

Stopping gonorrhoea's descent towards untreatability



Antimicrobial resistance is considered one of the main challenges to health at the global level. In 2024, WHO updated its list of bacterial priority pathogens, whose update is detailed in an Article published in this journal) and one bacterium highlighted in the list is *Neisseria gonorrhoeae*, the bacterium that causes the sexually transmitted disease gonorrhoea. Resistance is such a serious issue for *N gonorrhoeae* that the bacterium appears twice in the list, first for resistance to fluoroquinolones or then for resistance to third generation cephalosporins. Gonococci can easily pick up genetic material from other bacteria, including antibiotic resistance genes; this ability has fostered over the years resistance to tetracyclines, macrolides (including azithromycin), sulphonamides and trimethoprim combinations, and, more recently, quinolones. Resistance to the β -lactam ceftriaxone, which represents the first-line therapy (500 mg IM), is expanding, particularly in China, Cambodia, and Vietnam, where it ranges from 8.1% to 26.9%. The emergence of different forms of resistance in *N gonorrhoeae* is often followed by a rapid spread of disease, and in fact the prevalence of gonorrhoea has increased in the last five years. The current Global Health Sector Strategy on HIV, Hepatitis and STIs (2022–2030) has set targets to reduce the number of new cases of gonorrhoea among people aged 15–49 years old from 82.3 million per year in 2020 to 8.23 million per year in 2030, thus reducing the annual incidence by 90% by 2030. Yet, widespread resistance of *N gonorrhoeae* means that these targets might not be achievable and on the contrary, there is the risk that soon gonorrhoea will be impossible to treat in the absence of new drugs or strategies to curb the burden of disease.

Some good news is however on the horizon. A recent phase 3 trial of the first-in-class antibiotic zoliflodacin (single oral suspension dose of 3 g) demonstrated non-inferiority of microbiological cure at the urogenital site to 500 mg ceftriaxone IM plus 1 g oral azithromycin. An Article in *The Lancet* has reported similar results for another first-in-class antibiotic, gepotidacin, that in a phase 3 trial demonstrated non-inferiority to IM ceftriaxone (500 mg) plus oral azithromycin (1 g) for culture-confirmed bacterial eradication of urogenital gonorrhoea at day 4–8. In an assessment of efficacy at different body sites, gepotidacin performed better than

ceftriaxone plus azithromycin for rectal infections, but worse for pharyngeal infections, although sample sizes were small for these analyses so these observations require confirmation. The potential availability of two different new antibiotics which mechanisms of action are not affected by existing resistance genes could offer hope for managing gonorrhoea cases caused by panresistant bacteria. Moreover, on April 2, researchers from the universities of Konstanz, Germany, and Vienna, Austria, discovered a new class of antibiotic (called 2-nonyl-4-quinolone N-oxide) that selectively kills *N gonorrhoeae*, through activation of endogenous toxins. While very early, these results show that there is potential for further new drugs to be tested and possibly reach clinical development.

Another research area in which the use of antibiotics to reduce of gonorrhoea is being explored is post-exposure prophylaxis (PEP) with doxycycline: while recent trials such as DOXYVAC and DoxyPEP (also reported in this journal) have shown that the use of doxycycline after condomless sex may reduce the incidence of a first episode of chlamydia or syphilis, its impact on gonorrhoea is less clear. In the DoxyPEP trial, that was done in San Francisco, CA, USA, PEP with doxycycline was efficacious in reducing the number of new gonorrhoea cases while only a moderate efficacy was observed in the DOXYVAC trial done in Paris, France. In the French study, it is thought that the lower efficacy was due to the fact that many strains of *N gonorrhoeae* were highly resistant to tetracycline, something not observed in the US study. A similar lack of efficacy for PrEP with doxycycline was observed in a study done on women in Kenya where there are high levels of resistance to tetracyclines in *N gonorrhoeae* and adherence to PEP was low. Concerns also exist around the prophylactic use of doxycycline as a potential way to favour development of antimicrobial resistance.

What we are seeing with *N gonorrhoeae* is a challenge that could extend easily to other bacteria with worsening of the antimicrobial resistance landscape. Investment in research for new antimicrobials and efficacious prevention methods are key to prevent gonorrhoea from getting out of control in the coming years. ■ *The Lancet Infectious Diseases*



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For the trial on gepotidacin see **Articles** *Lancet* 2025; published online April 14. [https://doi.org/10.1016/S0140-6736\(25\)00628-2](https://doi.org/10.1016/S0140-6736(25)00628-2)

For the DOXYVAC trial see **Articles** *Lancet Infect Dis* 2024; **10**: 1093–1104

For the final analysis of the DoxyPEP trial see **Articles** *Lancet Infect Dis* 2025; published online March 25. [https://doi.org/10.1016/S1473-3099\(25\)00085-4](https://doi.org/10.1016/S1473-3099(25)00085-4)