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We declare that we have no conflicts of interest.

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Attention prescribers: be careful with antibiotics

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Microbiologists have known for some time that exposure to antimicrobial drugs leads to antimicrobial resistance. But trying to convince our scientific colleagues has not been easy. Quite simply, antibiotic consumption is difficult to measure accurately, along with surveillance of the corresponding resistance rates in different populations. These problems have led to the evidence being associative and not necessarily causal. The need to prove the link between antimicrobial consumption and increasing resistance has now gained momentum and the report by Surbhi Malhotra-Kumar and colleagues¹ in today's *Lancet* provides a robust challenge to attitudes

that maintain ambivalence over the consequences of inappropriate and uncontrolled antibiotic prescribing.

Malhotra-Kumar and co-workers undertook a randomised, double-blind, placebo-controlled study designed to satisfy scientists and persuade even the most disengaged of clinical readers. The effect of two macrolide antibiotics, azithromycin (500 mg once daily for 3 days) and clarithromycin (500 mg twice daily for 7 days), was measured against placebo in four groups of volunteers by use of oral streptococci as model organisms.¹ The researchers recorded a clearly defined effect on commensal pharyngeal streptococci, with both drugs selecting for macrolide resistance. Additionally, each antibiotic exerted its own distinctive selection pressure—azithromycin selected quantitatively more resistant organisms in the early post-therapy phases, whereas clarythromycin qualitatively selected for the higher resistance-conferring *erm(B)* gene. The acquisition of *erm(B)* represents a more efficient resistance mechanism for the organism. Not only does it confer increased resistance to the macrolide group of antibiotics, but it also induces resistance to the lincosamide, streptogramin B, and tetracycline groups. Just as acquisition of the *mec(A)* gene in *Staphylococcus aureus* wipes out susceptibility to flucloxacillin and all other β -lactam drugs, clarythromycin also seems to aid the acquisition of a whole package of resistance advantages for streptococci.



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Oral streptococci include *Streptococcus pneumoniae*, a normal inhabitant of the mouth and pharynx. The findings from Malhotra-Kumar and co-workers' study¹ imply that exposure to macrolides could encourage resistance in this community-associated pathogen. Perhaps we now have a reason for the varied rates of macrolide resistance in pneumococci across Europe.² Of course, penicillin is more often the drug of choice for the treatment of pneumococcal sepsis, but the potential for an allergic reaction to penicillin makes the macrolide antibiotics a popular and reliable alternative for family practitioners. Increased resistance will compromise treatment options greatly. Exposure to macrolides could also encourage resistance in *Streptococcus pyogenes*, another streptococcal pathogen found in the pharyngeal flora.

The UK has had a concerted drive to reduce antimicrobial prescribing in the community, especially for the management of infections in the upper respiratory tract. Reduced consumption of these drugs is clearly a result of this directive.³ The drive could even have affected penicillin resistance in pneumococci, which has remained at a consistently lower rate in the UK than in many other European countries.⁴ However, macrolide resistance is higher and more variable among pneumococci in the UK, in company with the rest of Europe. Clinical indications for erythromycin and clarythromycin encompass a far wider spectrum of disease than respiratory-tract infections, and the targeting of macrolide consumption in the community will need more than just a prescribing campaign. Indeed, if macrolide use was discouraged because of concern over their resistance potential, patients might end up receiving a drug that is more toxic, more expensive, and perhaps even better at selecting for resistance.

Malhotra-Kumar and colleagues should be commended for their careful and conscientious approach to providing the evidence we need to control antimicrobial prescribing.¹ Antibiotic use is driving antibiotic resistance at all levels, whether in an individual, on a ward, in a hospital, across a country, or throughout the international community.⁵⁻⁹ Such studies usually focus on the effect in human beings, but additional short-term and long-term effects of antibiotic consumption also occur in animals and various different environments.^{10,11} Even the antibiotics

consumed on a hospital ward can affect the amount and type of resistance in environmental organisms found on floors and hand-touch surfaces.¹² The key message is that antibiotic prescribing affects the patient, their environment, and all the people that come into contact with that patient or with their environment.¹³ Doctors who understand this point can influence the risk of antimicrobial resistance, not only for our current patients but also for patients in the future.

We now have strengthened evidence for the links between antibiotic use and resistance. Our only response to the delay in proving this association should be to get on and do something about it before the antibiotic era finally grinds to its apocalyptic halt.

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I declare that I have no conflict of interest.

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