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# Antimicrobial resistance in *Neisseria gonorrhoeae* isolates from foreign-born population in the European Gonococcal Antimicrobial Surveillance Programme

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## ABSTRACT

**Objectives** International spread has contributed substantially to the high prevalence of antimicrobial resistant (AMR) *Neisseria gonorrhoeae* infections worldwide. We compared the prevalence of AMR gonococcal isolates among native persons to foreign-born (reporting country different from country of birth) persons, and describe the epidemiological and clinical characteristics of foreign-born patients and their associations to AMR.

**Methods** We analysed isolates and patient data reported to the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) 2010–2014 (n=9529).

**Results** Forty-three per cent of isolates had known country of birth and 17.2% of these were from persons born abroad. Almost 50% of foreign-born were from the WHO European Region (13.1% from non-European Union [EU] and the European Economic Area [EEA] countries). Compared with isolates from natives, isolates from foreign-born had a similar level (p>0.05) of azithromycin resistance (7.5% vs 7.2%), ciprofloxacin resistance (50.0% vs 46.3%) and of decreased susceptibility to ceftriaxone (1.9% vs 2.8%); a lower rate of cefixime resistance (5.7% vs 3.6%, p=0.02), and a higher proportion of isolates producing penicillinase (8.4% vs 11.7%, p=0.02). Among isolates from persons born outside EU/EEA, the level of decreased susceptibility to ceftriaxone was higher (1.8% vs 3.5%, p=0.02), particularly in those from the WHO Eastern Mediterranean Region and non-EU/EEA WHO European countries (1.9% vs 9.6% and 8.7%, respectively, p<0.01). In multivariable analysis, foreign-born patients with AMR isolates were more likely to be from non-EU/EEA WHO European countries (adjusted OR [aOR]: 3.2, 95% CI 1.8 to 5.8), WHO Eastern Mediterranean countries (aOR: 1.8, 95% CI 1.1 to 3.3) and heterosexual males (aOR: 1.8, 95% CI 1.2 to 2.7).

**Conclusions** Importation of AMR strains remains an important threat in the EU/EEA. Research to improve understanding of sexual networks within foreign born and sexual tourism populations could help to inform effective tailor-made interventions. The Euro-GASP demonstrates the public health value of quality-assured surveillance of gonococcal AMR and the need for strengthened AMR surveillance, particularly in the non-EU/EEA WHO European Region.

## INTRODUCTION

*Neisseria gonorrhoeae* (gonococcus) has shown an extraordinary ability to develop antimicrobial resistance (AMR) to any antimicrobial introduced for gonorrhoea treatment. In the WHO European Region, a high prevalence of resistance to ciprofloxacin, penicillins and tetracycline has been observed for many years. In the last decade, in vitro and clinical resistance, resulting in treatment failures, to the extended-spectrum cephalosporins (ESCs) cefixime and ceftriaxone, as well as azithromycin have also emerged.[1–8]

To mitigate the emergence and/or dissemination of AMR gonococcal strains, ceftriaxone (500 mg single dose intramuscularly) plus azithromycin (2 g single oral dose) is currently recommended for empirical first-line dual therapy of uncomplicated gonorrhoea in Europe. Similar dual therapy regimens (ceftriaxone 250–500 mg plus azithromycin 1 g) are recommended in the USA, Canada, Australia, Brazil and globally by WHO, that is, when local, comprehensive, regular and quality-assured AMR surveillance is not supporting monotherapy. However, in some countries ceftriaxone high-dose monotherapy remains recommended, for example, Japan (1 g) and China (0.5–1 g).[1 8 9] The emergence of ceftriaxone resistance and relatively high rates of azithromycin resistance reported in Europe and globally[1–3 5–10] threaten the effectiveness of these regimens, which are currently the last evidence-based options for first-line empirical treatment. The first global failure to treat gonorrhoea with dual antimicrobial therapy was reported in 2016.[11] In early 2018, the first gonococcal strain with ceftriaxone resistance combined with high-level resistance to azithromycin was reported from England[12] followed by two similar cases in Australia.[13] Due to the development of difficult-to-treat or possibly untreatable gonorrhoea, AMR *N. gonorrhoeae* has been designated as a priority global health issue by WHO.[9]

Robust gonococcal AMR surveillance is essential to monitor the emergence and spread of AMR gonococcal strains,[2 3 6–8] which has been strongly emphasised by the Global Action Plan[14] and the European Response Plan,[3] developed by WHO

and the European Centre for Disease Prevention and Control (ECDC), respectively. Since 2009, ECDC has coordinated the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP), which is a sentinel surveillance system that monitors antimicrobial susceptibility of gonococcal isolates across Member States of the European Union (EU) and the European Economic Area (EEA). Linking the laboratory data to epidemiological data of the corresponding patients, Euro-GASP allows surveillance to be focused in subpopulations and analysis of patient risk groups.[3 6]

In Europe, international migration has been significant during recent decades.[15 16] Particular groups of migrants, especially those of lower socioeconomic status, refugees and sex workers, can be more at risk and suffer disproportionally from STIs,[17] including gonorrhoea.[18 19] Migrants and other mobile populations can play a significant role in the international transmission of AMR including AMR gonococcal strains, and are considered key populations for gonorrhoea control by WHO.[2 3 14 20] Historically, most gonococcal AMR is considered to have initially developed in the WHO Western Pacific Region (WPR), particularly in Japan, and subsequently spread globally.[2 8] The reasons for the initial emergence of gonococcal AMR in WPR are multifaceted and include the high rates of gonorrhoea, the lack of effective disease-control measures, the extensive use and misuse of antimicrobials and the lack of optimal monitoring of AMR and treatment failures.[2 8 9 14]

The objectives of this study were to investigate the prevalence of AMR gonococcal isolates among foreign-born cases of gonorrhoea reported through Euro-GASP from 2010 to 2014, compare isolates from such cases with gonococcal isolates from native born cases, and describe the epidemiological and clinical characteristics of foreign-born patients with AMR gonococcal isolates (resistance to at least one antimicrobial), with the purpose of improving the understanding of the distribution of AMR gonococcal strains among patient populations in the EU/EEA and inform targeted interventions.

## MATERIALS AND METHODS

### Data source

We analysed Euro-GASP isolates and corresponding patient data from 2010 to 2014. Euro-GASP has been described in detail elsewhere.[3 6 21] Briefly, participating sites in each Euro-GASP country collected around 100 gonococcal isolates (200 isolates in the UK, Spain and the Netherlands, which report higher numbers of gonorrhoea cases) from consecutive gonorrhoea patients (one isolate per patient and infection episode). The collection periods were April–May and October–November during 2010–2013, and September–November in 2014. We defined persons as foreign-born when the reporting country differed from the country of birth[20] and native as those with reporting country identical to country of birth.[22] Geographic region of origin was assigned based on WHO definitions.[7]

### Antimicrobial susceptibility testing

AMR testing was conducted using Etest for ceftriaxone and cefixime, agar dilution breakpoint method or Etest for azithromycin and ciprofloxacin and nitrocefin test for detection of penicillinase production.[3 6 21] The WHO gonococcal reference strains WHO G, K, M, O and P[23] should be used for quality control and all laboratories performing AMR testing are required to participate with acceptable results in the Euro-GASP external quality assessment. The minimum inhibitory concentrations (MICs; mg/L) of each antimicrobial were interpreted into resistance, intermediate susceptibility or susceptibility using breakpoints stated by the European Committee on Antimicrobial Susceptibility Testing.[24] Strains with a ceftriaxone MIC of 0.12 mg/L have previously caused gonorrhoea treatment failures and can be considered to have a decreased susceptibility.[8 25 26] Only whole MIC doubling dilutions were analysed.

### Epidemiological and clinical variables and statistical analysis

Epidemiological and clinical data analysed included: year of diagnosis, age (<25, 25–44, ≥45 years), area of origin (European Region [EUR; 28 EU countries, 3 EEA countries and 23 non-EU/EEA countries]; Eastern Mediterranean Region [EMR]; Region of the Americas [AMRO]; African Region [AFR]; South-East Asia Region [SEAR] and WPR), sexual orientation (heterosexual females, heterosexual males and men who have sex with men [MSM]), site of infection (anorectal, urogenital and pharyngeal), HIV status (positive, negative), previously diagnosed with gonorrhoea (yes, no) and probable country of infection (reporting country, others). AMR isolates from foreign-born patients were compared with those from native patients; and AMR isolates from patients born in EU/EEA were compared with AMR isolates from patients born outside EU/EEA. In our analysis, we excluded countries that had not reported consistently throughout the study period (Estonia, Iceland, Poland and Romania). Statistical significance was determined by Pearson's $\chi^2$ test or by Fisher's exact test if cell numbers were <5, with two-sided p values of <0.05 considered as significant. Data from 2010 to 2014 were combined. Among foreign-born patients, the association of gonococcal infection resistant to at least one antimicrobial with epidemiological and clinical characteristics were investigated using univariate and multivariable logistic regression analyses. Results were expressed with crude ORs (cORs) and adjusted ORs (aORs) and their 95% CI. Those variables that were associated with the outcome in univariate models at p<0.10 were included in the multivariable model. Using a backward stepwise approach, those that remained significant (p<0.05) were retained in the final model. Statistical analysis was performed in SPSS V.20.

### Ethical considerations

All examined gonococcal isolates were cultured and stored as part of routine diagnostics (standard care). Patient data were reported as part of a surveillance programme (EU Decisions 2119/98/EC and 1082/2013/EU) with no patient-identifiable information. Accordingly, separate ethical approval for the study was not required.

## RESULTS

### Study population

Out of the 9529 isolates, the patient's country of birth was known for 4098 (43%) isolates and was reported by 14 (60.8%) of the Euro-GASP countries (online supplementary table 1). Of these isolates (n=4098), 704 (17.2%) were from foreign-born patients. The Netherlands (34.9%), Ireland (13.1%) and the UK (12.9%) reported 60.9% of the isolates from foreign-born patients (online supplementary table 1). Among the foreign-born patients, 345 (49%) were from another country in WHO EUR (253 [35.9%] from EU/EEA and 92 [13.1%] from non-EU/EEA countries), 174 (24.7%) from WHO AMRO, 83 (11.8%) from WHO EMR, 55 (7.8%) from WHO AFR, 25 (3.6%) from WHO WPR and 22 (3.1%) from WHO SEAR. The proportion of isolates reported from foreign-born persons did not vary

significantly during the study period (ranging from 13.1% to 18.5%; p=0.19).

### Antimicrobial resistance and decreased susceptibility to ceftriaxone from persons born outside the reporting country

The proportion of isolates with AMR to at least one antimicrobial was similar for foreign-born persons compared with isolates from native persons (natives: 53.5%; foreign born: 52.0%, p=0.45). Compared with isolates from native persons, isolates from foreign-born had lower level of cefixime resistance (5.7% vs 3.6%, p=0.02), and similar rates of azithromycin resistance (7.5% vs 7.2%, p=0.8), ciprofloxacin resistance (50.0% vs 46.3%, p=0.07) and decreased susceptibility to ceftriaxone (1.9 vs 2.8, p=0.10). Only the proportion of isolates producing penicillinase was higher among foreign-born persons (8.4% vs 11.7%, p=0.02). All isolates from foreign-born persons were also susceptible to ceftriaxone; however, four (0.1%) isolates from natives (two MSM and two heterosexual males) were resistant to ceftriaxone, all with a ceftriaxone MIC of 0.25 mg/L (table 1).

The proportion of isolates with AMR to at least one antimicrobial was significantly higher among those born in non-EU/EEA WHO EUR countries and in WHO EMR countries than in native patients (53.5% vs 78.3% and 68.7%, respectively, p<0.01). Those born in non-EU/EEA WHO EUR countries had the highest rates of resistance to ciprofloxacin (71.7%), azithromycin (11.2%) and cefixime (9.1%), and the second highest rate of decreased susceptibility to ceftriaxone (8.7%). Isolates from patients born in WHO EMR had the highest level of decreased susceptibility to ceftriaxone (9.6%), and additionally the second highest rate of resistance to ciprofloxacin (66.3%) and cefixime (8.9%). The rates of decreased susceptibility to ceftriaxone in those coming from WHO EMR countries and non-EU/EEA WHO EUR were significantly higher than in native patients (1.9% vs 9.6% and 8.7%, respectively, p<0.01) (table 1). Data including isolates with unknown country of birth are summarised in online supplementary table 2.

### Antimicrobial resistance in isolates from persons born outside the EU/EEA

Isolates from patients born outside the EU/EEA when compared with patients born in the EU/EEA had similar levels of resistance to ciprofloxacin (n=1796, 49.4% vs n=223, 49.4%; p=1.0), azithromycin (n=268, 7.4% vs n=33, 7.5%; p=1.0), cefixime (n=198, 5.5% vs n=19, 4.3%; p=0.3) and penicillinase production (n=261, 8.6% vs n=36, 11.8%; p=0.07). All four ceftriaxone-resistant isolates were from patients born in the EU/EEA; however, the proportion of decreased susceptibility to ceftriaxone was higher among isolates from patients born outside the EU/EEA (n=67, 1.8% vs n=16, 3.5%; p=0.02).

### Epidemiological and clinical characteristics of antimicrobial resistant isolates from foreign-born patients compared with isolates from native patients

Foreign-born patients with AMR isolates had a mean age of 31.1 years (SD 9.1) and natives of 33.0 years (11.3). Compared with isolates from native persons, foreign-born persons were younger (82.9% vs 89.6% were <45 years, p<0.01), had higher proportions of anorectal (11.0% vs 18.4%, p<0.01) and lower frequency of urogenital (83.9% vs 74.7%, p<0.01) infections, as well as higher proportion of infections acquired abroad compared with the reporting country (5.7% vs 11.0%, p<0.01)

**Table 1** Antimicrobial resistance and decreased susceptibility to ceftriaxone by region of birth, Euro-GASP isolates 2010–2014

| | Country of birth of foreign-born* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | WHO EUR | | | | | | | | | |
| | EU/EEA, no. (%) | Non-EU/EEA, no. (%) | WHO EMR, no. (%) | WHO AMRO, no. (%) | WHO AFR, no. (%) | WHO SEAR, no. (%) | WHO WPR, no. (%) | Total foreign-born, no. (%) | Natives, no. (%) | P value† |
| Ciprofloxacin resistant (n=4088)‡§ | 103 (40.7) | 66 (71.7) | 55 (66.3) | 54 (31.0) | 20 (36.4) | 14 (63.6) | 14 (56.0) | 326 (46.3) | 1693 (50.0) | 0.07 |
| Azithromycin resistant (n=4048)§ | 17 (6.7) | 10 (11.2) | 6 (7.6) | 15 (8.6) | 0 (0.0) | 1 (4.8) | 1 (4.0) | 50 (7.2) | 251 (7.5) | 0.8 |
| Cefixime resistant (n=4050)§ | 6 (2.4) | 8 (9.1) | 7 (8.9) | 2 (1.1) | 1 (1.8) | 1 (4.5) | 0 (0.0) | 25 (3.6) | 192 (5.7) | 0.02 |
| Ceftriaxone resistant (n=4098)§ | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (0.1) | 1.0 |
| Decreased susceptibility to ceftriaxone (n=4098)§ | 4 (1.6) | 8 (8.7) | 8 (9.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 20 (2.8) | 63 (1.9) | 0.10 |
| Penicillinase production (n=3352) | 21 (11.6) | 9 (11.4) | 11 (16.7) | 7 (7.4) | 4 (10.3) | 1 (7.1) | 4 (28.6) | 57 (11.7) | 240 (8.4) | 0.02 |
| Resistant isolates (n=4098) | 118 (46.6) | 72 (78.3) | 57 (68.7) | 68 (39.1) | 22 (40.0) | 14 (63.6) | 15 (60.0) | 366 (52.0) | 1817 (53.5) | 0.45 |

The MIC ranges in the isolates resistant to ciprofloxacin, azithromycin, cefixime and ceftriaxone were 0.125–>32, 1–>256, 0.25–0.5 and 0.25 mg/L, respectively.
*Divided into WHO regions: EUR, European Region (28 European Union [EU] countries, 3 European Economic Area [EEA] countries and 23 non-EU/EEA countries).
†P value (Pearson's $\chi^2$ test or by Fisher's exact test if cell numbers were <5) between total number of isolates from foreign-born and native patients.
‡Number of isolates with known country of birth tested for each antimicrobial.
§The clinical breakpoints (susceptible, resistant) were as follows: ceftriaxone and cefixime (MIC ≤0.12 mg/L, MIC >0.12 mg/L), azithromycin (MIC ≤0.25 mg/L, MIC >0.5 mg/L) and ciprofloxacin (MIC ≤0.03 mg/L, MIC >0.06 mg/L). Furthermore, strains with a ceftriaxone MIC of 0.12 mg/L have previously caused gonorrhoea treatment failures and can be considered to have a decreased susceptibility.[8 25 26] Only whole MIC doubling dilutions were analysed.
AFR, African Region; AMRO, Region of the Americas; EMR, Eastern Mediterranean Region; Euro-GASP, European Gonococcal Antimicrobial Surveillance Programme; MIC, minimum inhibitory concentration; SEAR, South-East Asia Region; WPR, Western Pacific Region.

**Table 2** Epidemiological and clinical characteristics of patients with antimicrobial resistant isolates by country of birth (n=2183), Euro-GASP 2010–2014

| Epidemiological and clinical characteristics | | Country of birth: Native no. (%) | Country of birth: Foreign-born no. (%) | P value | P value* |
|---|---|---|---|---|---|
| Year of diagnosis (n=2183) | 2010 | 225 (12.4) | 31 (8.5) | 0.02 | 0.04 |
| | 2011 | 383 (21.1) | 66 (18.0) | | 0.2 |
| | 2012 | 393 (21.6) | 99 (27.0) | | 0.02 |
| | 2013 | 443 (24.4) | 84 (23.0) | | 0.59 |
| | 2014 | 373 (20.5) | 86 (23.5) | | 0.2 |
| Age (years) (n=2165) | <25 | 459 (25.5) | 96 (26.3) | <0.01 | 0.79 |
| | 25–44 | 1033 (57.4) | 231 (63.3) | | 0.04 |
| | ≥45 | 308 (17.1) | 38 (10.4) | | <0.01 |
| Sexual orientation (n=1737) | Heterosexual females | 169 (12.1) | 29 (8.5) | 0.14 | – |
| | Heterosexual males | 637 (45.7) | 158 (46.2) | | – |
| | Men who have sex with men | 589 (42.2) | 155 (45.3) | | – |
| Isolation site (n=2127) | Anorectal | 195 (11.0) | 66 (18.4) | <0.01 | <0.01 |
| | Urogenital | 1484 (83.9) | 268 (74.7) | | <0.01 |
| | Pharyngeal | 89 (5.0) | 25 (7.0) | | 0.15 |
| HIV status (n=1396) | Positive | 144 (12.7) | 42 (15.8) | 0.19 | – |
| | Negative | 987 (87.3) | 223 (84.2) | | – |
| Previous gonorrhoea (n=1478) | Yes | 181 (14.7) | 31 (12.8) | 0.48 | – |
| | No | 1054 (85.3) | 212 (87.2) | | – |
| Probable country of infection (n=1328) | Reporting country | 1081 (94.3) | 162 (89.0) | <0.01 | – |
| | Other country | 65 (5.7) | 20 (11.0) | | – |

*Calculated only for those variables with more than two categories and p value <0.05.
Euro-GASP, European Gonococcal Antimicrobial Surveillance Programme.

(table 2). Data including isolates with unknown country of birth are summarised in online supplementary table 3.

### Risk factors for antimicrobial resistant isolates among foreign-born patients

Among foreign-born persons, those with *N. gonorrhoeae* isolates resistant to at least one antimicrobial were found to be more likely from non-EU/EEA WHO EUR countries (cOR: 4.1, 95% CI 2.3 to 7.1) and from WHO EMR (cOR: 2.5, 95% CI 1.4 to 4.2), heterosexual males (cOR: 2.3, 95% CI 1.6 to 3.2), HIV negative (cOR: 1.7, 95% CI 1.1 to 2.7), without a previous gonorrhoea episode (cOR: 1.7, 95% CI 1.0 to 2.9) and with urogenital site of infection (cOR: 1.9, 95% CI 1.3 to 2.8). In the multivariable analysis, the associations remained significant for being from non-EU/EEA WHO EUR country (aOR: 3.2, 95% CI 1.8 to 5.8), from EMR (aOR: 1.8, 95% CI 1.1 to 3.3) and heterosexual male (aOR: 1.8, 95% CI 1.2 to 2.7) (table 3). There was no association with age and year of diagnosis.

## DISCUSSION

In our study, the proportion of overall AMR isolates among native and foreign-born patients (53.5%, n=1817, vs 52.0%, n=366; p=0.45) was similar. However, gonococcal AMR levels for cefixime (more common among native patients) and penicillinase production (more common among foreign-born patients) differed significantly depending on the region of birth of patients.

Over the last decade, international transmission of AMR gonococcal strains has been recorded in detail, for example, the multidrug-resistant NG-MAST genogroup 1407 clone associated with cefixime and ciprofloxacin resistance, increased MICs of ceftriaxone and azithromycin and causing the majority of verified cephalosporin treatment failures has been spreading in Europe, the USA and Canada.[2 8 27–29] Furthermore, resistance or decreased susceptibility to ceftriaxone and/or resistance to azithromycin has been described in many regions globally.[7] Recently, the first three cases of ceftriaxone resistance combined with high-level resistance to azithromycin[12 13] have been identified, two of them in men who had travelled to southeast Asia and had sexual intercourse with locally resident women. During recent years, in the EU/EEA, the level of cefixime resistance has decreased and appeared to stabilise at around 2%, ceftriaxone resistance has been exceedingly rare and azithromycin resistance has been stably relatively high (approximately 7%–8%).[6]

The role of importation of AMR strains in the transmission and prevalence of AMR in a country or region is difficult to elucidate and is largely unexplored. Global population mobility and international travel including sex tourism are providing additional challenges in the prevention and control of *N. gonorrhoeae* AMR internationally.[30] Recent data from Euro-GASP also showed that the majority (94%) of AMR gonococcal isolates are most likely acquired in the reporting country.[21] In the present study, the higher rate of decreased susceptibility to ceftriaxone in isolates from persons born outside the EU/EEA (1.8% vs 3.5%, p=0.02) and particularly in those from WHO EMR countries and non-EU/EEA WHO EUR (1.9% vs 9.6% and 8.7%, respectively, p<0.01), and the higher proportion of foreign-born patients likely infected abroad versus in the reporting country (5.7% vs 11.0%, p<0.01) indicate that importation of AMR gonococcal strains, and especially with decreased susceptibility to ceftriaxone, to the EU/EEA by foreign-born persons remains a threat. Despite this, native cases, although more likely to acquire gonorrhoea in the reporting country, are larger in number and therefore may represent a greater risk for importation of gonorrhoea. Further detailed molecular investigations of the international transmission of gonococcal strains with decreased susceptibility or resistance to ESCs and azithromycin are essential.[27]

Although absolute numbers were small, isolates from foreign-born persons from non-EU/EEA WHO EUR countries had the highest rates of resistance to ciprofloxacin (71.7%), azithromycin (11.2%) and cefixime (9.1%), and together with those from WHO EMR, of decreased susceptibility to ceftriaxone (8.7% and 9.6%, respectively). The major challenge in the non-EU/EEA part of the WHO EUR Region (former Soviet Union countries in Eastern Europe and Central Asia) is the very limited quality-assured surveillance of gonococcal AMR.[4 5 7] [w1,w2] In this region, the burden of gonorrhoea is estimated to be relatively high, and, together with suboptimal laboratory diagnostics, lack of gonococcal culture, scarce surveillance of both gonorrhoea cases and gonococcal AMR and misuse of antimicrobials of uncertain quality and origin without prescription from a physician predispose for emergence and rapid spread of gonococcal AMR.[7] [w1–w3] The rapid spread of AMR might be further accelerated by the introduction AMR gonococcal strains in more antimicrobial susceptible populations. For example, it has been shown that some ciprofloxacin resistance mutations enhance the fitness of the gonococcal strains,[w4] which can result in an out-competition of the ciprofloxacin-susceptible strains due to both the ciprofloxacin resistance and the enhanced fitness. Despite that quality-assured data are available from Russia and Belarus,[4 5] a quality-assured GASP in the Eastern and Central Asian part of

**Table 3** Univariate and multivariate analysis of foreign-born patients with antimicrobial resistant isolates (n=366), Euro-GASP 2010–2014

| Epidemiological and clinical characteristics | | Resistant isolates from foreign-born patients | | | | |
|---|---|---|---|---|---|---|
| | | | Crude OR | | Adjusted OR | |
| | | No. (%) | (95% CI) | P value | (95% CI) | P value |
| Year of diagnosis (n=704) | | | | 0.21 | – | – |
| | 2010 | 31/50 (62.0) | 1 | | | |
| | 2011 | 66/143 (46.2) | 0.5 (0.2 to 1.0) | 0.05 | | |
| | 2012 | 99/183 (54.1) | 0.7 (0.3 to 1.3) | 0.32 | | |
| | 2013 | 84/173 (48.6) | 0.5 (0.3 to 1.1) | 0.09 | | |
| | 2014 | 86/155 (55.5) | 0.7 (0.3 to 1.4) | 0.41 | | |
| Age (years) (n=701) | | | | 0.25 | – | – |
| | <25 | 96/177 (54.2) | 0.7 (0.4 to 1.4) | 0.4 | | |
| | 25–44 | 231/461 (50.1) | 0.6 (0.3 to 1.1) | 0.13 | | |
| | ≥45 | 38/63 (60.3) | 1 | | | |
| Area of origin (n=704) | | | | <0.01 | | <0.01 |
| | EU/EEA | 118/253 (46.6) | 1 | | 1 | |
| | Non-EU/EEA WHO EUR | 72/92 (78.3) | 4.1 (2.3 to 7.1) | <0.01 | 3.2 (1.8 to 5.8) | <0.01 |
| | WHO EMR | 57/83 (68.7) | 2.5 (1.4 to 4.2) | <0.01 | 1.8 (1.1 to 3.3) | 0.02 |
| | WHO AMRO | 68/174 (39.1) | 0.7 (0.4 to 1.0) | 0.12 | 0.7 (0.5 to 1.1) | 0.21 |
| | WHO AFR | 22/55 (40.0) | 0.7 (0.4 to 1.3) | 0.37 | 0.6 (0.3 to 1.2) | 0.17 |
| | WHO SEAR | 14/22 (63.6) | 2.0 (0.8 to 4.9) | 0.13 | 1.9 (0.7 to 5.0) | 0.13 |
| | WHO WPR | 15/25 (60.0) | 1.7 (0.7 to 3.9) | 0.2 | 1.6 (0.7 to 3.9) | 0.23 |
| Sexual orientation (n=677) | | | | <0.01 | | <0.01 |
| | Heterosexual females | 29/67 (43.3) | 1.0 (0.6 to 1.7) | 0.94 | 1.0 (0.6 to 1.8) | 0.81 |
| | Heterosexual males | 158/248 (63.7) | 2.3 (1.6 to 3.2) | <0.01 | 1.8 (1.2 to 2.7) | <0.01 |
| | Men who have sex with men | 155/362 (42.8) | 1 | | 1 | |
| Isolation site (n=694) | | | | <0.01 | – | – |
| | Ano-rectal | 66/164 (40.2) | 1 | | | |
| | Urogenital | 268/469 (57.1) | 1.9 (1.3 to 2.8) | <0.01 | | |
| | Pharyngeal | 25/61 (41.0) | 1.0 (0.5 to 1.8) | 0.92 | | |
| HIV status (n=555) | Positive | 42/115 (36.5) | 1 | <0.01 | – | – |
| | Negative | 223/440 (50.7) | 1.7 (1.1 to 2.7) | | | |
| Previous gonorrhoea (n=425) | Yes | 31/68 (45.6) | 1 | 0.03 | – | – |
| | No | 212/357 (59.4) | 1.7 (1.0 to 2.9) | | | |
| Probable country of infection (n=319) | Reporting country | 162/286 (56.6) | 1 | 0.66 | – | – |
| | Other country | 20/33 (60.6) | 1.1 (0.5 to 2.4) | | | |

EEA, European Economic Area; EU, European Union; Euro-GASP, European Gonococcal Antimicrobial Surveillance Programme; WHO AFR, WHO African Region; WHO AMRO, WHO Region of the Americas; WHO EMR, WHO Eastern Mediterranean Region; WHO SEAR, WHO South-East Asia Region; WHO WPR, WHO Western Pacific Region.

WHO EUR is still needed. As previously stressed,[7] such a GASP is crucial to also develop in the WHO EMR.

In the multivariable analysis, among foreign-born persons, those from non-EU/EEA WHO EUR (aOR: 3.2, 95% CI 1.8 to 5.8), from WHO EMR (aOR: 1.8, 95% CI 1.1 to 3.3) and heterosexual males (aOR: 1.8, 95% CI 1.2 to 2.7) were associated with AMR gonococcal isolates. Most likely, area of origin, country of infection, sexual orientation and additional epidemiological characteristics can play a major role in the spread of AMR gonococcal strains in many countries. These results are in line with recent data from Euro-GASP, where geometric means were higher for both cefixime and ceftriaxone MICs for heterosexual males compared with MSM (p<0.001) and females (cefixime: p=0.014, ceftriaxone: p=0.025).[w5] In England and Wales, a higher rate of decreased susceptibility to ceftriaxone has been reported within MSM compared with heterosexual males.[w6] Among heterosexual males, those with older age (especially ≥35 years), rapid partner turnover and sex abroad also had a higher proportion of decreased susceptibility to ceftriaxone.[w6] The emergence and spread of gonococcal AMR is such a dynamic phenomenon that transmission of AMR gonococcal strains may spread from heterosexual to MSM networks or vice versa very quickly. Further studies on the molecular epidemiology of AMR gonococcal strains[27] can contribute to a better understanding of epidemiology and population dynamics in the national and international spread of AMR gonococcal strains.

The present study includes other limitations such as the absence of participation of some countries along with differences in representativeness that limit the generalisability of the findings. In addition, the limited number of isolates resistant to ceftriaxone, cefixime and azithromycin did not allow for analysis by antimicrobial. When considering the AMR all together, the high levels of resistance to ciprofloxacin account for most of the AMR described. Missing patient data, particularly for country of birth (57%), and the different proportions of reported patient characteristics between different countries may bias the results. The results might also not be representative of all foreign-born cases of gonorrhoea as some categories of foreign-born persons such as refugees, undocumented migrants, trafficked people, migrant MSM and subgroups of migrant women can

face particular challenges in accessing healthcare services. Male heterosexuals are over-represented in Euro-GASP, likely because the majority of males with urogenital gonorrhoea are symptomatic and attend for testing, the high sensitivity of culture for these males, and possibly due to undeclared or misclassified MSM. In some Euro-GASP countries, under-reporting of patient data is also due to ethical or juridical restrictions around linking patient and isolate data. The under-representation of patients younger than 25 years in Euro-GASP may be due to *Chlamydia trachomatis* screening programmes targeting this group and their use of dual *C. trachomatis* and *N. gonorrhoeae* molecular tests instead of culture for diagnosis.

Increasing the number of participating countries and examined isolates, facilitating and promoting culture of *N. gonorrhoeae*, achieving more complete reporting of epidemiological data, particularly data on country of birth, country of infection and sexual orientation and increasing the representativeness are high priorities for Euro-GASP.[6]

## CONCLUSIONS

Importation of AMR gonococcal strains into the EU/EEA from other geographic regions worldwide poses a threat for emergence and subsequent rapid spread of gonococcal AMR in Europe. Effective disease-control measures targeted towards foreign-born originating from countries with higher levels of gonococcal AMR and those returning to their country of birth to visit friends and relatives could be valuable. These results from Euro-GASP demonstrate the public health value of quality-assured surveillance of gonococcal AMR, which is required throughout the WHO European Region. Improving the completeness of demographic and risk factor data in Euro-GASP would provide strengthened information for public health action. It is also essential to further strengthen and expand the WHO Global GASP,[7] particularly in regions with very limited AMR data such as WHO EMR and WHO AFR, but also in regions with high rates of AMR such as SEAR and especially WPR. Further research to improve the understanding of sexual networks within foreign-born and sexual tourism populations will help to inform effective tailor-made interventions.

Additional references can be found in the online supplementary file.

### Key messages

- Importation of antimicrobial resistant (AMR) gonococcal strains and particularly those with decreased susceptibility to ceftriaxone, into the European Union/European Economic Area from other geographic regions worldwide is of importance.
- Area of geographic origin and sexual orientation of patients are both important risk factors for AMR in gonococcal strains.
- Robust surveillance of *Neisseria gonorrhoeae* antimicrobial susceptibility globally is essential to identify emerging AMR, monitor AMR trends and inform treatment guidelines.
- Implementation of more effective disease-control measures, including these related to foreign-born populations that originate from countries with increased AMR, is needed.

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**APPENDIX, SUPPLEMENTARY FILE**

**Table 1** *Neisseria gonorrhoeae* isolates from foreign-born and native patients in countries reporting country of birth, Euro-GASP 2010-2014

| COUNTRIES REPORTING COUNTRY OF BIRTH | FOREIGN BORN No. (%) | NATIVE No. (%) | TOTAL No. (%) |
|---|---|---|---|
| THE NETHERLANDS | 246 (34.9) | 577 (17.0) | 823 (20.1) |
| IRELAND | 92 (13.1) | 162 (4.8) | 254 (6.2) |
| UNITED KINGDOM | 91 (12.9) | 216 (6.4) | 307 (7.5) |
| GREECE | 86 (12.2) | 315 (9.3) | 401 (9.8) |
| ITALY | 75 (10.7) | 293 (8.6) | 368 (9.0) |
| DENMARK | 52 (7.4) | 389 (11.5) | 441 (10.8) |
| MALTA | 19 (2.7) | 58 (1.7) | 77 (1.9) |
| SLOVAKIA | 10 (1.4) | 493 (14.5) | 503 (12.3) |
| BELGIUM | 10 (1.4) | 104 (3.1) | 114 (2.8) |
| SLOVENIA | 9 (1.3) | 197 (5.8) | 206 (5.0) |
| GERMANY | 7 (1.0) | 61 (1.8) | 68 (1.7) |
| HUNGARY | 4 (0.6) | 131 (3.9) | 135 (3.3) |
| CYPRUS | 3 (0.4) | 29 (0.9) | 32 (0.8) |
| PORTUGAL | 0 (0.0) | 369 (10.9) | 369 (9.0) |
| TOTAL | 704 (100.0) | 3394 (100.0) | 4098( 100.0) |



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**Table 2** Antimicrobial resistance and decreased susceptibility to ceftriaxone by known country of birth, Euro-GASP isolates 2010-2014

| | FOREIGN BORN, No. (%) | NATIVES, No. (%) | UNKNOWN COUNTRY OF BIRTH, No. (%) | TOTAL, No (%) |
|---|---|---|---|---|
| **CIPROFLOXACIN RESISTANT** (n=9519) | 326 (46.3) | 1693 (50.0) | 2791 (51.4) | 4810 (50.5) |
| **AZITHROMYCIN RESISTANT** (n=9479) | 50 (7.2) | 251 (7.5) | 283 (5.2) | 584 (6.2) |
| **CEFIXIME RESISTANT** (n=9479) | 25 (3.6) | 192 (5.7) | 289 (5.3) | 506 (5.3) |
| **CEFTRIAXONE RESISTANT** (n=9529) | 0 (0.0) | 4 (0.1) | 21 (0.4) | 25 (0.3) |
| **DECREASED SUSCEPTIBILITY TO CEFTRIAXONE** (n=9529) | 20 (2.8) | 63 (1.9) | 113 (2.1) | 196 (2.1) |
| **PENICILLINASE PRODUCTION** (n=8560) | 57 (11.7) | 240 (8.4) | 708 (13.6) | 1005 (11.7) |
| **RESISTANT ISOLATES** (n=9529) | 366 (52.0) | 1817 (53.5) | 3030 (55.8) | 5213 (54.7) |



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**Table 3** Epidemiological characteristics of antimicrobial resistant Euro-GASP isolates (n=5213) by country of birth, 2010-2014

| | COUNTRY OF BIRTH | | |
|---|---|---|---|
| | **UNKNOWN COUNTRY OF BIRTH** | **FOREIGN BORN** | **NATIVES** |
| **YEAR OF DIAGNOSIS** (n=5213) | | | |
| 2010 | 733 (24.2) | 31 (8.5) | 225 (12.4) |
| 2011 | 521 (17.2) | 66 (18.0) | 383 (21.1) |
| 2012 | 552 (18.2) | 99 (27.0) | 393 (21.6) |
| 2013 | 578 (19.1) | 84 (23.0) | 443 (24.4) |
| 2014 | 646 (21.3) | 86 (23.5) | 373 (20.5) |
| **AGE** (years) (n=5046) | | | |
| <25 | 828 (28.7) | 96 (26.3) | 459 (25.5) |
| 25-44 | 1589 (55.2) | 231 (63.3) | 1033 (57.4) |
| ≥45 | 464 (16.1) | 38 (10.4) | 308 (17.1) |
| **AREA OF ORIGIN** (n=704) | | | |
| EU/EEA | - | 118 (32.2) | - |
| Non-EU/EEA WHO EUR | - | 72 (19.7) | - |
| WHO EMR | - | 57 (15.6) | - |
| WHO AMRO | - | 68 (18.6) | - |
| WHO AFR | - | 22 (6.0) | - |
| WHO SEAR | - | 14 (3.8) | - |
| WHO WPR | - | 15 (4.1) | - |
| **SEXUAL ORIENTATION** (n=2666) | | | |
| Heterosexual females | 189 (20.3) | 29 (8.5) | 169 (12.1) |
| Heterosexual males | 407 (43.8) | 158 (46.2) | 637 (45.7) |
| Men who have sex with men | 333 (35.8) | 155 (45.3) | 589 (42.2) |
| **ISOLATION SITE** (n=4852) | | | |
| Ano-rectal | 208 (7.6) | 66 (18.4) | 195 (11.0) |
| Urogenital | 2392 (87.8) | 268 (74.7) | 1484 (83.9) |
| Pharyngeal | 125 (4.6) | 25 (7.0) | 89 (5.0) |
| **HIV STATUS** (n=1726) | | | |
| Positive | 72 (21.8) | 42 (15.8) | 144 (12.7) |
| Negative | 258 (78.2) | 223 (84.2) | 987 (87.3) |



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| **PREVIOUS GONORRHOEA** (n=2042) | | | |
|---|---|---|---|
| Yes | 161 (28.5) | 31 (12.8) | 181 (14.7) |
| No | 403 (71.5) | 212 (87.2) | 1054 (85.3) |
| **PROBABLE COUNTRY OF INFECTION** (n=1794) | | | |
| Reporting country | 428 (91.8) | 162 (89.0) | 1081 (94.3) |
| Other country | 38 (8.2) | 20 (11.0) | 65 (5.7) |



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**RESUMEN**

**Objetivos** La transmisión internacional tiene un papel relevante en la elevada prevalencia global de la infección *Neisseria gonorrhoeae* resistente a los antibióticos (NGR). Comparamos la prevalencia de muestras de infección gonocócica resistente entre personas autóctonas y extranjeras (país que reportó el caso diferente del país de nacimiento), y describimos las características epidemiológicas y clínicas de los pacientes extranjeros y su asociación con la NGR.

**Métodos** Analizamos muestras y la información de los pacientes reportada al European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) entre 2010-2014(n=9529).

**Resultados** El 43% de las muestras eran de personas con país de nacimiento conocido, y de ellas, el 17.2% eran nacidas en el extranjero. Casi el 50% de los extranjeros procedían de la Región Europea de la OMS (13,1% de países no-UE/EEA). En comparación con las muestras procedentes de autóctonos, las muestras de los extranjeros tenían niveles similares (p>0.05) de resistencia a la azitromicina (autóctonos: 7.5%; extranjeros 7.2%), a ciprofloxacino (50.0% vs. 46.3%), y de sensibilidad disminuida a la ceftriaxona (1.9% vs. 2.8%); menor frecuencia de resistencia a la cefixima (5.7% vs. 3.6%, p=0.02) y mayor frecuencia de muestras que producían penicilinasa(8.4% vs. 11.7%, p=0.02). Entre las personas nacidas fuera de la UE/AEE la proporción de sensibilidad disminuida a la ceftriaxona fue superior (1.8% vs. 3.5%, p=0.02), particularmente en aquellos que procedían de la Región de la Mediterránea Oriental y de países europeos no-UE/AEE (1.9% vs. 9.6% and 8.7% respectivamente, p<0.01). En el análisis multivariado, los pacientes extranjeros con NGR presentaban mayor probabilidad de proceder de países europeos no-UE/AEE (ORa: 3,2; 95%IC 1,8-5,8), de la

Región de la Mediterránea Oriental (ORa: 1,8; 95%IC 1,1-3,3), y hombres heterosexuales (ORa: 1,8; 95%IC 1,2-2,7).

**Conclusiones** La importación de NGR persiste como una amenaza importante en la UE/AEE. Mejorar el conocimiento de las redes sexuales en la población extranjera y el turismo sexual permitirá informar de intervenciones efectivas y específicas para estos grupos. Los resultados muestran la relevancia de los programas de vigilancia de la NGR y la necesidad de reforzar la vigilancia de la NGR, en particular en los países europeos no-UE/AEE.

**Palabras clave:** Gonorrea, Tratamiento, Ceftriaxona, Resistencia a los Antibióticos, Vigilancia, Euro-GASP, Europa, Inmigración