



Gonorrhoea antimicrobial resistance in Ireland, 2010-2017: Summary

On behalf of the Irish National Forum on Antimicrobial Resistance in *Neisseria gonorrhoeae*

January 2019

Key Points

- Antimicrobial susceptibility data on 7% of all gonorrhoea notifications in Ireland have been reported to the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) between 2010 and 2017
- Irish isolates were highly susceptible to cephalosporins:
 - 99% of isolates were susceptible to cefixime
 - 99.9% of isolates were susceptible to ceftriaxone
- Resistance to azithromycin among Irish isolates has been above the European average since 2004
 - 13% of isolates were resistant to azithromycin
- Resistance to ciprofloxacin was observed in 37% of isolates
- Production of β -lactamase was observed in 9% of isolates
- Data included in this summary originated mainly from two large STI clinics in Dublin
 - Future work will involve improving and increasing the national representativeness of the reported gonorrhoea antimicrobial susceptibility data

Suggested citation: HSE Health Protection Surveillance Centre and Interim National Gonococcal Reference Laboratory. Gonorrhoea antimicrobial resistance in Ireland, 2010-2017: Summary. Dublin: HSE HPSC and INGRL; 2019

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Introduction

Gonorrhoea antimicrobial resistance is routinely monitored in Ireland through participation in the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) (1). Data on antimicrobial susceptibility profiles of 775 Irish isolates have been reported to Euro-GASP since 2010, covering 7% of the total national notifications reported during that time. Between 2010 and 2016, the Department of Clinical Microbiology in St. James's Hospital in Dublin provided laboratory data for the Irish submission to Euro-GASP. In 2017, the Interim National Gonococcal Reference Laboratory (INGRL) was established within St. James's Hospital and continued laboratory testing for the Irish submission to Euro-GASP for 2017. Epidemiological data were provided by STI clinics, GPs and Departments of Public Health. Epidemiological and laboratory data were collated by HPSC and reported to the European Centre for Disease Prevention and Control (ECDC) via The European Surveillance System (TESSy).

Prior to designation of the INGRL, samples mainly originated from two large STI clinics in Dublin, one of which was a men who have sex with men (MSM)-specific clinic, and from GPs based in the Dublin area. Following designation of the INGRL, external microbiology laboratories were invited to submit gonococcal isolates suspected of being resistant to therapeutically-relevant antimicrobials to the INGRL for confirmation, determination of antibiogram and/or molecular analysis. A small number of isolates from external sources were included in the 2017 data submission, however the learnings and processes put in place for the collection of the 2017 laboratory and epidemiological data will allow for increased national representativeness in future Euro-GASP data collections.

Epidemiology

Table 1 provides details on the epidemiology of cases reported to Euro-GASP from 2010-2017 and on the cases reported via routine national notifiable disease surveillance of gonorrhoea during the same time period. The male to female ratio of cases reported to Euro-GASP was higher than of cases reported via national surveillance. The median age of cases reported to Euro-GASP also tended to be slightly older than those reported via routine surveillance, although the age range of cases reported via routine surveillance was larger, than those reported to Euro-GASP.

The proportion of cases reported among MSM was higher in the Euro-GASP dataset, while the proportion of cases among females was higher in the national surveillance data. Data on mode of transmission were more complete in the Euro-GASP dataset but the higher representation of MSM cases in the Euro-GASP dataset may also be attributed to the fact that the majority of cases were reported from an MSM-specific clinic.

Table 1. Data on the epidemiology of cases reported via Euro-GASP and via the routine national surveillance system, 2010-2017

Euro-GASP variable	Epidemiology	Euro-GASP		National	
		% available	Data	% available	Data
Sex		100%		99.7%	
	Male		92%		83%
	Female		8%		17%
Age		100%		99.9%	
	Range		15-65 years		15-81 years*
	Median		27 years		26 years*
	Male range		15-65 years		15-81 years*
	Male median		28 years		27 years*
	Female range		17-63 years		15-76 years*
	Female median		23 years		21 years*
Mode of transmission		92%		64%	
	MSM		77%†		61%†
	Heterosexual males		14%†		12%†
	Females		9%†		27%†
HIV status		84%		N/A‡	
	HIV positive		12%†		N/A
Previous gonorrhoea		88%		N/A‡	
	Yes		21%†		N/A
Concurrent STI		94%		N/A‡	
	Yes		20%†		N/A
	Most common: Chlamydia		76%		N/A
Region of birth		75%		30%	
	Ireland		60%†		74%†
	Latin America		18%†		10%†
	Western Europe		10%†		5%†
	Central or Eastern Europe		8%†		6%†
	Other§		4%†		5%†
Area of residence		98%		100%	
	Ireland		97%†		100%
	Dublin region		77%†		64%
Clinical service type		100%		96%	
	General Practice		9%		34%†
	STI clinic		87%		62%†
Treatment prescribed		75%¶		N/A	
	Dual therapy regimen**		89%†		N/A

*Excludes those aged ≤14 years (n=5)

†Percentage where data were known

‡Limited data on HIV status, previous gonorrhoea infection and concurrent STI diagnosis for patients diagnosed with gonorrhoea during this time period available on CIDR

§Other regions include: Asia, Africa, North America and Canada, the Middle East, Australia and New Zealand

||In routine national surveillance system, county of clinic or laboratory is assigned as patient county of residence if information on county of residence is not available

¶Percentage known since data on treatment prescribed for gonorrhoea infection began to be collected as part of the Euro-GASP dataset in 2015

**The recommended treatment regimen for gonorrhoea infection was changed in December 2018 to monotherapy with ceftriaxone (1g). Dual therapy with azithromycin is no longer recommended (See Discussion)

Region of birth was available for 75% of cases reported to Euro-GASP but only for 30% of cases reported via routine national surveillance, making comparison of this variable, between the two surveillance systems, difficult. Area of residence was well completed in both surveillance systems and a higher proportion of Euro-GASP cases were reported to live in the Dublin region, compared with those reported nationally. Area of residence may be assigned in the national surveillance system based on location of clinic or laboratory, which is likely to result in an over-estimate of cases reported as resident in Dublin. These data may also reflect the fact that only cases who attended clinics or GPs in the Dublin area were included in the Euro-GASP dataset between 2010 and 2016.

Information on the clinical service type where gonorrhoea was diagnosed was available for most patients. In the Euro-GASP dataset, 87% of patients were diagnosed in an STI clinic, while 9% were diagnosed by a GP, compared with 62% of gonorrhoea cases notified nationally that were diagnosed in an STI clinic and 34% of cases diagnosed by a GP. Data on treatment prescribed for gonorrhoea infection were collected as part of the Euro-GASP dataset since 2015 and were available for 75% of cases reported during that time. Where known, there was compliance with the recommended dual therapy regimen¹ of ceftriaxone (500mg) and azithromycin (1g) in 89% of cases.

The highlighted differences in sex, mode of transmission, area of residence and clinical service type attended between cases reported to Euro-GASP and those reported via routine national surveillance highlight the need to increase the national representativeness of the Euro-GASP dataset.

Gonorrhoea antimicrobial resistance

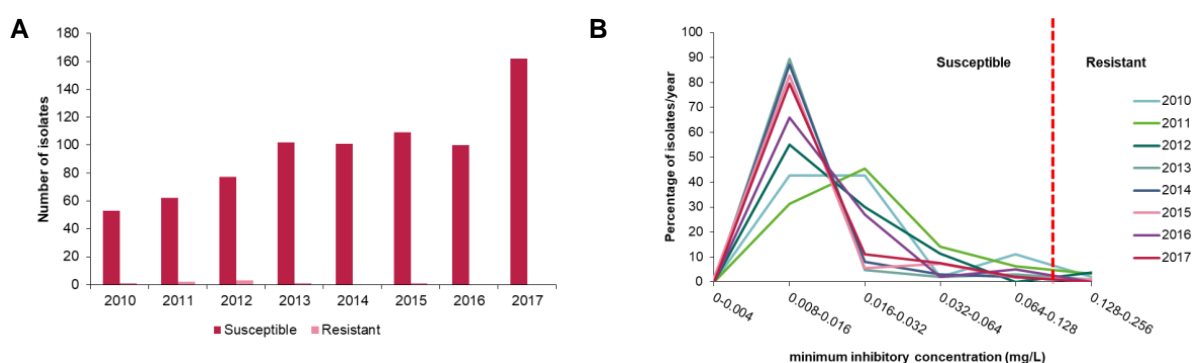
Gonococcal susceptibility to a panel of clinically relevant antimicrobials (cefixime, ceftriaxone, azithromycin, and ciprofloxacin) and β -lactamase production were tested annually.

¹ The recommended treatment regimen for gonorrhoea infection was changed in December 2018 to monotherapy with ceftriaxone (1g). Dual therapy with azithromycin is no longer recommended (See Discussion).

Cefixime

Susceptibility to cefixime was high, with only 1% (n=8) of reported isolates resistant to cefixime (minimum inhibitory concentration (MIC) ≥ 0.125 mg/L). The highest number of cefixime resistant isolates was reported in 2012 and no resistant isolates were reported since 2015 (Figure 1A). Prior to 2013 the Irish isolates displayed a broad range of cefixime MICs. Between 2013 and 2017 the majority of isolates had low cefixime MICs, in the range 0.008-0.016 mg/L. The shift towards higher susceptibility to cefixime in recent years was mirrored in other European countries and reflects the move away from oral third generation cephalosporin (cefixime) to injectable third generation cephalosporin (ceftriaxone) as frontline therapy for gonorrhoea infection (Figure 1B) (1).

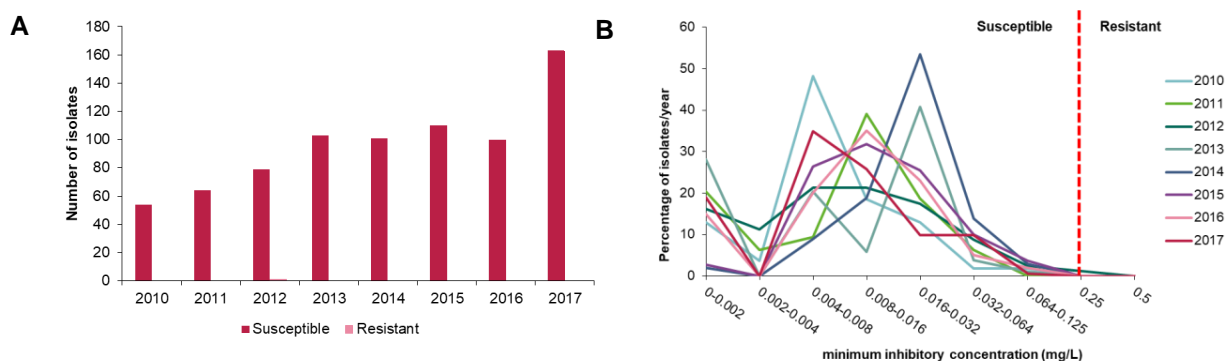
Figure 1. Cefixime susceptibility and MICs among gonococcal isolates in Ireland, 2010-2017



Ceftriaxone

Susceptibility to ceftriaxone was high, with 99.9% (n=774) of reported isolates sensitive to ceftriaxone (MIC < 0.125 mg/L). One ceftriaxone resistant isolate was reported in 2012 (Figure 2A), however the proportion of less susceptible isolates with MICs ≥ 0.032 mg/L was 10% in 2017, compared with 7% in 2016 (Figure 2B).

Figure 2. Ceftriaxone susceptibility and MICs among gonococcal isolates in Ireland, 2010-2017

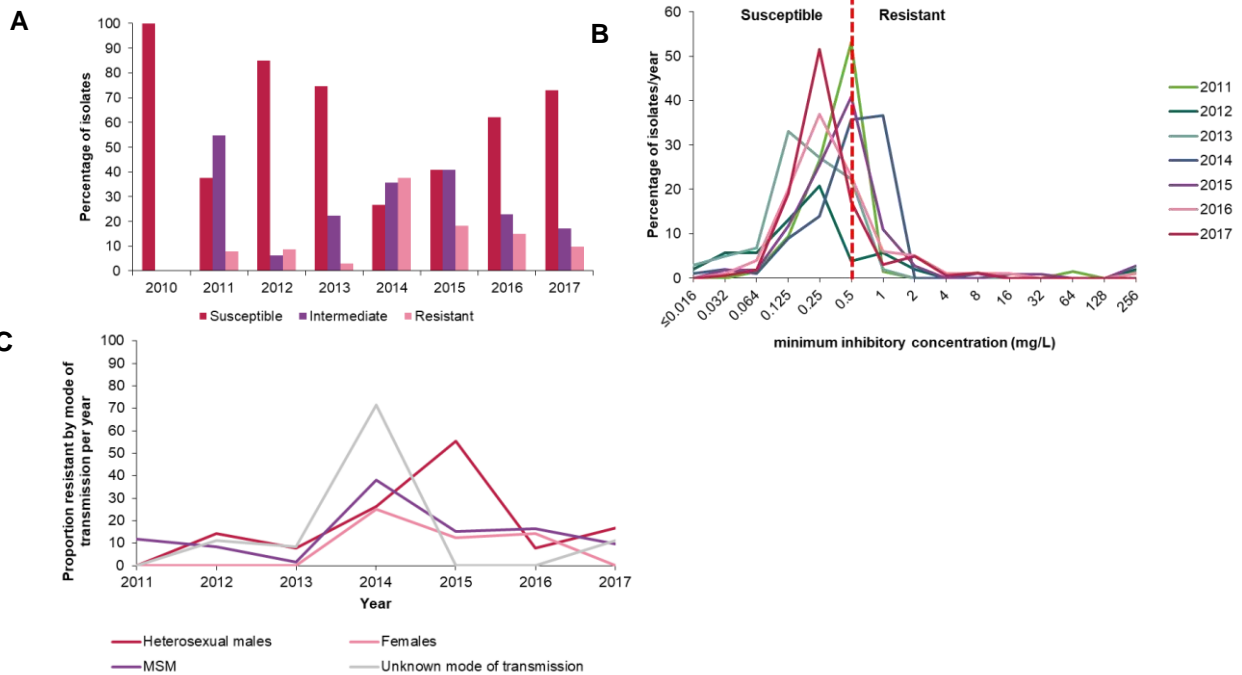


Azithromycin

Resistance to azithromycin was observed in 13% (n=104) of reported isolates (MIC > 0.5 mg/L) and a further 25% (n=195) displayed intermediate resistance to azithromycin (MIC

0.5 mg/L) (Figure 3A). Seven isolates displayed high level azithromycin resistance (HL-AziR; MIC ≥ 256 mg/L). The proportion of Irish isolates displaying resistance to azithromycin has been above the European average since 2014 and the proportion of isolates with MICs ≥ 2.0 mg/L has ranged from 7-9% since 2014 (Figure 3B). Azithromycin resistant isolates were observed in 16% of heterosexual males, 14% of MSM and 7% of females (Figure 3C).

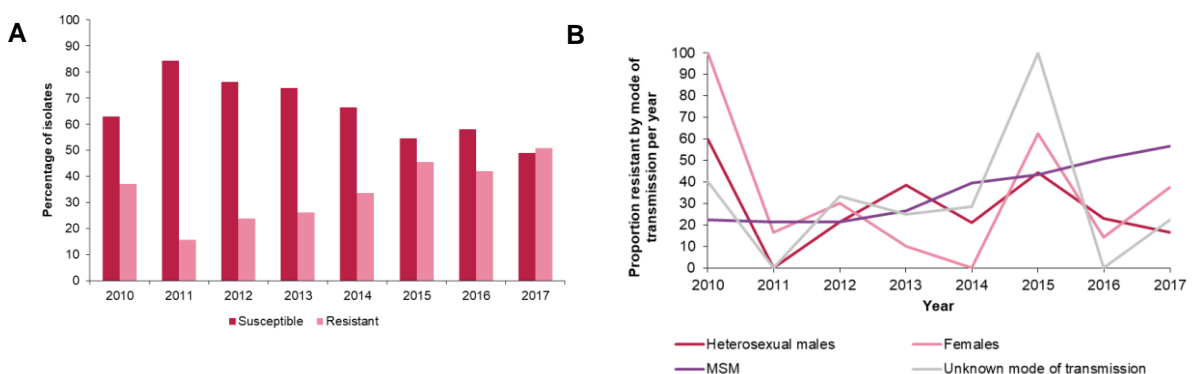
Figure 3. Azithromycin susceptibility, MICs and distribution of resistant isolates by mode of transmission among gonococcal isolates in Ireland, 2010-2017



Ciprofloxacin

Susceptibility to ciprofloxacin was low, with 37% of reported isolates displaying ciprofloxacin resistance (MIC >0.06 mg/L). The numbers of ciprofloxacin resistant isolates have been increasing since 2011, and in 2017 there was a higher proportion of resistant than susceptible isolates (Figure 4A). Resistance to ciprofloxacin was more likely among MSM as 40% of MSM cases displayed ciprofloxacin resistance, compared to 28% of cases among heterosexual males and 27% of cases among females (Figure 4B).

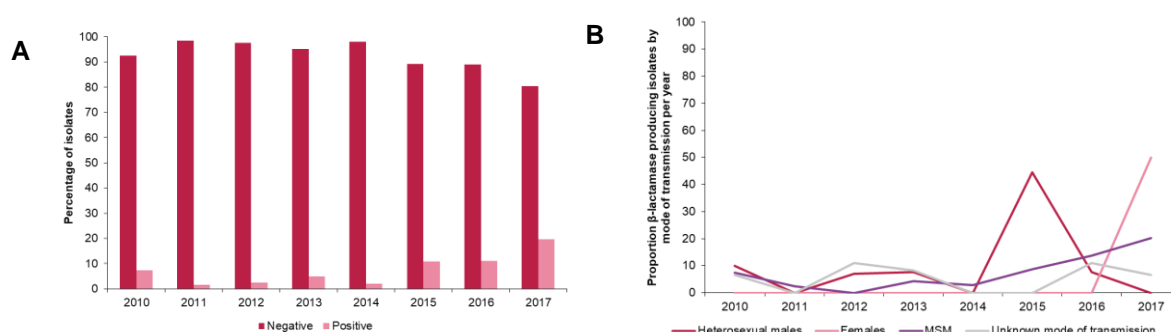
Figure 4. Ciprofloxacin susceptibility and distribution of resistant isolates by mode of transmission among gonococcal isolates in Ireland, 2010-2017



β -lactamase

Production of β -lactamase, which confers high level resistance to penicillin, was observed in 9% of all Irish isolates reported between 2010 and 2017, and increased from 2% in 2011 to 20% in 2017 (Figure 5A). The proportion of β -lactamase producing isolates among MSM was 10%, compared with 8% among heterosexual males and 6% among females, and increased significantly in MSM from 3% in 2014 to 20% in 2017 (Figure 5B).

Figure 5. β -lactamase production and distribution of β -lactamase producing isolates by mode of transmission in Ireland, 2010-2017



Discussion

Susceptibility to the extended spectrum cephalosporins, cefixime and ceftriaxone, was high among Irish isolates as has been reported in other European countries (1). Azithromycin resistance was above 10% among Irish isolates since 2014, this proportion has been above the European average since 2014. These data have important implications for the treatment of gonorrhoea. In December 2018 the clinical subgroup of the Irish National Multidisciplinary Forum on Antimicrobial Resistance in *Neisseria gonorrhoeae* reviewed the Irish treatment guidelines and recommended changing to ceftriaxone (1g) monotherapy. Dual therapy with ceftriaxone and azithromycin is no longer recommended. Ciprofloxacin resistance was over 50% in 2017, which also has important implications as the national treatment guidelines recommend the use of ciprofloxacin for treatment of gonorrhoea in cases in adults with cephalosporin allergy or hypersensitivity to β -lactam antibiotics, where antimicrobial susceptibility data are available prior to treatment and the isolate is sensitive to ciprofloxacin. Whilst the isolates reviewed may not be representative of ciprofloxacin susceptibility nationally, this highlights the importance of submitting samples for antimicrobial susceptibility testing and the need for test of cure when using ciprofloxacin to treat gonorrhoea.

Continued surveillance of gonorrhoea antimicrobial susceptibility in Ireland is necessary to monitor existing and emerging threats. The national representativeness of the data reported to Euro-GASP needs to be improved in order to accurately inform the development of guidelines and recommendations for the management of gonorrhoea infection. The INGR, HPSC and the Irish National Forum on Antimicrobial Resistance in *Neisseria gonorrhoeae* will continue to collaborate to improve the national representativeness of available gonorrhoea antimicrobial susceptibility data.

Technical note

The national gonorrhoea surveillance data reported in Table 1 were extracted from the Computerised Infectious Diseases Reporting (CIDR) system on 21/01/2019 and were correct at the time of publication.

Further information on gonorrhoea antimicrobial resistance and management of gonorrhoea infection

Accompanying slide set available at: <http://www.hpsc.ie/a-z/hivstis/sexuallytransmittedinfections/gonorrhoea/amrgonorrhoea/surveillancereports/>

Information on gonorrhoea antimicrobial resistance: <http://www.hpsc.ie/a-z/hivstis/sexuallytransmittedinfections/gonorrhoea/amrgonorrhoea/>

Gonorrhoea national guidelines: <http://www.hpsc.ie/a-z/hivstis/sexuallytransmittedinfections/gonorrhoea/publications/AMR%20Gonorrhoea%20guidelines%20documetn%20FINAL%202017.pdf>

Antibiotic prescribing guidelines for gonorrhoea: <https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/conditions-and-treatments/genital/gonorrhoea/gonorrhoea.html>

Interim National Gonococcal Reference Laboratory:
<http://www.stjames.ie/Departments/DepartmentsA-Z/N/NationalGonococcalReferenceLaboratory/DepartmentOverview/>

Acknowledgements

Laboratory data were provided by Public Health England, Brendan Crowley, Sinéad Saab, Mary Kelleher, Lisa Rose and members of the Central Pathology Laboratory, SJH and Interim Gonococcal Reference Laboratory, SJH.

Surveillance data were provided by Mary Kelleher, Aoife Colgan, Gillian Cullen, GUIDe, Gay Men's Health Service, Representatives in Local Departments of Public Health, STI/GUM clinicians and GPs.

Collation and analysis of the data was performed by Mary Kelleher, Brendan Crowley, Stephen Murchan, Gillian Cullen, Aoife Colgan and Derval Igoe.

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References

1. ECDC. Gonococcal antimicrobial susceptibility surveillance in Europe, 2016. Stockholm: ECDC 2018.