

The serious threat of multidrug-resistant and untreatable gonorrhoea: the pressing need for global action to control the spread of antimicrobial resistance, and mitigate the impact on sexual and reproductive health



EDITOR'S
CHOICE

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STIs remain a major cause of morbidity and mortality worldwide. The WHO estimated that >498 million new cases of syphilis, gonorrhoea, chlamydial infection and trichomoniasis occurred globally in 2008 in adults (15–49 years of age). More than 106 million were gonococcal infections.¹ Accordingly, gonorrhoea remains a major global public health problem with serious health, social and economic consequences. Inadequate control and treatment can result in severe complications, such as pelvic inflammatory disease, leading to infertility or ectopic pregnancy, and neonatal eye infections which can cause blindness. Up to 10% of women who remain untreated (or inadequately treated) for chlamydial and gonococcal infections may become infertile. Urogenital gonorrhoea is also asymptomatic in at least 50% of women, which leaves the infections undetected and untreated with the risk of severe complications. On a global scale, up to 4000 newborn babies, annually, may become

blind because of gonococcal and chlamydial ophthalmia neonatorum.² In men, gonococcal infections cause symptomatic urethritis which, if untreated, can result in epididymitis in 10%–30% of cases,^{w1} that may lead to infertility. Gonorrhoea also significantly enhances the transmission of HIV. The burden of gonococcal infections is highest in countries that are least able to manage them because of several factors, including stigma, inadequate resources and lack of appropriate diagnostics, surveillance and antimicrobial treatment. The problem is further compounded by the ability of *Neisseria gonorrhoeae* to develop antimicrobial resistance (AMR) within a relatively short time span.^{3 w2 w3}

Historically, since the advent of the antibiotic era, gonococcal infections have been easy to treat. However, the susceptibility of *N gonorrhoeae* to sulphonamides and penicillins from the mid-1930s and mid-1940s, respectively, gradually eroded as the organism developed a number of mechanisms for antimicrobial resistance. The mid-1980s and early 1990s were promising with the introduction of effective single-dose treatments that could be administered orally, such as fluoroquinolones (mainly ciprofloxacin and ofloxacin) and oral third-generation cephalosporins (cefixime being the most potent one). The macrolide azithromycin was even more exciting as it could treat both gonococcal and chlamydial infections with a single oral dose regimen. However, resistance to fluoroquinolones emerged only after about a decade, and these

were abandoned as first-line empiric treatment for gonorrhoea in the Asia-Pacific region already in the mid-to-late 1990s and, subsequently, in the USA, Europe and parts of Africa.^{3 w2 w3–w6} Azithromycin-resistant *N gonorrhoeae* emerged in the mid-to-late 1990s,^{4 w7} and, subsequently, also high-level azithromycin resistance has been described from several countries.^{5 w8–w11} Thus, since the early 2000s, third-generation cephalosporins (mainly cefixime and ceftriaxone) have been the sole class of antimicrobials recommended as first-line empiric treatment.^{3 w2 w3}

Worryingly, resistance and treatment failures to cefixime have been verified in Japan⁶ and recently in Europe.^{7–9} The recent report of a strain of *N gonorrhoeae* in Japan that was highly resistant to the parenteral ceftriaxone, and associated with a probable treatment failure with ceftriaxone,¹⁰ the last remaining option for empiric treatment, sounded alarm bells of significant future challenges to the treatment and control of gonococcal infections and their complications. This was also followed by the identification of a highly ceftriaxone-resistant strain in France¹¹ and in Spain.¹² Furthermore, many regions, worldwide, describe a decreasing susceptibility to ceftriaxone, and reports of ceftriaxone treatment failure of gonococcal pharyngeal infections have been published.^{3 13 w2 w3} Given the ability of *N gonorrhoeae* to develop AMR within a relatively short time span compounded with its ability to retain the resistance to previous antibiotics, even after their use has been discontinued, the threat of a widespread ceftriaxone resistance and untreatable gonorrhoea in certain circumstances is real.^{3 10 11 w2 w3}

The global trend of AMR in *N gonorrhoeae*, and decreased susceptibility and resistance to the third-generation cephalosporins, in the age of easy international travel dictated that a global approach needed to be elaborated to respond to the emerging menace of untreatable gonorrhoea. This was especially important because gonococcal AMR data were not available in many settings, and the true global magnitude of the problem is unknown. Therefore, the WHO Global Gonococcal Antimicrobial Surveillance Programme (WHO Global GASP), initially established in the 1990s, was revisited and revamped in 2009 as a network of collaborators in order to enable a global, coordinated response. The WHO Global GASP network consists of the WHO Headquarters, Geneva, as the managing focal centre working with interregional collaborators in Africa, Asia, the Americas, Europe and the

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Western Pacific, and aims to encourage and recruit national laboratories to monitor gonococcal AMR data, with particular attention to third-generation cephalosporins, and identify treatment failures using recommended treatment.

To facilitate the functioning of the GASP network and engage the support of governments and the international community and donors in this venture, the WHO published the 'Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in *N gonorrhoeae*' in June 2012.¹⁴ The Global Action Plan aims to facilitate early detection of strains resistant to recommended treatment, combined with a public health response to mitigate the impact of cephalosporin-resistant *N gonorrhoeae* on sexual and reproductive health morbidity. The WHO Global Action Plan calls for the public health approach to the control of gonococcal infections and the emergence of multidrug-resistant and untreatable gonorrhoea. Some of the main components and actions of the Global Action Plan are:

- ▶ Advocacy for increased awareness on correct use of antibiotics among healthcare providers and the consumers, particularly in key populations, including men-who-have-sex-with-men and sex workers.
- ▶ Effective prevention, diagnosis and control of gonorrhoea, using prevention messages, interventions, recommended diagnosis and treatment regimens.
- ▶ Systematic monitoring and early detection of treatment failures with recommended treatment (cefixime and ceftriaxone) by developing a standard case definition of treatment failure, and protocols for verification, reporting and management of failure.
- ▶ Effective drug regulations and prescription policies.
- ▶ Strengthened AMR surveillance, especially in countries with a high burden of gonococcal infections (and/or gonococcal AMR), other STIs and HIV.
- ▶ Capacity building to establish regional networks of laboratories to perform quality-assured gonococcal culture and antimicrobial susceptibility testing.
- ▶ Research to identify new molecular methods for detecting and monitoring antimicrobial resistance.
- ▶ Research (basic science, in vitro and clinical studies) to identify alternative

effective treatment strategies and/or antimicrobials (or other effective compounds) for gonorrhoea.

This Global Action Plan will be implemented within the WHO's 'Global Strategy for the prevention and control of sexually transmitted infections: 2006–2015' which was adopted by the WHO Member States at the 59th World Health Assembly in May 2006.² To ensure harmonisation and sustainability, the WHO GASP network will be linked to, and operate within, the WHO Policy Package to Combat AMR which was launched on World Health Day 2011 in Geneva.¹⁵

The implementation of the WHO GASP activities both at the global and national levels can only be achieved with the formation of partnerships for funding and training among different but related programmes, and adequate funding for surveillance of STIs, in general, and quality-assured gonococcal AMR testing, in particular. Several region-specific and even country-specific action plans to control the spread of gonococcal antimicrobial resistance, are also under preparation, these plans are also crucial for the global response to the serious threat of untreatable gonorrhoea. Ultimately, it is essential to identify new strategies and/or antimicrobials (or other effective compounds) for effective treatment of gonorrhoea. It is imperative that this research is adequately supported and funded by national and international partners.

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▶ Additional references are published online only. To view these references please visit the journal online (<http://sti.bmj.com/content/88/5.toc>).

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