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Commentary

Now Is the Time to Implement Whole Genome Sequencing in the Global Antimicrobial Resistance Surveillance for *Neisseria gonorrhoeae*?

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Neisseria gonorrhoeae causes gonorrhoea, the second most prevalent global bacterial sexually transmitted infection with 87 million new cases estimated in 2016 [1]. Untreated gonorrhoea can lead to severe sequelae including ectopic pregnancy, infertility, and increased HIV transmission. Public health management of gonorrhoea relies on effective prevention, early diagnosis and particularly antimicrobial treatment. However, *N. gonorrhoeae* has developed resistance to all antimicrobials introduced for treatment. In the past decade, resistance to the last option for empirical first-line monotherapy, ceftriaxone, has resulted in recommendations of dual antimicrobial therapy (ceftriaxone + azithromycin) in many countries globally [2]. Worryingly, treatment failure with dual therapy was reported in UK [3] and isolates with decreased susceptibility or resistance to both ceftriaxone and azithromycin have been reported worldwide [4], with highest levels in Asia including China [4,5]. In China, 115,000 gonorrhoea cases are reported annually (likely highly underestimated), making gonorrhoea one of the most frequently reported infections in China with a population of 1·4 billion inhabitants [5,6]. China has the second highest antimicrobial consumption globally [7] and high-levels of gonococcal antimicrobial resistance (AMR), making appropriate AMR surveillance essential.

The high prevalence of gonorrhoea and gonococcal AMR are global threats, and AMR surveillance but also epidemiological surveillance is imperative for timely and effective infection control. Whole genome sequencing (WGS) provides ideal resolution and can resolve true clonalities of *N. gonorrhoeae*. WGS can adequately assess the emergence, spread and persistence of AMR strains and AMR determinants locally, nationally and internationally over time and provide additional information, e.g., AMR prediction [8,9].

In EClinicalMedicine, Peng and colleagues [10] present the first gonococcal WGS study from China, where 435 selected isolates (25·6% with decreased ceftriaxone susceptibility), mainly urethral isolates from males (90·6%), were sequenced. The isolates were collected in 2012–2013 in 11 of the 31 Chinese provinces through the China Gonococcal Resistance Surveillance Programme (China-GRSP). The isolates were compared to published reference genomes [11] and WGS sequences from over 2000 clinical isolates from USA [12] and UK [13] to elucidate how Chinese isolates relate to strains circulating in two other countries and regions. The researchers used a genomic approach as well as traditional molecular typing methods, i.e., *N. gonorrhoeae* multi-antigen sequence typing (NG-MAST) and multilocus sequence typing (MLST). The genomic approach elucidated two lineages (L1 and L2), where L2 was further divided into nine sub-lineages (L2·1-L2·9). All Chinese isolates belonged to L2 (mainly L2·4, L2·5, and L2·9), which was suggested to predominantly include more recently evolved and globally circulating strains [10]. Interestingly, MLST ST1901, prevailing and associated with cephalosporin resistance in USA [12] and Europe [9], was not found in China. MLST ST1901 isolates belonged to L2·1 and L2·6, where L2·1 isolates were susceptible to ceftriaxone. These findings suggest that L2·6 has evolved from L2·1 and that isolates in L2·6 are less susceptible to ceftriaxone. Notably, most (86.2%) Chinese ceftriaxone-resistant isolates contained a non-mosaic penA allele, possibly selected by the high-level of β-lactam use in China. However, ST7363/L2·8 isolates, harboring a mosaic penA-10 allele, were also associated with decreased susceptibility and/or resistance to ceftriaxone [10]. Particularly the L2·6 and ST7363/L2·8 lineages are important to monitor in China and internationally. Obviously, MLST (examining seven genes) and NG-MAST (examining two genes) have highly suboptimal and inaccurate resolution [9,12], which makes the description and nomenclature of circulating gonococcal strains biased, less dynamic, and difficult to interpret, i.e., microbiologically, epidemiologically, and clinically. The nomenclature is one of the main challenges in phylogenomics and only well-defined clades should guide epidemiology and public health interventions. Peng et al. [10] defined lineages based on lineage-determining single nucleotide polymorphisms in a low number of the 2200–2450 genes in the gonococcal genome and the utilized genes are not standardized. The gonococcal scientific community should develop harmonized methods and nomenclature based on complete WGS data to uniformly define clades.

Peng and colleagues [10] enhance the understanding of the transmission and dynamics of the AMR gonococcal population in China and

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internationally, which can inform AMR surveillance programmes and public health, including infection control, globally. As strongly emphasized by the WHO [4], enhanced, quality-assured global surveillance of gonococcal AMR, ideally including treatment failures, is essential to identify emerging AMR, monitor AMR trends, and inform refinements of empirical treatment guidelines. Where feasible, now is the time to implement WGS, in conjunction with linked clinical, epidemiological, and phenotypic data, in the global gonococcal AMR surveillance programmes. Ideally, this WGS surveillance should use harmonized protocols and nomenclature for WGS (including nationwide sampling, quality assurance, and sequence analysis), and examine selected AMR strains but also consecutive and representative isolates (geographically and numerically representative; from both genders, symptomatic and asymptomatic patients, and all anatomical sites) to provide baseline data about the complete gonococcal population as has been done in the European gonococcal AMR surveillance [9]. WGS is revolutionizing our understanding of gonococcal AMR, AMR prediction, and emergence, transmission and persistence of AMR strains and AMR determinants locally, nationally and internationally over time, and is informing the development of gonococcal diagnostics, including point-of-care tests for detection of *N. gonorrhoeae* and its AMR, novel antimicrobials, and vaccine(s).

Conflict of Interest Statement

None of the authors has a conflict of interest with regard to this publication.

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