Antibiotic resistance—to treat...

To the editor—The medical community has been criticized frequently for contributing to a pandemic of antibiotic resistance by overprescribing antibiotics, and reduced antibiotic use has been suggested as one solution to the growing problem of antibiotic resistance¹. However, it is important to note that reducing treatment rates is not a viable option for many infections that, if left untreated, have serious morbidity effects and high fatality rates. Using a previously published theoretical framework for tuberculosis^{2–4}, we show that it is in fact possible (in certain circumstances) to increase antibiotic use and simultaneously reduce antibiotic resistance.

Drug-resistant tuberculosis cases can be treated, but the efficacy of treatment of drug-resistant cases is reduced compared with that of drug-sensitive cases. We have developed an epidemic model that can be used to predict the differential effects of treatment on drug-sensitive and drug-resistant strains of *Mycobacterium tuberculosis*^{2–4}. Here we apply the model to predict the effects of increasing antibiotic use levels (horizontal axis) on the prevalence of tuberculosis (vertical axis), the dotted lines show the prevalence of the drug-sensitive and the drug-resistant strains and the solid line shows the overall prevalence of disease (see Fig.). The predicted epidemics differ only in the efficacy of treatment of drug-resistant cases (low in *a* and fairly high in *b*). As shown, increasing antibiotic use can result in two very different outcomes: the

Fig. Predictions derived from a model that links the transmission dynamics of drug-sensitive and drug-resistant strains of *M. tuberculosis*^{2–4}. The predicted epidemics in *a* and *b* differ only in the efficacy of treatment of drug-resistant cases. In *a*, the minimum prevalence of disease occurs at moderate treatment rates; and very high levels of antibiotic use will lead to a paradoxical effect (increasing prevalence of disease). However in *b*, the minimum prevalence of disease (and levels of antibiotic resistance) occurs at a high treatment rate.

'conventional wisdom' outcome (*a*) and the 'unconventional wisdom' outcome (*b*). If treatment efficacy of drug-resistant tuberculosis is low, then increasing antibiotic use results in monotonically increasing levels of antibiotic resistance (*a*) and the prevalence of antibiotic resistance could only be decreased if levels of antibiotic use were decreased. However, if the treatment efficacy of drug-resistant cases is fairly high (but still lower than that of drug-sensitive cases), levels of antibiotic resistance could be decreased by increasing antibiotic use, from a moderate to a high level (*b*). Under such conditions, increasing antibiotic use would monotonically reduce the prevalence of disease, and could eliminate both drug-sensitive and drug-resistant epidemics of *M. tuberculosis* (*b*).

It is essential to treat life-threatening infections, but fortunately, increasing levels of antibiotic resistance are not necessarily always a consequence of increasing antibiotic use.

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...or not to treat?

To the editor—An earlier article emphasized the need to carefully reconsider the use of antibiotics in medicine and to complete the body of scientific evidence before any specific prescribing or control policy is effected¹. In orthopedic surgery, the use of antibiotics is common in joint replacement with biomaterials. The biofilm mode of growth protects infectious microorganisms on implants against the host immune system and antibiotics⁵. Therefore, infected orthopedic implants must be removed from the patient and the infection cured before a new implant can be placed. To prevent implant-related infections, about 90% of the orthopedic surgeons in the US use prophylactic antibiotic-releasing bone cements, even though it is known that these cements only release up to 10% of the antibiotic incorporated and little is known

about the antibiotic concentration around an actual orthopedic implant in the body^{6,7}. Most surgeons are aware of the lack of scientific evidence regarding the efficacy of antibiotics in these applications but nonetheless use antibiotic-loaded bone cements "to be on the safe side."

Recently, a 67-year-old patient of the University Hospital Groningen complained of pain associated with a hip prosthesis that was cemented in his right hip 4 years earlier. His left hip was revised 5 years ago with gentamicin-impregnated cement and was without symptoms. X-rays showed loosening of the right hip prosthesis and, consequently, the hip was revised. As the removed hip was covered with a slimy layer positive for Gram staining, 60 gentamicin-loaded cement beads were left in the patient, as is usual in these cases, to cure the

infection. After 2 weeks, the gentamicin-loaded cement beads were removed aseptically, and a gentamicin-resistant staphylococcal strain was isolated from them.

This observation evokes the question "Did we help this patient or did we stimulate the development of an antibiotic-resistant strain in his body?" Without overinterpreting this single case, the adhesion and growth of a staphylococcal strain on gentamicin-loaded bone cement beads in a patient is worrisome. Given the growing doubts about the efficacy of prophylactic use of antibiotic-releasing cements for the fixation of implants, the conclusion seems to be justified that the current generation of antibiotic-releasing bone cements contribute to the development of antibiotic resistance, as their release rates are insufficient.

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