

National Interim Gonococcal Reference Laboratory

Annual Report 2017

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Contents

1.	The Establishment and Funding of the Service	1
2.	Gonorrhoea	1
3.	Services Available	2
■	Monitoring, alert and response	2
■	Technical advice	2
■	Clinical advice	2
■	Collaboration and research	2
4.	2017 Isolates	3
■	Patient demographics	3
5.	Antimicrobial resistance	3
■	High-Level Azithromycin in Ireland 2017	4
6.	Euro-GASP collection 2017	5
7.	Continuous Education and Professional Development	7
8.	Publications and presentations	8
9.	Acknowledgements	8
10.	References:.....	9

1. The Establishment and Funding of the Service

The Interim National Gonococcal Reference Laboratory (GCRL) Service was established in April 2016 by the Health Service Executive (HSE). The laboratory is funded by a central allocation to St. James's Hospital. Funding is provided for consumable costs and staffing, which consists of a medical scientist, a senior medical scientist and a surveillance scientist. This is the first Annual Report of the GCRL and details the output of the GCRL service in 2017.

The National Interim Gonococcal Reference Laboratory is located within the Central Pathology Laboratory Microbiology Department within St. James's Hospital and is administered within the Laboratory Medicine (LabMed) Directorate.

2. Gonorrhoea

Gonorrhoea is a sexually transmitted infection (STI) caused by the bacterium *Neisseria gonorrhoea* (*N. gonorrhoea*); these infections primarily involve the mucosal surfaces of urethra, endocervix, rectum, pharynx and conjunctiva¹.

There is a significant burden of gonococcal disease globally with higher rates in less developed countries². In Ireland gonorrhoea is the second highest notifiable STI after chlamydia and provisional 2017 data from HSPC indicates that there were 2,260 reported gonorrhoea cases, giving a notification rate of 47.5 per 100,000 population in 2017 representing a 15.6% increase from 2016 rates.

For further information the website of the HSE – HPSC provides a useful guide <http://www.hpsc.ie/a-z/hivstis/sexuallytransmittedinfections/gonorrhoea/>

3. Services Available

The interim Gonococcal Reference Laboratory provides the following services:

■ Monitoring, alert and response

- Antimicrobial susceptibility testing – provision of extended antimicrobial susceptibility testing for *N. gonorrhoeae* to identify and monitor current resistance profiles in Ireland.
- In collaboration with the HPSC, determining what is representative gonococcal sentinel sampling
- Contribution to and participation in gonococcal surveillance including the European - Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) and relevant Public Health Departments
- Participation and provision of technical advice/expertise in the context of an outbreak.
- Provision of an annual report on activity and future objective to the Sexual Health and Crisis Pregnancy programme (SHCPP).

■ Technical advice

- Development and dissemination of guidance on appropriate diagnostic methods, including storage and transport of isolates.
- Proactive and reactive provision of advice and information to other laboratories that carry out *N. gonorrhoeae* identification and antimicrobial susceptibility testing.
- Support and advice to other laboratories that carry out *N. gonorrhoeae* nucleic acid amplification testing (NAAT).

■ Clinical advice

- A point of contact for clinical queries from clinicians and other clinical microbiologists.
- Proactive dissemination of information to clinicians and other clinical microbiologists in relation to gonococcal diagnostics

■ Collaboration and research

- International research collaboration
- Supporting clinical and laboratory based research, at both MSc and PhD level

4. 2017 Isolates

In 2017 The GCRL received a total of eighty five *N. gonorrhoea* isolates.

These isolates were recovered from patients attending community medical practitioners, GUIDE clinics, Gay Men's Health Service and hospitals and were submitted to the GCRL from hospital microbiology laboratories throughout the Republic of Ireland.

■ Patient demographics

Of the isolates received 43.5% (37/85) were received from University Hospital Limerick, 42.3% (36/85) were received from University Hospital Galway, 5.9% (5/85) received from Beaumont Hospital, 4.7% (4/85) from the National Maternity Hospital Holles Street and the remaining 3.5% (3/85) were received from Waterford Regional Hospital, Mayo General Hospital and Tallaght University Hospital.

Of the eighty five isolates received, 12.9% (11/85) were female, 74.1% (63/85) were male and the remaining 12.9% (11/85) of isolates the sex was not stated. Among female patients the predominant site from which isolates were recovered was cervical at 63.6% (7/11) although GC was also recovered from eye swabs (27.3%, 3/11). In one incidence the site of recovery was not specified (9%, 1/11). The age range among female patients was 15 - 43 years old. Urethral was the predominant site of recovery in male patients representing 61.9% (39/63) while the remaining sites included penile (11.1% 7/63), eye (11.1% 7/63), rectal (7.9% 5.63), throat (1.6% 1/63), and unknown (6.3% 4/63). The age range among males isolate was 14 - 51 years old.

5. Antimicrobial resistance

Neisseria gonorrhoea has rapidly acquired resistance to all antimicrobial drugs used as front-line monotherapy to treat gonorrhoea infection, including the extended spectrum cephalosporin class of antimicrobials which is typically considered to be the last remaining treatment option³. Current clinical guidelines recommend the use of a dual therapy regimen comprising the cephalosporin, ceftriaxone, and the macrolide, azithromycin, for treatment of gonorrhoea infections¹. The use of dual antimicrobial therapy is expected to extend the useful life of ceftriaxone, as it is considered unlikely that resistance to two classes of antimicrobial will develop simultaneously. However, resistance to azithromycin threatens

the success of the dual therapy regimen and if azithromycin becomes ineffective against gonorrhoea there will be no further barriers to the development of ceftriaxone resistance with the risk that gonorrhoea may become untreatable in the future⁴.

The isolates received in the GCRL were tested against six antimicrobials (azithromycin, ceftriaxone, cefixime, ciprofloxacin, tetracycline and spectinomycin) using Gradient minimum inhibitory concentration (MIC) strips from Biomérieux and liofilchem®. Interpretations were based upon the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints- bacteria table V7.1⁵. β -lactamase testing was performed using the Hodge plate and confirmed when positive by Cefinase™ discs (Biomérieux).

In 2017 98% (84/85) of isolates tested susceptible to the third generation cephalosporin's cefixime and ceftriaxone. Ceftriaxone MICs ranged from <0.002 - 0.064 $\mu\text{g/ml}$ where all isolates (100% 85/85) tested susceptible according to EUCAST breakpoints. Cefixime MICs ranged from <0.016- 0.25 $\mu\text{g/ml}$, 98.9% (84/85) of isolates tested displayed a susceptible MICs (<0.016-0.125 $\mu\text{g/ml}$) however one isolate displayed reduced susceptibility to cefixime with an MIC of 0.25 $\mu\text{g/ml}$.

Resistance to ciprofloxacin and tetracycline varied among the isolates. In 2017 ciprofloxacin MICs ranged from ≤ 0.002 - ≥ 32.0 $\mu\text{g/ml}$. Ciprofloxacin resistance was seen in 28.3% (24/85) of isolates where MICs were > 0.06 $\mu\text{g/ml}$, the remaining 71.7% (61/85) displayed MICs ranging from ≤ 0.002 - 0.032 $\mu\text{g/ml}$. Similar to ciprofloxacin the MICs to tetracycline varied among 2017 isolates. Of the 85 isolates 77.6% (66/85) tested susceptible to tetracycline MIC ≤ 0.5 $\mu\text{g/ml}$, 14.1% (12/85) tested resistant to tetracycline with MICs > 1.0 $\mu\text{g/ml}$ and the remaining 8.2% (7/85) tested intermediate.

All 85 isolates tested against spectinomycin in 2017 display a susceptible phenotype with MICs ≤ 64.0 $\mu\text{g/ml}$.

■ High-Level Azithromycin in Ireland 2017

There have been 18 cases of high level azithromycin resistant gonorrhoea (HL-AziR; azithromycin minimum inhibitory concentration ≥ 256 $\mu\text{g/ml}$) reported in Ireland since 2011 to date⁶. Five further cases of HL-AziR gonorrhoea were reported in Ireland in 2017. All cases were diagnosed in the first two quarters of the year, from January to April. The cases were reported from HSE-East, HSE-Midwest and HSE-West, and high level azithromycin

resistance was confirmed for all 5 cases, as well as extended antimicrobial susceptibility testing, in the Interim Gonococcal Reference Laboratory.

All isolates were recovered from male patients ranging in age from 21 – 29 years. Four of the cases were reported as heterosexual while the remaining patient was reported as a man who has sex with men (MSM). In three cases the site of infection was the urethral while the remaining two cases were recovered from pharyngeal and rectal swabs. All HL-AziR isolates were susceptible to ceftriaxone, with MICs ranging from 0.004 µg/ml to 0.032 µg/ml. One HL-AziR isolate displayed reduced susceptibility to cefixime (MIC 0.125 µg/ml) while one was resistant to ciprofloxacin (MIC 8.0 µg/ml). All other isolates were susceptible to cefixime and ciprofloxacin and no isolates produced β-lactamase.

6. Euro-GASP collection 2017

The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP) is a sentinel surveillance programme, run by the European Centre for Disease Control (ECDC), established to detect emerging and increasing trends in antibiotic resistance in gonorrhoea isolates throughout the participating member states in Europe. The annual de-centralised testing model requires that sentinel laboratories perform antimicrobial susceptibility testing on a selection of isolates, enhanced surveillance is collected on the selected isolates and this information is reported to the ECDC. Linking susceptibility and epidemiological information informs disease prevention interventions. The programme ensures quality and comparability across all participating laboratories and provides training in gonococcal culturing and antimicrobial susceptibility testing. Ireland has participated in Euro-GASP since 2010, and has participated via de-centralised testing since 2013. The GCRL in St. James's Hospital is the Irish sentinel laboratory.

The collection period for Euro-GASP samples commences annually in September. Euro-GASP guidelines recommend that 100 consecutive samples should be collected but countries should aim to capture approximately 10% of the total number of national Gonorrhoea cases per year. For countries where 100 isolates is much lower than 10% of the national total of gonorrhoea cases, additional isolates should be collected to achieve a more representative sample size. Samples should be selected from groups that represent different geographical

regions and patient groups to reflect the distribution of gonorrhoea cases nationally. When more than one isolate is submitted for a patient it is considered one episode of infection if the specimens were recovered ≤ 4 weeks apart. In these cases only one isolate should be submitted for Euro-GASP according to the following hierarchy:

Male: 1) pharyngeal, 2) rectal, 3) urethral, 4) other

Female: 1) pharyngeal, 2) cervical, 3) other anogenital (high vaginal swab, rectal, urethral), 4) other

By August 2017 the number of gonorrhoea notifications in Ireland had already exceeded 1000 so 165 consecutive gonorrhoea isolates were selected for submission to Euro-GASP for 2017.

In Ireland 95% ($n=157$) of the isolates in the 2017 Euro-GASP submission were recovered from male patients while the remaining 5% ($n=8$) were recovered from females. The male patients ranged in age from 15-59 years (median age=28 years) while female patients were 17-37 years (median age=23 years). The majority of isolates (88%) came from patients who attended the GUIDE or Gay Men's Health Service STI clinics in Dublin. Table 1 shows the original clinical or laboratory source of all isolates included the 2017 Euro-GASP submission.

Table 1. 2017 Euro-GASP isolates

Clinic/laboratory	Number of isolates
Gay Men's Health Service	90
GUIDE	56
General Practitioners	8
University Hospital Limerick	6
Beaumont Hospital	2
Mayo General Hospital	1
National Maternity Hospital	1
Tallaght Hospital	1

All isolates were investigated for susceptibility against ciprofloxacin, cefixime, azithromycin, ceftriaxone and for the production of β -lactamase. Isolates submitted from external laboratories, outside the clinical microbiology laboratory in SJH, were also further investigated for susceptibility to tetracycline and spectinomycin. Fifty percent of isolates

($n=83$) were resistant to ciprofloxacin, 19% ($n=32$) of isolates were β -lactamase positive, 10% ($n=16$) were resistant to azithromycin and a further 17% ($n=28$) were azithromycin intermediate according to EUCAST breakpoints. No high level azithromycin resistant (HL-AziR; MIC \geq 256 mg/l) isolates were included in the Euro-GASP collection for 2017. All isolates were sensitive to the extended spectrum cephalosporins, cefixime and ceftriaxone.

Enhanced surveillance information on patients linked to each Euro-GASP isolate is collected to combine antimicrobial susceptibility patterns with epidemiological data to inform public health policy and health promotion strategies. Data on patient country of birth, area of residence, probable country of infection, probable mode of transmission, antimicrobial treatment used to treat current incidence of infection, history of gonorrhoea infections and concurrent sexually transmitted infections is provided by clinicians and Departments of Public Health. The laboratory and epidemiological data is collated at the Health Protection Surveillance Centre (HPSC) and will be reported to the ECDC via The European Surveillance System (TESSy) in April 2018.

7. Continuous Education and Professional Development

The Staff of the GCRL maintains their expertise and knowledge through participation at both national and international meetings, workshops and conferences. Throughout the year all staff continued their professional development through attendance various meetings including;

- HIV club evening meetings
- SJH Journal clubs
- Focus on Infection
- Microbiology Advisory Body

GCRL staff also ensured mandatory training requirements were met in areas such as Manual Handling & Fire safety, Quality Management and Hand Hygiene.

8. Publications and presentations

The Staff of the GCRL have presented for the Society for the Study of Sexually Transmitted Diseases in Ireland (SSTD) and the Academy of Clinical Science and Laboratory Medicine (ACSLM)

“Epidemiological report on high level azithromycin resistant gonorrhoea infections in Ireland 2011 - 2017” By Aoife Colgan, Gillian Cullen, Brendan Crowley and Derval Igoe. SSTD Autumn Meeting in the Royal Marine Hotel in Dun Laoghaire on the 25th of November 2017.

“*Nisseria gonorrhoea* resistance is futile” By Sinéad Saab and Brendan Crowley. ACSLM Winter meeting 2017.

9. Acknowledgements

We would like to thank the Staff of the GCRL for their hard work in providing this service; The Department of Laboratory Medicine, St. James’s Hospital, the Health Protection Surveillance Centre (HPSC) and users of this service for the support provided to the GCRL.

10. References:

¹ Health Protection Surveillance Centre Scientific Advisory Committee. National Guidelines for Prevention and Control of Gonorrhoea and for Minimising the Impact of Antimicrobial Resistance in *Neisseria gonorrhoeae*.

² Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. PLoS ONE. 2015; 10(12):e0143304. <https://doi.org/10.1371/journal.pone.0143304> PMID: 26646541.

³ Unemo M, Shafer WM. Antimicrobial resistance in *Neisseria gonorrhoeae* in the 21st century: past, evolution, and future. Clin Microbiol Rev. 2014;27(3):587-613. doi:10.1128/CMR.00010-14

⁴ WHO. Antimicrobial Resistance: Global Report on Surveillance. Geneva: WHO 2014

⁵ The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, version 7.1, 2017.

http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1/Breakpoint_Tables.pdf

⁶ Health Protection Surveillance Centre. High level azithromycin resistant (HL-AziR) gonorrhoea in Ireland 2011 - 2017. Health Protection Surveillance Centre 2017