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HIV risk and gonococcal genotype: Opportunities to improve passive surveillance for prompt identification of syndemics?

Sara FE Bell, Stephen B Lambert, Amy V Jennison, Christine JD Guglielmino, Robert S Ware, David M Whiley

To understand the risk of HIV associated with gonococcal genotypes, we analysed linked Queensland datasets of genotyped *Neisseria gonorrhoeae* isolates with phenotypic resistance data with HIV notifications. Further research into the association of gonococcal genotypes and risk of HIV acquisition may be helpful to develop targeted public health interventions.

Keywords: *Neisseria gonorrhoeae*, genotype, HIV, Queensland

Syndemics arise when health conditions act together, increasing morbidity and mortality.¹ For example, human immunodeficiency virus (HIV) transmission increases in the presence of other sexually transmissible infections, including *Neisseria gonorrhoeae* (NG).² To understand potential associations between HIV infection and gonococcal genotypes and antimicrobial sensitivity, we analysed linked Queensland datasets of genotyped NG isolates (using *N. gonorrhoeae* multiantigen sequence typing, NG-MAST)^{3,4} with phenotypic resistance data, ascertained by standardised methods,⁵ in the period 1 January 2010 to 31 December 2015 and new HIV notifications from 1 January 2009 to 31 December 2016 (before widespread use of HIV pre-exposure prophylaxis). Currently, empirical dual therapy, ceftriaxone and azithromycin, is recommended treatment for uncomplicated NG cases.⁶ Susceptibility was established for all positive NG isolates referred from public and private pathology services to the Queensland state reference laboratory. Only one positive NG isolate per case from each episode of care, at least one month from a previous NG detection, was included for analysis.

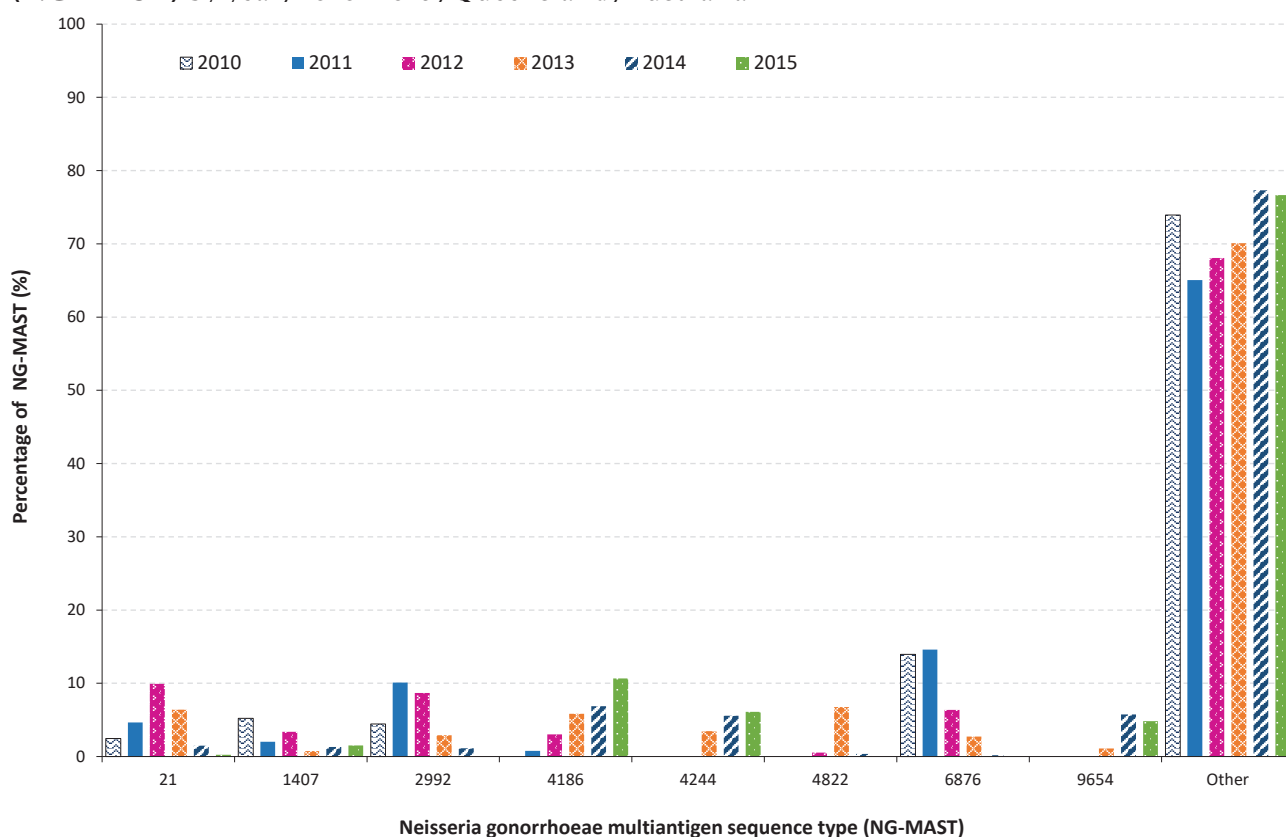
A total of 3340 NG isolates, representing 29.9% (3340/11170) of all unique NG notifications, from 3082 unique cases were genotyped using NG-MAST. There were 732 unique sequence

types (ST) identified; most prevalent was ST6876 (7.1%, 237/3340) (Table 1). Prevalence of STs changed over time: ST6876, dominant in 2010 (14.0%, 91/652) and 2011 (14.6%, 94/644) was absent in 2015; ST4186, absent in 2010, accounted for 10.7% (42/394) of NG genotypes in 2015 (Figure 1).

There were 156 (4.5%, 156/3340) genotyped NG isolate results linked to 128 (4.9%, 128/2592) HIV notifications. Of linked HIV notifications, 106, 18, 2 and 2 were associated with 1, 2, 3 or 4 genotyped results, respectively. Of the 22 HIV notifications linked to two or more genotyped results, only 1/22 (4.5%) had a repeat NG genotype (ST4951) notified 40 days following the first notification; the remainder had different NG genotypes identified. Repeat infections were more common among NG infections linked to HIV notifications (17.9%, 28/156) compared to those unlinked (7.2%, 230/2954) (odds ratio (OR) 2.5, 95% CI 1.7–3.6). This association may be due to greater testing rates, or greater rates of gonorrhoea reinfection, for people living with HIV.

HIV notifications were linked to 65 NG genotypes (8.9%, 65/732), suggesting, like other studies,⁷ that HIV is not necessarily associated with a limited number of gonococcal genotypes. Across the study period, two NG genotypes had

Figure 1: Percentage of *Neisseria gonorrhoeae* isolates by Multiantigen Sequence Type (NG-MAST) by year, 2010–2015, Queensland, Australia



significantly increased risk of same-calendar-year HIV diagnosis (ST1407 [from 2012 to 2015]: OR 5.1, 95% CI 1.8–14.8; and ST2992 [from 2010 to 2012]: OR 3.2, 95% CI 1.2–8.3) when compared to all other NG genotypes from the same calendar year. Both ST1407, harbouring a mosaic *penA* gene, and ST2992, harbouring a mosaic *mtrR* gene, are internationally recognised successful clones.⁸ A high degree of antimicrobial resistance was exhibited by ST1407, with 97.6% (81), 67.5% (56) and 7.2% (6) of isolates being resistant to ciprofloxacin, penicillin and azithromycin, respectively, and 27.7% (23) exhibiting decreased susceptibility to ceftriaxone. Only 2.4% of isolates (2/83) were susceptible to all four antimicrobials. Sequence type 1407 has been identified in men who have sex with men (MSM) and heterosexual networks, as have interrelated strains with key genetic markers, suggesting men who have sex with men and women present opportunities for strains to bridge between sexual networks.⁹ Bridging networks represent the potential for enabling HIV entry into heterosexual

networks.¹⁰ Conversely, ST2992 exhibited a high degree of antimicrobial susceptibility, with 7.3% of isolates (12/165) being resistant to azithromycin only. A Melbourne study¹⁰ suggests ST2992 is associated more exclusively with MSM sexual networks.

Further research into the association of gonococcal genotypes and risk of HIV acquisition may be helpful, noting there is increasing concern of HIV becoming established in Far North Queensland, syndemic with syphilis.¹¹ Analyses such as ours could help develop targeted public health interventions to identify and respond to important syndemic relationships. Routine NG genotyping to identify risk NG genotypes could provide real-time feedback to clinicians to promote HIV testing and awareness of HIV pre-exposure prophylaxis (PrEP). On-going surveillance of NG genotypes and HIV notifications might assist to minimise outbreaks, within and between sexual networks; however, the success of this strategy is highly dependent on the information technology infrastructure available.

Table 1: Descriptive summary of *Neisseria gonorrhoeae* Multiantigen Sequence Typing (NG-MAST), HIV notifications and linked cases, ^a 2009–2016, Queensland, Australia

	NG-MAST result		Linked to HIV notification	
	Number	%	Number	%
<i>Neisseria gonorrhoeae</i> Multiantigen Sequence Type (NG-MAST) tested	3340	100.0	156 ^b	100.0
NG-MAST				
6876	237	7.1	0	0.0
2992	165	4.9	23	14.7
21	146	4.4	9	5.8
4186	133	4.0	4	2.6
6879	100	3.0	0	0.0
1407	83	2.5	10	6.4
6937	75	2.2	0	0.0
4244	73	2.2	5	3.2
Other NG-MAST (724 sequence types)	2328	69.7	105	67.3
Anatomical site of collection				
Urethra	1707	51.1	68	43.6
Vagina	617	18.5	0	0.0
Rectum	432	12.9	70	44.9
Pharynx	224	6.7	17	10.9
Cervix	146	4.4	0	0.0
Other anatomical site	214	6.4	1	0.6
Year of collection				
2010	652	19.5	22	14.1
2011	644	19.3	27	17.3
2012	564	16.9	27	17.3
2013	548	16.4	19	12.2
2014	538	16.1	38	24.4
2015	394	11.8	23	14.7
	HIV notification		Linked to NG-MAST result	
New Queensland HIV notifications	2592	100.0	128 ^b	100.0
Sex				
Male	2233	86.1	128	100.0
Female	357	13.8	0	0.0
Not specified	2	0.1	0	0.0
Aboriginal and or Torres Strait Islander person				
No	2475	95.5	126	98.4
Yes	114	4.4	2	1.6
Not specified	3	0.1	0	0.0
First HIV diagnosis in Qld				
No	924	35.6	18	14.1
Yes	1668	64.4	110	85.9
Reported HIV exposure (% of cases) ^c				
Men who have sex with men / bisexual	1748	67.4	124	96.9
Person/partner with origin from a high prevalence country	512	19.8	3	2.3
Heterosexual	355	13.7	3	2.3
Injecting drug use	202	7.8	11	7.8
Not reported/unknown	127	4.9	0	0.0
Partner with/at risk of infection	107	4.1	0	0.0
Maternal	25	1.0	0	0.0
Year of notification				
2009	277	10.7	20	15.6
2010	310	12.0	17	13.3
2011	282	10.9	29	22.7
2012	350	13.5	23	18.0
2013	309	11.9	10	7.8
2014	366	14.1	16	12.5
2015	340	13.1	9	7.0
2016	358	13.8	4	3.1

a Significant HIV/NG-MAST associations are bolded.

b The numbers of 'linked' cases differ owing to an individual HIV notification being linked to one or more NG-MAST results.

c Multiple exposures possible.

Ethics

Ethical approval was granted by the Prince Charles Hospital Human Research Ethics Committee HREC/15/QPCH/44. Approval for the provision of data held by Queensland Government Department of Health for public interest was granted (PHA 27230).

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