National Gonococcal Reference Laboratory

Annual Report 2018

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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 and, in addition to consumable costs, includes staffing of a medical scientist, a senior medical scientist and a surveillance scientist. This is the second Annual Report of the GCRL and details the output of the GCRL service in 2018.

The 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 conjunctiva[1].

There is a significant burden of gonococcal disease globally with higher rates in less developed countries[2]. Gonorrhoea has been a notifiable disease in Ireland since 1948[3] and is the second highest notifiable STI behind chlamydia. Health Protection Surveillance Centre (HPSC) Data 2018 data indicates that there were 2,450 cases of gonorrhoea, giving a notification rate of 50.5% per 100,000 population in 2018 representing a 7% increase from 2017 rates and 86% increase since 2015[4].

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
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4. 2018 Isolates

Isolates received in the GCRL were recovered from patients attending community medical practitioners, Genitourinary and Infectious Disease clinics (GUIDe), Gay Men's Health Services and from all hospital microbiology laboratories in the Republic of Ireland. In 2018 the GCRL received seven hundred and forty seven isolates.

Patient demographics

Of the isolates received 47.52% (*n*= 355) were received from Gay Men's Health Services, 38.88% (*n*=288) from GUIDE clinics, 4.95% (*n*= 37) from the University Hospital Limerick, 2.68% (*n*= 20) from general practitioner clinics and the remaining 6.29% (*n*= 47) isolates were received from Beaumont Hospital, Mid-regional Hospital Portlaoise, Letterkenny General Hospital, University Hospital Galway, Mater Hospital Dublin, Waterford Regional Hospital, Mayo General Hospital, Cork University Hospital, Eurofins Biomnis Ireland, the National Maternity Hospital, Our Lady of Lourdes Hospital Navan and Our Lady of Lourdes Hospital Drogdhea.

Of the seven hundred and forty seven isolates received, 7.10% (*n*= 53) were female, 92.5% (*n*= 691) were male and the remaining 0.40% (*n*=3) the sex was not stated. Among female isolates the predominant site from which *N. gonorrhoea* was recovered was the cervical at 66.04% (*n*= 35) other sites included pharyngeal, rectal, high vaginal swabs and a blood stream isolate. In three incidences (5.66% *n*= 3) the site of recovery was not specified. The age range among female patients was 18- 43 years old (median age =29 years old). Urethral was the predominant site of recovery in male patients representing 43.85 % (*n*= 303) while the remaining sites included rectal, pharyngeal, eye, penile and endocervical (transgender). In 10 incidences the site of recovery was not specified 1.45 % (*n*= 10). The age range among males isolate was 17-59 years old (median age = 29 years old).

5. Antimicrobial resistance

Antimicrobial resistance is an on-going threat to the management of gonorrhoea infections *N. 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 option[5]. In 2018 Clinical guidelines traditionally recommend the use of a dual therapy comprising the cephalosporin, ceftriaxone, and the macrolide, azithromycin, for treatment of gonorrhoea infections[1]. The use of dual antimicrobial therapy was expected to extend the useful life of ceftriaxone. This dual therapy was comprised in 2018 when the first global report of a high level azithromycin resistant *N. gonorrhoea* which is also resistant to ceftriaxone was imported to the UK[6]. As a result of this and a case of imported ceftriaxone resistant in Ireland in 2018[7], in December 2018 on the advice of the clinical subgroup of the National Forum on Antimicrobial Resistance in *N. gonorrhoea,* the recommended treatment of uncomplicated gonorrhoea (without a cephalosporin allergy) changed to ceftriaxone 1g intramuscularly[8].

The isolates received in the GCRL were tested against varying panel of antimicrobials (azithromycin, ceftriaxone, cefixime, ciprofloxacin, tetracycline and spectinomycin) using 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 V8.0/8.1[9]. B-lactamase testing was performed using hodge plates and confirmed when positive by nitrocefin™ discs (MastID).

In 2018, 98.93% (*n*= 739) isolates underwent antimicrobial susceptibility testing, as eight isolates failed to be recovered. 99.73% (*n*= 737) of these isolates tested susceptible to the third generation cephalosporin cefixime, susceptible MICs ranged from <0.016-0.125 µg/ml. According to EUCAST 2018 breakpoints, only 0.27% (*n*= 2) displayed a resistant phenotype to cefixime where MICS were 0.25 µg/ml and 0.5 µg/ml respectively.

Resistance to ciprofloxacin and tetracycline varied among the isolates. In 2018 ciprofloxacin MICs ranged from <=0.002 - >=32.0 µg/ml. Ciprofloxacin resistance was seen in 54.85% (*n*= 198) of isolates, where MICs range >=0.125 µg/ml - >=32 µg/ml, the remaining 44.88% (*n*= 162) displayed MICs ranging from <=0.002 – 0.032 µg/ml, one isolates display an MIC 0.064 µg/ml. Similar to ciprofloxacin the MICs to tetracycline varied among 2018 isolates. Of the 102 isolates 70.59% (*n*= 72) tested susceptible to tetracycline MIC <=0.5 µg/ml, 18.63% (*n*= 19) tested intermediate to tetracycline with an MIC 1.0 µg/ml and the remaining 10.78% (*n*= 11) tested resistant.

All 102 isolates tested against spectinomycin in 2018 display a susceptible phenotype with MICs <=64.0 µg/ml, MIC ranged from 0.5ug/ml- 32.0 ug/ml.

High-Level Azithromycin in Ireland 2018

There have been 18 cases of high level azithromycin resistant gonorrhoea (HL-AziR; azithromycin minimum inhibitory concentration ≥256 µg/ml) reported in Ireland since 2011 to 2017[10]. Seven further cases of HL-AziR gonorrhoea were reported in Ireland in 2018 (six male and one female), these cases were reported HSE-East (n=3), HSE-Southeast (n=2), and HSE-Midwest (n=1) and HSE-West (n=1). High level azithromycin resistance was confirmed for all 7 cases, as well as extended antimicrobial susceptibility testing, the GCRL.

Of the HL-AziR cases in males ages ranged from 19-35 years old (median age= 27 years old) Sites of infection reported were urethral, cervical and unknown in one case. All HL-AziR isolates were susceptible to the 3rd generation cephalosporin's ceftriaxone and cefixime, with ceftriaxone MICs ranging from <0.016 µg/ml to 0.008 µg/ml and cefixime MICs ranging from <0.016 µg/ml – 0.032 µg/ml. All other isolates were susceptible to ciprofloxacin, tetracycline spectinomcyin and no isolates produced β-lactamase.

Ceftriaxone resistance in Ireland 2018

In August 2018 the second documented case of ceftriaxone resistant gonorrhoea was reported in Ireland[11]. The isolate was recovered from a heterosexual male who reported having recent sexual contact with a female during a visit to a country in Asia[7].

Both phenotypic and genotypic testing was performed in the GCRL on the isolate. Antimicrobial susceptibility profiling of the isolate demonstrated resistance to ceftriaxone, cefixime, cefotaxime and ciprofloxacin (ceftriaxone (MIC = 0.5 mg/L), cefixime (MIC = 1–2 mg/L), cefotaxime (MIC = 2–4 mg/L), ciprofloxacin (MIC > 32 mg/L)). The isolate displayed intermediate resistance to azithromycin (MIC = 0.38–0.5 mg/L). The isolate susceptible to spectinomycin (MIC = 16 mg/L) and tetracycline (MIC = 0.5 mg/L) and did not produce β-lactamase[7]. Whole Genome sequencing of the isolate was performed in the Swedish Reference laboratory for sexually transmitted infections. The isolate is thought to belong to the internationally Japanese spreading clone FC 428[7].

6. Euro-GASP collection 2018

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, that enhanced surveillance is collected on the selected isolates and that 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. By August 2018 the number of gonorrhoea notifications in Ireland had already exceeded 1000 so 211 consecutive gonorrhoea isolates were selected for submission to Euro-GASP for 2018. 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

In Ireland 94% (*n*=198) of the isolates in the 2018 Euro-GASP submission were recovered from male patients while 5% (*n*=11) were recovered from females and in two incidence sex

was unidentified. The male patients ranged in age from 17-59 years (median age= 29 years) while female patients were 18-30 years (median age=29 years). The majority of isolates (85%) 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 2018 Euro-GASP submission.

Table 1. 2018 Euro-GASP isolates

Clinic/laboratory	Number of isolates
Gay Men's Health Service	102
GUIDe	77
University Hospital Limerick	11
General Practitioners	10
Beaumont Hospital	3
MRH Portlaoise	3
Mayo General Hospital	1
Letterkenny General Hospital	1
Mater University Hospital	1
Our Lady of Lourdes Drogheda	1
Waterford Regional 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 seven percent of isolates (*n*= 120) were resistant to ciprofloxacin, 22% (*n*= 46) of isolates were β-lactamase positive, 8% (*n*= 17) were resistant to azithromycin and a further 9% (*n*= 20) were azithromycin intermediate according to EUCAST V8.0/ 8.1 breakpoints[9]. One high level azithromycin resistant (HL-AziR; MIC ≥ 256 mg/l) isolate was included in the Euro-GASP collection for 2018. All isolates were sensitive to the extended spectrum cephalosporin's, 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

- Poster presentation at IUSTI meeting, June 2018: Developing a national sentinel surveillance system for antimicrobial resistance in *Neisseria gonorrhoeae* in Ireland
- Oral presentation at SSSTDI Autumn meeting, November 2018: Gonorrhoea antimicrobial resistance in Ireland, 2010-2017
- Epi Insight vol. 19 issue 4, April 2018: Public Health England reports multi-drug resistant gonorrhoea strain
- Epi Insight vol. 19 issue 9, September 2018: Imported case of ceftriaxone resistant gonorrhoea in Ireland, 2018
- ICGP Forum, October 2018 issue: Gonorrhoea antimicrobial resistance in Ireland
- Golparian D, Rose L, Lynam A, Mohamed A, Bercot B, Ohnishi M, et al. Multidrug resistant *Neisseria gonorrhoeae* isolate, belonging to the internationally spreading

Japanese FC428 clone, with ceftriaxone resistance and intermediate resistance to azithromycin, Ireland, August 2018. Euro Surveill. 2018;23(47).

9. Acknowledgements

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10. Useful links

For more useful links and further information can be found at

https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/conditions-and-treatments/genital/gonorrhoea/

https://www.hpsc.ie/a-z/sexuallytransmittedinfections/gonorrhoea/

https://www.hpsc.ie/a-z/sexuallytransmittedinfections/gonorrhoea/amrgonorrhoea/

https://www.sexualwellbeing.ie/

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[9] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters, version 8.0/ 8.1, 2018.

https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf

https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.1_Breakpoint_Tables.pdf

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[11]HSE, Health Protection Surveillance Centre. Imported case of ceftriaxone resistant gonorrhoea in Ireland, 2018. Epi Insight HPSC, Volume 19, Issue 9, September 2018.