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- 1 Dhallan R, Guo X, Emche S, et al. A non-invasive test for prenatal diagnosis based on fetal DNA present in maternal blood: a preliminary study. *Lancet* 2007; published online Feb 2. DOI:10.1016/S0140-6736(07)60115-9.
- 2 Lo YM, Corbetta N, Chamberlain PF, et al. Presence of fetal DNA in maternal plasma and serum. *Lancet* 1997; **350**: 485–87.
- 3 Costa JM, Benachi A, Gautier E. New strategy for prenatal diagnosis of X-linked disorders. *N Engl J Med* 2002; **346**: 1502.
- 4 Bianchi DW, Avent N, Costa JM, van der Schoot CE. Non invasive prenatal diagnosis of fetal rhesus D: ready for prime(r) time. *Obstet Gynecol* 2005; **106**: 841–44.
- 5 Tong YK, Ding C, Chiu RW, et al. Noninvasive prenatal detection of fetal trisomy 18 by epigenetic allelic ratio analysis in maternal plasma: theoretical and empirical considerations. *Clin Chem* 2006; **52**: 2194–202.
- 6 Li Y, Wenzel F, Holzgreve W, Hahn S. Genotyping fetal paternally inherited SNPs by MALDI-TOF MS using cell-free fetal DNA in maternal plasma: influence of size fractionation. *Electrophoresis* 2006; **27**: 3889–96.
- 7 Tsui NB, Chiu RW, Ding C, et al. Detection of trisomy 21 by quantitative mass spectrometric analysis of single-nucleotide polymorphisms. *Clin Chem* 2005; **51**: 2358–62.
- 8 Lo YM, Tein MSC, Lau TK, et al. Quantitative analysis of fetal DNA in maternal plasma and serum: implications for noninvasive prenatal diagnosis. *Am J Hum Genet* 1998; **62**: 768–75.
- 9 Dhallan R, Au WC, Mattagajasingh S, et al. Methods to increase the percentage of free fetal DNA recovered from the maternal circulation. *JAMA* 2004; **291**: 1114–19.
- 10 Lo YM, Tsui NB, Chiu RW, et al. Plasma placental RNA allelic ratio permits noninvasive prenatal chromosomal aneuploidy detection. *Nat Med* 2007; published online Jan 7. DOI:10.1038/nm1530.
- 11 Anon. ACOG practice bulletin no. 77: screening for fetal chromosomal abnormalities. *Obstet Gynecol* 2007; **109**: 217–27.
- 12 Malone FD, Canick JA, Ball RH, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. *N Engl J Med* 2005; **353**: 2001–11.

## 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 colleagues<sup>1</sup> 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.<sup>1</sup> 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  $\beta$ -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' study<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>1</sup> 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.<sup>5-9</sup> 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.<sup>10,11</sup> 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.<sup>12</sup> 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.<sup>13</sup> 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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- 1 Malhotra-Kumar S, Lammens C, Coenen S, Van Herk K, Goossens H. Effect of azithromycin and clarythromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet* 2006; **369**: 482-90.
- 2 European Antimicrobial Resistance Surveillance System (EARSS) Annual Report. Bilthoven, Netherlands: Rijksinstituut voor Volksgezondheid en Milieu (RIVM), 2004.
- 3 Majeed A, Wrigley T. Antibiotic prescribing rates in England are falling. *BMJ* 2002; **325**: 340.
- 4 Vardhan MS, Allen KD, Bennett E. Antibiotic prescribing and penicillin-resistant pneumococci in a Merseyside Health District. *J Infect* 2003; **46**: 30-34.
- 5 Muller A, Mauny F, Talon D, Donnan PT, Harbarth S, Bertrand X. Effect of individual- and group-level exposure on MRSA isolation: a multilevel analysis. *J Antimicrob Chemother* 2006; **58**: 878-81.
- 6 Schentag JJ, Hyatt JM, Carr JR, et al. Genesis of methicillin-resistant *Staphylococcus aureus* (MRSA), how treatment of MRSA infections has selected for vancomycin-resistant *Enterococcus faecium*, and the importance of antibiotic management and infection control. *Clin Infect Dis* 1998; **26**: 1204-14.
- 7 Meyer E, Jonas D, Schwab F, Gastmeier P, Ruden H, Daschner FD. SARI: surveillance of antibiotic use and bacterial resistance in German intensive care units: correlation between antibiotic use and the emergence of resistance. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2004; **47**: 345-51.
- 8 MacDougall C, Powell JP, Johnson CK, Edmond MB, Polk RE. Hospital and community fluoroquinolone use and resistance in *Staphylococcus aureus* and *Escherichia coli* in 17 US hospitals. *Clin Infect Dis* 2005; **41**: 435-40.
- 9 Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365**: 579-87.
- 10 Smith DL, Harris AD, Johnson JA. Animal antibiotic use has an early but important impact on the emergence of antibiotic resistance in human commensal flora. *Proc Natl Acad Sci USA* 2002; **99**: 6434-39.
- 11 Kummerer K. Significance of antibiotics in the environment. *J Antimicrob Chemother* 2003; **52**: 5-7.
- 12 Dancer SJ, Coyne M, Robertson C, Thomson A, Guleri A, Alcock S. Antibiotic use is associated with resistance of environmental organisms in a teaching hospital. *J Hosp Infect* 2006; **62**: 200-06.
- 13 Dancer SJ. How antibiotics can make us sick: the less obvious adverse effects of antimicrobial chemotherapy. *Lancet Infect Dis* 2004; **4**: 611-19.