2. Surveillance and epidemiology of gonorrhoea and AMR in gonorrhoea

Surveillance of AMR in *N. gonorrhoeae* is crucial for monitoring local, national and international trends in antimicrobial resistance. It can inform and shape public health policy for the control of gonococcal infections and containment of antimicrobial resistance.

The WHO Action Plan states that strengthened surveillance systems are needed in order to notify and investigate drug-resistant *N. gonorrhoeae* in a timely manner [1]. STI surveillance, including gonococcal antimicrobial susceptibility surveillance, conducted in a systematic and regular manner, enables the early detection of resistant microorganisms and monitors their spread among people and geographic areas. Drug-resistant infections can be verified and notified early and allow correct decisions to be taken about treatment of individual patients, as well as informing national and international treatment guidelines.

Current surveillance activities for gonorrhoea and for surveillance of AMR in *N. gonorrhoeae* in Ireland are described below. The epidemiology of AMR in *N. gonorrhoeae* in Ireland is described, as well as an analysis of current surveillance strengths and limitations, and recommendations for improvement.

2.1 Gonorrhoea notification

Gonorrhoea is a notifiable disease in Ireland under the Infectious Disease Regulations [24]; laboratory directors and clinicians are required to notify any cases detected to the local Medical Officer of Health (local Director of Public Health or Consultant in Public Health Medicine, MOH), who in turn notifies the Health Protection Surveillance Centre (HPSC). There is an agreed case definition for gonorrhoea [25] (Appendix 2). Up to 2013, the information available nationally was limited; aggregate information by gender, area and age group on a quarterly basis only.

National case based reporting of gonorrhoea commenced in January 2013; data from all laboratories and STI clinics on gonorrhoea is held in the national computerised infectious disease surveillance system, CIDR. National data on laboratory diagnosed cases of gonorrhoea is now comprehensive, since its inclusion in CIDR [26]. In addition, since 2014, for cases notified by laboratories, mode of transmission information and county of residence (if not provided by the laboratory) has been routinely requested from STI clinicians. This latter information is less comprehensive at present.

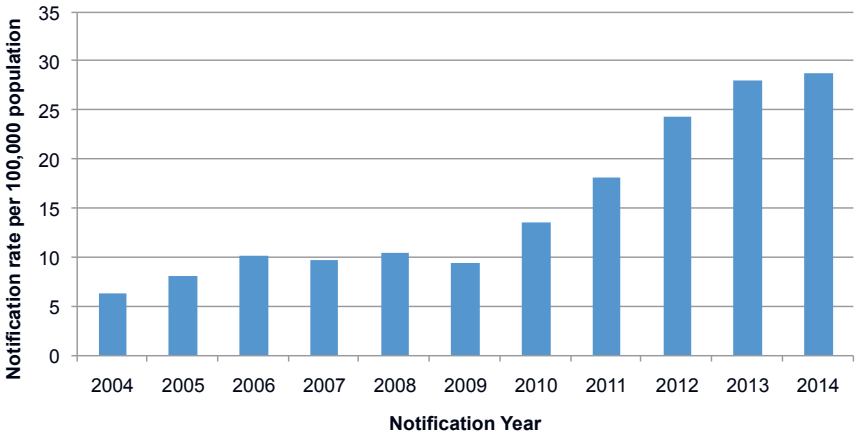
2.2 Epidemiology of gonorrhoea

Gonorrhoea is the second most common notifiable bacterial STI in Ireland, mainly affecting young people (aged 15-24 years) and MSM. The number of notifications of gonorrhoea has been rising in the past few years, but stabilised somewhat in 2014[1]. In 2014, a total of 1,320 cases of gonorrhoea were reported in Ireland, giving a notification rate of 28.8 per 100,000 population. Figure 1 shows the trend in gonorrhoea notifications from 2004 to 2014. The overall trend has increased by 200% between 2009 and 2014. The increase may be due to a number of factors, such as more sensitive diagnostic tests i.e. the nucleic acid amplification test (NAAT), increased testing of extragenital sites in MSM, increase in routine STI screening and ongoing high-levels of unsafe sexual behaviour. This increasing trend in gonorrhoea has been seen in other countries also. Latest figures for the UK show that between 2013 and 2014, there was a 19% increase in cases of gonorrhoea; 52% occurred in MSM, and 55% of cases occurred in young people aged 15-24 years [27]. In Europe, the number of cases of gonorrhoea increased by 58% between 2008 and 2012, with most countries reporting increasing trends. Rates in the European Union (EU) and European Economic Area (EEA; this incorporates the EU as well as Iceland, Liechtenstein and Norway) have increased since 2008, among both males and females; however there has been a more pronounced rise in rates among men [28].

1 Notifications of gonorrhoea in males increased in 2016. See www.hpsc.ie for latest data

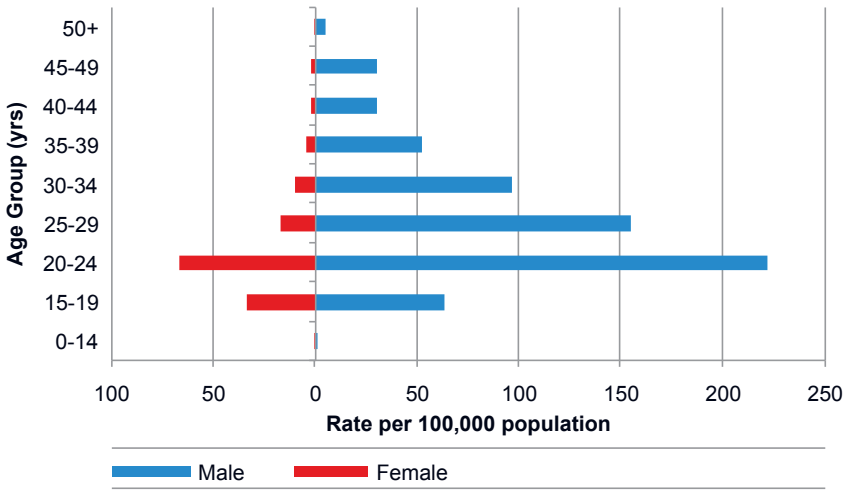
An upsurge in gonorrhoea occurred in the Health Service Executive (HSE) East region (Dublin, Kildare and Wicklow) in late 2012/2013, and a retrospective enhanced surveillance review of cases in the first quarter of 2013 was undertaken [20]. Over half of the cases were in MSM and 44% in heterosexuals (28% males and 16% females). The proportion of cases in MSM increased with increasing age, peaking in the 35-39 year age group, with 95% of the cases in this age group being MSM. Forty two percent (n=53) of MSM cases were born outside Ireland. Only 35% of the MSM cases were symptomatic. Thirteen per cent of cases were HIV positive. Fifteen per cent of cases had had an STI in the previous 12 months. Nearly two thirds of cases had pharyngeal infection (61%). One third of cases had infection at two or more sites. Cases in heterosexuals were significantly younger than MSM. Almost two thirds of the cases (62%) in those less than 25 years of age were heterosexual and approximately two thirds of cases were symptomatic.

Figure 1 Notification rates per 100,000 for gonorrhoea in Ireland 2004 - 2014



In all, a third (32%) of gonorrhoea cases notified in 2014 were among those aged between 20 and 24 years old and 71% were aged between 20 and 35 years old. The highest rate among males was in the 20-24 year old age group followed by the 25-29 year old group. The highest rate among females was also in the 20-24 year age group followed by the 15-19 year old age group (Figure 2). Mode of transmission was available for 419 (32%) of gonorrhoea notifications in 2014. Of the 419 cases, mode of transmission was reported as MSM for 71% of cases (n=297) and heterosexual for 29% (78 male and 44 female). This information on mode of transmission needs to be strengthened so that the effect of prevention and control interventions targeted to those groups most at risk can be evaluated.

Figure 2 Notification rates per 100,000 for gonorrhea cases notified in Ireland in 2014 by age group and gender



2.3 Surveillance of AMR in *N. gonorrhoeae*: Euro-GASP

Although there is currently no dedicated funding allocated for AMR surveillance, at either laboratory or HPSC level, Ireland participates in the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) [29]. This programme was established in 2009 by ECDC as a surveillance system across the countries of the EEA to monitor *N. gonorrhoeae* AMR in the EU/EAA.

The objectives of Euro-GASP are to:

- Develop and implement surveillance of gonococcal antimicrobial susceptibility to a range of therapeutically relevant antimicrobials in a timely manner to allow accurate information on trends in gonococcal AMR across Europe;
- Link susceptibility data with epidemiological information to inform prevention interventions;
- Ensure quality and comparability across countries, laboratories and samples through an external quality assurance (EQA) scheme for AMR testing;
- Provide training in gonococcal culture and antimicrobial susceptibility testing.

There are 21 countries participating in the network. Sentinel laboratories are chosen by individual member states based on local epidemiological patterns as well as convenience. Participating laboratories aim to test a minimum of 100 isolates per year. Isolates are selected from among consecutive patients during April/May and October/November each year. Testing was undertaken biannually until 2014 when it moved to annual testing. Laboratories can participate through decentralised testing, via supplying their own susceptibility test results, rather than submitting the samples for testing in the international reference laboratory hub. Laboratories are required to perform consistently well on EQA prior to moving from centralised to decentralised testing.

Euro-GASP detected the rapid spread of isolates with decreased susceptibility to cefixime in 2010 and 2011 across Europe [29]. Euro-GASP has also undertaken molecular epidemiological typing on a subset of the isolates within Euro-GASP using *Neisseria gonorrhoeae* multi-antigen sequence typing (NG-MAST) [30]. They found associations between antimicrobial resistance and molecular type.

Molecular typing work has been carried out in Ireland. Lynagh *et al.* published detailed characterisation of the first two high-level azithromycin resistant *Neisseria gonorrhoeae* cases in Ireland in 2015 [12]. They reviewed all available urethral isolates of *N. gonorrhoeae* (n=300) collected at St James's Hospital, Dublin from 2008-2014 and detected high-level resistance in two isolates. An association between antimicrobial resistance and molecular type in these two isolates was identified.

2.4 Report on Euro-GASP Ireland, 2010-2014

2.4.1 Isolate collection

2.4.1.1 Source of isolates

The Irish isolates for Euro-GASP come from a major STI clinic (87% of cases) and from GPs (12% of cases) who submit them to one laboratory in the HSE-Eastern region (St James's Hospital). The laboratory liaises with the STI clinic to get the epidemiological data for their cases which is then linked locally to the isolate data using the patient's medical record number (subsequently replaced with unique patient identifier for Euro-GASP in advance of submitting to HPSC who sends it to ECDC).

2.4.1.2 Sampling

The isolates are generally sampled consecutively but any isolates where one of the following phenotypic resistances has been detected are also included:

- β-Lactamase-positive
- Penicillin-Resistant
- Penicillin-Intermediate PLUS Ciprofloxacin-Resistant
- Ceftriaxone zone diameter ≤40mm

2.4.2 Antimicrobial susceptibility testing

Between 2010 and 2012, the laboratory in Ireland participated in centralised testing, i.e. they were asked to submit 110 isolates per year (55 isolates for each 3-month time period monitored: April-June and October-December) with the aim of retrieving and testing 100 isolates. Centralised testing was performed by Public Health England (Colindale).

In 2013, decentralised testing, in which the laboratory performed its own susceptibility testing, was first introduced for all Irish isolates reported to Euro-GASP.

In 2014, the collection period was changed from twice yearly as described above to just one continuous period, starting in August, until the 100 isolates were collected.

The following antimicrobials were tested:

- azithromycin
- ciprofloxacin
- spectinomycin
- cefixime
- ceftriaxone
- penicillinase production

All results were interpreted using European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints with the exception of azithromycin and ciprofloxacin which use more clinically relevant breakpoints as recommended by Euro-GASP (Table 1).

2.4.3 Limitations

The data presented here originate from one laboratory only and so the findings need to be interpreted with caution.

In general, the isolates were selected consecutively over the required study period; however, "non-consecutive" isolates with specific resistance profiles as described above were also included in the study sample. Thus the proportions of isolates with resistance to particular antibiotics may be over-estimated. The sample selected is not necessarily representative of the population from which it is taken (i.e. there are selection biases) and is not representative of the Irish population.

Table 1 Minimal Inhibitory Concentration breakpoints for specific antimicrobials tested

Antimicrobial	Guideline	MIC breakpoint (mg/L)		
		R ≥	I	S ≤
Azithromycin	Euro-GASP	1		0.5
Cefixime*	EUCAST	0.25		0.125
Ceftriaxone*	EUCAST	0.25		0.125
Ciprofloxacin	Euro-GASP	1	0.12-0.5†	0.06
Spectinomycin	EUCAST	128		64

* Decreased susceptibility reported as Intemediate (I) by Euro-GASP (in TESSy)
† Resistant according to EUCAST but recorded as I by Euro-GASP

2.4.4 Results

2.4.4.1 Number of isolates tested

In 2014, 1,320 notifications of gonorrhoea were made in Ireland via CIDR. In the same year 101 isolates were reported to Euro-GASP. This represents 8% of the total (Table 2) and is in accordance with the Euro-GASP aims of testing at least 5% of all cases reported nationally. Between 2010 and 2014, 7-9% of all cases have consistently been tested. However, the isolates tested are from just one laboratory and therefore the results are not geographically representative of national data.

Table 2 Number of *N. gonorrhoeae* isolates tested, number of gonorrhoea cases notified nationally and percentage of isolates tested nationally, 2010-2014

Year	Number of isolates tested	Number of cases notified	% isolates tested
2010	54	625	9%
2011	64	834	8%
2012	80	1108	7%
2013	103	1293*	8%
2014	101	1336*,†	8%

* Cases first notified via the Computerised Infectious Diseases Reporting (CIDR) system
† Provisional data

2.2.4.2 Patient demographics

The majority of gonococcal isolates (cases) were collected from samples from males (Table 3; 370 of 402; 92%).

The age range for all patients was from 16 to 63 years with a median of 27 years. For males (n=370) the age range was from 16 to 63 years with a median of 27 years. For females (n=32), the age range was from 18 to 63 years with a median of 22 years.

Table 3 Patient age distribution, 2010-2014

	2010-2014						
	Number	**Range**	**IQR**	**Mean**	**Median**	**Mode**	**<25 years**
All patients	402	16-63	23-34	28	27	23	143 (35.6%)
Gender							
Female	32 (8.0%)	18-63	20-26	25	22	19	21 (66%)
Male	370 (92.0%)	16-63	23-34	29	27	23	122 (33.0%)
Mode of transmission							
Heterosexual (female and male)	92 (22.9%)	16-63	21-28	26	24	21	47 (51%)
Female heterosexual	*28 (7.0%)*	*18-63*	*20-26*	*25*	*22*	*23*	*19 (68%)*
Male heterosexual	*64 (15.9%)*	*16-57*	*21-29*	*26*	*25*	*19*	*28 (44%)*
Men who have sex with men	255 (63.4%)	18-51	24-34	29	28	23	77 (30.2%)
Unknown	55 (13.7%)	18-63	23-37	31	28	20	19 (35%)

2.4.4.3 Mode of transmission

Between 2010 and 2014, the majority of cases (63.4%) were MSM with heterosexual transmission accounting for 22.9%. The mode of transmission for 13.7% of cases was unknown (Table 4).

2.4.4.4 Site of infection

Genital isolates accounted for the majority of cases (55.7%), followed by anorectal (22.4%) and pharyngeal (21.9%) isolates (Table 4).

2.4.4.5 Previously diagnosed cases

Between 2010 and 2012, 6-8% of cases had a previous diagnosis of gonorrhoea. This increased to 18% in 2013 and 22% in 2014 (Table 4).

2.4.4.6 Concurrent STIs

Between 2011 and 2014, the proportion of cases with a concurrent chlamydia infection increased from 8% to 19% (Table 4).

Table 4 Overall patient characteristics, 2010-2014

	2010	2011	2012	2013	2014	2010-2014
Total number of isolates	54	64	80	103	101	402
Gender						
Female	2 (4%)	6 (9%)	10 (12.5%)	10 (10%)	4 (4%)	32 (8.0%)
Male	52 (96%)	58 (91%)	70 (87.5%)	93 (90%)	97 (96%)	370 (92.0%)
Age (years)						
<25	13 (24%)	27 (42%)	41 (51%)	32 (31%)	28 (28%)	141 (35.1%)
>=25	41 (76%)	37 (58%)	39 (49%)	71 (69%)	73 (72%)	261 (64.9%)
Median	33	26.5	24	27	26	27
Mode of transmission						
Heterosexual (female and male)	12 (22%)	12 (19%)	24 (30%)	21 (20%)	23 (23%)	92 (22.9%)
Female heterosexual	2 (4%)	4 (6%)	10 (13%)	8 (8%)	4 (4%)	28 (7.0%)
Male heterosexual	10 (19%)	8 (13%)	14 (18%)	13 (13%)	19 (19%)	64 (15.9%)
Men who have sex with men	27 (50%)	42 (66%)	47 (59%)	68 (66%)	71 (70%)	255 (63.4%)
Unknown	15 (28%)	10 (16%)	9 (11%)	14 (14%)	7 (7%)	55 (13.7%)
Site of infection						
Anorectal	5 (9%)	20 (31%)	16 (20%)	23 (22%)	26 (26%)	90 (22.4%)
Genital	43 (80%)	33 (52%)	51 (64%)	47 (46%)	50 (50%)	224 (55.7%)
Pharyngeal	6 (11%)	11 (17%)	13 (16%)	33 (32%)	25 (25%)	88 (21.9%)
Previously diagnosed						
Yes	4 (7%)	5 (8%)	5 (6%)	18 (18%)	22 (22%)	54 (13.4%)
No	50 (93%)	58 (91%)	72 (90%)	84 (82%)	73 (72%)	337 (83.8%)
Unknown	0 (0%)	1 (2%)	3 (4%)	1 (1%)	6 (6%)	5 (1.7%)
Concurrent STIs						
Concurrent chlamydia	14 (26%)	5 (8%)	9 (11%)	13 (13%)*	19 (19%)*	41 (13.6%)†
Concurrent other STIs (not HIV)	4 (7%)	6 (9%)	0 (0%)	1 (1%)*	4 (4%)*	11 (3.7%)†
No concurrent STI	35 (65%)	31 (48%)	68 (85%)	89 (86%)	73 (72%)	223 (74.1%)
Unknown	1 (2%)	22 (34%)	3 (4%)	1 (1%)	6 (6%)	27 (9.0%)
HIV status						
Positive	0 (0%)	5 (8%)	7 (9%)	4 (4%)	11 (11%)	27 (6.7%)
Negative	0 (0%)	18 (28%)	68 (85%)	98 (95%)	82 (81%)	266 (61.2%)
Unknown	54 (100%)	41 (64%)	5 (6%)	1 (1%)	8 (8%)	109 (27.1%)

* includes one case with both concurrent chlamydia and syphilis;
† includes 2 cases with both concurrent chlamydia and syphilis

2.4.4.7 HIV status

In 2014, 11% of cases were HIV-positive (Table 4). This represents an increase from 4% in 2013. There were five gonorrhoea cases reported, all MSM, where the patient was HIV-positive and also had concurrent chlamydia infection.

2.4.4.8 Probable country of infection

Between 2012 and 2014, the probable country of infection was provided for the majority of cases (178 of 284, or 63%). Most of these (169, or 95%) were probably infected in Ireland. The nine cases probably infected outside of Ireland originated in six countries: the UK (n=3), Thailand (n=2) and one case each from the Netherlands, Pakistan, Poland and Romania. The mode of transmission was heterosexual for four cases and MSM for four cases.

2.4.4.9 Country of birth

Between 2011 and 2014, the country of birth was provided for the majority of cases (254 of 348, or 73%). Most of these (162, or 64%) were born in Ireland. Of the 92 cases born outside Ireland, 29 countries were represented, including Brazil (n=26), Poland (n=12), UK (n=8) and Venezuela (n=6). The majority of cases born outside of Ireland were MSM (n=80, or 87%).

In 2014, the country of birth was provided for 92% (93 of 101) of cases. The majority were born in Ireland (n=56), but 37 cases from patients born in 17 other countries (including 11 from Brazil and five each from the UK and Venezuela) were reported. The majority of cases born outside of Ireland were MSM (n=31, or 84%).

2.4.4.10 Antimicrobial resistance patterns

A summary of the numbers of isolates tested and their susceptibility to key antibiotics is provided in Table 5 and Figure 3.

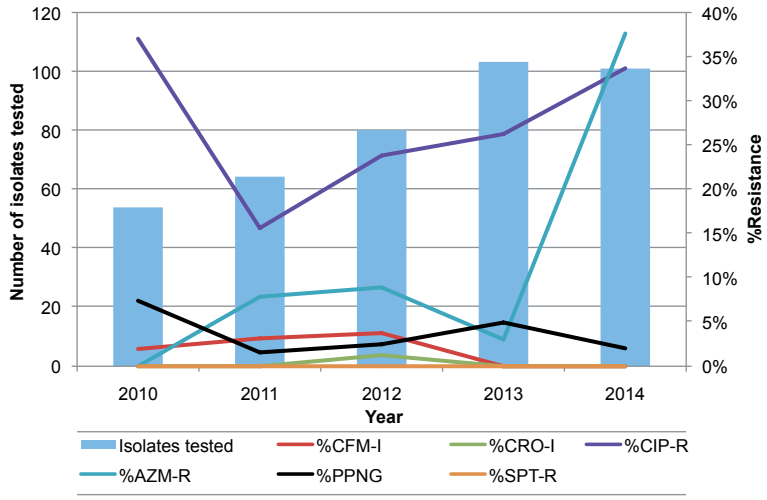
A more detailed discussion of resistance of *N. gonorrhoeae* to individual antibiotics from 2010-2014, and providing the European context is provided in Appendix 3.

Table 5 Antimicrobial susceptibility to key antibiotics (numbers and proportions that are resistant or have decreased susceptibility, i.e. with intermediate levels of resistance), 2010-2014

		Number antibiotic-resistant / proportion antibiotic-resistant											
Time period	**Isolates tested**	**CFM-I**	**%CFM-I**	**CRO-I**	**%CRO-I**	**CIP-R**	**%CIP-R**	**AZM-R**	**%AZM-R**	**PPNG**	**%PPNG**	**SPT-R**	**%SPT-R**
2010	54	1	2%	0	0%	20	37%	0	0%	4	7%	0	0%
2011	64	2	3%	0	0%	10	16%	5	8%	1	2%	0	0%
2012	80	3	4%	1	1%	19	24%	7	9%	2	3%	0	0%
2013	103	0	0%	0	0%	27	26%	3	3%	5	5%	0	0%
2014	101	0	0%	0	0%	34	34%	38	38%	2	2%	0	0%
2010-2014	**402**	**6**	**1.5%**	**1**	**0.2%**	**110**	**27.4%**	**53**	**13.2%**	**14**	**3.5%**	**0**	**0.0%**

CFM-I, cefixime-intermediate; CRO-I, ceftriaxone-intermediate; CIP-R, ciprofloxacin-resistant; AZM-R, azithromycin-resistant; PPNG, penicillinase-producing *N. gonorrhoeae*; SPT-R, spectimomycin-resistant

Figure 3 Numbers of *N. gonorrhoeae* isolates tested and proportions of isolates with resistance or decreased susceptibility (i.e. with intermediate levels of resistance) to key antibiotics, 2010-2014



CFM-I, cefixime-intermediate; CRO-I, ceftriaxone-intermediate; CIP-R, ciprofloxacin-resistant; AZM-R, azithromycin-resistant; PPNG, penicillinase-producing *N. gonorrhoeae*; SPT-R, spectimomycin-resistant

In summary, resistance levels in Ireland are low compared with the Euro-GASP data (see limitations highlighted earlier):

- No reduced susceptibility (or intermediate resistance) to cefixime and ceftriaxone reported for past two years (2013 and 2014);
- No resistance to spectinomycin reported since surveillance began in 2010;
- Increase in azithromycin resistance reported in 2014, but the majority of isolates (37 of 38) were at the resistance breakpoint (Minimum Inhibitory Concentration, MIC = 1 mg/L) and no treatment failures were reported from these cases;
- Increase in previously diagnosed cases in 2013 and 2014 compared with the period 2010-2012;
- Increase in cases with a concurrent STI in 2014;
- Increase in HIV-positive status in 2014 including five cases where the patient had a concurrent chlamydia infection.

2.5 High level azithromycin resistant (HL-AziR) gonorrhoea in Ireland (2011-2016)

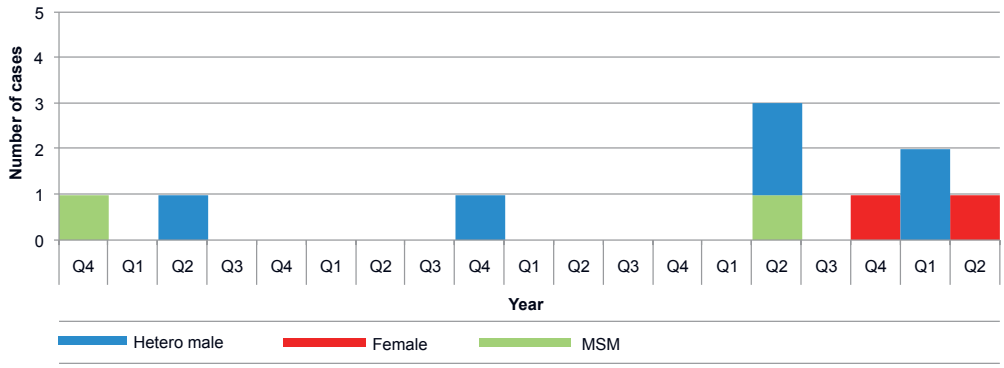
In Ireland, a total of 10 cases of high-level azithromycin resistant (HL-AziR) gonorrhoea have been reported since 2011, with three cases reported in the first half of 2016 (Figure 4). Surveillance forms were distributed to clinicians for six cases notified within the past year, to date, 66% of which have been completed. Data on the others have been collated from EURO GASP upload data (n=4) and initial notification data provided to Departments of Public Health (n=2). HPSC has convened a group to monitor and make recommendations in relation to the surveillance of HL-AziR gonorrhoea in Ireland with representation from clinical microbiology, laboratory, public health, and HPSC. As of September 2016, enhanced epidemiological surveillance forms and mechanisms to gather and collate information to monitor HL-AziR gonorrhoea are in development.

In summary:

- There were two cases in females and eight in males. The median age is 20 years (range 18 to 35 years). Sexual orientation is reported as MSM for two of the male cases (20%), heterosexual for seven cases (70%) and is missing for one case.
- Nine of the cases were reported from the GUIDE clinic and one from the Midwest via Public Health England.
- Site of infection was reported as urethra for four cases (40%), pharynx for three (30%) and rectum for one. Site of infection is missing for two others.
- Of the six cases for whom surveillance forms have been requested:
  - County of residence is available for four cases, three of whom live in Dublin, the fourth in Kildare.
  - Four cases were reported as symptomatic, one asymptomatic and unknown for one.
  - Two cases have been successfully treated and have had a negative test of cure. Two cases were treated but have not had a negative test of cure. These data are missing for the other two cases.
  - A total of six partners have been reported for four cases. Only one contact has been contacted, treated and has had a negative test of cure.

During the period 2010-2015, details of six isolates with HL-AziR have been reported to EURO GASP. One isolate was reported each year for the period 2011-2013 and three in 2015. None was reported in 2014.

Figure 4 Epidemiological curve of HL-AziR gonorrhoea in Ireland by sexual orientation, 2011-2016



Recommendations

- Funding is required at local and reference laboratory level and at HPSC for gonorrhoea AMR surveillance (cephalosporin, azithromycin and other emerging), so that a representative national sample of isolates can be submitted for AMR testing, epidemiological data can be collected, and this information can be reviewed, analysed and regularly reported on, nationally and internationally.

- Provision of information to the MOH on mode of transmission for all cases of gonorrhoea needs to be improved (http://www.hpsc.ie/).