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Antibiotic resistance: long-term solutions require action now

A crisis looms. In the very near and rapidly approaching future, the wonder-drugs of the 20th century, antibiotics, may cease to be useful. The benefits of antibiotics hardly need to be restated, but their availability has contributed to major advances in health and substantially increased life expectancy. Yet, despite warnings from many, including Alexander Fleming, that resistance would be a problem, antibiotics have been used with great profligacy—prescribed pointlessly for viral infections, added to animal feed to boost growth of livestock, and handed out like cough sweets in the community.

The antibiotic soup that now permeates health-care facilities, farms, and our bodies, has exerted a selection pressure on pathogens and commensal organisms alike, and resistance has proliferated and spread such that many bacteria can withstand almost all drugs. The golden age of antibiotic discovery, when the rate of discovery of new molecules kept pace with bacterial innovation, is now a distant memory, and the drug discovery pipeline for antibiotics is not so much dry as arid.

Against this bleak backdrop, the global activities of Antibiotic Awareness Week, starting November 18, seek to draw attention to a dire situation that threatens to take us back to a preantibiotic era. For our part, *The Lancet Infectious Diseases* launches a Commission, entitled *Antibiotic resistance—the need for global solutions*. The goal of the Commission is not to convince readers that there is an urgent problem with dire consequences if we do not act now. Our readers know this. Rather, the Commission explores why antibiotic resistance has become such a problem worldwide, and, most importantly, proposes solutions to avert the impending crisis.

The Commission is a collaboration coordinated by the journal under the guidance of Otto Cars, who, as the head of ReAct, has done more than almost anyone to put antibiotic resistance on the global policy and research agendas. The journal editors are incredibly grateful for Otto's insight, guidance, and tireless enthusiasm for the project.

In deciding what to cover in the Commission, we also had to decide what to leave out—from the starting point of wanting to address the issue of antimicrobial resistance, we quickly decided to focus on Gram-negative and Gram-positive bacteria to the exclusion of tuberculosis. To include drug resistance in tuberculosis would lead to a lack of focus. Indeed, drug-resistant tuberculosis could easily be the subject of a Commission on its own.

Having chosen the overarching theme, we selected the topics to cover. Antibiotic resistance arises because of actions in health care, the pharmaceutical industry, agriculture, and the community. Through a complex web, the effects of resistance are also felt in all these realms. This is partly the reason for producing a Commission rather than a series of separate articles, to reflect the interconnectedness of the problem. We recruited experts in the various topics and asked them to write pieces focusing on how we got to this point and potential solutions to the problem. The individual contributions were peer-reviewed, revised, and assembled into a single document. Naturally there was some overlap between sections, and although we have endeavoured to remove redundancies, some topics recur from different perspectives. Analysis of these points of intersection may provide clues to opportunities for collaboration and intervention.

The final section of the Commission, a call to action, identifies specific points for which urgent responses are needed as well as longer-term goals. Successful examples of hospital stewardship, responsible use in agriculture, provision of access in countries with weak health systems, community education, and environmental management provide templates that can be tailored to new settings now. Other areas, however, need far greater innovation and radical thinking. We have seemingly exhausted the potential of the antibiotic classes in use so far, and new drugs—either antibiotics or from other approaches—are needed, but academia and pharmaceutical companies have not focused on this problem for so long that antibacterial drug-development programmes have withered. To stimulate drug discovery, novel incentives for industry and new approaches to funding, licensing, and patenting may be needed.

The Commission is launched at a pivotal time when there is global academic, industry, and governmental recognition that action is urgently required. To maintain and build on current interest, antibiotic resistance should feature prominently in discussions of post-2015 development goals. We hope that the Commission will provide encouragement that, although the picture is bleak, there is hope. ■ *The Lancet Infectious Diseases*

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Antibiotic resistance in Ghana

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Ghana's 24·5 million people face a double disease burden of communicable and non-communicable diseases equally causing morbidity and mortality. Malaria, HIV/AIDs, neonatal diseases, maternal issues, diabetes, cardiovascular diseases, cancers, and diahorreal diseases are the major causes of mortality. Among bacterial infections, the most important pathogens are *Escherichia coli, Klebsiella* spp, *Salmonella* spp, pneumococci, and *Staphylococcus aureus*.

In 2007, Enweronu-Laryea and Newman[1] found that minimum inhibition concentration for these pathogens to basic antibiotics like cefuroxime, ciprofloxacin, and gentamicin suggested some level of resistance, likely to erode substantial gains made in infection control and treatment. Since 2007, no more studies were done until the establishment of the Antibiotic Drug Use and Monitoring and Evaluation of Resistance (ADMER) project in March 2010, with support from the Danish Ministry of Foreign Affairs.

Although *E coli* and *Klebsiella* spp remain the main challenge, intestinal colonisation by organisms capable of producing extended spectrum β lactamases (ESBLs) is becoming a worrying problem. The widespread use of cephalosporins, hospital-acquired infections, and CTX-M15-producing *E coli* are also big problems. Resistance of *Salmonella* spp to commonly used antibiotics such as chloramphenicol, ampicillin, and tetracycline, is widespread (LA Andoh, ADMER, personal communication). Obeng-Nkrumah and co-workers[2] found that more than 87% of salmonella strains produce ESBLs. Meticillin-resistant *S aureus* carriage is uncommon, but there is a high risk of nasal carriage of multidrug-resistant *S aureus*.[3]

Monitoring of antibiotic use is poor, with nascent surveillance systems and scarce reporting of treatment failures. Weak regulatory systems generally allow free movement of goods within the Economic Community of West African States. In this setting, the potential negative effects of substandard, spurious, falsely labelled, or falsified counterfeit medical products cannot be overemphasised, but information about such products is generally difficult to obtain or almost unavailable. In Ghana the capacity to link results of laboratory diagnostic tests to selection of medicines is lacking, and immediate action is needed to ensure value for money. Finally, uncontrolled use of antibiotics in agriculture, especially veterinary use, is worrying, and clear evidence and policy directions for the veterinary community are needed. Unfortunately, data are scant.

The establishment of an antimicrobial resistance working group, supported by Swedish International Development Agency, has helped to move research into practice. This working group brings together all researchers, policy makers, non-governmental organisations, civil society groups, media, academia, professional bodies, veterinary practitioners, industry, and those who work in infection prevention, control, and treatment. Civil society is also being engaged through a study to find out knowledge, attitudes, beliefs, and practices to develop appropriate messages and change attitudes to antibiotic use. The continuous review of Standard Treatment Guidelines has also been useful.[4] In 2011, Ghana developed and launched its very first infection-control policy,[5] which sets out basic guidelines and strategies to control infection in our health facilities and households.

For more on the **study to change attitudes on antibiotic use** see http://www.cso.reactgroup.org

For the **ADMER project** see http://www.admerproject.org

Moving policy into action remains a challenge. In February 2012, one of our top teaching hospital's neonatal intensive care unit (Korle Bu Teaching Hospital, Ghana) had to close down because of an MRSA outbreak. The unit reopened after a couple weeks with strict infection control strategies to prevent further outbreaks. The uncontrolled and unregulated private sector is another challenge that could be described as a failed state. Prescription and dispensation are not done on a rational basis, with 41·4% of patients in outpatient departments receiving one or more antibiotics. Economic incentives for prescription have a big effect on the private sector and lead to a weak gatekeeper system, because prescribing levels are not enforced.

There is a strategic need to build capacity for research into key issues related to antibiotic resistance. The ADMER programme and the culture it has engendered could sustain the interest in this topic; so far it has produced eight PhD candidates and several MPhils. The research findings should provide evidence for policy decision making. Surveillance systems should be linked to global actions and initiatives to move the agenda forward both nationally and internationally. To improve surveillance of resistance and drug use, a

small percentage (at least 2%) of funds from President's Emergency Plan For AIDS Relief (PEPFAR) or the Global Fund to Fight AIDS, Tuberculosis and Malaria could be used across their areas of operation.

Rational prescription would be supported by better diagnostic capacity than is available. Improved supply chains with consistent integrity of both diagnostic tests and drugs are urgently needed. Finally, when it comes to any new antibiotic, there must be responsible access to medicines with stringent regulatory mechanisms to curtail misuse. In effect, any new antibiotics would need similar distribution mechanisms to those in place for dangerous drugs.

Martha Gyansa-Lutterodt
Ministry of Health Ghana, Infection Prevention and Control Policy 2011, Accra, Ghana
martha.lutterodt@moh.gov.gh

I declare that I have no conflicts of interest.

1 Enweronu-Laryea CC, Newman MJ. Changing pattern of bacterial isolates and antimicrobial susceptibility in neonatal infections in Korle Bu Teaching Hospital, Ghana. *East Afr Med J* 2007; **84:** 136–40.
2 Obeng-Nkrumah N, Twum-Danso, Krogfelt KA, Newman MJ, High levels of extended-spectrum Beta-lactamases in a major teaching hospital in Ghana: the need for regular monitoring and evaluation of antibiotic resistance. *Am J Trop Med Hyg* 2013; published online Sept 16. DOI:10.4269/ajtmh.12-0642.
3 Egyir B, Guardabassi L, Nielsen SS, et al. Prevalence of nasal carriage and diversity of Staphylococcus aureus among inpatients and hospital staff at Korle Bu Teaching Hospital, Ghana. 2024; published online July 16. DOI:10.1016/j.jgar.2013.05.006.
4 Ministry of Health, Ghana. Standard Treatment Guidelines, 6th edn. 2010. http://apps.who.int/medicinedocs/documents/s18015en/s18015en.pdf (accessed Oct 22, 2013).
5 Ministry of Health, Ghana. National manual for infection prevention and control policy and a standard operating procedure for airborne diseases for healthcare practitioners. Accra: Ministry of Health, Ghana, 2011.

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Antibiotic resistance: global response needed

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In 1945, Sir Alexander Fleming famously warned of the danger of over-reliance on antibiotics and the threat of bacteria developing resistance.[1] 68 years later, his prediction has been realised; in *The Lancet Infectious Diseases* Commission on antibiotic resistance and use,[2] Laxminarayan and colleagues warn that "we are at the dawn of a postantibiotic era", with "almost all disease-causing bacteria resistant to the antibiotics commonly used to treat them".

Rarely has modern medicine faced such a grave threat. Without antibiotics, treatments from minor surgery to major transplants could become impossible, and health-care costs are likely to spiral as we resort to newer, more expensive antibiotics and sustain longer hospital admissions. Infection-related mortality rates in developed countries might return to those of the early 20th century.

This is a global problem, with many examples of the rapid spread of new resistances between continents; however, we lack the surveillance systems and the policy methods needed to tackle it. The paucity of basic information about prescribed antibiotic use is compounded by the fact that antibiotics are used across the world in animal feed and on a non-prescription basis. Indeed, antibiotic sales are sometimes incentivised, with up to a quarter of revenues in some Chinese hospitals deriving from antibiotic sales.[2]

An improvement to antibiotic stewardship is essential. As outlined by Qamar and colleagues, the prescribing behaviour of health-care practitioners is affected by many factors,[2] including demands from patients, the threat of competition from alternative systems of health care, and financial incentives to prescribe. Yet, as Wertheim and coworkers show, because the effect of antibiotic use extends beyond individual patients,[2] there is a public health imperative for use to be closely monitored and regulated.

So and colleagues argue that a balance needs to be struck between limiting the availability of antibiotics and ensuring timely treatment for severe infections.[2] Such a balance is difficult to strike in countries with robust health-care systems, but is exponentially more difficult in those with limited facilities. However, the increasing resistance shown by Enterobacteriaceae, the leading cause of newborn sepsis in developing countries,[2] shows that resistance is a serious threat in these countries. Concerted global action is needed to tackle this problem and, at the same time, ensure equity of access to effective treatments.

Microbiological diagnostic tests help to prevent unnecessary antibiotic use and narrow the spectrum of coverage needed to treat an infection, but these are often slow, and delays in treatment can be associated with increased mortality. Hence, broad-spectrum antibiotic treatment is often used. Development of rapid diagnostics could eliminate this delay, enabling targeted antibiotic or non-antibiotic treatment from the outset. This, and education of prescribers about the importance of making use of the results of such tests, would reduce overuse of broad-spectrum agents, and hence reduce the speed with which resistance develops.

Antimicrobial resistance extends far beyond human medicine: the majority of the 100 000–200 000 tonnes of antibiotics manufactured every year is used in the agricultural, piscicultural, and veterinary sectors.[2] More research is needed on the associations between non-human use of antibiotics and the development of resistance in human beings. Reduction of antibiotic use in animal rearing must be achieved while maintaining the security of the food supply.

Only two new classes of antibiotic have reached the market since the 1970s; Coates and Bergstrom state a clear need exists for the development of new products.[2] However, economic challenges around the potential profitability (and hence incentive to invest in research and development) of new antibiotics remain. Innovative funding solutions are needed to promote research in this specialty, while removing the incentive for pharmaceutical companies to attempt to maximise sales volume of any newly developed product. Figures from the Office of Health Economics show that the value of a new musculoskeletal drug to a pharmaceutical company is likely to be 20 times higher than the value of a new antibiotic, and make the scale of the funding challenge plain. New models of collaboration, including academia, research funders, and not-for-profit organisations, could restart the stalled engine of antibiotic discovery.

The lack of new antibiotics in the pipeline has prompted research on alternative approaches, including new vaccines and new interventions, such as antibiotic adjuvants and antivirulence agents—eg, inhibitors of quorum sensing mediated by diffusible small molecules.

In tackling the threat of antibiotic resistance, we must not underestimate the part that can be played by the

rediscovery of assiduous hygiene practices. The effect of reimplementation of regular and effective hand-washing in health-care settings on incidence rates of meticillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* is well documented.[3] However, this simple message can be spread wider: improved sanitation and hygiene practices in the community are likely to reduce both the burden of infection and the spread of resistant organisms; improved farming hygiene practices would help to reduce non-human use of antibiotics.

It is also important that the public is educated about antibiotic resistance, not only to improve the standard of hygiene in society, but also because measures to mitigate the effect of resistance will involve substantial financial costs. These costs will ultimately be met by the public, both through taxation and, probably, through higher direct costs of products whose manufacturing methods are altered. A pricing paradox exists in farming whereby antibiotics, a scarce natural resource, cost less than implementation of more effective hygiene practices. Reversal of this paradox might lead to higher food prices.

In the UK, a cross-government antimicrobial strategy has been launched. The key elements are: improvement of infection prevention and control practices in human and animal health; optimisation of prescribing practice; improvement of professional education, training, and public engagement; development of new drugs, treatments, and diagnostics; better access to and use of surveillance data; better identification and prioritisation of research into antimicrobial resistance; and strengthened international collaboration. The UK Government is working alongside other governments under the auspices of the WHO to improve global antimicrobial stewardship and surveillance.

Simon J Howard, Mike Catchpole, John Watson, Sally C Davies
Office of the Chief Medical Officer, Department of Health, London, UK (SJH, JW, SCD); and Public Health England, London, UK (MC)
simon.howard@dh.gsi.gov.uk

SCD is chair of the WHO Science and Technical Advisory Group on Antimicrobial Resistance and the Antimicrobial Resistance Forum of the World Innovation Summit for Health. We declare that we have no conflicts of interest.

1 Fleming A. Penicillin. Nobel Lecture Dec 11, 1945. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf (accessed Oct 23, 2013).
2 Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013; published online Nov 17. http://dx.doi.org/10.1016/S1473-3099(13)70318-9.
3 WHO. WHO Guidelines on hand hygiene in health care: a summary. First gobal patient safety challenge. Clean care is safer care. 2009. http://whqlibdoc.who.int/hq/2009/WHO_IER_PSP_2009.07_eng.pdf (accessed Oct 23, 2013).

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Light at the end of the tunnel of antibiotic development

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It is reassuring to see the escalating state of awareness and support regarding antibiotic resistance. Over the past decade, it has become clear that bacteria are eminently armed to outsmart our best efforts to defeat them. The *Lancet Infectious Diseases* Commission on antibiotic resistance[1] covers several themes that are not typically covered when experts are asked to review emergence of resistance among bacteria and the possible consequences.

Several issues have been raised that need to be addressed so various new initiatives not only gain momentum, but also actually succeed. Perhaps one of the most important issues is the true effect of infections on both morbidity and mortality. The number of deaths directly attributable to infection is large, and exceeds many other disorders that have much higher profiles. In fact, the precise number of deaths due to infection as an incidence is poorly defined, but recent estimates of deaths caused by multidrug-resistant organisms exceeded 25 000 in Europe alone.

Infection does not have a clear advocacy group and as such, receives no airplay and little interest or support from the general public. Unless the populace see clear outcome such as increased deaths or hospitalisations, then the relevance of the problem is diluted by the louder advocate groups, such as the cancer and colitis societies.

The big pharmaceutical companies are slowly returning to the therapeutic area—expanding their research teams and resources to identify new molecules and bacterial targets. However, the key to this investment is the implied assurance that the eventually approved antibiotics will, to some extent, repay their investment by being premium priced. The Pew Foundation recently polled various stakeholders and deduced that for drugs approved for a limited population, a course of treatment could exceed US$10 000.[3] As shown by the fidaxomicin story, payers and clinicians are unwilling to prescribe a drug that is better than the current treatment at some endpoint, despite the overall potential cost and health quality savings. Perhaps the newly approved limited population antibiotic drugs are only prescribed when the patient has received many other drugs and is close to death with a low probability of success. The new drugs need to be given sooner to the right patients at the right time.

Companies developing these diagnostic tests have fewer resources than do the large pharmaceutical companies, and development costs of these new assays should be shared. The use of point-of-care tests will improve enrolment of patients in clinical trials (a positive for the pharmaceutical industry in many ways), might reduce empiricism, and could reduce overall management costs, length of stay in hospitals or specialist units, and even mortality. However, the regulatory process for diagnostics needs help. New tests must be accurate, specific, convenient (ie, do not need complex equipment to run them), and, most importantly, quick, in both actual test time and getting the results to prescribers. Speed in treating infections is often crucial, and early appropriate antibiotic treatment has positive outcomes for patients.[2]

Finally regulators have been severely criticised over the past decade, but recent efforts by both the US and European Union authorities have been very encouraging. Perhaps what the industry needs is a unified approach by both groups to the assessment of drugs that are being developed for serious infections. The increasing openness of authorities is encouraging and dialogue between companies and agencies will hopefully lead to a clear pathway to the development of drugs for infections for which no solutions presently exist.

I am slightly optimistic about the development of new antibiotics based on these recent shifts in the environment. I hope my optimism is not misplaced.

Glenn S Tillotson
TranScrip Partners LLC, Downingtown, PA 19335, USA
Glenn.tillotson@transcrip-partners.com

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1 Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013; published online Nov 17. http://dx.doi.org/10.1016/S1473-3099(13)70318-9.
2 Moehring RW, Sloane R, Chen LF, et al. Delays in appropriate antibiotic therapy for gram-negative bloodstream infections: a multicenter, community hospital study. *PLoS One* 2013; **8:** e76225.
3 The Pew Charitable Trusts. A new pathway for antibiotic innovation. A summary of a conference on exploring drug development for limited populations. June 2013. http://www.pewhealth.org/uploadedFiles/PHG/Content_Level_Pages/Issue_Briefs/AntibioticsReport.pdf (accessed Nov 1, 2013).

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Antibiotic effectiveness and child survival

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The latest estimates of child mortality show that although the global mortality rate in children younger than 5 years has roughly halved, from 90 deaths per 1000 live births in 1990 to 48 per 1000 live births in 2012, an estimated 6·6 million children died in 2012.[1]

As noted in *The Lancet Infectious Diseases* Commission on antibiotic resistance and use,[2] most of these deaths are caused by preventable infectious diseases; the largest cause is pneumonia (1 137 766 deaths; 17%), although neonatal sepsis (350 661; 5%) and meningitis (165 360; 3%) are also important.[3] The poorest and most marginalised children are most often exposed to disease-causing pathogens, and most likely to develop severe illness caused by malnutrition or comorbidities. But despite these children being in greater need of effective treatment, they are least likely to receive it. In high-burden countries, treatment remains critically low, with antibiotics reaching about only a third of children in need.[4]

Because few data exist for causes of non-severe pneumonia, antibiotics have been targeted at the pathogens known to cause severe pneumonia. The common causes are *Streptococcus pneumoniae* (17–37% of severe pneumonia infections), *Haemophilus influenzae* (0–31%), and *Staphylococcus aureus* (1–33%).[5] Likewise, few data are available for the effect of antibiotic resistance in childhood pneumonia, although findings show an association between in-vitro resistance to co-trimoxazole and poor clinical outcome in acute otitis media.[5] Amoxicillin and co-trimoxazole are the most widely available oral antibiotics for non-severe pneumonia; however, data from at least one study[6] suggest higher treatment failure in patients with severe pneumonia given co-trimoxazole than in those given amoxicillin. As a result, WHO recommends oral amoxicillin as the preferred first-line treatment for childhood pneumonia in settings with low HIV prevalence. Amoxicillin is also preferred in settings with high HIV prevalence because oral co-trimoxazole is recommended as prophylaxis to prevent pneumonia caused by *Pneumocystis jirovecii*.

To achieve Millennium Development Goal 4, child killers like pneumonia need to be more effectively targeted; good quality, cheap, and accessible antibiotics will be essential for success.[7] Therefore, aggressive actions to overcome challenges related to antibiotic resistance are crucial.[1] Evidence from large-scale programmes in Ethiopia, Malawi, Uganda, Zambia, and other settings show that community health workers can provide good quality treatment services and contribute to rational drug use.[8,9] Community health workers have shown themselves to be competent in illness classification, ability to follow treatment algorithms, and correct prescription of treatment, including non-prescription of antibiotics for children who did not need them. Although supportive supervision and close monitoring is needed to maintain skills, community health workers need to be an essential part of national strategies for child survival. At the health facility level, the WHO Integrated Management of Childhood Illness strategy has improved quality of care and rational prescribing by health workers.[10]

The contribution of antibiotics for treatment of childhood pneumonia to the total selection pressure for antibiotic resistance is probably lower than the overall (and often indiscriminate) use of antibiotics for adult illness in most countries. However, increased access to improved and adequate diagnostic methods and antibiotics that are suitable for children is crucial in the prevention of antibiotic resistance. Innovation by the public and private sector is underway to improve pneumonia diagnostic methods and the outcome of such research should be available in the next 1–2 years. Innovative preparations of antibiotics suitable for children are now widely available—notably dispersible tablets provided in unit-dose, user-friendly packs.

Flexible, solid, and oral dosing (eg, a dispersible tablet) removes the need for refrigeration, which is important in resource-limited settings with no power supply, and reduces the bulkiness of the product, and therefore lowers the cost of transportation and storage. Making the right form of antibiotic available at the right level of health care contributes to the correct use of antibiotics. Further studies are needed of the association between pharmaceutical technology aspects of medicines such as formulations and outcomes.

The best way to avoid antibiotic resistance is to reduce pneumonia and meningitis infections through

wide coverage of effective prevention strategies. These include handwashing[11] and introduction and scale-up of vaccines.

With political will and coordinated engagement of public, private, and civil society sectors, the world can fulfil the promise to give every last child the opportunity to survive and thrive. The availability of good quality antibiotics effective against childhood pneumonia and neonatal sepsis will be essential to success.

Mark Young, Mickey Chopra, Atieno Ojoo
UNICEF, Programme Division, New York, USA (MY, MC); and Supply Division, Copenhagen, Denmark (AO)
myoung@unicef.org

All authors are employed by UNICEF. We declare that we have no conflicts of interest.

1 UNICEF. Committing to child survival: a promise renewed. Progress report 2013. Sept 2013. http://www.unicef.org/publications/files/APR_Progress_Report_2013_9_Sept_2013.pdf (accessed Oct 23, 2013).
2 Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013; published online Nov 17. http://dx.doi.org/10.1016/S1473-3099(13)70318-9.
3 UNICEF analysis based on IGME 2013, drawing on provisional analyses by WHO and CHERG 2013. http://progressreport.apromiserenewed.org/ (accessed Oct 25, 2013).
4 WHO, UNICEF. Countdown to 2015. Building a future for women and children. The 2012 report. http://www.countdown2015mnch.org/documents/2012Report/2012-complete-no-profiles.pdf (accessed Oct 23, 2013).
5 Grant GB, Campbell H, Dowell SF, et al. Recommendations for treatment of childhood non-severe pneumonia. *Lancet Infect Dis* 2009; **9:** 185–96.
6 Straus WL, Qazi SA, Kundi Z, Nomani NK, Schwartz B. Antimicrobial resistance and clinical effectiveness of co-trimoxazole versus amoxycillin for pneumonia among children in Pakistan: randomised controlled trial. *Lancet* 1998; **352:** 270–74.
7 United Nations. UN Commission on life-saving commodities for women and children: commissioners' report. Sept 2012. New York: United Nations, 2012.
8 Hamer DH, Brooks ET, Semrau K, et al. Quality and safety of integrated community case management of malaria using rapid diagnostic tests and pneumonia by community health workers. *Pathog Glob Health* 2012; **106:** 32–39.
9 Miller NP, Amouzou A, Bryce J, Victora C, Hazel E, Black RE. Assessment of iCCM implementation strength and quality of care in Oromia, Ethiopia. Baltimore, Addis Ababa: Institute for International Programs, Johns Hopkins Bloomberg School of Public Health, 2013.
10 Chopra M, Patel S, Cloete K, Sanders D, Peterson S. Effect of an IMCI intervention on quality of care across four districts in Cape Town, South Africa. *Arch Dis Child* 2005; **90:** 397–401.
11 Luby SP, Agboatwalla M, Feikin DR, et al. Effect of handwashing on child health: a randomised controlled trial. *Lancet* 2005; **366:** 225–33.

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Global collaboration to encourage prudent antibiotic use

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For more on **EAAD** see http://antibiotic.ecdc.europa.eu

For more on **Get Smart About Antibiotics Week** see http://www.cdc.gov/GetSmart/campaign-materials/week/index.html

For more on **AAW** see http://antibioticawareness.ca/

For more on **Australian Antibiotic Awareness Week** see http://www.safetyandquality.gov.au/our-work/healthcare-associated-infection/antimicrobial-stewardship/antibiotic-awareness-week-2013/

For more on **the Australian Commission on Safety and Quality in Health Care** see http://www.safetyandquality.gov.au/our-work/healthcare-associated-infection/antimicrobial-stewardship/antibiotic-awareness-week-2013

For more on **NPS MedicineWise** see http://www.nps.org.au/antibiotics

For more on **Combating Resistance: Getting Smart About Antibiotics** see http://www.cdc.gov/about/grand-rounds/

During November, awareness-raising activities promoting the prudent use of antibiotics in communities and hospitals are taking place in Europe, the USA, Canada, and Australia. Many health-related and professional organisations have partnered with governmental organisations and agencies to prepare communications materials and plan activities targeting patients, doctors, nurses, pharmacists, academics, industrialists, scientists, farmers, veterinarians, and the general public. Here we offer a snapshot of common themes, goals, and activities planned as part of European Antibiotic Awareness Day (EAAD), US Get Smart About Antibiotics Week, Canadian Antibiotic Awareness Week (AAW), and Australian Antibiotic Awareness Week .

Under the banner of European Antibiotic Awareness Day, national campaigns on prudent antibiotic use are anticipated in more than 40 European countries, with the target audiences selected by campaign organisers at the national level, including both public and prescribers. In the USA, a national campaign aims to educate the general public, health-care providers, administrators, and policy makers about appropriate antibiotic use in outpatient and inpatient health-care settings. Canada aims to build awareness among health-care practitioners, animal health experts, patients, and the general public about the prudent use of antibiotics. In Australia, activities to promote awareness of safe and judicious use of antibiotics among health-care professionals, veterinarians, food producers, and consumers are taking place with the tagline "no action today—no cure tomorrow", adopted from World Health Day 2011.

Across all the regions, communication materials are available to download from campaign websites. The EAAD website includes communications materials in all European Union official languages targeting the general public, primary care prescribers, and hospital prescribers. The Get Smart website of the US Centers for Disease Control and Prevention (CDC) provides a toolkit for its partners, and educational information for the general public and health-care providers. The Canadian Antibiotic Awareness website is linked to a visual campaign, including attention-grabbing posters and fact sheets. Equally, various materials and methods are available through the Australian Commission on Safety and Quality in Health Care and NPS MedicineWise.

To launch the campaigns, public stakeholder events, press conferences, and social media activities (eg, Twitter conversations) are taking place. A European Commission press conference preceded a stakeholder event entitled *Everyone is responsible* at the Brussels Press Club to launch EAAD on Nov 15, including presentations to launch the results of a survey of public attitudes towards antibiotics, new initiatives in research, and the latest surveillance data for resistance trends. The European Centre for Disease Prevention and Control is planning a Twitter chat on Nov 18 as well as promotional tweets and postings (#EAAD). The US CDC is hosting public health grand rounds called *Combating Resistance: Getting Smart About Antibiotics* on Nov 19 and a Twitter conversation on Nov 20. The observance will feature the release of an American Academy of Pediatrics Clinical Report in the *Journal of Pediatrics* on the principles of judicious antibiotic prescribing for paediatric upper respiratory tract infections. In Canada, social media and e-blasts will be used by all AAW partner organisations to build public health awareness about antimicrobial resistance. A campaign highlight will be webinars featuring talks by expert speakers on antimicrobial resistance. Various events and promotional activities are planned to take place across Australia covering both human and animal health, including Twitter and Facebook discussions. Health professionals and consumers will be invited to make an online pledge to help tackle the problem of antibiotic resistance, and hospitals will be invited to take part in a national antibiotic prescribing survey.

As *The Lancet Infectious Diseases* Commission on antibiotic resistance and use[1] makes clear, antibiotic-resistant infections are increasing at an alarming pace, posing a great threat to human health on every continent. Of the steps that need to be taken, we believe that improvement of antibiotic use practices is the most important to slow development and spread of resistant bacteria. Antibiotics are frequently used inappropriately in both human beings and animals. We highlight an example of coordinated action, and our hope is to foster further cooperation worldwide to ensure prudent use of

antibiotics and preservation of the gains made to reduce morbidity and mortality due to infectious diseases.

Sarah Earnshaw, Andrea Mendez, Dominique L Monnet, Lauri Hicks, Marilyn Cruickshank, Lynn Weekes, Howard Njoo, Stacie Ross

European Centre for Disease Prevention and Control, Stockholm, Sweden (SE, AM, DLM); US Centers for Disease Control and Prevention, Atlanta, GA, USA (LH); Australian Commission on Safety and Quality in Health Care, Sydney, Australia (MC); NPS MedicineWise, Sydney, Australia (LW); Public Health Agency of Canada, Ottawa, Canada (HN); and Communication and Education Task Group on Antimicrobial Resistance, Winnipeg, Canada (SR)

Sarah.Earnshaw@ecdc.europa.eu

MC is Director of the national healthcare associated infection programme at the Australian Commission on Safety and Quality in Health Care, and Chair of the Antimicrobial Resistance Standing Committee. LW is CEO of NPS MedicineWise, a not-for-profit company that received contract funding from the Department of Health. We declare that we have no conflicts of interest.

1 Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance–the need for global solutions. *Lancet Infect Dis* 2013; published online Nov 17. http://dx.doi.org/10.1016/S1473-3099(13)70318-9.

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Perseverance, persistence, and the Chennai declaration

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> "The darkest places in hell are reserved for those who maintain their neutrality in times of moral crisis"
>
> *Dante Alighieri, The Divine Comedy*

The Drug Controller General of India and Indian Health Ministry spared themselves from the darkest places and earned a glimpse of heaven when they published a law regulating over-the-counter sale of antibiotics.[1] Patients in India will no longer be able to walk into a roadside pharmacy and buy the antibiotics of their choice, but will have to have a prescription.

Antibiotic dispensing in Indian hospitals and pharmacies has been unregulated until recently, leading to rampant misuse. India has one of the highest prevalences of resistant Gram-negative bacteria in the world, with antibiotic misuse being the main cause of this disastrous scenario. 20–40% of *Klebsiella* spp isolates are resistant to carbapenems in major Indian hospitals, and the prevalence is even higher in some centres.[2] Even healthy individuals who have never visited a hospital carry these bacteria.[3]

The new rule issued by the ministry of health includes 24 antibiotics and 11 antituberculosis drugs in the schedule H1 category, designed to regulate over-the-counter dispensing of drugs, whereby pharmacists not only have to insist on a prescription from a registered medical practitioner, but they also need to enter details about patients, drugs, and prescribers in a register. Drug inspectors will monitor compliance with the regulation and offenders are answerable to the law. First-line antibiotics are excluded from the list and so will not come under the strict monitoring. The new H1 list is based on a step-by-step strategy, by contrast with the earlier published and withheld list that included all antibiotics. The Chennai declaration had recommended the step-by-step strategy, starting with second-line and third-line antibiotics.[4]

The road map meeting[4] held on Aug 24, 2012, in Chennai, was the first ever summit of all major stakeholders in India on the issue of tackling antibiotic resistance, with the participation of medical societies, representatives of government bodies such as the Drugs Controller General of India, the Medical Council of India, the Indian Council of Medical Research, state government representatives, WHO, and media.[4] The ensuing document, the Chennai declaration, was widely discussed in medical journals and public media. Before the declaration, medical professional societies in India were largely silent on the issue of antibiotic resistance. Rulings on over-the-counter regulation and antibiotic policy published immediately after the NDM-1 controversy were withheld because the main recommendations could not be implemented.[5] The Chennai declaration helped the Ministry of Health to move in the right direction, by providing a practical and implementable solution suitable to the background scenario of heterogeneity of health-care system in the country.

The declaration led to a change in attitude among the Indian authorities and medical community by convincing them to be more open about the issue of antimicrobial resistance. The international medical community and policy makers became less critical and more sympathetic towards understanding the reality in developing countries. Chennai declaration efforts—through relentless interaction with the ministry, creation of public and professional awareness via media, journals, and meetings, and inspiration of political leadership to discuss the issue in the Indian parliament—have undoubtedly sped up the publication of the new over-the-counter rule and also been crucial in convincing the ministry to initiate efforts to publish a new national antibiotic policy. As Herman Goossens predicted in his Comment in *The Lancet Infectious Diseases* early this year, the wind has changed.[6] UK Chief Medical officer Dame Sally Davies applauded India's new over-the-counter rule describing it as a "fantastic example of political leadership that will protect the integrity of life-saving treatments".[7]

The new over-the-counter rule will definitely make prescribers, patients, and the pharmacists show antibiotics the respect they deserve. This attitude change will lead to sensible and rational prescription of antibiotics included in the list and might also be followed by reasonable use of antibiotics off list and other groups of drugs. With more than 600 000 pharmacies in India, implementation of this new rule will be a huge challenge and if successful, will be an inspiration to other countries in the region. A new antibiotic policy and an over-the-counter rule are

not expected to stop the spread of antibiotic resistance immediately. However, this daring move will serve as a trigger for further, bolder steps—better late than never.

Abdul Ghafur
Infectious Diseases and Clinical Microbiology, Apollo Hospital, Chennai, India
drghafur@hotmail.com

I am coordinator of the Chennai Declaration. I declare that I have no conflicts of interest.

1 Department of Health and Family Welfare. The Gazette of India. 441, part 2. August 30, 2013. http://www.cdsco.nic.in/588E30thAug2013.pdf (accessed Oct 22, 2013).
2 Sir Ganga Ram Hospital. Microbiology news letter, May 2, 2013. 2013; **19:** 2.
3 Mittal G, Gaind R, Kumar D, Verma PK, Deb M. Faecal carriage of NDM-1 in hospitalized and non hospitalized patients. HISICON 2013; Mumbai, India. Feb 7–9, 2013. OC17.
4 Ghafur A, Mathai D, Muruganathan A, et al. The Chennai declaration: a roadmap to tackle the challenge of antimicrobial resistance. *Indian J Cancer* 2013; **50:** 71–73.
5 Nikita, CNN-IBN. Antibiotic Policy put on hold indefinitely. Oct 14, 2011. http://ibnlive.in.com/news/antibiotic-policy-put-on-hold-indefinitely/192878-17.html (accessed Oct 12, 2013).
6 Goossens H. The Chennai declaration on antimicrobial resistance in India. *Lancet Infect Dis* 2013; **13:** 105–06.
7 The Hindu. UK hails India's move on antibiotics sale. http://www.thehindu.com/todays-paper/tp-national/uk-hails-indias-move-on-antibiotics-sale/article5223564.ece (accessed Oct 17, 2013).

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Comment

Antibiotic Action: helping deliver action plans and strategies

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The Lancet Infectious Diseases Commission on antibiotic resistance and use[1] provides a global overview of antibiotic resistance, the paucity of new drugs to treat multidrug-resistant bacterial infections, and some of the key issues and proposals to resolve the present difficulties. Insufficient understanding of the complex and myriad reasons for the crisis of antibiotic resistance and scarcity of new treatments has complicated and compounded the predicament. For these reasons, the British Society for Antimicrobial Chemotherapy (BSAC) public engagement initiative Antibiotic Action was launched in November 2011,[2] to inform and educate everyone about the need for discovery, research, and development of new treatments for bacterial infections. The initiative contributes to national and international activities, and acts as a conduit for the sharing of information about antibiotic resistance and paucity of new drugs with all stakeholders.

It is very important that health-care professionals are informed about the scientific basis of antibacterial drug resistance, how bacteria with different antibiotic resistances emerge and are disseminated, and strategies that could be used to minimise resistance. As outlined in the Commission, much work remains to be done. All stakeholders (eg, patients, veterinarians, and health-care professionals) need information because ignorance, or worse, uninformed opinion, will fuel profligate antibiotic use. Therefore, Antibiotic Action has engaged with the general public, policy makers, and politicians worldwide. To help with the delivery of key messages, the initiative has worked with similar organisations including ReAct, the Infectious Diseases Society of America (IDSA), Alliance for the Prudent Use of Antibiotics (APUA), World Alliance against Antibiotic Resistance (WAAAR), Global Antibiotic Resistance Partnership (GARP), and those associated with the Chennai Declaration. Antibiotic Action differs from these organisations in that its remit is focused on public engagement. This method has been successful, and was aided in 2013 by the advocacy of the UK Chief Medical Officer, Dame Sally Davies. UK politicians are also engaged, and the government has just issued its 5 year strategy on antimicrobial resistance.[3] Furthermore, the All Party Parliamentary Group on Antibiotics was established in June 2013 (for which BSAC provides the secretariat), and a Science and Technology Select Committee inquiry into antibiotic resistance is underway.[4]

Antibiotic resistance affects practice in many different medical disciplines, and resolution needs to move beyond infectious diseases, microbiology, and pharmacy. To achieve this goal, Antibiotic Action's public engagement activities have included conference presentations to health care, veterinary, and pharmaceutical science professionals, and much engagement via the lay media. This action has led to more than 7000 articles in digital, print, and broadcast media directly quoting the information provided by the initiative. Importantly, patients are becoming increasingly aware of the issues and their concerns will need to be addressed.

One concern is the inadequate commercial and public funding for the discovery and development of new treatments for bacterial infections. The European Union Innovative Medicines Initiative and US Biomedical Advanced Research and Development Authority schemes are one avenue for funding, discovery, and development of new treatments, but, as highlighted in the Commission, many more different mechanisms will be needed. Unfortunately, in the UK and many other countries, funding for medical and scientific research seems unlikely to be increased, so additional research on antibiotics will be at the expense of other disciplines. In the 1980s, the AIDS pandemic led to public pressure that stimulated funding for new antiviral drugs; perhaps similar pressures will lead to more funding for discovery and development plus improved diagnosis of bacterial infections.

The development of new treatments will be in vain if these are squandered and used as widely as present antibacterial compounds. Therefore, BSAC and Antibiotic Action will work to inform everyone about the essentiality of preservation, and how to use available antibacterial drugs properly while maintaining equitable access, especially to the most vulnerable populations. Professional and public education will be equally important. An understanding of when antibiotics are needed,

For more on **Antibiotic Action** see http://antibiotic-action.com

For more on **ReAct** see http://www.reactgroup.org

For more on **the IDSA** see http://www.idsociety.org/topic_antimicrobial_resistance/

For more on **APUA** see http://www.tufts.edu/med/apua/

For more on **WAAAR** see http://www.waaar.org/

For more on **GARP** see http://www.cddep.org/projects/global_antibiotic_resistance_partnership

For more on the **Chennai Declaration** see http://chennaideclaration.org/

and more importantly when they are not, will reduce use. For health-care professionals, adequate undergraduate and postgraduate education about infection and antibiotics is essential so these individuals know how to use antibacterial treatments appropriately and recognise how, unlike other treatments, their use has affects that reach beyond individual patients.

Now is the time to establish strategies for the treatment of bacterial infections that prevent the widespread, wasteful use of valuable antibacterial compounds in many different environments outside of human medicine. For instance, new treatments with novel modes of action and new chemical classes of inhibitors could be restricted to only one area of use—for example, either human beings or animals, but not both, and available on prescription only. Furthermore, the use of antibacterial compounds in domestic and other environments should be restricted to those that do not select resistance to antibacterial drugs used to treat infections. Many solutions to the reduction of bacterial colonisation and treatment of bacterial infections need to be found. Antibiotic Action will continue to publicly engage on all aspects of antimicrobial chemotherapy to help deliver national and global action to tackle antibiotic resistance and the paucity of new treatments for bacterial infections.

Laura JV Piddock
Institute of Microbiology and Infection and School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
l.j.v.piddock@bham.ac.uk

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1 Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013; published online Nov 17. http://dx.doi.org/10.1016/S1473-3099(13)70318-9.
2 Piddock LJV. The crisis of no new antibiotics–what is the way forward? *Lancet Infect Dis* 2012; **12:** 249–53.
3 Department of Health, Department for Environment, Food, and Rural Affairs. UK five year antimicrobial resistance strategy 2013 to 2018. Sept 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf (accessed Oct 3, 2013).
4 Commons Select Committee. Antimicrobial resistance (AMR). Sept 11, 2013. http://www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-committee/inquiries/parliament-2010/antimicrobial-resistance-amr/ (accessed Oct 3, 2013).