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Delaying the widespread emergence of cephalosporin-resistant gonorrhoea: what is the best target?

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Neisseria gonorrhoeae is associated with high morbidity worldwide. The emergence of cephalosporin and macrolide resistance represents a grave threat to the control of a disease, which, if untreated, can lead to serious reproductive complications in women, blindness in neonates, facilitated spread of HIV and, in rare cases, life-threatening disseminated infections.^{1, 2} A plenary was convened at the Centers for Disease Control and Prevention's (CDC) sexually transmitted disease (STD) Prevention Conference held in Atlanta, Georgia, 9–12 June 2014, to discuss several key aspects pertaining to this issue. The Scientific Committee, including Drs Matthew Golden from the University of Washington, Kevin Karem from CDC and Khalil Ghanem from Johns Hopkins University School of Medicine, invited three experts to discuss challenges to the control of drug-resistant gonorrhoea. The presentations focused on the antibiotics, the microbe and population-specific dynamics. The three contributors were then asked to develop their presentations into full-length papers, which are compiled here.

In an effort to delay the emergence of cephalosporin and macrolide resistance, several public health agencies now recommend combination therapy with ceftriaxone and azithromycin to treat gonorrhoea.^{3, 4} In his provocative paper, 'Can the treatment of GC with dual antibiotics delay the emergence of drug-resistant GC?', Louis Rice highlights some important considerations that may hinder the long-term success of this approach. Gonorrhoea is capable of quickly acquiring resistance through mutations and horizontal gene transfer. Gonorrhoea routinely and asymptotically colonises the rectum and the upper respiratory tract. It is not clear, however, whether antibiotics achieve the necessary concentrations at these anatomical sites, particularly in the absence of inflammation, to treat these infections and prevent the emergence of resistance. To further complicate matters, azithromycin and ceftriaxone are often used separately for the treatment of common non-gonococcal infections, so patients with asymptomatic gonococcal carriage may be effectively exposed to monotherapy. In addition, azithromycin has a much longer half-life than ceftriaxone, and therefore, monotherapy may be an unintended consequence of combination therapy. Finally, both antibiotics have the potential to select for resistance to each other. Dr Rice points to

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reports of the emergence of some strains that demonstrate reduced susceptibility to both antibiotics as a worrisome sign.

In his paper, ‘Will targeting oropharyngeal gonorrhoea delay the further emergence of drug resistant *Neisseria gonorrhoeae* strains?’, David Lewis further explores the important role that oropharyngeal infections may play in the development and spread of gonococcal antibiotic resistance. While usually asymptomatic, and often self-limited, oropharyngeal gonococcal infections are an important source for transmission to urogenital sites. The oropharynx provides an excellent environment for genetic exchange and therefore may facilitate the development of gonococcal resistance. Even single courses of antibiotics have been shown to increase the carriage of antibiotic-resistant genes by oropharyngeal commensals. Given the significantly higher prevalence of non-gonococcal *Neisseria* spp in the oropharynx than in the urogenital tract, antibiotics may select for resistance in these commensals, which is then, in turn, transferred to gonococci. The asymptomatic nature of oropharyngeal gonococcal infections as well as their prevalence in high-risk groups makes them both difficult to diagnose and important to treat.

Finally, in their paper, ‘Targeting core groups for gonorrhea control: Feasibility and impact’, Katia Giguere and Michel Alary define members of a core group as a population of people with high STD burden, large numbers of sexual partners and high rates of sexual partner change. Core groups are important because these individuals bear a disproportionate burden of disease and also play an important role in the spread and persistence of infections in the general population. Giguere and Alary also introduce the concept of ‘bridging’ groups who help to maintain an epidemic in the general population. Core groups are difficult to identify, but interventions that target them have been shown to have a broader impact by decreasing STD and HIV prevalence in the general population. However, this approach of targeting core groups for treatment of STDs is more complicated in the era of gonococcal drug resistance. Epidemiological evidence suggests that drug-resistant gonorrhoea strains seem to be emerging from or may be amplified by core groups. Indeed, a recent modelling study suggested that the treatment of core groups in the presence of antimicrobial resistance may maximise the dissemination of antimicrobial-resistant gonorrhoea, leading to a rebound of drug-resistant gonorrhoea in the general population. In the face of these concerns, the authors call for a better-functioning worldwide system to track gonococcal drug resistance and stress the importance of STD prevention efforts targeting core groups to increase condom use as critical in helping to prevent the spread of drug-resistant gonorrhoea.

The development of antibiotic resistance in *N. gonorrhoeae* continues to threaten our efforts to effectively treat and control this infection. Choosing the right antimicrobial therapy, targeting infections at specific anatomical sites and focusing prevention and treatment efforts on certain high-risk groups may be important, but as these three papers make clear, significant challenges abound and the path forward is fraught with uncertainty.

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