Society's failure to protect a precious resource: antibiotics

Jean Carlet, Peter Collignon, Don Goldmann, Herman Goossens, Inge C Gyssens, Stephan Harbarth, Vincent Jarlier, Stuart B Levy, Babacar N'Doye, Didier Pittet, Rosana Richtmann, Wing H Seto, Jos W M van der Meer, Andreas Voss

Since their discovery last century, antibiotics have served society well by saving tens of millions of lives. Too many individuals—including illustrious composers and writers such as Schubert, Mahler, Mozart, and Wilde—died prematurely in the pre-antibiotic era from bacterial infections that are now treatable. Antibiotics are called miracle drugs because they kill bacteria, and thereby cure people of potentially fatal infectious diseases. Antibiotics are also unique drugs, because they act not only on the bacteria causing the infections, but also on a myriad of commensal bacteria, which can then disseminate widely, creating a reservoir of resistant organisms.

Unfortunately, from the moment antibiotics were discovered, they have been used excessively and with little attention to the inevitable consequence of resistance. Although they are a treasure for all humanity, they have been regarded as inexhaustible gifts, without full appreciation that they are a limited resource that can be renewed only with great difficulty and expense. More recently, antibiotic discovery and development has almost stopped, in part because of a vast underestimation of the implications of antibiotic resistance. Some people pointed out the potential of indiscriminate antibiotic use to give rise to resistant bacteria,[1] but these warnings had limited effect on practice. Additionally, although we focus on resistance to antibiotics here, it should be borne in mind that resistance is also a problem for most antimicrobials, including agents used for treating parasites, fungi, mycobacteria, and viruses.

In view of the casual attitude towards antibiotics that prevails, it is hardly surprising that resistance has increased worldwide over the past few decades, closely correlated with their usage.[2] Antibiotic use facilitates both the development and spread of resistant bacteria in the community, hospitals, and long-term care facilities. Only a few countries have had the foresight to implement more stringent policies and programmes to prevent or mitigate the emergence and spread of resistance by reducing inappropriate antibiotic use, and improving hygiene standards to prevent cross transmission.[3] However, even in these more careful countries, resistance can still be an issue, often after the importation of multiresistant bacterial strains[4] or the overuse of antibiotics in farmed animals.[5]

There are many alarming examples of increasing resistance in bacteria that commonly infect patients in the community and health-care settings. Among gram-positive bacteria, meticillin-resistant *Staphylococcus aureus* (MRSA) has attracted media and public policy attention.[6] Some MRSA strains have shown a disturbing creep towards resistance to glycopeptides and some of the more recently introduced agents, such as daptomycin and oxazolidinones.[7] Community-acquired MRSA strains have spread globally, and are also now becoming increasingly common in healthcare settings. Glycopeptide-resistant enterococci are a concern in many countries, and new mechanisms of resistance continue to develop.[8]

The resistance problem is even worse for gram-negative bacteria, both in community and hospital settings. Gonococci, which were easily treated until recently with standard antibiotics, are becoming more resistant to fluoroquinolones and cephalosporins.[9] *Salmonella*, many strains of which have become resistant to many antibiotics, complicate treatment—especially in countries where access to remaining effective antibiotics is limited.[10] Mounting resistance in *Enterobacteriaceae*, such as *Escherichia coli* and *Klebsiella pneumoniae*,[11] complicates the treatment of common community-acquired infections. Although third-generation cephalosporin resistance in *E coli* is still below 5% in many European countries, it has increased substantially in others, exceeding 25% and even reaching 50% in bacteria isolated from invasive infections in the European Antimicrobial Resistance network.[3]

In health-care settings, multi-drug resistance in gram-negative bacillary infections has severely restricted therapeutic options, and sometimes no effective drugs are available to treat life-threatening infections.[12] Advanced cephalosporins can no longer be used as empirical therapy in many countries. Hence, carbapenems, an antibiotic class that represents the last available weapon against many gram-negative bacilli, are being used increasingly for empirical therapy. Resistance to these agents will accelerate if carbapenems become standard first-line therapy worldwide, particularly in intensive care, where selective pressure and transmission risks are highest. *Pseudomonas aeruginosa* and *Acinetobacter* species can be highly resistant to ceftazidime, fluoroquinolones, and carbapenems. An increasing number of organisms are resistant to all antibiotics, including colistin.[12] *K pneumoniae* and *E coli* will probably become increasingly resistant to carbapenems by harbouring carbapenemases or nucleoside diphosphate enzymes, such as the New Delhi metallo-betalactamase (NDM1).[13] The spread of these resistant gram-negative organisms should be regarded as a growing but insufficiently publicised pandemic.

Some drug resistance among *Enterobacteriaceae* came from the use of antibiotics in animals in the retail food chain. *E coli* and *Salmonella* strains resistant to fluoroquinolones and third-generation cephalosporins have been associated with meat and poultry products.[14] The non-therapeutic use of antibiotics in animals

Lancet 2011; 378: 369–71
Published Online
April 7, 2011
DOI:10.1016/S0140-6736(11)60401-7

WHO, African Partnership for Patient Safety programme, Paris, France (J Carlet MD); **Infectious Diseases Unit and Microbiology Department, The Canberra Hospital, and School of Clinical Medicine, Australian National University, Woden, ACT, Australia** (Prof P Collignon MB); **Institute for Healthcare Improvement, Cambridge, MA, USA, and Division of Infectious Diseases, Children's Hospital Boston and Harvard Medical School, Boston, MA, USA** (D Goldmann MD); **Laboratory of Medical Microbiology, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium** (H Goossens MD); **Department of Internal Medicine and Medical Microbiology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands** (I C Gyssens MD, J W M van der Meer MD); **Hasselt University, Diepenbeek, Belgium** (I C Gyssens, A Voss MD); **Infection Control Program and WHO Collaborating Centre on Patient Safety, University of Geneva Hospitals and Faculty of Medicine, University of Geneva, Geneva, Switzerland** (S Harbarth MD, Prof D Pittet MD); **Bactériologie-Hygiène Pitié Salpétrière Hospital, Assistance Publique–Hôpitaux de Paris (AP–HP), UPMC Université de Paris, Paris, France** (V Jarlier MD); **Center for Adaptation Genetics and Drug Resistance and Departments of Molecular Biology/Microbiology and Medicine, Tufts University School of Medicine, Alliance for the Prudent Use of Antibiotics, Boston, MA, USA** (S B Levy MD); **Programme National de Lutte contre les Infections Nosocomiales (PRONALIN), Ministère de la Santé et de la Prévention, Dakar, Senegal** (B N'Doye MD); **Infectious Diseases Department, Emilio**

Ribas Infectious Diseases Institute, Sao Paulo, Brazil (R Richtmann MD); **and Department of Quality and Safety, Hong Kong Hospital Authority, SAR Hong Kong, China** (Prof W H Seto MD)

Correspondence to:
Dr Jean Carlet, 9 rue de la Terrasse, 94000 Creteil, France
jeancarlet@gmail.com

continues to increase, despite recommendations from WHO[15] and others to have this practice stopped, as has been done in the European Union.

Faced with these daunting therapeutic challenges, physicians in some countries have had to resort to antibiotics with unfavourable toxicity profiles and limited pharmacodynamic guidance (eg, colistin),[16] as well as unconventional combinations of antibiotics that have not been investigated properly. Old ideas are being resurrected, such as the use of lytic bacteriophages, but with little evidence of clinical effectiveness. New approaches, such as defensins, targeted monoclonal antibodies, and agents designed to interrupt mechanisms of pathogenesis (eg, toll-like receptors, quorum sensing) have yet to fulfill their therapeutic potential. Essentially, even as we are forced to revisit treatments that are more than 30 years old while waiting desperately for new research to bear fruit, we sense a pervasive belief in the scientific community that increasing resistance is the new norm. This is a misleading and costly attitude, both in human and economic terms.

Some action has been taken in response to the mounting crisis. For example, the Infectious Diseases Society of America,[17] US Centers for Disease Control and Prevention (CDC),[18] European commission,[19] European Centre for Disease Prevention and Control (ECDC),[20] and other expert groups and non-governmental organisations have worked hard to raise awareness and provoke action by government and industry. National awareness campaigns to educate the public and health-care workers about appropriate outpatient antibiotic use have been undertaken in many countries.[21] The effect of these campaigns in curbing antibiotic use is difficult to assess, but seems positive.[21] The ECDC holds a European Antibiotic Awareness Day (EAAD) on Nov 18 each year.[22] In 2010, Canada joined the EAAD, and the CDC Get Smart programme was highlighted during the same week in November as the EAAD. Under the Swedish presidency of the European Union, a cooperative venture was set up between the USA and Europe in 2009 (the Transatlantic Task Force for Antibiotic Resistance). WHO has also voiced its serious concern by designating antimicrobial resistance as the focus of World Health Day on April 7, 2011.

Unfortunately, it is doubtful that these efforts will have the resources, leverage, and influence on policy makers to have a meaningful effect on antibiotic use and resistance. How high-level recommendations can have a global effect on antibiotic prescribing and transmission control in the real world of physicians' offices, hospital wards, and long-term care facilities is not clear. Nor is it clear how these efforts can change public attitudes about antibiotic use. Those leading these international efforts urgently need to develop an understanding and recognition of the most successful approaches, wherever they are working, so that these strategies can be repeated and spread. It will be very useful to examine how the attitudes, culture, and practices of one community can be transferred to another, and how stewardship programmes in one country can be implemented in diverse settings.[21] For example, how will the strict infection-control standards in northern European countries have to be amended to be palatable and effective in other nations? Words and pronouncements will not be sufficient to bend the antibiotic resistance curve and preserve what remains of a precious therapeutic resource that benefits all humanity.

No matter how vigorous and successful the efforts to combat antibiotic resistance might be, new antibiotics will still be urgently needed.[17,20,23] Since the net present value of antibiotics is low, the development of new antibiotics is not a high priority for pharmaceutical companies. New approaches to overcoming the barrier to drug development have been proposed, including orphan drug benefits, government support for antibiotic development, prolonged patents, expedited approval, and other strategies.[17] Again, talk will not be enough, and efforts to stimulate new antibiotic development must be paired with even more aggressive programmes and policies to limit inappropriate use in human beings, animal husbandry, and aquaculture.

For practising physicians, the call for responsible action is especially acute and personal. Clinical work is founded on principles of professionalism and stewardship.[24] Our responsibility is both collective and personal. People still misuse, and physicians still prescribe, antibiotics to treat viral infections. Health-care providers still treat infections, such as pneumonia and sinusitis, longer than indicated by the latest evidence, and fail to de-escalate antibiotic therapy promptly on the basis of culture results and sensitivity testing.[24] We should be raising our voices to curtail the widespread use of crucial antibiotics in food production animals. We should argue for the need to strengthen local, national, and international global antimicrobial use and resistance surveillance. We should work with our institutions and health systems to ensure fastidious adherence to antibiotic use policies, hand hygiene, and other important infection-control measures.[25]

We have watched too passively as the treasury of drugs that has served us well has been stripped of its value.[26] We urge our colleagues worldwide to take responsibility for the protection of this precious resource. There is no longer time for silence and complacency.

Contributors

JC, DP, IG, and JWMvdM conceived the idea for the paper. JC wrote the paper with critical contributions from DP, SL, DG, PC, and input from IG, AV, HG, JWMvdM, SH, VJ, BN, RR, and WHS. All authors had full access to all the data in the study, and read and approved the final version. The corresponding author had final responsibility for the decision to submit for publication.

Conflicts of interest

We declare we have no conflicts of interest.

References

1 Kunin CM, Tupasi T, Craig WA. Use of antibiotics: a brief exposition of the problem and some tentative solutions. *Ann Intern Med* 1973; **79:** 555–60.

2 Goossens H, Ferech R, Van der Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross national database study. *Lancet* 2005; **365:** 579–87.

3 European Centre for Disease Prevention and Control. EARS-Net Database. http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.aspx (accessed March 4, 2011).

4 Kennedy K, Collignon P. Colonisation with *Escherichia coli* resistant to "critically important" antibiotics: a high risk for international travellers. *Eur J Clin Microbiol Infect Dis* 2010; **29:** 1501–506.

5 Grave K, Torren-Edo J, Mackay D. Comparison of the sales of veterinary antibacterial agents between 10 European countries. *J Antimicrob Chemother* 2010; **65:** 2037–40.

6 Boucher H, Miller LG, Razonable RR. Serious infections caused by methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 2010; **51:** S183–97.

7 van Hal SJ, Paterson DL, Gosbell IB. Emergence of daptomycin resistance following vanvomycin-unresponsive *Staphylococcus aureus* bacteremia in a daptomycin-naïve patient-a review of the literature. *Eur J Clin Microbiol Infect Dis* 2010; Published online Dec 30. DOI:10.1007/s10096-010-1128-3.

8 Johnson PD, Ballard SA, Grabsch EA, et al. A sustained hospital outbreak of vancomycin-resistant *Enterococcus faecium* bacteremia due to the emergence of van B *E faecium* sequence type 203. *J Infect Dis* 2010; **202:** 1278–86.

9 Chisholm SA, Mouton JW, Lewis DA, et al. Cephalosporin MIC creep among gonococci: time for a pharmacodynamic rethink. *J Antimicrob Chemother* 2010; **65:** 2141–48.

10 Uma B, Prabhakar K, Rajendran S, et al. Prevalence of extended spectrum beta lactamases in *Salmonella* species isolated from patients with acute gastroenteritis. *Indian J Gastroenterol* 2010; **29:** 201–204.

11 Ofner-Agostini M, Simor A, Mulvey M, et al. Risk factors for and outcomes associated with clinical isolates of *Escherichia coli* and *Klebsiella* species resistant to extended-spectrum cephalosporins among patients admitted to Canadian hospitals. *Can J Infect Dis Med Microbiol* 2009; **20:** 43–48.

12 Koo SH, Kwon KC, Cho HH, Sung JY. Genetic basis of multi-resistant *Acinetobacter baumannii* clinical isolates from three university hospitals in Chungcheong Province, Korea. *Korean J Lab Med* 2010; **30:** 498–506.

13 Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010; **10:** 597–602.

14 Li J, Ma Y, Hu C et al. Dissemination of cefotaxime-M producing *Escherichia coli* isolates in poultry farms, but not in swine farms, in China. *Foodborne Pathog Dis* 2010; **7:** 1387–92.

15 Collignon P, Powers JH, Chiller TM, Aidara-Kane A, Aarestrup FM. World Health Organization ranking of antimicrobials according to their importance in human medicine: a critical step for developing risk management strategies for the use of antimicrobials in food production animals. *Clin Infect Dis* 2009; **49:** 132–41.

16 Jajoo M, Kumar V, Jain M, Kumari S, Manchanda V. Intravenous colistin administration in neonates. *Pediatr Infect Dis J* 2011; **30:** 218–21.

17 Infectious Diseases Society of America. Bad bugs, no drugs. http://www.idsociety.org/workarea/showcontent.aspx?id=5554 (accessed March 4, 2011).

18 United States Centers for Disease Prevention and Control. Get Smart programme. http://www.cdc.gov/getsmart (accessed Dec 4, 2010).

19 Council of the European Union. Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC). *Official Journal of the European Communities L34* 2002; **45:** 13–16.

20 European Centre for Disease Prevention and Control and European Medicines Agency. ECDC/ EMEA Joint Technical Report. The bacterial challenge: time to react. http://ecdc.europa.eu:en:publications/forms/ECDC dispForm.aspx?ID=444 (accessed March 4, 2011).

21 Huttner B, Goossens H, Verheij TJ, Harbarth S. Characteristics and outcomes of public health campaigns with the aim to improve outpatient antibiotic use in high income countries. *Lancet Infect Dis* 2010; **10:** 17–31.

22 Earnshaw S, Monnet DL, Duncan B, et al. European antibiotic awareness day 2008: the first Europe-wide public information campaign on prudent antibiotic use; methods and survey activities in participating countries. *Eurosurveillance* 2010; **14:** 23–30.

23 Hughes JM. Preserving the lifesaving power of antimicrobial agents. *JAMA* 2011; **305:** 1027–28.

24 Dellit TH, Owens RC, McGowan JE, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; **44:** 159–77

25 Seto WH, Otaiza F, Pessoa-Silva CL, World Health Organization infection prevention and control network. Core comp onents for infection prevention and control programs: a World Health Organization networks report. *Infect Control Hosp Epidemiol* 2010; **31:** 948–51.

26 Hulscher ME, Grol RP, van der Meer JW. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. *Lancet Infect Dis* 2010; **10:** 167–75.