     | 4 (1.5, 0.6-3.8)                     |            |           | 0.08*            |
| No (940)                                      | 4 (0.4, 0.2-1.1)                     |            |           |                  |
| <b>HIV status (n=1424)</b>                    |                                      |            |           |                  |
| Positive (224)                                | 0 (0.0, 0.0-1.7)                     |            |           | 0.37*            |
| Negative (1200)                               | 9 (0.8, 0.4-1.4)                     |            |           |                  |
| <b>Age (n=3253)</b>                           |                                      |            |           |                  |
| <25 years (923)                               | 13 (1.4, 0.8-2.3)                    | 1          |           | 0.86             |
| ≥25 years (2330)                              | 31 (1.3, 0.9-1.9)                    | 0.94       | 0.49-1.81 |                  |

\* Expected value for one cell < 5, so Fisher's exact test performed

**Table A 3. Univariate association of azithromycin MICs >0.5 mg/L (previously recommended EUCAST resistance breakpoint) and patient characteristics, Euro-GASP, 2018**

|   | Azithromycin MIC<br>>0.5 mg/L N<br>(%, 95% CI) | Odds<br>ratio | 95% CI    | P<br>value |
|---|--|---------------|-----------|------------|
| <b>Site of infection (n=3061)</b>             |  |               |           |            |
| Genital (2155)                                | 275 (12.8, 11.4-14.2)                          | 1             |           |            |
| Anorectal (570)                               | 91 (16.0, 13.2-19.2)                           | 1.3           | 1.00-1.68 | 0.05       |
| Pharyngeal (259)                              | 35 (13.5, 9.9-18.2)                            | 1.07          | 0.73-1.56 | 0.73       |
| Other (77)                                    | 8 (10.4, 5.4-19.2)                             | 0.79          | 0.38-1.67 | 0.54       |
| <b>Sexual orientation and gender (n=2264)</b> |  |               |           |            |
| MSM (1186)                                    | 146 (12.3, 10.6-14.3)                          | 1             |           |            |
| Male heterosexual (595)                       | 81 (13.6, 11.1-16.6)                           | 1.12          | 0.84-1.50 | 0.44       |
| Female (483)                                  | 47 (9.7, 7.4-12.7)                             | 0.77          | 0.54-1.09 | 0.14       |
| <b>Previous GC (n=982)</b>                    |  |               |           |            |
| Yes (264)                                     | 35 (13.3, 10.3-15.2)                           | 1.07          | 0.70-1.62 | 0.76       |
| No (718)                                      | 90 (12.5, 9.7-17.9)                            | 1             |           |            |
| <b>Concurrent chlamydia (n=1215)</b>          |  |               |           |            |
| Yes (270)                                     | 35 (13.0, 9.5-17.5)                            | 1.07          | 0.72-1.61 | 0.73       |
| No (945)                                      | 115 (12.2, 10.2-14.4)                          | 1             |           |            |
| <b>HIV status (n=1428)</b>                    |  |               |           |            |
| Positive (224)                                | 24 (10.7, 7.3-15.4)                            | 0.92          | 0.51-1.26 | 0.34       |
| Negative (1204)                               | 157 (13.0, 11.3-15.1)                          | 1             |           |            |
| <b>Age (n=3257)</b>                           |  |               |           |            |
| <25 years (925)                               | 117 (12.7, 10.7-14.9)                          | 0.27          | 0.74-1.18 | 0.6        |
| ≥25 years (2332)                              | 311 (13.3, 12.0-14.8)                          | 1             |           |            |

**Table A 4. Univariate association of azithromycin MICs above/below ECOFF (>1 mg/L) and patient characteristics, Euro-GASP, 2018**

|   | Azithromycin ECOFF N<br>(%, 95% CI) | Odds<br>ratio | 95% CI    | P value |
|---|-------------------------------------|---------------|-----------|---------|
| <b>Site of infection (n=3061)</b>             |                                     |               |           |         |
| Genital (2155)                                | 163 (7.6, 6.5-8.8)                  | 1             |           |         |
| Anorectal (570)                               | 47 (8.3, 6.3-10.8)                  | 1.1           | 0.78-1.54 | 0.59    |
| Pharyngeal (259)                              | 20 (7.7, 5.1-11.6)                  | 1.02          | 0.63-1.66 | 0.93    |
| Other (77)                                    | 5 (6.5, 2.8-14.3)                   | 0.85          | 0.34-2.13 | 0.73    |
| <b>Sexual orientation and gender (n=2264)</b> |                                     |               |           |         |
| MSM (1186)                                    | 86 (7.3, 5.9-8.9)                   | 1             |           |         |
| Male heterosexual (595)                       | 45 (7.6, 5.7-10.0)                  | 1.04          | 0.72-1.52 | 0.81    |
| Female (483)                                  | 27 (5.6, 3.9-8.0)                   | 0.76          | 0.48-1.18 | 0.22    |
| <b>Previous GC (n=982)</b>                    |                                     |               |           |         |
| Yes (264)                                     | 19 (7.2, 4.7-11.0)                  | 1             |           |         |
| No (718)                                      | 52 (7.2, 5.6-9.4)                   | 0.99          | 0.58-1.71 | 0.98    |
| <b>Concurrent chlamydia (n=1215)</b>          |                                     |               |           |         |
| Yes (270)                                     | 15 (5.6, 3.4-9.0)                   | 0.82          | 0.46-1.47 | 0.51    |
| No (945)                                      | 63 (6.7, 5.2-8.4)                   | 1             |           |         |
| <b>HIV status (n=1428)</b>                    |                                     |               |           |         |
| Positive (224)                                | 8 (3.6, 2.8-6.9)                    | 0.48          | 0.23-1.01 | 0.05    |
| Negative (1204)                               | 86 (7.1, 5.8-8.7)                   | 1             |           |         |
| <b>Age (n=3257)</b>                           |                                     |               |           |         |
| <25 years (925)                               | 72 (7.8, 6.2-9.7)                   | 1.04          | 0.78-1.38 | 0.79    |
| ≥25 years (2332)                              | 175 (7.5, 6.5-8.6)                  | 1             |           |         |

**Table A 5. Univariate association of ciprofloxacin resistance/susceptibility and patient characteristics, Euro-GASP, 2017**

|   | Ciprofloxacin resistance N (% , 95% CI) | Odds ratio | 95% CI    | P value      |
|---|---|------------|-----------|--------------|
| <b>Site of infection (n=3059)</b>             |   |            |           |              |
| Genital (2154)                                | 1036 (48.1, 46.0-50.2)                  | 1          |           |              |
| Anorectal (570)                               | 317 (55.6, 51.1-59.6)                   | 1.35       | 1.12-1.63 | <b>0.001</b> |
| Pharyngeal (258)                              | 144 (55.8, 49.7-61.7)                   | 1.36       | 1.05-1.77 | <b>0.01</b>  |
| Other (77)                                    | 42 (54.55, 43.5-65.2)                   | 1.29       | 0.82-2.04 | 0.27         |
| <b>Sexual orientation and gender (n=2262)</b> |   |            |           |              |
| MSM (1184)                                    | 634 (53.6, 50.7-56.4)                   | 1.26       | 1.03-1.54 | <b>0.02</b>  |
| Male heterosexual (595)                       | 284 (47.7, 43.7-51.7)                   | 1          |           |              |
| Female (483)                                  | 200, (41.4, 37.1-45.9)                  | 0.77       | 0.61-0.99 | <b>0.04</b>  |
| <b>Previous GC (n=980)</b>                    |   |            |           |              |
| Yes (262)                                     | 134 (51.2, 45.1-52.5)                   | 1.09       | 0.82-1.45 | 0.5          |
| No (718)                                      | 351 (48.9, 45.2-52.5)                   | 1          |           |              |
| <b>Concurrent chlamydia (n=1213)</b>          |   |            |           |              |
| Yes (270)                                     | 115 (42.6, 36.8-48.6)                   | 1          |           |              |
| No (943)                                      | 482 (51.1, 47.9-54.2)                   | 1.4        | 1.07-1.85 | <b>0.01</b>  |
| <b>HIV status (n=1426)</b>                    |   |            |           |              |
| Positive (223)                                | 109 (48.9, 42.4-55.4)                   | 1.02       | 0.77-1.36 | 0.03         |
| Negative (1203)                               | 581 (48.3, 45.5-51.1)                   | 1          |           |              |
| <b>Age (n=3255)</b>                           |   |            |           |              |
| <25 years (925)                               | 431 (46.6, 43.4-49.8)                   | 1          |           |              |
| ≥25 years (2330)                              | 1207 (51.8, 49.7-53.8)                  | 1.23       | 1.06-1.44 | <b>0.007</b> |

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