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Doxycycline post-exposure prophylaxis: let the debate begin

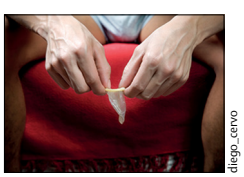
Should physicians prescribe doxycycline to prevent syphilis? In their study published in *The Lancet Infectious Diseases*, Jean-Michel Molina and colleagues[1] report on the findings of the first large, open-label randomised control trial to help answer this question.[2] Their findings show that, among men who have sex with men (MSM) who were using pre-exposure prophylaxis (PrEP) for HIV and who had a median of ten partners every 2 months, taking doxycycline within 24 h after sex reduced the incidence of chlamydia by 70% when compared with no prophylaxis (hazard ratio [HR] 0·30, 95% CI 0·13–0·70; p=0·006); similar results were observed for syphilis (0·27, 0·07–0·98; p=0·047), but not for gonorrhoea (0·83, 0·47–1·47; p=0·52).[1]

We can now debate the merits and limitations of this paper, including, the high sexual risk profile of these men compared with those attending most sexual health services, the substantial attrition in the use of doxycycline over time and therefore the concerns about the sustainability of the effect, or the possible underestimation of the effect size because a substantial number of individuals in the no-prophylaxis group were actually taking doxycycline. But although all these discussions matter, patients and the community will rightly ask what is being done about the relentlessly rising rates of syphilis, particularly in the absence of successful interventions and falling rates of condom use.[3] Syphilis is a serious infectious disease, with significant ocular, otic, and other neurological complications in about 8% of affected individuals.[4]

The pressure from patients will be substantial. Indeed, health practitioners might find it challenging to tell patients that the benefits of reducing their risk of acquiring syphilis and its substantial complications outweigh the harms of intermittent doxycycline. Patients could rightly argue that the antibiotic is commonly prescribed for many conditions, including in 6-month courses for acne.[5] A key issue to discuss with patients, however, is the number of doses of doxycycline that are required to prevent one case of syphilis. In the present study, men had a median of 120 sexual acts a year (based on a median of 10 per month) and had an incidence of syphilis of about 13 per 100-person years.[1] Most MSM have substantially fewer partners and are less sexually active and have a lower incidence of syphilis than those enrolled in this study, so the number of doses needed for most MSM to prevent a case of syphilis would be higher than reported in this paper.[6]

But although arguments about the individual risks and benefits to patients are important, so too are the population risks and benefits. The global community is desperately trying to reduce antibiotic use in an attempt to slow the seemly inexorable rises in antibiotic resistance, and doxycycline is an important antibiotic for several common infections, including in the respiratory tract, and not just for the treatment of sexually transmitted infections.[7] Data from patients taking doxycycline for acne indicate that its use will lead to doxycycline resistance in other bacteria, including potential pathogens, and calls have been made to limit the use of doxycycline for acne.[5] Theoretical concerns also exist about resistance to syphilis or chlamydia and the inevitable increased resistance to *Neisseria gonorrhoeae*.

However, population-wide benefits could be observed with doxycycline prophylaxis, particularly in the absence of successful interventions to slow the rising incidence of syphilis in MSM.[3] Selective introduction of doxycycline post-exposure prophylaxis for the highest-risk MSM could substantially reduce the reproductive rate for



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syphilis in MSM, and hence the rates of syphilis might fall significantly. Indeed, modelling has shown that doxycycline prophylaxis will moderate the incidence of syphilis.[8] However, for large declines to occur, doxycycline prophylaxis needs to be at least 70% effective and be taken by over half of MSM with more than 40 partners a year.[8] Substantial reductions in syphilis in MSM might also lead to simultaneous reductions in heterosexual men if bisexual men are the key bridge to the heterosexual population.[9] For example, the rising rates of syphilis in MSM have been temporarily associated with rising rates in women in the USA,[10] and congenital syphilis has appeared in Victoria, Australia, for the first time since 2004.[11]

Given the absence of data on population-wide benefits and antibiotic resistance, we agree with Molina and colleagues that any recommendation in favour of doxycycline prophylaxis is premature. The absence of a recommendation, however, will not prevent clinicians from prescribing doxycycline in individual circumstances, but we should use this use of doxycycline as an opportunity to accurately define the risks and benefits of doxycycline prophylaxis in this setting.

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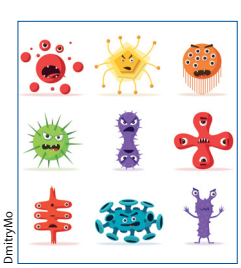
A crucial list of pathogens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In this issue of *The Lancet Infectious Diseases*, Evelina Tacconelli and colleagues, and the WHO Pathogens Priority List Working Group,[1] describe how WHO created a priority list of antibiotic-resistant bacteria to support research into and development of effective drugs. The authors used a multicriteria decision analysis method to prioritise antibiotic-resistant bacteria: 20 bacterial species with 25 patterns of acquired resistance and ten criteria to assess priority were used to generate the list.

The authors are to be commended on the development of a sound scientific approach to the identification of problem pathogens. Through the establishment of the WHO priority list of antibiotic-resistant bacteria, the authors aim to affect the long-term antibiotic research and development plans of pharmaceutical companies and research centres, and to reduce the burden of antibiotic-resistant infections. The list is the fourth such effort in the past 5 years.[2–4] It is easy to criticise these often labour-intensive projects—as Reuters[5] did of the US Centers for Disease Control and Prevention list and de Kraker[6] of the O'Neill report—but it is important that their merits are also discussed.

The statistical approach used by Tacconelli and colleagues[1] to establish the list of antibiotic-resistant bacteria was of the highest standard, with multiple experts enlisted to provide input into a complex process. A factor that stood out was the use of six WHO regions to support the overall process. From the perspective of antibiotic resistance, the Americas and