From zero to zero in 100 years: gonococcal antimicrobial resistance

The threat of antimicrobial resistance (AMR) in bacteria has been escalated to a rightful seat on the global health agenda. In September 2016, for only the fourth time in United Nations (UN) history, the UN General Assembly in New York will meet to focus on a health threat – antimicrobial resistance. Other diseases afforded this level of consultation at the UN were human immunodeficiency virus (HIV), non-communicable diseases and Ebola virus. There are grim predictions for the future in terms of AMR and health security that span income settings. These predictions challenge the premise that minor bacterial infections of childhood are innocuous, and threaten to halt the medical advancements dependant on antibiotic therapy. Those with compromised immune systems, whether endogenous or induced, will be at highest risk. The development and spread of AMR has been, and will continue to be, fanned by...
the relentless selection pressure of exposure to antibiotics whether used appropriately, unnecessarily or suboptimally, in human health, animal health and agriculture. The distribution of antibiotic resistant bacteria is facilitated by travel and transport. Antimicrobial resistance will affect those in the community and the hospital.

A well-documented example that demonstrates the development and spread of AMR involves *Neisseria gonorrhoeae* (Figure 1). The expansion of AMR to each successive therapeutic recommendation has left limited options for treatment of this once easy-to-treat infection. International travel remains a major factor in the dissemination of drug-resistant *Neisseria gonorrhoeae* strains and this has been highlighted most recently by the global spread of strains with resistance to extended spectrum cephalosporin antibiotics, the so-called last single dose therapy. Now a combination of two antibiotics are generally recommended for the treatment of gonorrhoea, ceftriaxone and azithromycin, and resistance to both has been documented\(^1,2\). Resistance to azithromycin is typically caused by alteration of the 23S ribosomal RNA gene (the drug target), but may also arise via mutations causing increased activity of efflux pumps (which pump drugs out of the cell)\(^3\). Resistance to cephalosporin antibiotics is characterised by a mosaic penicillin binding protein-2 (PBP-2) (this mosaic PBP-2 occurs as a result of integration of DNA sequences from other bacteria producing a changed drug target). Mosaic PBP-2 strains belonging to multi-locus sequence type 1901, first reported in Japan at the turn of the millennium, have become a successful clone in several continents. Whilst genetic data are lacking to confirm what happened with the previous first-line antibiotic classes, it is likely that a similar global transmission event was responsible for limiting the use of fluoroquinolones in the early 1990s.

Many questions remain regarding how to best deal with AMR in *Neisseria gonorrhoeae*. A gonococcal vaccine remains elusive and other primary prevention strategies, such as safer sex behaviour change strategies have not prevented the spread of gonococcal AMR. Many regions of the world remain unaware (particularly at the population level) of the nature and extent of gonorrhoea prevalence and the incidence of antimicrobial resistance. In addition, international travel continues to threaten AMR containment and border screening is not a realistic option for preventing spread of AMR. For these reasons, ongoing monitoring of AMR, both at national and global levels, remains the central tenet of the public health response to the threat of untreatable gonorrhoea. In our opinion, this can only be achieved through combined use of both bacterial culture and molecular AMR testing strategies. Culture based surveillance remains optimal for detecting new resistance mechanisms. However, mechanism and strain-specific molecular assays add rapid, important and clinically relevant data for situational analysis and to inform treatment guidelines, to monitor the effect of interventions and to provide data in countries or remote areas with limited laboratory capacity.

Gonococcal diagnostic and AMR testing strategies in remote and regional communities of Australia provide an ideal fine scale example of the above. These communities represent one of the few globally where penicillin can still be used for treatment of locally acquired gonorrhoea. Penicillin is an ideal treatment option as it is orally administered, and can be stored without need for refrigeration hence there is considerable motivation to maintain

In Focus

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**Figure 1.** Gonococcal antimicrobial resistance over the past 100 years. Bars indicate the number of clinically tested antimicrobial classes available for *Neisseria gonorrhoeae* treatment.
this therapeutic option. Incursion of penicillin resistant strains from elsewhere in Australia, where resistance rates exceed 40%, or from international travellers, is an ever-present threat. Optimal surveillance is pivotal to identify such incursions and initiate rapid public health interventions. Whilst gonococcal culture is promoted, the majority of infections (~90%) are diagnosed by molecular based testing. To facilitate surveillance locally, an in-house polymerase chain reaction (PCR) assay has been developed and implemented to screen for penicillinase-producing *Neisseria gonorrhoeae* (PPNG) strains. This approach has a key benefit: rather than simply responding to emerging trends in aggregate data, the assay provides immediate results at an individual level that can readily be acted upon.

The recent incursion of the ceftriaxone resistant A8806 strain into Australia exemplifies how the dual culture-molecular approach supports public health initiatives to contain gonococcal AMR. The A8806 isolate was first identified by culture (highlighting the importance of maintaining bacterial culture). After the phenotypic AMR profile was established using conventional culture-based techniques, the isolate was sequenced, and a strain-specific PCR method developed. The PCR was utilised in clinical practice to determine the spread and prevalence of the A8806 strain across the two states where the infected patient had travelled. We are currently investigating an outbreak of azithromycin resistance in Australia, and further intend to use molecular assays to gauge the importance of maintaining bacterial culture. After the phenotypic AMR profile was established using conventional culture-based techniques, the isolate was sequenced, and a strain-specific PCR method developed. The PCR was utilised in clinical practice to determine the spread and prevalence of the A8806 strain across the two states where the infected patient had travelled. We are currently investigating an outbreak of azithromycin resistance in Australia, and further intend to use molecular assays to gauge the extent of the outbreak. Increasingly the availability of genome sequencing is facilitating the identification and characterisation of such clusters, permitting tracking and tracing of AMR strains and investigation of transmission dynamics.

The WHO’s *Report on global sexually transmitted infection surveillance 2015* shows that in many regions where disease rates are high there is limited data to determine the scope and extent of AMR. This is a function of a number of factors including limited resources and syndromic management of patients. Paradoxically, best resource settings often test relatively few gonococcal isolates for AMR, due to a preference for nucleic acid tests which do not characterise AMR profiles of well documented resistance genes. Gonococcal antimicrobial susceptibility testing remains expensive and technically difficult. Strategies are required to strengthen local laboratory capacity and capability, to increase the number of isolates for testing, with all options available to gather timely and reliable information considered.

A population-based approach that identifies those at risk for gonococcal infections, possibly linked to other health interventions, such as HIV screening of high risk people, may be reasonable. Containing gonococcal AMR should be program oriented, linking patient and contact management with the best treatments to prevent disease and reduce transmission. Merging cutting edge molecular technologies that can diagnose known and emerging AMR determinants with new ways of case finding, and bringing effective treatment to patients and partners in a timely fashion will improve health outcomes. Thus a strategy that focusses only on the acquisition of AMR data and which is isolated from other components of an active program to ensure treatment and elimination of transmission is bound to fail. Such programs may entail a shift in thinking regarding how AMR is diagnosed, how and what patients are identified, and the criteria for which treatment guidelines are modified.

Critically *N. gonorrhoeae* infects only humans and can therefore be potentially eradicated. Future success in the current context will rely on adaptive thinking, exploiting both new and pre-existing technologies to gather information and inform health care strategies. However, primary prevention must remain the principle focus.

### References


### Biographies

**Professor Monica Lahra** is the Director of the Division of Bacteriology and Director of the World Health Organization Collaborating Centre (WHO-CC) for STDs, at Prince of Wales Hospital, Sydney, Australia. She is also Director of the National Neisseria Network and conjoint Professor at The University of New South Wales. Professor Lahra leads the team at the WHO-CC Sydney to coordinate national and international networks for laboratory surveillance of pathogenic Neisseria, including antimicrobial resistance surveillance using phenotypic and genotypic testing.

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transmissible diseases, in particular *Neisseria gonorrhoeae* and the surveillance and molecular biology of antimicrobial resistance. Dr Dillon has extensive academic and public sector administrative leadership experience, has led several national and international scientific organisations, and has consulted nationally and internationally in the area of STIs and public health. Dr Dillon has authored numerous publications with a special focus on international trends in antimicrobial resistance, molecular typing of bacterial pathogens and the cell biology of *Neisseria gonorrhoeae*. She is a Fellow of the Canadian Academy of Health Sciences.

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**Professor David Lewis**, FRCP (UK), is Director of the Western Sydney Sexual Health Centre and Professor at the University of Sydney. He is also the Discipline Leader for STI/HIV within the Marie Bashir Institute for Infectious Diseases and Biosecurity. David’s research interests focus on gonorrhoea, genital ulcer disease, STI care in resource-poor settings, outreach STI services and men’s sexual health. He serves as the current President of the International Union against STIs (IUSTI). David frequently assists the World Health Organization as a Technical Advisor in matters related to STI treatment guidelines, the proposed 2016–2025 STI strategy, point-of-care diagnostic tests and the Gonococcal Antibiotic Susceptibility Programme (GASP).

**Dr Teodora E Wi**, MD, FPSVI is currently the Medical Officer, Human Reproduction Team, Department of Reproductive Health and Research, World Health Organization (WHO), Geneva, Switzerland. In WHO HQ she is leading the development of STI guidelines, antimicrobial resistance in *N. gonorrhoeae* and interventions for key populations, in addition to providing technical support to regional and country offices of WHO. She has over 20 years of experience in HIV and STI programming. She was the acting team leader for HIV/AIDS and STI, Western Pacific Region Office, WHO. Prior to WHO, she was the Director, STI Capacity Raising, Family Health International (FHI) India under the Avalahan India AIDS Initiative of the Bill & Melinda Gates Foundation (BMGF).

**Associate Professor David Whiley** is based at The University of Queensland Centre for Clinical Research and Pathology Queensland. His research is principally focused on the development of novel molecular diagnostic and typing tools for infectious diseases. He has a particular research interest in *Neisseria gonorrhoeae*.

### Foodborne disease associated with travel

![Prue Bramwell](image)

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The most important determinant of developing foodborne disease is travel destination. The risk is proportional to regions where there is a high level of unsanitary water supply, lack of food hygiene, lack of food safety regulation, fluctuating electricity supply and lack of education. In medium to high risk regions a travel kit, designed to prevent, minimise or treat the effects should be carried. After a decade of comprehensive work gathering data to estimate the world burden of foodborne disease the World Health Organization (WHO) has produced a report in which it has calculated that 600 million people develop foodborne disease after eating contaminated food each year. The report also determined which regions and countries had the highest incidence and which foodborne pathogens caused the majority of outbreaks. This has great significance on the varying degrees of danger of developing a foodborne disease when travelling in these regions because the most important determinant of risk is travel destination. Risk also depends on the season of travel.