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Resistant gonorrhoea: east meets west

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In 2016 and 2018, two treatment failures of ceftriaxone and azithromycin, used in combination, were reported in the UK in men who contracted gonococcal infections in Asia,[1,2] once again suggesting that antimicrobial resistance of *Neisseria gonorrhoeae* is spreading. These treatment failures indicate the potentially waning efficacy and usefulness of this combination, which is currently recommended as the first-line therapy. Surveillance of antimicrobial resistance is paramount if resistance patterns of these and other antimicrobials are to be recognised in a timely manner that enables meaningful intervention and prevention of the spread of resistant organisms. Antimicrobial susceptibility testing (phenotyping) for antimicrobial resistance is considered the gold-standard test. There are some key limitations to the more commonly used methods of genotyping, such as *N gonorrhoeae* multi-antigen sequence typing (NG-MAST) and multilocus sequence typing (MLST), which indicate associated antimicrobial resistance determinants but do not directly identify antimicrobial resistance. The genotypes of *N gonorrhoeae* strains that are identified by use of these methods, which include antimicrobial resistance determinants, often do not correlate directly with the mean inhibitory concentrations of antimicrobials against these strains.

In their Article in *The Lancet Infectious Diseases*, Simon Harris and colleagues[3] used whole genome sequencing (WGS) for comprehensive genetic analyses of more than 1000 *Neisseria gonorrhoeae* strains that were isolated in 2013 in 20 European countries that participated in the European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP). As expected, NG-MAST genogroups (designated from the closely related NG-MAST sequence types) fit the WGS phylogeny relatively well; however, separation into clades (the branches of the WGS phylogeny trees) avoided separation of clinically important, phylogenetically related isolates while also excluding phylogenetically unrelated (less relevant) isolates. WGS therefore maintains the breadth of analysis that is necessary to identify known antimicrobial resistance determinants and can also identify new antimicrobial resistance determinants. MLST and NG-MAST, although sensitive in their association with known antimicrobial resistance determinants, can be non-specific.

An advantage of WGS or MLST and NG-MAST over phenotyping is that these genotyping methods enable detection of modest changes to the genetic organisation of strains before changes to antimicrobial resistance (phenotypic) patterns occur; monitoring genes, therefore, makes for a timely sentinel-based, surveillance system. However, superior resolution of WGS versus NG-MAST and MLST, when WGS is linked to epidemiological data, could enable even earlier identification of antimicrobial resistance outbreaks and novel high-risk clones. Harris and colleagues evaluated pairwise geographical and cophenetic distances (phylogenetic distances between pairs of isolates) at the level of single nucleotide polymorphisms, which provided the resolution for comparison at the whole genome level by WGS that is not possible with MLST or NG-MAST. With WGS, these baseline comparisons showed patterns in the same locations, the same country, and bordering countries. WGS used in this manner enables recognition of genetic mixing as would occur in transmission from one of these locations to another, allowing identification of local hot spots or outbreaks.[4,5] This method adds a dynamic feature to WGS, making it potentially capable of recognising small genomic changes that might be clinically or epidemiologically important as quickly as the sequences are generated and examined, almost in real time. Harris and colleagues also used bioinformatics[6] to model evolving phenotypes. In this case, the authors analysed distribution of degree of sensitivity (susceptible, intermediate, and resistant) of gonococcal strains to three antimicrobials and, independently, sexual orientation of the patients, which is a novel use of WGS that provides information in a separate dimension.

But how do sensitive and specific genomic techniques inform and address the problem represented by the two cases with failed combined therapy? The NG-MAST genogroup G1407 was the predominant serogroup in Euro-GASP in 2013, and accounted for the greatest extent of cephalosporin resistance. However, G1407 decreased from 23% prevalence[7] in 2009–10 to 17% in 2013 in Harris

and colleagues' subsequent study. Since 2009–10, antimicrobial resistance patterns of *N gonorrhoeae* have changed in the EU/EEA. In 2012, combination therapy (ceftriaxone plus azithromycin), which was already being used in several countries, was officially recommended for all European countries.[8] Cefixime resistance declined to 4·8%; however, azithromycin resistance rose to 6·7% overall,[9,10] with strains from Cyprus and Greece together showing 28·6% resistance to azithromycin. Much of the antimicrobial resistance originates in Asia and is transmitted to Europe (such as in the two patients with treatment failure). Between 2013 and 2016, China reported a significant increase (from 1·9% to 3·3%) in gonococcal strains that showed both resistance to azithromycin and decreased susceptibility to ceftriaxone.[11] The proportion of isolates with decreased susceptibility to ceftriaxone fluctuated between 9·7% and 12·2%, and the prevalence of azithromycin-resistant isolates was 18·6% during this period.[11] Further, in eastern Chinese cities, resistance to azithromycin rose more than four-fold (from 7% to 32%) from 2008 to 2014.[12] A key step in management of antimicrobial resistance of gonococci in Europe will be global collaboration in identifying gonococcal WGSs from Asian strains, some of which are likely to spread to Europe. The 2017 International Forum on Gonococcal Infections and Resistance, held in Shenzen in Guangdong, China, and led by Xiang-Sheng Chen was a crucial step forward in establishing these ties.[13]

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We declare no competing interests.

1 Fifer H, Natarajan U, Jones L, et al. Failure of dual antimicrobial therapy in treatment of gonorrhea. *N Engl J Med* 2016; **374:** 2504–06.
2 Public Health England. UK case of *Neisseria gonorrhoeae* with high-level resistance to azithromycin and resistance to ceftriaxone acquired abroad. March 29, 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/694655/hpr1118_MDRGC.pdf (accessed April 25, 2018).
3 Harris SR, Cole MJ, Spiteri G, et al. Public health surveillance of multidrug-resistant clones of *Neisseria gonorrhoeae* in Europe: a genomic survey. *Lancet Infect Dis* 2018; published online May 15. http://dx.doi.org/10.1016/S1473-3099(18)30225-1.
4 Lahra MM, Martin I, Demczuk W, et al. Cooperative recognition of internationally disseminated cetriaxone-resistant *Neisseria gonorrhoeae* strain. *Emerg Infect Dis* 2018; **24:** 735–43.
5 Fifer H, Cole M, Hughes G, et al. Sustained transmission of high-level azithromycin-resistant *Neisseria gonorrhoeae* in England: an observational study. *Lancet Infect Dis* 2018; **18:** 573–81.
6 Ansari MA, Didelot X. Bayesian inference of the evolution of a phenotype distribution on a phylogenetic tree. *Genetics* 2016; **204:** 89–98.
7 Chisholm SA, Unemo M, Quaye N, et al. Molecular epidemiological typing within the European Gonococcal Antimicrobial Resistance Surveillance Programme reveals predominance of a multidrug-resistant clone. *Euro Surveill* 2013; **18**.
8 Bignell C, Unemo M. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. *Int J STD AIDS* 2013; **24:** 85–92.
9 Cole MJ, Spiteri G, Jacobsson S, et al. Overall low extended-spectrum cephalosporin resistance but high azithromycin resistance in *Neisseria gonorrhoeae* in 24 European countries, 2015. *BMC Infect Dis* 2017; **17:** 617.
10 European Centre for Disease Prevention and Control. Surveillance report. Gonococcal antimicrobial susceptibility surveillance in Europe 2012. July, 2014. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/gonococcal-antimicrobial-susceptibility-surveillance-Europe-2012.pdf (accessed April 25, 2018).
11 Yin YP, Han Y, Dai XQ, et al. Susceptibility of *Neisseria gonorrhoeae* to azithromycin and ceftriaxone in China: a retrospective study of national surveillance data from 2013 to 2016. *PLoS Med* 2018; **15:** e1002499.
12 Wan C, Li Y, Le WJ et al. Increasing resistance to azithromycin of *Neisseria gonorrhoeae* in eastern Chinese cities: mechanisms and genetic diversity of resistant Nanjing isolates. *Antimicrob Agents Chemother* 2018; published online March 12. DOI:10.1128/AAC.02499-17.
13 Chen, XS. Proceedings of the 2017 International Forum on Gonococcal Infections and Resistance (2017 IFGIR) in Shenzhen, China. *Sex Transm Dis* 2018; published online Apr 17. DOI:10.1097/OLQ.0000000000000859.

Eliminating cystic echinococcosis in the 21st century

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Cystic echinococcosis is a helminthic disease caused by the larval stage of the cestode *Echinococcus granulosus*. This parasitic disease is regarded as a zoonosis because adult worms and eggs are found in the small intestine of carnivores, whereas the larval stage infects humans. As a definitive host, dogs play a major part in transmitting the infection to humans: tapeworms pass proglottids and eggs in dogs' faeces and humans become infected through faecal-oral contact. The presence of a cyst-like mass in a person with a history of exposure to dogs in areas where *E granulosus* is endemic supports the diagnosis of cystic echinococcosis. The diagnosis can be made non-invasively with ultrasonography and other imaging techniques.[1] Cystic echinococcosis is endemic in sheep-raising areas and is among the most neglected diseases in the world.[2–4]

The study in *The Lancet Infectious Diseases* by Francesca Tamarozzi[5] and colleagues describes results