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SEXUAL HEALTH

The changing epidemiology of *Neisseria gonorrhoeae* genogroups and antimicrobial resistance in Queensland, Australia, 2010–15: a case series analysis of unique *Neisseria gonorrhoeae* isolates

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ABSTRACT

Background. *Neisseria gonorrhoeae* (NG) can lead to serious reproductive and sexual health outcomes, and the annual number of NG notifications in Australia increased steadily from 10 329 in 2010 to 29 549 by 2020. Australian populations most affected are urban men who have sex with men and First Nations peoples living in remote areas, and a resurgence in urban heterosexuals has been observed since 2012. **Methods.** A case series analysis of Queensland NG isolates (2010–15) exploring temporal trends and antimicrobial resistance by demographic and geographic distribution and genotype was performed. Proportions describe age, sex, strain, genogroup (NG multi-antigen sequence typing), region, swab site, antimicrobial sensitivity and isolate rates per 100 000 population. Dominant genogroups were identified. **Results.** Among 3953 isolates, the median age was 25 years (IQR 20–34 years) and most (n = 2871/3915, 73%) were men. Brisbane city (68.8) and Far North Queensland (54.1) excluding Cairns showed the highest rates. Forty-six genogroups were documented, seven (G2992, G6876, G1415, G4186, G5, G1407 and G6937) comprised half of all isolates. The predominant male genogroup was G2992 (16%), and G6876 (20%) for females; G5 was predominantly male from 2010 to 2011, but equal in both sexes from 2012 to 2015. **Conclusion.** Considerable temporal, geographical and demographical diversity was observed in Queensland NG isolates, which has public health implications. Certain genogroups are more transient than others, and evidence suggests bridging from male-dominant networks to heterosexual networks. Molecular surveillance can enhance tracking the epidemiology and movement of NG in Australia, highlighting the necessity of genotyping to expose potentially prevalent strains circulating in undetected or underrepresented networks by current screening methods.

Keywords: Australasia, epidemiology, genotype, gonorrhoea, isolates, molecular epidemiology, *Neisseria*, Queensland.

Background

Gonorrhoea is a bacterial infection caused by *Neisseria gonorrhoeae* (NG), and can lead to serious reproductive and sexual health outcomes including pelvic inflammatory disease and infertility, as well as increasing the risk of transmission of HIV.[1] The number of NG cases notified each year in Australia has increased steadily from 10 329 in 2010 to 29 549 by 2020.[2] The populations most affected in Australia are urban men who have sex with men (MSM), and Aboriginal and Torres Strait Islander (First Nations) people living in remote areas,[3] but a resurgence in urban heterosexuals has been observed since 2012.[4,5]

Antimicrobial resistance (AMR) to NG is increasing globally, with the World Health Organization prioritising control of this serious public health threat.[6] In Australia, dual antibiotic treatment with ceftriaxone and azithromycin is currently recommended for NG infections, having replaced ceftriaxone monotherapy in 2014.[7,8] Locally, AMR in NG isolates is monitored by the Australian Gonococcal Surveillance Programme. Recent data show an increase in low-level resistance to azithromycin in all jurisdictions of Australia

from 2012 to 2018.[8] Surprisingly, isolates exhibiting decreased susceptibility to ceftriaxone decreased to 0.9% in 2020 from 8.8% in 2013.[9] However, the need for ongoing surveillance is critical, with two extensively drug-resistant isolates reported in Queensland in 2018.[8] Although there are limited alternative options for NG antibiotic treatment of proven safety and efficacy, surveillance, prevention and efficient diagnosis are key strategies for control.[10]

Queensland began slowly transitioning to polymerase chain rection (nucleic acid amplification test-based diagnosis) from the late 1990s.[11] Technological advances in genotyping of NG isolates and its increasing affordability have legitimised its use as an important public health tool, enabling enhanced surveillance, investigation of the geographical spread of AMR and identification of epidemiological changes over time.[6,10] Analysis of NG isolate data from 1991 to 1999 in New South Wales showed considerable variability in genotype prevalence, further highlighting the need for ongoing, timely surveillance.[12] We aimed to describe NG isolates in Queensland from January 2010 to August 2015 to better understand the epidemiology in this jurisdiction in terms of demographics, temporal trends, geographic distribution, genotypes and resistance patterns. This is the first time such comprehensive analyses have been undertaken in Queensland.

Methods

Study design

We conducted case series analyses for a sample of de-identified, coded NG isolates for cases reported in Queensland between 1 January 2010 and 24 August 2015, inclusive.

NG laboratory data

Data for isolates were provided by the Queensland reference laboratory for *Neisseria* located in the Public Health Microbiology Laboratory, Forensic Scientific Services (FSS), Queensland Health, which collates isolates from pathology services for Brisbane and surrounding areas. These isolates were a proportion of total Queensland notifications of NG. One isolate per patient episode was included. Testing for AMR to azithromycin, ciprofloxacin and ceftriaxone was performed by the agar dilution method, and interpreted using the Australian Gonococcal Surveillance Program criteria.[9]

Molecular typing of NG isolates was conducted at FSS using NG multi-antigen sequence typing, as previously described.[13] Briefly, this is based on sequencing two genes, *porB* and *tbpB*, coding for variable NG outer membrane proteins. Following sequence-type (ST) assignment via the NG multi-antigen sequence typing protocol, genetically similar strains were categorised into genogroups. A genogroup was defined as: (1) STs that shared one allele and showed >99% similarity in the other allele (≤5 base pair (bp) difference for *porB* and ≤4 bp for *tbpB*), or (2) STs with two different alleles, but the concatenated sequence of both alleles (880 base pairs) displayed ≥99.4% (875 bp) similarity to the concatenated sequence of both alleles of the main ST in the genogroup.[14]

Other data sources

The postcode of case isolates was used to categorise regions of residence, according to the Australian Bureau of Statistics (ABS) regions of Queensland.[15] The regions were defined as Brisbane city, Brisbane surrounds, Gold Coast, Sunshine Coast, Wide Bay–Burnett, Darling Downs and South West, Fitzroy, Central West and North West, Mackay, Northern, Cairns, Far North (FNQ) excluding Cairns (Supplementary Fig. S1), overseas, and interstate. National Notifiable Diseases Surveillance System data were used to calculate total annual Queensland notifications, and notification rates per 100 000 Queensland population.[2]

Data analysis

Isolates were described in terms of region of residence, year of notification, age group, sex, swab site, ST, genogroup and AMR. Genogroups with >10 isolates over the study period were identified and analysed by year of notification, sex, region, swab site and AMR. As dual treatment with ceftriaxone and azithromycin is currently recommended in Australia for NG infections, our study focused on the resistance/sensitivity to these antibiotics and ciprofloxacin. We analysed resistance/sensitivity by sex, year of notification, region and genogroup. Specimen swabs were categorised into six sites: urethral/penile, male rectal, female rectal, vaginal/cervical, male pharyngeal and female pharyngeal. Swab sites were analysed by sex and genogroup (Supplementary Box S1).

Data were analysed using Stata statistical software v.16.1 (StataCorp),[16] and graphs and figures were constructed using Microsoft Excel. Summary statistics were calculated for isolates using proportions, counts, ratios and average annual notifications per 100 000 Queensland population, by year of notification, age, sex, AMR and region. Some regions were combined due to small numbers to protect confidentiality and privacy. Age-specific ABS estimates of Queensland resident population size for the years 2010–15 were used as the denominator when calculating the average annual rates for each region.[17,18] Data for isolates reported in 2015 were only available for January to August, and as such, rates were adjusted to reflect the incomplete data.

Ethics

This project was conducted for the purposes of public health surveillance under the Queensland Public Health Act, and approved by the Office of Research and Governance as application HEC18_01 by the Queensland Health FSS Ethics Committee (FSS-HEC EC00305).

Results

Between 1 January 2010 and 24 August 2015, 3953 individual NG isolates were identified. Data included one isolate per patient episode (defined as not collected within 1 month of previously included strain). The median age was 25 years, with an interquartile range (IQR) of 20–34 years; men (median age 26 years, IQR 21–36 years) were older than women (median age 22 years, IQR 19–29 years). The overall male:female (M:F) ratio was 2.7, and ratios for individual study years are shown in Table 1.

The number of isolates per 100 000 population decreased from 2010 to 2015; however, the M:F ratio increased. The total isolates included in this study comprise 25% of the overall notifications for the study period. The highest number of isolates identified in men were in the 20–24 year-old age group, whereas the highest number of isolates in women were those aged <19 years. There were more isolates from men than women in every age group (Table S1).

Regions and isolate rates

Of the 3953 isolates, the highest proportion was from Brisbane city (25%, 1007). The isolate rate by region per 100 000 population was also highest in Brisbane city (68.8), followed by FNQ (54.1), excluding Cairns. Geographically, there was an increasing trend in isolate rates for regions heading in a northward direction from Mackay to Far North surrounds (Table S2), and these isolates showed a more balanced 1:1 M:F ratio compared with higher male M:F ratios from Brisbane city, Brisbane surrounds and the Gold Coast. The majority of isolates from Brisbane city were in men aged 20–29 years, and this was consistent for each year of our study. Isolates from Mackay to FNQ showed higher isolate rates in younger age groups (≤24 years). Isolate rates were higher in women than men for some age groups and locations, in particular FNQ (Fig. S2).

Swab site

There were 3701 (94%) swabs where data on sampling site were available. Of these, 2061 (56%) were urethral/penile, 469 (13%) low vaginal, 482 (13%) high vaginal/cervical, 446 (12%) male rectal, 10 (<1%) female rectal, 216 (6%) male pharyngeal and 17 (<1%) female pharyngeal.

Genogroups

There were 46 genogroups documented, comprising 825 unique strain types. Clusters of each genotype fluctuated over time (Fig. 1), with only seven genogroups (G2992, G6876, G1415, G4186, G5, G1407 and G6937) representing half of the isolate population throughout the study period (Fig. 2).

Most genogroups were male dominant, although some – G6937, G758, G7343 and G7807 – had more equal proportions of men and women (35–65% women; Fig. 2). Genogroups also varied by sex over time; where G2992, G5 and G1407 were consistently found predominantly in men, other commonly reported genogroups, G6876, G1415, G4186 were identified in both men and women (Fig. S3), and G5 was found predominantly in men from 2010 to 2011, but the proportion in women increased in 2012 to 2015. Common genogroups identified by individual swab site were: urethral/penile G2992, G1415, G6876, G5 and G4186; penile G6876, G1415, G2992, G4186 and G6937; rectal G2992, G1407, G5, G4244 and G9654; pharyngeal- G2992, G5, G4186, G1407 and G3995; and combined low vaginal/high vaginal and cervical G6876, G1415, G4186, G6937 and G7343 (Fig. S4).

Antimicrobial resistance

Reduced antimicrobial susceptibility was highest for azithromycin and ciprofloxacin. Overall, 15 genogroups showed reduced susceptibility (0.06–0.125 mg/L) to azithromycin and 15 to ciprofloxacin (Fig. S5). No genogroups showed resistance to

Table 1. *N. gonorrhoeae* isolates (by year, sex and rate) and notifications (by year and rate), Queensland, Australia (2010–15).

Isolates	Males	Females	All	M:F ratio	Isolates[A] (per 100 000)	Notifications[B]	Isolates/notifications[C] (%)	Notifications[A,D] (per 100 000)
2010	553	229	782	2.4	17.3	2384	33	54.1
2011	548	206	754	2.7	16.3	2947	26	65.8
2012	480	200	680	2.4	14.1	2690	25	58.9
2013	472	178	650	2.6	13.5	2728	24	58.6
2014	488	145	633	3.3	12.7	2725	23	57.7
2015[E]	357[E]	97[E]	454	3.7	13.3[F]	2274[F]	20	63.5[F]
Total	2898	1055	3953	2.7	–	15 748	25	–

[A]Total number of isolates per 100 000 Queensland population per study year.
[B]Total annual Queensland notifications, and notification (National Notifiable Diseases Surveillance System 2010–15).[2]
[C]Yearly proportion of total isolates from the total notifications.
[D]Notifications include NAT detections with no isolate.
[E]Incomplete data for this year (data available are January–August).
[F]Adjusted to reflect incomplete data for this year.

Fig. 1. Timeline of *N. gonorrhoeae* isolates by genogroup, Queensland, January 2010 to August 2015. Listed in order of time of first identification. Each circle represents the timing of detection of each isolate.

ceftriaxone, although six showed reduced sensitivity (G5, G1407, G3995, G6876, G7705, G10193). Twenty-two genogroups showed 100% sensitivity to ciprofloxacin, whereas sensitivity ranged from 0% to 99% for other genogroups (G25, G225, G436, G225, G758, G1217, G1407, G2018, G2400, G3995, G4644, G6863 (for women only), G6882, G10039 and G10193 (Fig. S5). No specific changes in patterns of ciprofloxacin resistance over time were identified (Table S3). Resistance varied across regions and by sex. Regions with the highest rates of AMR were Wide Bay–Burnett and the Sunshine Coast. Resistance was higher in men for all regions, with the exception of these same two areas, Wide Bay–Burnett and the Sunshine Coast (Fig. S6).

Thirty genogroups showed 100% sensitivity to azithromycin. Sensitivity ranged from 23% to 99% for others (G1478, G10193, G2992, G2400, G26, G1407, G3995, G5, G1119, G2018, G190, G225, G1415, G4244, G9654; Fig. S7). Resistance appeared to increase over time for G5, but fluctuated for others

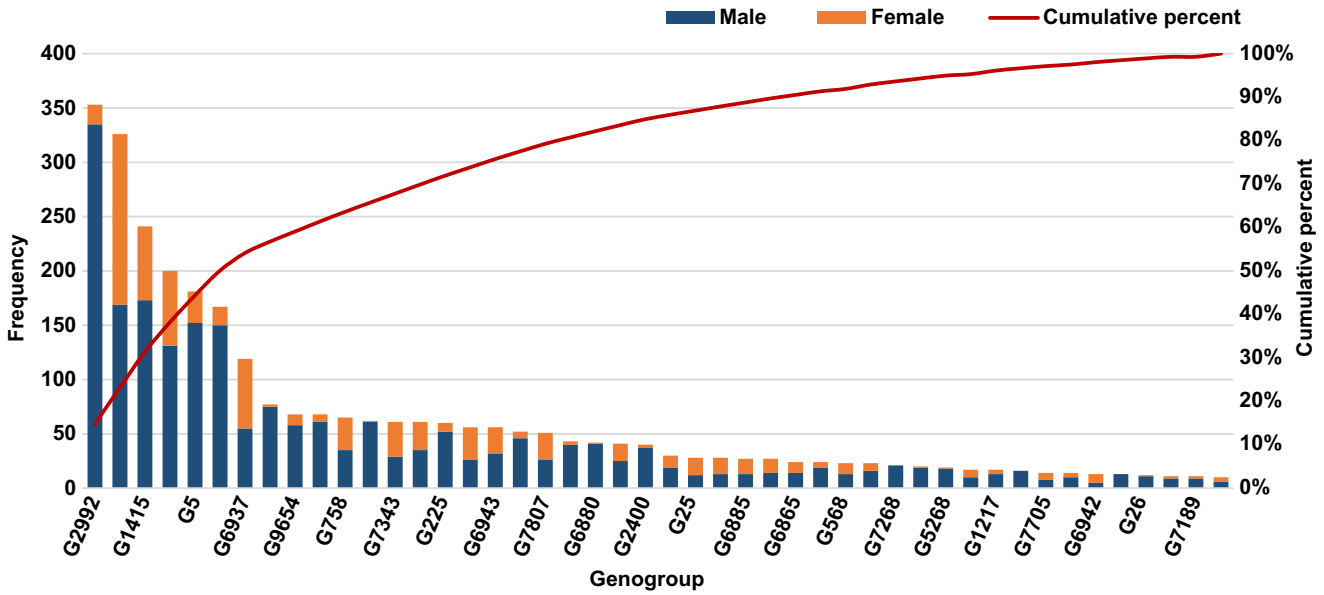

Fig. 2. Frequency and cumulative frequency of *N. gonorrhoeae* genogroups by sex in isolates from Queensland, January 2010 to August 2015.

(Table S4). Resistance (≥1 mg/L) varied across regions and by sex. Regions with the highest rates of resistance to azithromycin were Wide Bay–Burnett, Brisbane city and Mackay. Resistance was higher in men for all regions, with the exception of Wide Bay–Burnett, Darling Downs and South West, and the Gold Coast (Fig. S8).

Discussion

Our study of Queensland NG isolates over a period of 5 years showed considerable variation, transiency and prevalence in strains and genogroups over time, place and sex, and provides important insights into changes in AMR patterns. In Australia, the majority of NG infections occur in urban men, and primarily among MSM.[3] This is consistent with our findings that the highest proportion of isolates were in men, and the highest rates of infection in Brisbane, the largest city in Queensland. The diversity and unpredictability of genogroups and AMR we observed in the male population in South East Queensland suggests bridging between the MSM and heterosexual populations, which has significant public health implications around the importance of treatment options being person-, time- and place-specific. An example is G5, which transitioned from historically infecting only men, to infecting both women and men by the end of our study. Previous Australian behavioural and genomic data have provided some evidence of genotype bridging across these populations, hypothesised to be attributable to a subgroup of men having sex with both men and women.[19] The predominance of men in some genogroups and male rectal swab sites suggests potentially higher transmission in the MSM population; however, our dataset did not include information on sexual behaviour. Therefore, these results should be interpreted with caution. Furthermore, NG cultures are more highly represented in the metro regions of Queensland, and therefore, may be biased towards MSM populations and harbour more AMR, whereas nucleic acid amplification test-positive people in remote/regional areas are more likely to carry NG susceptible strains, and more likely to be heterosexual men and women. Altogether, NG-positive people are not well-represented/tested using culture, particularly in remote/regional Queensland. In contrast, younger women represented a higher proportion of isolates in FNQ, which is potentially due to higher rates among First Nations peoples in this area.[20] Although our data did not specify Indigenous status, our findings are consistent with historically high-risk groups for NG in Queensland: the heterosexual First Nations populations in the remote north, and in MSM from South East Queensland.[20]

Few studies have examined changes of NG genogroups over time in Australia.[21] Our study also showed considerable variation and transiency in genogroups geographically; for example, G6879 showed significant geographical changes over time (e.g. moving from predominantly central to North Coast and North Queensland from 2010 to 2013) compared with G2992, which had consistently high proportions of isolates in Brisbane. Confirmation of the transient nature of NG genogroups highlights the importance of ongoing and timely surveillance, as this can inform prevention, efficient diagnosis and facilitate planning for more targeted treatment, which are the established key strategies for control.[10]

Recent Australian data have identified an increase in low level resistance to azithromycin. We identified one genogroup that showed increasing resistance to azithromycin over time,

with resistance to ciprofloxacin identified in a number of genotypes varying by sex and region. Specifically, the two regions with the highest resistance rates were also the only regions that reported the highest resistance in women. A 2018 systematic review of AMR NG in Australia and New Zealand also found variations in ciprofloxacin AMR between states and territories.[22] More recently, a study investigating AMR gonorrhoea in NSW found that resistance was occurring across multiple genotypes, and many of these displayed transiency.[12] In our study, the highest resistance rate was identified in men across the majority of regions, which is also consistent with previous trends observed in Australia.[12] Our results have demonstrated that AMR patterns can change rapidly, providing evidence to support the potential utility of a (near) real-time gonococcal surveillance system to inform timely clinical decision-making.

Regarding swab sites, our data suggest that women are not potentially being screened for pharyngeal and rectal gonorrhoea, or if they are being screened, fewer cases are being detected. We do acknowledge the potential for ascertainment bias in this scenario though, given that penile infections are more likely to be symptomatic, and therefore, more likely to be swabbed and cultured. Increasing pharyngeal and rectal testing for women during routine sexual health screening checks is still warranted, however, to ascertain whether there are undiagnosed cases of NG circulating in the community, because research shows that men may only be positive at one site.[23] Swab results following a period of increased testing for women at multiple sites is needed to provide updated clinical guidelines about which sites should be sampled.

The primary strength of this study is the large number of individual NG isolates tested over time, with key demographic indicators, such as age, sex and location. This study was limited by the fact that isolates were available for ~25% of total Queensland notifications for this time period. Isolate collection is also more common in urban areas, leading to an underrepresentation of rural and remote areas. The data showed that NG notifications have been stable over time, but the proportion of notifications for which isolates are collected has decreased which may also affect the representation of the isolate AMR data. Data relating to sexual orientation, behavioural risk factors or modes of transmission were not available, limiting our ability to interpret these factors. Indigenous status for isolates was also not available, hence we were unable to specifically investigate the epidemiology of NG in First Nations peoples living in Queensland. Given the large population of First Nations peoples living in FNQ,[18] future epidemiological studies that include Indigenous status, and that also involve First Nations researchers, would strengthen our findings.

Conclusion

The findings from this study have significant clinical and public health implications. The diversity, unpredictability and spread of genotypes over time and place highlights the need for strengthened surveillance at the local level, particularly with evidence of bridging between the MSM and heterosexual populations. These data highlight the gaps in culture collection, coupled with the importance of consistent molecular geographic surveillance over time to capture 'unidentified' or underrepresented strains/populations to inform the most effective treatment of NG moving forward. Clinical guidelines should also be strengthened in relation to testing and treatment, with both genogroups and levels of AMR displaying changes over time. This includes ensuring testing for pharyngeal and rectal gonorrhoea in the female population.

Supplementary material

Supplementary material is available online.

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Data availability. The data that support this study cannot be publicly shared due to ethical or privacy reasons and may be shared upon reasonable request to the corresponding author if appropriate.

Conflicts of interest. The authors declare that they have no conflicts of interest.

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