Editorial

Neisseria gonorrhoeae Is Evolving into a ‘Superbug’ – what Measures Can Be Implemented to Combat the Emergence of Multidrug and Extensively-drug Resistant Gonorrhoea in Latin America and Globally?

Infections with Neisseria gonorrhoeae remains an important public health concern worldwide. In 2008, the World Health Organization (WHO) estimated the global burden of gonorrhoea among adults to be 106 million cases, which represented a 21% increase since 2005. Most of those cases (64%) were in the WHO Western Pacific Region (42 million cases) and WHO South-East Asia Region (25 million cases), however, 11 (10%) million cases were in the WHO Region of the Americas (including both North America and Latin America)(1). Gonorrhoea may result in pelvic inflammatory disease, ectopic pregnancy, infertility and enhanced transmission of HIV. These complications cause substantial morbidity and economic costs, particularly in those resource-poor regions of the world where gonorrhoea is most prevalent.

Public health control of gonorrhoea requires treatment with appropriate antimicrobials, as well as generalized and targeted prevention efforts, use of reliable diagnostics, effective partner notification processes and quality-assured surveillance activities. Antimicrobial therapy should cure individual cases in order to reduce the risk of complications and prevent further transmission of the infection. However, from the beginning of the antimicrobial era (1930s), N. gonorrhoeae has consistently shown its extraordinary genetic capacity to develop antimicrobial resistance (AMR) to all drugs introduced for treatment of gonorrhoea(2-4). Currently, in most countries globally the extended-spectrum cephalosporins (ESCs) cefixime (oral) and ceftriaxone (injectable) are the only remaining antimicrobials recommended for monotherapy. However, treatment failures, particularly with cefixime but also more rarely with ceftriaxone, have been verified in Japan, Australia, several European countries, South Africa and Canada(4-7).

Furthermore, it is of most grave concern that the three first extensively-drug resistant (XDR)(5) N. gonorrhoeae strains, which also display high-level ceftriaxone resistance, have now been verified. These XDR N. gonorrhoeae strains were identified in high-risk frequently transmitting populations, i.e. a commercial sex worker (CSW) and men-who-have-sex-with-men (MSM), and their isolation raises concern that gonorrhoea may become untreatable in the future(6). The gonococcus may thus be evolving into a ‘superbug’ and, in order to meet the public health challenges associated with the emergence and spread of both multidrug resistant (MDR) and XDR N. gonorrhoeae, the WHO has recently published a global action plan(8). In addition, the European Centre for Disease Prevention and Control(9) and the US Centers for Disease Control and Prevention(10) have published regional response plans. Furthermore, dual antimicrobial treatment regimens for uncomplicated anogenital gonorrhoea have been introduced in the USA(11) and Europe(12). Those dual antimicrobial therapies mainly recommend single-dose combinations of intramuscular ceftriaxone (250-500 mg) together with oral azithromycin (1-2 g).

One key component of the international action/response plans(8,10) is to enhance the timely and quality-assured surveillance of AMR (preferably using WHO gonococcal control strains(13)) and treatment failures. This is imperative because gonococcal AMR data are lacking in many settings and the true global problem remains unknown. In 2009, the WHO’s Global Gonococcal Antimicrobial Surveillance Programme (GASP) was revitalized, in close liaison with other existing AMR surveillance programmes. The WHO Global GASP network aims to recruit laboratories worldwide to monitor quality-assured gonococcal AMR data (with particular attention to ESCs), to provide support to establish gonococcal culture and AMR testing, to inform public health authorities and treatment guidelines on trends in gonococcal AMR, to optimize early detection of emerging resistance and, finally, to identify and verify treatment failures with ESCs. Worryingly, longitudinal quality-assured gonococcal AMR surveillance programmes remain sporadic, limited or even lacking in large parts of many regions worldwide, including Eastern Europe, Central Asia and Africa as well as Latin America and the Caribbean (LAC). These regions also suffer from a high burden of gonorrhoea, creating the prerequisites for rapid emergence and spread of gonococcal AMR.

In LAC, a strong and quality-assured GASP was established in the 1990s(14) and there have been recent attempts to revitalize this GASP network. The connections and programmes of the GASP-LAC have been maintained in many LAC countries, and, in response to the WHO 2009 call for revitalization, the GASP-LAC regional network has been renewed(15,16). Several countries in Latin America have on-going national GASP networks. Gono-
coccocal AMR surveillance efforts, such as the one reported from Brazil in the current issue by Medeiros et al., will help catalyse enhanced regional and national GASP networks that are important not only for Brazil, but also for the entire LAC region. Recent GASP-LAC surveillance established that several countries in the region, including Brazil, still recommend ciprofloxacin for the treatment of gonococcal infections(15). The paper by Medeiros et al., which reports on high percentages of isolates resistant to ciprofloxacin, underscores the importance of GASP surveillance to inform the development and implementation of updated treatment guidelines for gonorrhoea infections. It is also notable that early GASP regional surveillance in Brazil also reported the first emerging resistance to azithromycin, a trend that has continued and is reflected in the Medeiros paper(17). Based on the results reported by Medeiros et al., although the sample size of isolates was low, it appears that ceftriaxone might be the only antimicrobial that can be recommended for national first-line empiric monotherapy of gonorrhoea in Brazil.

Recently, Brazil banned the sale of over-the-counter antibiotics, an essential first step in ensuring the prudent use of antibiotics for treatment. In addition, well-conducted microbiological surveys or, ideally, a sustainable national GASP network, testing substantial numbers of consecutive non-selected gonococci from multiple sites within a country, should provide the evidence base for local and national treatment guidelines. To achieve this, it is essential to strengthen and further develop regional and national capacity to undertake gonococcal culture and AMR testing. This requires substantial political will and funding as well as an investment in laboratory infrastructure and staff training. Brazil may now be ready to undertake this national challenge (Franchini M, personal communication).

Although enhanced surveillance of gonococcal AMR and treatment failures are critical, more holistic views and actions are required to truly combat the emergence and spread of possibly untreatable gonorrhoea nationally and internationally. Substantially enhanced and broad disease control activities (i.e., improved prevention, better diagnostics, effective treatment and surveillance) are needed to reduce the global burden of gonorrhoea combined with the implementation of wider strategies for general antimicrobial control (such as guidelines for antimicrobial use, appropriate selection of therapeutic agents, uninterrupted supplies and quality of generic drugs), sustainable implementation of most components of the action/response plans and an increased awareness among clinicians, microbiologists, epidemiologists and policy-makers in respect of the public health threat of MDR/XDR gonorrhoea. Internationally, there is an urgent need for an enhanced focus on reducing gonorrhoea burden in high-risk frequently transmitting populations (such as CSWs and MSM) as well as appropriate diagnosis and treatment of pharyngeal gonorrhoea, which is harder to eradicate and is an asymptomatic reservoir for gonorrhoea and emergence of AMR.

In conclusion, essential public health actions are required to retain gonorrhoea as a treatable infection including enhanced awareness; implementing action/response plans for potentially untreatable gonorrhoea infections nationally and globally; enhancing surveillance of gonococcal antimicrobial resistance, treatment failures and antimicrobial use/misuse; and improving both prevention and early diagnosis and treatment of gonorrhoea in index cases and their sexual contacts. Unfortunately, all these actions are likely only to mitigate the spread of MDR and XDR N. gonorrhoeae in the short-term. It thus remains imperative to develop novel treatment strategies, new antimicrobial agents (or other compounds) and ideally a vaccine for effective treatment and prevention of gonorrhoea in the longer term.

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REFERENCES