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The ticking time bomb: escalating antibiotic resistance in *Neisseria gonorrhoeae* is a public health disaster in waiting

David M. Whiley[1,2]*, Namraj Goire[1,2], Monica M. Lahra[3], Basil Donovan[4,5], Athena E. Limnios[3], Michael D. Nissen[1,2,6] and Theo P. Sloots[1,2,6]

[1]Queensland Paediatric Infectious Diseases Laboratory, Queensland Children's Medical Research Institute, Children's Health Service, Brisbane, Queensland, Australia; [2]Clinical Medical Virology Centre, Sir Albert Sakzewski Virus Research Centre, The University of Queensland, Brisbane, Queensland, Australia; [3]WHO Collaborating Centre for STD, Microbiology Department, South Eastern Area Laboratory Services, The Prince of Wales Hospital, Sydney, New South Wales, Australia; [4]The Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia; [5]Sydney Sexual Health Centre, Sydney Hospital, Sydney, New South Wales, Australia; [6]Microbiology Division, Pathology Queensland Central Laboratory, Herston, Queensland, Australia

*Corresponding author. Queensland Paediatric Infectious Diseases Laboratory, Sir Albert Sakzewski Virus Research Centre, Royal Children's Hospital & Health Service District, Herston Road, Herston, Queensland, Australia 4029. Tel: +61-7-3636 1623; Fax: +61-7-3636 1401; E-mail: d.whiley@uq.edu.au

From a once easily treatable infection, gonorrhoea has evolved into a challenging disease, which in future may become untreatable in certain circumstances. International spread of extensively drug-resistant gonococci would have severe public health implications. It seems clear that under the current treatment pressure from extended-spectrum cephalosporins, and owing to *Neisseria gonorrhoeae*'s remarkable evolutionary adaptability, further rise of ceftriaxone-resistant strains around the world is inevitable. Simply increasing the doses of extended-spectrum cephalosporins will likely prove ineffective in the long run, and has been a lesson learnt for all single-agent therapies used for gonorrhoea to date. We recommend that dual therapy, especially those consisting of extended-spectrum cephalosporins and azithromycin, be adopted more widely and complemented by strengthening of antimicrobial resistance surveillance. Unless there is urgent action at international and local levels to combat the problem of *N. gonorrhoeae* antimicrobial resistance, we are in for gloomy times ahead in terms of gonorrhoea disease and control.

Keywords: dual therapy, ceftriaxone, azithromycin, surveillance

Introduction

Gonorrhoea now poses a potential public health disaster, with a very real threat that it may soon be untreatable in certain circumstances. The recent isolation of two extensively drug-resistant strains (H041 and F89) in Japan and France, respectively,[1,2] which exhibited resistance to ceftriaxone, epitomizes these concerns. The story of drug-resistance development in *Neisseria gonorrhoeae* spans several decades and has a recurring theme, usually beginning with tell-tale signs of gradually increasing MIC in each case. The gonococcus has managed to develop resistance to multiple classes of antibiotics, including the penicillins, tetracyclines, macrolides and quinolones.[3] Therefore, it really does not come as a surprise that we are now observing signs of resistance to extended-spectrum cephalosporins (ESCs), including cefixime and ceftriaxone, after a steady rise in MICs over the last decade. However, the alarm bells are resounding this time round given there are now no ideal alternative therapies to fall back on, with all current options having significant drawbacks. In addition, there are serious inadequacies in antimicrobial resistance (AMR) surveillance globally.

Therapeutic options

As gonorrhoea is a sexually transmitted disease, the ideal treatment strategy is to use a single agent that is effective when given orally and as a single dose, and that has few or no side effects. Unfortunately, drug resistance is leading us further and further from such possibilities and our current regimens, including the ESCs, may soon be redundant. Although spectinomycin,[4] gentamicin[5] and ertapenem[6] have all been considered as alternatives, data are currently limited (or, in the case of spectinomycin, dated) and more studies are urgently needed to investigate and assess these drugs as current viable treatment options. Spectinomycin, unfortunately, can almost certainly be discounted as a single-agent therapy given its propensity to select for resistance when used as a first-line treatment,[7] and is not effective in eradicating pharyngeal gonorrhoea.[8] Azithromycin (2 g) is another alternative option but, as in the case of spectinomycin, resistance readily develops if it is used regularly as a single therapy[3] and there are increasing reports of gonococcal isolates with high-level resistance to azithromycin, including a recent case in the USA.[9]

A dual therapy regimen of ceftriaxone (intramuscularly; 250–500 mg) and azithromycin (orally; 1 g), is now recommended in the UK and USA for treatment of uncomplicated anogenital gonococcal infections.[8,10] It is worthwhile to note that combination therapy regimens have been widely adopted as strategies for the treatment of other bacterial infections in the face of development of multidrug resistance, e.g. *Mycobacterium tuberculosis*. A synergistic effect has been reported for cephalosporins and azithromycin for the treatment of *N. gonorrhoeae*,[11] and there are also promising data to suggest improved treatment of pharyngeal gonorrhoea using such an approach.[12] Pharmacodynamic data produced by Chisholm *et al.*[13] provide further support for the use of dual therapy rather than single therapies for treatment of gonorrhoea. Thus, in the absence of other viable options, and as a strategy recognized as effective in the management of resistant organisms, we recommend that wherever possible these dual therapies be more widely adopted in a bid to delay development of widespread *N. gonorrhoeae* resistance. From Australia there is anecdotal evidence to support improved efficacy of dual therapies in remote Aboriginal communities. First-line syndromic treatment of urethritis in these remote communities is amoxicillin (3 g), azithromycin (1 g) and probenecid (1 g), with the original reason to include azithromycin being to cover chlamydial infections.[14] Notably, these areas represent one of the few remaining pockets in the world where penicillin resistance remains sufficiently low for penicillins to be used as a first-line treatment,[14,15] and this is despite penicillin resistance being widespread in all other parts of Australia.[15] Nevertheless, this anti-gonococcal dual therapy by happenstance could have contributed to the surprisingly low levels of *N. gonorrhoeae* resistance in these remote communities,[15] although social isolation from populations with higher AMR levels and less antibiotic exposure could also be factors.

While dual therapy strategies may be readily implementable in the developed world, factors including cost and compliance issues may prevent these from being a viable option in under-resourced countries. It should also be noted that there are *N. gonorrhoeae* isolates currently circulating in China[16] and likely elsewhere that are resistant to azithromycin but also exhibit reduced susceptibility to ESCs, including ceftriaxone. Thus, we cannot be complacent with dual therapies as they may only form a partial solution, with the other prominent part to be played by AMR surveillance.

Surveillance

Accurate and up-to-date information on *N. gonorrhoeae* AMR is pivotal to the formulation of successful gonorrhoea control policies. Surveillance activities need to be optimized and, depending on the countries/populations targeted, could involve the implementation of surveillance, enhancement of surveillance or otherwise rethinking surveillance approaches. Currently, a lack of data in both developed and developing countries places serious limitations on the ability to control the *N. gonorrhoeae* AMR problem. An unlikely, and to an extent undeserving, culprit in this is the popularity of nucleic acid amplification tests (NAATs) for gonococcal diagnosis. No longer can we continue to resort to the convenience of NAATs at the expense of bacterial culture. Maintaining bacterial culture services to test all or representative samples of *N. gonorrhoeae* isolates from all anatomical sites for AMR is paramount in containing the problem. Secondly, and an important component of surveillance, is test of cure (TOC), for which data are lacking globally. TOC for all cases of gonorrhoea is now recommended by the UK guidelines.[10] Widespread implementation of TOC needs to be considered seriously, particularly for pharyngeal infections, which are effectively a melting pot of resistance development, and for which current TOC studies are unearthing increasing numbers of treatment failures. Thirdly, novel surveillance approaches, including molecular surveillance, need to be investigated, and may include direct detection of resistance mechanisms or direct application of database-driven typing strategies. While it is not currently conceivable that molecular surveillance could replace culture-based AMR testing, especially in resource-poor settings, molecular tools can certainly be used to complement it. Increasing the number of well-equipped reference centres in strategic locations around the world to complement the AMR surveillance of the region may help address the problem of infrastructure disparity. In this regard, we could take a leaf out of the influenza surveillance book; after the advent of the H1N1 (swine flu) virus in 2009, through concerted efforts of health agencies around the world, PCR assays were readily developed and implemented to successfully track influenza strains of public health importance.[17] There is no reason why such approaches could not be applied to resistant *N. gonorrhoeae*. That is, specific molecular methods could be developed for the detection of significant *N. gonorrhoeae* strains, such as H041 or F89, so that they could be promptly detected in non-cultured (*N. gonorrhoeae* NAAT-positive) samples. Our laboratory has demonstrated the feasibility of this for the *N. gonorrhoeae* H041 strain and other *N. gonorrhoeae* resistance markers.[18,19] Implementation could initially be local or in a broader setting if the strain becomes widespread. Dedicated sequence databases for the genes of AMR interest, particularly the *N. gonorrhoeae penA* gene, would go a long way in aiding these developments.

Conclusions

The problem of *N. gonorrhoeae* AMR is complex and unfortunately is gaining momentum. It is probably only a matter of time before extensively drug-resistant *N. gonorrhoeae* strains become widespread and treatment failures, particularly for pharyngeal gonorrhoea, become commonplace. The history of resistance in this bacterium is such that many of the current strategies, including dual therapies, may by themselves only provide a reprieve rather than a solution. Action is therefore urgently needed at local and international levels to combat the problem. We advise that government agencies take this threat seriously and provide urgently needed funds for increased research, surveillance activities and vaccine development.

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None to declare.

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