

Surveillance report

Gonococcal antibiotic surveillance in Scotland (GASS): prevalence, patterns and trends in 2018



Prepared by: Jill Shepherd,¹ Lesley Wallace,² Martin McHugh,¹ Beth Cullen,² Ross Cameron² and David Goldberg²

1. Scottish Bacterial Sexually Transmitted Infections Reference Laboratory
2. Health Protection Scotland

Key Points

- The number of episodes of gonorrhoea submitted to the Scottish Bacterial Sexually Transmitted Infections Reference Laboratory (SBSTIRL) increased by 24% in 2018. Around half of episodes were diagnosed by nucleic acid amplification only. The resistance surveillance in 2018 was, therefore, based on 52% of gonococcal infections in Scotland.
- One patient had resistance to both ceftriaxone and cefixime. This isolate was also resistant to ciprofloxacin, but susceptible to azithromycin. The infection was acquired in China, highlighting the need to understand the global epidemiology of gonorrhoea.
- Resistance to azithromycin was seen in 7.0% of isolates. Of concern are the 35 isolates which demonstrated high-level resistance to azithromycin (HL-AziR; >256 mg/l), corresponding to 2.1% of all isolates. This increase has been noted throughout the UK, which has led to a change in the UK guidelines for gonorrhoea treatment from azithromycin plus ceftriaxone dual therapy, to ceftriaxone monotherapy.¹
- The proportion of isolates resistant to ciprofloxacin has remained steady at 35%. This suggests that although ciprofloxacin could play a role in the treatment of gonorrhoea¹, it can not be used empirically.
- Continued surveillance for antibiotic resistance is essential for guiding the choice of effective therapeutic regimens for gonorrhoea and every effort should be made to maintain culture from a high proportion of gonococcal episodes of infection. This is highlighted by the increase in numbers of isolates demonstrating HL-AziR, and the reports of extensively drug-resistant (XDR) gonorrhoea reported elsewhere.²

Methodology

The Scottish Bacterial Sexually Transmitted Infections Reference Laboratory (SBSTIRL) provides surveillance data on antimicrobial resistance for all gonococci isolated in Scotland. All cultured organisms are tested against seven antibiotics using the agar dilution method³ and by Etests (bioMérieux) when the minimum inhibitory concentration (MIC) exceeds the dilution series. Due to an increase in the number of isolates received from July 2018, Etests are no longer routinely carried out for ciprofloxacin, tetracycline and penicillin. *Neisseria gonorrhoeae* multi-antigen sequence typing (NG-MAST)⁴ is performed on a proportion of isolates and specimens positive by *N. gonorrhoeae* nucleic acid amplification tests (NAAT) submitted to SBSTIRL where a culture is not available.

Episodes of gonorrhoea in Scotland

The number of episodes of gonorrhoea is obtained by the manual removal from the database of duplicate samples from the same patient taken within a six week period, and presumed duplicate patients who appear to have been tested both in primary care and at sexual health services. A total of 3168 episodes of gonococcal infection were reported by SBSTIRL in 2018; of these, nine were cultures non-recoverable on receipt in the laboratory and a further 1507 were diagnosed by NAAT with no culture available. Antibiotic susceptibility testing was, therefore, performed on isolates from 1652 episodes (52% of all gonococcal infections). Since April 2015, NG-MAST has only been performed on a proportion of samples; these data can be a useful predictor of antibiotic susceptibility profile for those sequence types (STs) that occur commonly and for which no cultured isolate exists.⁵ NG-MAST data are available for 436 (14%) episodes.

Table 1 shows gonorrhoea episodes and trends by gender. Total gonorrhoea episodes increased in comparison with 2017 (2536 in 2017 versus 3168 in 2018). Men accounted for 73% of episodes in 2018. As has been the case for every year for which such data have been available, a larger proportion (54%) of diagnoses in women were by NAAT only, compared with 45% in men and 48% overall.

TABLE 1: Episodes of gonorrhoea: isolates and NAAT specimens sent to SBSTIRL, 2014-2018

	2014			2015			2016			2017			2018		
	Culture positive	NAAT positive	Total	Culture positive	NAAT positive	Total	Culture positive	NAAT positive	Total	Culture positive	NAAT positive	Total	Culture positive	NAAT positive	Total
Men	747	616	1363	932	896	1828	847	820	1667	1053	852	1905	1267	1041	2308
Women	189	268	457	168	259	427	253	269	522	296	325	621	388	464	852
Unknown	0	0	0	1	1	2	1	3	4	3	7	10	6	2	8
Total¹	936	884	1820 (51%)	1101	1156	2257 (49%)	1101	1092	2193 (50%)	1352	1184	2536 (53%)	1661	1507	3168 (52%)

1 The proportion of the total which are culture positive are shown in parentheses

General antibiotic susceptibility trends

Previous GASS reports have used antibiotic breakpoints particular to the SBSTIRL. In this year's report, the antibiotic breakpoints have changed to those of EUCAST (European Committee on Antimicrobial Susceptibility Testing) v9 breakpoints⁶ – these are now used routinely by SBSTIRL to report patient results. Antibiotic susceptibility data are presented for the past four years, 2015-2018. EUCAST have changed their definition of susceptible and resistant⁶, which is reflected in the 2018 data.

Table 2 and Figure 1 provide resistance data for the antibiotics tested over the last four years and Table 3 gives the pattern of resistance for isolates in 2018. Given that Etests were not performed on all tetracycline resistant isolates, it has not been possible to provide more detailed information about whether this is plasmid- or chromosomally-mediated resistance.

In total, 802 (49%) of the 1652 episodes for which susceptibility data were available exhibited resistance to one or more antibiotics tested; this is comparable with previous years.

TABLE 2: Gonococcal antibiotic resistance trends; number and proportion, 2015-2018

Antimicrobial resistance	2015 (n=1101)		2016 (n=1087)		2017 (n=1338)		2018 (n=1338)	
Ceftriaxone resistance (MIC > 0.125 mg/l)	0%		0%		0%		0.1%	(1)
Cefixime resistance (MIC > 0.125 mg/l)	0.2%	(2)	0.5%	(5)	0.1%	(2)	0.1%	(1)
Azithromycin resistance (MIC > 0.5 mg/l)	2.3%	(25)	1.0%	(11)	2.5%	(34)	7.0%	(115)
<i>Azithromycin high-level resistance</i> (> 256 mg/l)	0.3%	(3)	0.2%	(2)	1.6%	(21)	2.1%	(35)
Ciprofloxacin resistant (MIC > 0.06 mg/l)	34.4%	(379)	34.9%	(379)	31.4%	(420)	34.6%	(571)
PPNG (β -lactamase positive)	11.6%	(128)	7.4%	(80)	8.1%	(109)	9.5%	(157)
PenR (chromosomally mediated resistance to penicillin - MIC >1 mg/l but β -lactamase negative)	7.2%	(79)	1.2%	(13)	1.7%	(23)	3.2%	(53)
Tetracycline resistance (> 1 mg/l)	32.2%	(355)	23.4%	(254)	29.4%	(393)	32.0%	
Spectinomycin resistance (MIC > 64 mg/l)	0%		0%		0%		0%	
Resistant to one or more antibiotics	50.1%	(552)	42.4%	(461)	49.3%	(659)	48.6%	(802)

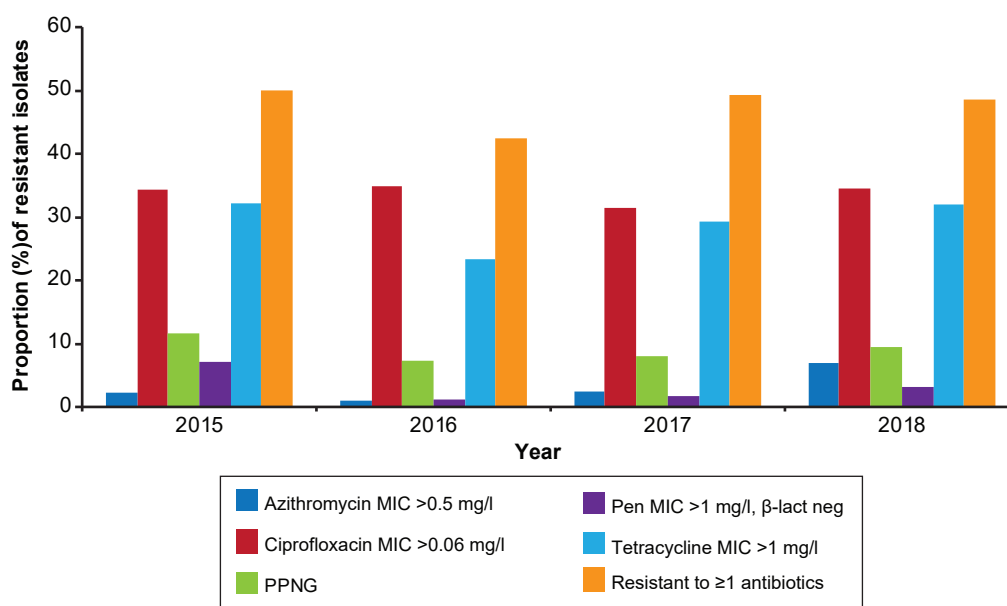
FIGURE 1: Four-year trends in gonococcal resistance, 2015-2018

TABLE 3: Antibiotic resistance and commonly occurring sequence types, 2018

Resistance category	Sequence type	No. resistant isolates	No. non-resistant isolates	No. identified by NAAT only ¹	Total No episodes in 2018
Cefixime & ceftriaxone	9659	1	0	0	1
Azithromycin ²	649	6 (6)	5	5	16
	2475	1 (1)	0	0	1
	5802	4 (0)	0	0	4
	11842	1 (0)	0	0	1
	12302	18 (0)	1	1	20
	13892	17 (17)	19	9	45
	16404	7 (7)	0	0	7
	17288	1 (0)	0	0	1
	17338	2 (0)	0	0	2
Ciprofloxacin	51	1	8	12	21
	9153	12	0	0	12
	10386	17	0	0	17
	11421	21	0	5	26
	12302	19	0	1	20
	12547	13	0	0	13
	14769	19	0	0	19
	15845	9	0	1	10
	16020	10	0	0	10
	16169	11	0	0	11
PPNG	51	1	8	12	21
	14769	18	1	0	19
	15845	8	1	1	10
Tetracycline	51	2	7	12	21
	649	10	1	5	16
	9153	7	5	0	12
	10386	17	0	0	17
	11421	5	16	5	26
	11461	24	0	13	37
	12302	19	0	1	20
	14769	19	0	0	19
	16020	10	0	0	10

1 No antibiotic resistance data available from samples positive by NAAT only.

2 Numbers in parentheses represent high-level azithromycin resistance (>256 mg/l).

Cephalosporin resistance

Resistance to ceftriaxone (MIC >0.125 mg/l) and to cefixime (MIC >0.125 mg/l) was found in one isolate (0.1%) in 2018. This isolate was also resistant to ciprofloxacin but susceptible to azithromycin and was acquired in China. Prior to 2018, ceftriaxone resistance had not been detected in Scotland. Cefixime resistance continues at a low level with one isolate in 2018 (0.1%), two isolates in 2017 (0.1%), five isolates in 2016 (0.5%) and two isolates in 2015 (0.2%). The 2019 UK guidance for the management of gonorrhoea¹ now recommends monotherapy with ceftriaxone as the first-line empirical treatment rather than dual therapy with azithromycin plus ceftriaxone. It is, therefore, vital to continue to monitor cephalosporin resistance in Scotland to determine any change to resistance.

Azithromycin resistance

Resistance to azithromycin (>0.5 mg/l) has increased from 2.5% in 2015 to 7.0% in 2018. Although some of this is due to an increase in the proportion of HL-AziR isolates (from 1.6% to 2.1%), most of this rise is associated with low-level resistance. Although direct comparison with the situation in England and Wales is not possible as these data are not available, in 2017, 9.2% of isolates examined as part of their sentinel surveillance programme were resistant to azithromycin (>0.5 mg/l)⁷. The latest European surveillance data from 2016 revealed that 7.5% of isolates were resistant to azithromycin.⁸

Azithromycin high-level resistance

Over the past three years the number of HL-AziR episodes in Scotland has increased considerably from less than five in 2015 and 2016 to 21 in 2017 (1.6%) and 35 (2.1%) in 2018. This mirrors the situation recorded in England and Wales⁷.

Of the 35 individuals diagnosed with HL-AziR gonorrhoea in 2018, 20 were men, giving a male to female ratio of diagnoses of 1.33:1; however, the rate was higher among women with the proportion of isolates with HL-AziR being 3.9% compared to 1.6% among men. The majority of resistant isolates were reported from NHS Greater Glasgow & Clyde (13) and NHS Lothian (6) with the remainder coming from six other NHS board areas. This finding is consistent with almost two thirds of all gonorrhoea diagnoses being made in these [two largest NHS board areas](#). There were no reported treatment failures as all gonococcal strains were sensitive to ceftriaxone. The HL-AziR strain is infecting predominantly young adults with a median age of 20 years. From the information available on sexual orientation, the majority were young, of white Scottish ethnicity and heterosexual. Of 32 isolates where sequence type (ST) data were available, the most common STs were: ST 649 (n=6); ST 16404 (n=7); or ST 13892 (n=20). The former was associated with an outbreak of gonorrhoea in Scotland in 2007.⁹

Due to the increase in azithromycin resistance in Scotland, in the rest of the UK⁷ and across Europe,⁸ and the sustained transmission of HL-AziR gonorrhoea across the UK,¹ the 2019 UK guidance for the management of gonorrhoea has been amended with azithromycin no longer being recommended as an empirical first-line treatment.¹

Ciprofloxacin resistance

Ciprofloxacin resistance (MIC > 0.06 mg/l) has remained steady over the past four years with 571 (35%) of 1652 episodes resistant. The 2019 UK guidance for the management of gonorrhoea suggests that ciprofloxacin can be used as the first-line treatment in infections known to be susceptible to this agent.¹ These data show that at this level of resistance, empirical treatment is not possible and that determination of resistance prior to treatment is essential.

Penicillin and tetracycline resistance

Overall, resistance to penicillin and tetracycline was found in 13% and 32% of culture episodes, respectively. There has been little change from 2017 to 2018.

Sequence type and antibiotic resistance

NG-MAST is a highly discriminatory typing scheme that differentiates between isolates on the basis of the sequence variation observed in two genes, coding for the por protein and transferrin binding protein b (tbpb). Each ST is unique and differs from any other by at least one nucleotide. Clusters of isolates sharing the same ST can be observed and both phenotypic and demographic data support the validity of the clusters as containing related isolates. Sequence types represented by ten or more antibiotic resistant episodes are shown in Table 3, along with sequence types associated with cefixime plus ceftriaxone and with azithromycin resistance.

There were 19 STs detected with ten or more episodes. Not all of these are associated with antibiotic resistance. The individual with ceftriaxone and cefixime resistance was infected with ST 9659, which was not detected in any other patient analysed. The most commonly detected ST was 13892 which can be associated with HL-AziR, although it is ceftriaxone and ciprofloxacin susceptible.

Azithromycin resistance was seen in a number of different STs, the most frequently observed being 13892 and 649, both of which are associated with HL-AziR. A proportion of these STs did not have MIC data available due to the lack of a cultured isolate; only a NAAT sample was received by SBSTIRL. For ST 649, five (31%) of 16 samples had no MIC data available, and for ST 13892, nine (20%) of 45 samples were missing data. Therefore, the number of patients with HL-AziR gonorrhoea is likely to be an underestimate for 2018. Seven episodes of infection with ST 16404 were detected in 2018 – this ST was not recorded in 2017. It is also associated with HL-AziR. One episode of ST 12302 was detected in 2017; in 2018, this increased to 20. This ST is associated with LL-AziR (low-level azithromycin resistance), as well as resistance to ciprofloxacin and tetracycline, but it is susceptible to ceftriaxone.

Discussion

The threat of antibiotic-resistant gonorrhoea is a major public health concern and *N. gonorrhoeae* is on the WHO priority list as part of the Global Action Plan on antimicrobial resistance.¹⁰ The number of cases of extensively drug-resistant (XDR) gonorrhoea, the presence of HL-AziR strains, which are now established and circulating, and the detection of a ceftriaxone resistance in Scotland indicate the importance of continued surveillance of isolates for antibiotic resistance. With the implementation of new guidance recommending ceftriaxone only for the treatment of gonorrhoea, it is hoped that the rate of HL-AziR detection will decline. Clearly, resistance information is essential for guiding the choice of effective therapeutic regimens for gonorrhoea infection.

Encouragingly, to date, there have been no documented treatment failures and no resistance to spectinomycin observed; however, almost half of all strains are resistant to one or more antibiotics previously used in treatment regimens. A small number of ceftriaxone-resistant isolates have been detected in Europe.¹⁰ While prevention of infection is the primary goal, the continuing importance of effective partner notification, along with a documented test of cure test to reduce transmission of infection is evident.

Acknowledgements

We would like to acknowledge all Microbiologists and Virologists who have submitted isolates and specimens to SBSTIRL throughout the year, and all Sexual Health clinicians for their support. Thanks are also due to staff at SBSTIRL for performing susceptibility testing, NG-MAST typing and maintaining the SBSTIRL databases.

References

1. Fifer H, Saunders J, Soni, S, Sadiq, ST, FitzGerald M. British Association for Sexual Health and HIV national guideline for the management of infection with *Neisseria gonorrhoeae* (2019). Available from <https://www.bashhguidelines.org/media/1208/gc-2019.pdf>
2. European Centre for Disease Prevention and Control. Extensively drug-resistant (XDR) *Neisseria gonorrhoeae* in the United Kingdom and Australia. 7 May 2018. Stockholm. ECDC.
3. Young H, Moyes A, Robertson DHH, et al. Gonococcal infection within Scotland: antigenic heterogeneity and antibiotic susceptibility of infecting strains. *European Journal of Epidemiology* 1990; **6**:1-8.
4. Martin IMC, Ison CA, Aanensen DM, Fenton KA, Spratt BG. Rapid sequence-based identification of gonococcal transmission clusters in a large metropolitan area. *Journal of Infectious Diseases* 2004; **189**: 1479-1505.
5. Palmer HM, Young H, Graham C, Dave J. Prediction of antibiotic resistance using *Neisseria gonorrhoeae* multi-antigen sequence typing. *Sexually Transmitted Infections* 2008; **84**(4):280-4.
6. European Committee on Antimicrobial Susceptibility Testing www.eucast.org
7. Public Health England. Surveillance of antimicrobial resistance in *Neisseria gonorrhoeae* in England and Wales. 2018. Key findings from the Gonococcal Resistance to Antimicrobials Surveillance Programme GRASP.

8. European Centre for Disease Prevention and Control Gonococcal antimicrobial susceptibility surveillance in Europe 2016. ECDC Surveillance Report. Available from <https://ecdc.europa.eu/sites/portal/files/documents/EURO-GASP-report-2016.pdf>
9. Palmer HM, Young H, Winter A, Dave J. Emergence and spread of azithromycin- resistant *Neisseria gonorrhoeae* in Scotland. *Journal of Antimicrobial Chemotherapy*. 2008; 62(3): 490-94.
10. World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Geneva: World health Organization, 2017. Available from: <http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/>

NHS board abbreviations

AA Ayrshire & Arran	BR Borders	DG Dumfries & Galloway	GGC Greater Glasgow & Clyde
FF Fife	FV Forth Valley	GR Grampian	HG Highland
LO Lothian	LN Lanarkshire	OR Orkney	SH Shetland
TY Tayside	WI Western Isles		

HPS Surveillance Report

Published by: Health Protection Scotland

Meridian Court, 5 Cadogan Street, Glasgow G2 6QE

T: 0141 300 1100 **F:** 0141 300 1170

W: <http://www.hps.scot.nhs.uk> **Email:** NSS.HPSEnquiries@nhs.net

© Health Protection Scotland 2018