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European Surveillance of Sexually Transmitted Infections (ESSTI): the first combined antimicrobial susceptibility data for *Neisseria gonorrhoeae* in Western Europe

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***Objectives*: To conduct a sentinel surveillance study for antimicrobial resistance in *Neisseria gonorrhoeae* in Western Europe in 2004 as part of the European Surveillance of Sexually Transmitted Infections (ESSTI) Programme.**

***Methods*: Gonococcal isolates were collected from centres in 12 countries and transferred to two reference centres for testing. The same methodology of agar dilution was used to determine susceptibility to a range of antimicrobials used for the treatment of gonorrhoea including azithromycin, ceftriaxone, ciprofloxacin, penicillin and tetracycline. Quality control between the two laboratories was assessed during the testing.**

***Results*: A total of 1055 gonococcal isolates were collected, of which 965 (91.5%) were retrievable for susceptibility testing. Resistance was found to be high to ciprofloxacin (30.9%), but also present to penicillin (21.3%) and tetracycline (59.8%). Azithromycin resistance was above 5%, the first time this has been documented in Europe. Three isolates had a low level of resistance to ceftriaxone. With regard to quality control between the two reference laboratories, 92% of MIC results were within two dilutions.**

***Conclusions*: These are the first sentinel surveillance data for Western Europe for *N. gonorrhoeae* and they have implications for choice of antimicrobial for treatment of gonorrhoea on a European and a local level. This is the start of the formation of a European gonococcal antimicrobial surveillance programme (EURO-GASP).**

Keywords: GASP, gonococci, antimicrobial resistance, antimicrobial surveillance, ciprofloxacin

Introduction

Within many Western European countries rates of gonorrhoea declined between the 1970s and 1990s. However, since the mid-1990s diagnoses have increased throughout the European Union (EU).[1] With increased migration and travel within Europe there is a need for enhanced European-wide surveillance data for gonorrhoea as well as other sexually transmitted infections (STIs), for timely information on outbreaks, changing disease epidemiology and early identification of problems with antimicrobial resistance.[2]

Neisseria gonorrhoeae, the causative bacterium of gonorrhoea, is genetically diverse and competent for genetic exchange throughout its lifecycle. This ability has led to the acquisition and selection of resistance to most antimicrobials used for treatment of gonorrhoea.[3–6] Resistance to antimicrobials creates challenges for successful treatment of gonorrhoea and therefore timely and accurate surveillance data on the distribution of determinants of resistance is essential to inform national treatment guidelines. European guidelines for the management of gonorrhoea exist and for urethral, cervical and rectal infections currently recommend either ciprofloxacin 500 mg,

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ofloxacin 400 mg, ceftriaxone 250 mg, cefixime 400 mg or spectinomycin 2 g.[7]

The European Surveillance of Sexually Transmitted Infections (ESSTI) Programme was established in 2002 with funding from the European Commission (DG SANCO) to determine the feasibility of establishing epidemiological and laboratory surveillance for STIs within Western Europe. In 2004 ESSTI collaborators undertook a sentinel surveillance study to determine the prevalence of antimicrobial-resistant *N. gonorrhoeae* in Western Europe.

Methods

Participating centres

One reference laboratory or specialist centre for laboratory diagnosis of *N. gonorrhoeae* that had previously been identified in each of the 12 collaborating ESSTI countries across the EU participated in the surveillance project (Austria, Belgium, Denmark, England and Wales, France, Greece, Italy, The Netherlands, Portugal, Scotland, Spain and Sweden).[8] Of the 12 participating centres, 9 are national reference laboratories for *N. gonorrhoeae* in their respective countries (Belgium, Denmark, England and Wales, France, Greece, Portugal, Scotland, Spain and Sweden) and the remaining 3 are specialist or expert centres in their respective countries (Austria, Italy and The Netherlands). Of the 12 countries, 3 had complete coverage of all diagnosed gonorrhoea in their respective countries (Denmark, Scotland and Sweden), 5 had good national coverage (Belgium, England and Wales, France, Greece and Spain) and 4 had good regional coverage (Austria, Italy, The Netherlands and Portugal).

Collection of isolates

Gonococcal isolates were collected at each laboratory in the 12 different EU countries from consecutively referred patient samples, allowing one isolate per patient. Where multiple sites were infected in the same patient an order of preference was assigned (rectal isolate before a urethral before a cervical followed by any other site). Isolates were collected from June 2004 up to a maximum of 100 isolates per country and the collection was stopped in November 2004. Isolates were purified and stored on cryo-beads at –80°C at each centre. Information on sex, age and anatomical site of isolation was also collected for each isolate. Isolates were sent frozen on dry ice to one of the two testing centres (Sexually Transmitted Bacteria Reference Laboratory, Health Protection Agency Centre for Infections, London, UK or the Neisseria and Streptococcus Reference Laboratory, Statens Serum Institut, Copenhagen, Denmark) for antimicrobial susceptibility testing. Isolates were retrieved and purified where necessary from the cryo-beads on GC agar plates and subcultured once before susceptibility testing.

Susceptibility testing

Antimicrobial susceptibility testing was performed by the agar dilution technique as described previously.[9] Agar plates were prepared containing Diagnostic Sensitivity Test Agar (DST agar, Oxoid) supplemented with 1% IsoVitaleX and 5% lysed horse blood and doubling dilutions of each antimicrobial agent in the following ranges, azithromycin (0.03–4 mg/L), ceftriaxone (0.002–0.12 mg/L), ciprofloxacin (0.002–32 mg/L), penicillin (0.03–4 mg/L) and tetracycline (1–32 mg/L). Each batch was quality controlled using standard WHO *N. gonorrhoeae* control strains (WHO A-E) and 81-10 (ciprofloxacin reduced susceptible) and the controls were also included in each run. A suspension of each isolate was prepared in saline and 10^4 cfu were inoculated onto each plate using a multipoint inoculator. Plates were incubated for 24 h before growth was recorded and the MIC was determined as the lowest concentration giving complete inhibition of growth. Penicillinase production was detected using a chromogenic cephalosporin (nitrocefin).

Quality control

A panel of 20 gonococcal isolates was exchanged between London and Copenhagen at the beginning of the study and a separate panel of 20 isolates between Copenhagen and London mid-way through the testing. The panel of isolates was chosen to have a range of susceptibilities. The isolates were tested at each centre using the same methodology. Results were compared by MIC, within one dilution and within two dilutions and by category of susceptibility.

Analysis of results

All data were entered into and analysed in MS Access. MIC values of azithromycin, ceftriaxone, ciprofloxacin, penicillin and tetracycline were transferred into categories and resistance rates determined. Penicillinase-producing *N. gonorrhoeae* (PPNG) are β-lactamase-positive; chromosomally resistant *N. gonorrhoeae* (CMRNG) have penicillin MICs ≥1 mg/L and are β-lactamase-negative and have tetracycline MICs 2–8 mg/L; tetracycline-resistant *N. gonorrhoeae* (TRNG) have tetracycline MICs ≥16 mg/L and are β-lactamase-negative; *N. gonorrhoeae* with chromosomal resistance to tetracycline (tetR) have tetracycline MICs 2–8 mg/L and penicillin MICs <1 mg/L; quinolone-resistant *N. gonorrhoeae* (QRNG) have ciprofloxacin MICs ≥1 mg/L; azithromycin-resistant *N. gonorrhoeae* have azithromycin MICs ≥1 mg/L; and ceftriaxone-resistant *N. gonorrhoeae* have ceftriaxone MICs >0.125 mg/L. Multiresistant isolates were defined as QRNG and PPNG; QRNG and TRNG; QRNG, PPNG and TRNG; QRNG and azithromycin-resistant.

Results

A total of 1055 gonococcal isolates were collected from the 12 countries, ranging from 18 to a maximum of 102 isolates (Table 1). The gonococci were isolated from 849 men (80%), 200 women (19%) and the gender was unknown for the remaining six isolates. The age range of the patients with the referred isolates was between 0 and 73 years. The site of isolation in men was predominantly the urethra (85.2%), rectum (7.1%) or pharynx (4.8%) and from women the cervix (68%), vagina (12.5%) and urethra (10.5%). A total of 965 (91.5%) isolates were successfully retrieved and susceptibility tested, the retrieval rates varying between 81% in The Netherlands and 100% in Belgium, England and Wales, Denmark and Sweden (Table 1).

Quality control: Concordance between the two testing centres on the two exchanges for azithromycin, ceftriaxone, ciprofloxacin, penicillin and tetracycline within one dilution was 79% and within two dilutions was 91.6%. By examining the concordance by category of susceptibility between the two result sets, 82.5% of results gave the same category.

Susceptibility results

Azithromycin: The overall prevalence of resistance to azithromycin was 8.2% (79/965), with considerable variation between the countries ranging from 31.2% to 0% (Table 1). The prevalence from countries with complete coverage of all diagnosed gonorrhoea was higher compared with the rate from countries with good national or good regional coverage (Table 2) ($P \leq 0.001$,

Table 1. Resistance rates by antimicrobial, overall and by country

Country	No. isolates received	No. isolates retrieved and tested	Azithromycin (%)	Ceftriaxone (%)	QRNG (%)	Ciprofloxacin reduced susceptible (%)	CMRNG (%)	PPNG (%)	PPNG/TRNG (%)	TRNG (%)	tetR (%)
Overall combined	1055	965	79 (8.2)	3 (0.3)	298 (30.9)	22 (2.3)	84 (8.7)	65 (6.7)	57 (5.9)	60 (6.2)	376 (39.0)
Austria	100	96	30 (31.2)	0	51 (53.1)	0	3 (3.1)	15 (15.6)	4 (4.2)	1 (1.0)	45 (46.9)
Belgium	64	64	2 (1.6)	0	30 (46.9)	0	7 (10.9)	3 (4.7)	7 (10.9)	8 (12.5)	23 (35.9)
Denmark	99	98	8 (8.2)	0	45 (46)	5 (5.1)	11 (11.2)	1 (1.0)	16 (16.3)	5 (5.1)	43 (43.9)
England & Wales	100	100	1 (1)	0	12 (12)	0	8 (8)	1 (1.0)	4 (4.0)	6 (6.0)	20 (20.0)
France	102	101	0	0	33 (32.7)	2 (2)	11 (10.9)	2 (2.0)	0	7 (6.9)	58 (57.4)
Greece	81	79	0	0	6 (7.6)	1 (1.3)	3 (3.8)	7 (8.9)	1 (1.3)	5 (6.3)	32 (40.5)
Italy	43	42	4 (9.5)	2 (4.8)	15 (33.3)	2 (4.8)	4 (9.5)	4 (9.5)	0	0	18 (42.9)
The Netherlands	100	81	14 (17.3)	0	13 (16)	0	11 (13.6)	7 (8.6)	3 (3.7)	7 (8.6)	27 (33.3)
Portugal	18	17	0	0	3 (17.6)	0	0	2 (11.8)	0	6 (35.3)	6 (35.3)
Scotland	100	99	5 (5.1)	0	30 (30.3)	1 (1)	17 (17.2)	7 (7.1)	5 (5.1)	1 (1)	25 (25.3)
Spain	96	92	2 (2.2)	0	14 (15.2)	8 (8.7)	2 (2.2)	6 (6.5)	2 (2.2)	6 (6.5)	40 (43.5)
Sweden	96	96	13 (13.5)	1 (1)	46 (48)	3 (3.1)	7 (7.3)	10 (9.6)	15 (15.6)	8 (8.3)	39 (40.6)

Table 2. Resistance rates by antimicrobial, overall and by degree of coverage of diagnosed gonorrhoea in each country

Degree of coverage of laboratory diagnosed gonorrhoea in country	No. retrieved and tested	Azithromycin (%)	Ceftriaxone (%)	QRNG (%)	Ciprofloxacin reduced susceptible (%)	CMRNG (%)	PPNG (%)	PPNG/TRNG (%)	TRNG (%)	tetR
Overall combined	965	79 (8.2)	3 (0.3)	298 (30.9)	22 (2.3)	84 (8.7)	65 (6.7)	57 (5.9)	60 (6.2)	376 (39.0)
Complete[a]	293	26 (8.9)	1 (0.3)	121 (41.3)	9 (3.1)	35 (11.9)	18 (6.1)	36 (12.3)	14 (4.8)	107 (36.5)
Good national[b]	436	5 (1.1)	0	95 (21.8)	11 (2.5)	31 (7.1)	19 (4.4)	14 (3.2)	32 (7.3)	173 (39.7)
Good regional[c]	236	48 (20.3)	2 (0.8)	82 (34.7)	2 (0.8)	18 (7.6)	28 (11.9)	7 (3.0)	14 (5.9)	96 (40.7)

[a]Complete coverage of all diagnosed gonorrhoea in the country (Denmark, Scotland and Sweden).
[b]Good national defined as representations from all areas of the country but not every case of diagnosed gonorrhoea (Belgium, England and Wales, France, Greece and Spain).
[c]Good regional defined as good coverage of a particular region of the country but not national coverage (Austria, Italy, The Netherlands and Portugal).

Table 3. MIC_{50} and MIC_{90} values of each antimicrobial

Antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Azithromycin	0.25	0.5
Ceftriaxone	<0.002	0.015
Ciprofloxacin	0.015	32.0
Penicillin	0.125	1.0
Tetracycline	2.0	32.0

χ^2 = 72.8). The MIC_{90} value of 0.5 mg/L indicates that the majority of isolates were susceptible to azithromycin with resistance defined as ≥1 mg/L (Table 3).

Ceftriaxone: Three isolates from two different countries were determined as having an MIC of 0.25 mg/L, which is above the concentration used to define reduced susceptibility to ceftriaxone (>0.125 mg/L) and exhibited *in vitro* resistance (Table 1). All other isolates were fully susceptible to ceftriaxone (Table 1) and the MIC_{90} value of 0.015 mg/L indicates that the majority of isolates were very susceptible to ceftriaxone (Table 3).

Ciprofloxacin: Overall resistance to ciprofloxacin was 30.8% (298/965) (Table 1) and the resistance was widespread in the countries ranging between 53.1% and 7.6% (Table 1). The MIC_{90} value of 32 mg/L indicates that the resistance was of a high level (Table 3) and not close to the concentration used to define resistance (1 mg/L). 2.3% (22/965) of isolates demonstrated reduced susceptibility to ciprofloxacin, varying from 0% in five countries to the highest of 8.7% (Table 1). The highest levels of resistance and reduced susceptibility to ciprofloxacin were from countries with complete coverage (Table 2) ($P \leq 0.001$, χ^2 = 33.4).

Penicillin: Plasmid-mediated resistance to penicillin, PPNG, was determined to be 6.7% (65/965) and combined PPNG and TRNG was 5.9% (57/965), giving a total plasmid-mediated resistance to penicillin of 12.6% (122/965) (Table 1). Penicillin resistance was variable in the countries ranging from the highest of 26% in one country to 2.0% (Table 1). Chromosomally mediated resistance was lower at 8.7% (84/965) (Table 1) and ranged from 17.2% to 0% (Table 1). There was little variation in resistance by degree of coverage, though the highest rates were seen in countries with complete coverage of diagnosed gonorrhoea (Table 2) ($P \leq 0.001$, χ^2 = 25.9).

Tetracycline: High-level plasmid-mediated resistance to tetracycline, TRNG, was 6.2% (60/965) and combined with penicillin, PP/TRNG, was 5.9% (57/965), giving a total tetracycline plasmid-mediated resistance of 12.1% (122/965) (Table 1), ranging from 24% to 0% (Table 1). Chromosomally mediated resistance to tetracycline, tetR, was determined to be present in 39% of isolates (Table 1), with little variation in incidence by the degree of coverage of gonococcal isolates (Table 2). Total chromosomally mediated resistance to tetracycline, including CMRNG, was 47.7%. The MIC_{50} value of 2 mg/L and the MIC_{90} value of 32 mg/L indicate that the majority of isolates were not susceptible to tetracycline (Table 3).

Multiresistant isolates: QRNG was found in combination with PPNG in 4.9% (47/965) of isolates (QRNG/PPNG), with TRNG in 2.2% (21/965) (QRNG/TRNG) and with both PPNG and TRNG in 3.6% (35/965) (PP/TR/QRNG). High-level resistance to both penicillin and tetracycline (PP/TRNG) was found in 5.9% (57/965) of isolates. Resistance to azithromycin and QRNG was found in 5.0% (48/965). Total high-level multiresistance was determined to be 21.6%.

Discussion

This sentinel study undertaken by ESSTI is the first combined surveillance report for antimicrobial-resistant *N. gonorrhoeae* in Western Europe tested using the same methodology. It is a unique collection of gonococcal isolates from 12 sentinel sites in Western Europe, nine of which are the national reference centres in their countries for *N. gonorrhoeae* and three of which are expert or specialist centres for *N. gonorrhoeae* in their countries.

The number of isolates collected varied between countries, from 18 to 102, but all were consecutively selected. However, within each centre there was an element of selection due to the type of isolates referred to each centre. This was best expressed by stratifying countries into those that have complete coverage, i.e. isolates from consecutive patients of all gonorrhoea diagnosed in the country; those centres that have national coverage, i.e. selected centres but with good national representation; and those centres with regional coverage within their country. There is always a possibility that specialist centres that do not receive all strains will be referred a higher percentage of resistant isolates due to active selection by the submitting laboratories. However in this study the highest levels of ciprofloxacin, penicillin and tetracycline resistance were found among those laboratories that receive all diagnosed gonococcal isolates with no selection bias (Table 2).

The resistance levels reported here may differ from nationally published figures for individual countries because of minor differences in methodology, classification of resistance and temporal sampling.[10–14] A limitation of this sentinel surveillance study was that demographic and behavioural data, other than age and sex, were not collected which would have allowed further analysis of the determinants of resistance in Western Europe. It also involved the collection of a maximum of 100 gonococcal isolates over a 5 month period, rather than continuous surveillance, due to logistical reasons, and may have resulted in monitoring some seasonal variation.

In the most recent European guidelines for the treatment of gonorrhoea in adults, one of the recommended therapies for gonorrhoea is a fluoroquinolone, ciprofloxacin or ofloxacin.[7] Very high levels of resistance to ciprofloxacin were detected in this surveillance study, with resistance rates above 5% in all of the participating countries. Ciprofloxacin or ofloxacin is therefore unlikely to achieve a 95% or greater treatment success rate in individuals where the susceptibility of the gonococcal isolate is unknown prior to treatment.[15] This raises issues regarding treatment for individuals infected with gonorrhoea in each of the countries and also for individuals returning to their home country having reported sexual contact within Western Europe. Ciprofloxacin has been the antimicrobial of choice for treatment of gonorrhoea in most Western European countries and is recommended by other agencies such as the Centres for Disease Control (CDC) and it has been a very effective antimicrobial agent for over a decade.[16] Resistance reports to ciprofloxacin have been increasing worldwide in recent years, with very high levels in South East Asia and with many QRNG diagnosed in Europe

resulting from sex tourism to these areas of high incidence.[17–19] Many countries have now made changes to treatment guidelines and of the 12 participating countries six have treatment guidelines, of which two still recommend the use of fluoroquinolones and four recommend third-generation cephalosporins.[10,20–25]

Three isolates from two different countries (Table 1) had *in vitro* resistance to ceftriaxone (MIC > 0.125 mg/L), a tentatively defined concentration as there are currently no confirmed reports of treatment failure with third-generation cephalosporins with pre- and post-treatment isolates available anywhere in the world. For this study, data on the antimicrobial treatment used and subsequent outcome were not available for the individuals with these three isolates. There are reports of increasing gonococcal MICs to third-generation cephalosporins and it is very important for all surveillance programmes to closely monitor susceptibility to the cephalosporins.[17,26] These data support the use of third-generation cephalosporins, ceftriaxone or cefixime, for the treatment of gonorrhoea within Western Europe.

Resistance to azithromycin was also surprisingly high in the collected isolates, with six countries having a prevalence greater than 5% (Table 1). Azithromycin is not recommended for treatment of gonorrhoea as a 2 g dose is required and is poorly tolerated due to adverse gastrointestinal effects.[27,28] There are increasing reports of gonococcal resistance or reduced susceptibility to azithromycin from around the world, hence the findings from ESSTI are not totally unexpected.[29–31] Azithromycin is widely used for treatment of chlamydia, usually a 1 g dose, and it is possible that gonococcal resistance is selected for by this use if an individual has a co-infection with both bacterial pathogens. The European guidelines for the management of gonorrhoea state that co-infection is common and that treatment for gonorrhoea should be routinely followed by treatment for chlamydial infection.[7]

Overall resistance to penicillin, of combined chromosomal (8.7%) and plasmid-mediated resistance (12.6%), was high at 21.3%, with considerable variation between the 12 countries. The European guidelines do state that penicillin regimens (amoxicillin with probenecid) are appropriate when the isolate is known to be penicillin-susceptible, but these surveillance data show that 1 in 12 infections in 2004 had plasmid-mediated resistance to penicillin and therefore may have been unsuccessfully treated with this regimen. The prevalence of chromosomal resistance to penicillin was less than plasmid-mediated resistance and treatment failures following the use of penicillin in an individual with a CMRNG are lower, usually less than 5% as MICs are lower.[32]

Tetracycline is not recommended for gonococcal therapy in Western Europe or the developed world and the plasmid-mediated resistance rate of 12.1% and the chromosomally mediated resistance rate of 47.7% detected in this study may be due to selection of resistance by the use of tetracycline or tetracycline derivatives for chlamydial infection. Isolates with chromosomally mediated resistance to tetracycline have a lower MIC than isolates with plasmid-mediated resistance and hence a lower risk of treatment failure if tetracycline were to be used.

This first antimicrobial surveillance programme for Western Europe organized through the ESSTI network is the start of the formation of a European Gonococcal Antimicrobial Surveillance Programme (EURO-GASP). Other GASPs exist such as the WHO Western Pacific programme, GASP-WAR in West Africa, Caribbean GASP and WHO-SEAR in South East Asia, providing essential data on antimicrobial susceptibility in various regions.[17,33–35] The ESSTI data and methodology are interesting to compare with the other GASPs that are established around the world. The WHO Western Pacific programme has been in existence since 1992 and collects data from 15 countries. Different methodologies are used in the testing centres and centralized quality assurance is used to ensure comparability. High levels of resistance to the quinolones continue to be reported, with an incidence of 99.3% in Hong Kong in 2004; penicillin and tetracycline plasmid-mediated resistance are widespread, with the highest PPNG rates of 85% in Brunei and 72% TRNG in Singapore; isolates with decreased susceptibility to the third-generation cephalosporins continue to occur in this region.[17] These Western Pacific resistance rates are much higher than those reported from ESSTI. Agreement to commence surveillance in West Africa has recently occurred involving eight countries, with an agreed common methodology, quality assurance and reporting. Data were only available up to 2001 for six countries, with high levels of resistance to penicillin and tetracycline reported.[33] The WHO South East Asia surveillance programme was formed in 1997 and currently involves seven countries. Each country undertakes its own testing by disc diffusion and external quality assurance is provided from Australia which leads the WHO WP programme. The 2000/2001 data show increasing penicillin and quinolone resistance, decreasing tetracycline resistance with wide ranges of incidence between the countries and five of the seven laboratories reported isolates with reduced susceptibility to ceftriaxone.[35] Data from the WHO South American and Caribbean GASP have not been continuous since its inception in 1990, with the latest available data from 1997, due to problems with funding, public interest and commitment. CLSI agar dilution methodology is used, as well as central quality control, to ensure comparability. The data from the 1990s showed decreasing penicillin resistance, increasing plasmid-mediated tetracycline resistance and very few isolates with resistance to the quinolones.[34] ESSTI differs from these WHO surveillance programmes in that the susceptibility testing was performed in two reference laboratories rather than by the individual countries with central reporting. Either method requires time commitment, rigorous quality assurance to ensure result comparability and funding. Continued surveillance is essential to monitor ongoing resistance to fluoroquinolones and potential emergence of resistance to third-generation cephalosporins within Europe.

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Transparency declarations

None to declare.

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