

Antimicrobial resistance: A global threat

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In 1945, when accepting his Nobel Prize for discovering penicillin, Sir Alexander Fleming predicted that antibiotics would eventually develop resistance and that we would once again see an increase in deaths from infection. We are now facing the reality of this prediction. Every year in Europe, approximately 25,000 people die due to antimicrobial resistance (AMR) and in Asia, one child dies every five minutes from a resistant infection that cannot be treated with simple antibiotics.¹ The United States Centers for Disease Control and Prevention (CDC) have given a conservative estimate of two million cases of antibiotic-resistant illnesses and 23,000 deaths from AMR a year in the US.²

Rarely has modern medicine faced such a grave threat as infection-related mortality rates in the developed world return to those last seen in the early 20th century. Without antibiotics, treatments from minor surgery to major transplants will carry with them too great a risk of infection and modern chemotherapy will become impossible. Health care costs are also likely to spiral upwards as we sustain longer hospital admissions and resort to newer, more

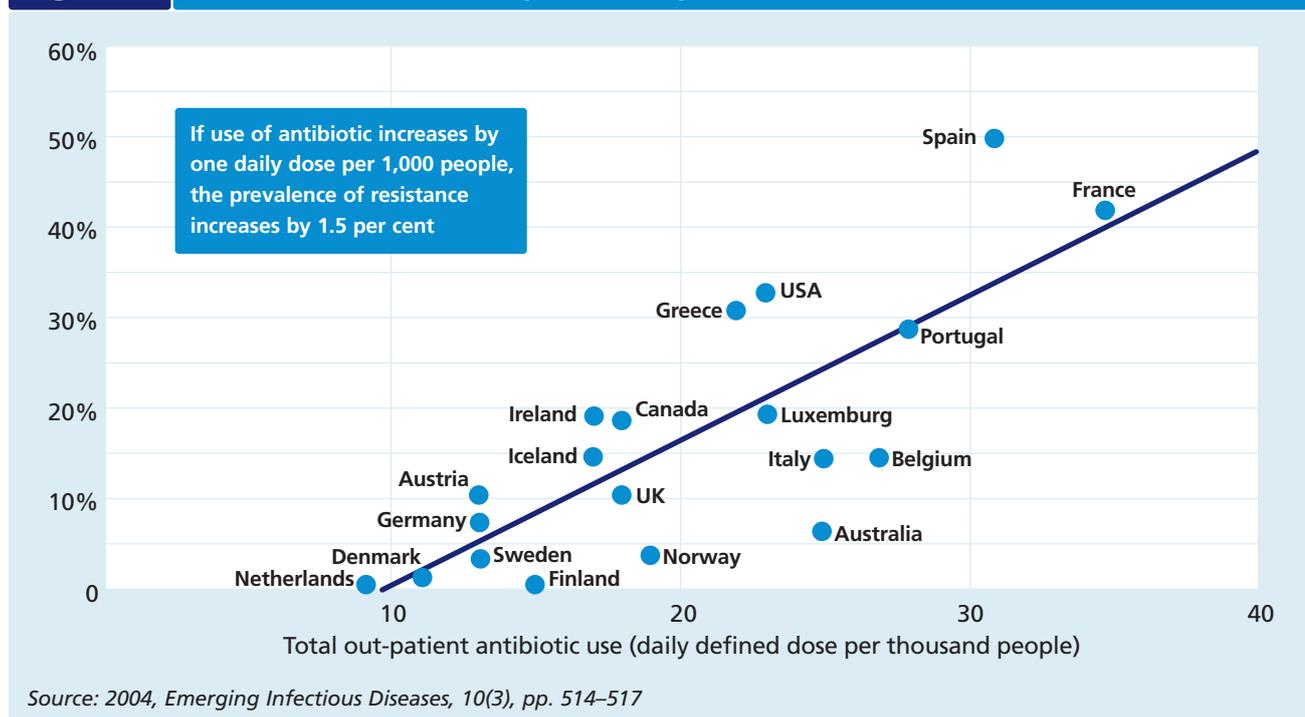
expensive antibiotics, and it is estimated that health care costs and productivity-loss as a result of AMR already costs Europe approximately €1.5 billion a year.³ In the USA, the CDC has reported a loss of US\$35 billion per year, including both health care and wider productivity costs, compared with the costs if those infections had been totally preventable.⁴

Surveillance and conservation

The development of resistance is due to the natural Darwinian process of evolution. Any bacteria will eventually develop some form of resistance. However, with antibiotics we are responsible for exacerbating and expediting the process through excessive and inappropriate use.

Immediate and co-ordinated action is essential to slow down the development of further resistance. Action is needed at the personal, national and global levels to preserve our remaining antibiotics and the effectiveness of any new antibiotics that are developed, an approach we can best understand as stewardship.

Figure 1 Penicillin-resistant *Streptococcus pneumoniae*





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Seventy per cent of antibiotics manufactured each year are used in the agricultural, aquacultural and veterinary sectors

At the personal level, patients and general practitioners (GPs) need to ensure that they are taking and prescribing the right antibiotics for the right amount of time and at the right dosage. A complex web of influence plays upon the prescribing behaviour of health care practitioners, including demands from patients, the threat of competition from alternative systems of health care and, in some countries, financial incentives to prescribe. Yet, as the impact of antibiotic use extends beyond individual patients, there is a public health imperative for use to be closely monitored and regulated.

At the societal level we need systems of surveillance and monitoring for resistant bacteria and antibiotic use, in both humans and animals. This is a global problem, with many examples of the rapid spread of new resistances between continents, yet we lack the surveillance systems and the policy tools required to tackle it. The lack of basic information on prescribed antibiotic use is compounded by the fact that antibiotics are used across the world in animal feed and often on a non-prescription basis.

At the global level, international collaboration is therefore required to foster commitment, and develop and enforce guidance regarding the appropriate use of antibiotics in humans and animals. Antimicrobial resistance extends far beyond human medicine: approximately 70 per cent of the 100,000 to 200,000 tonnes of antibiotics manufactured each year is used in the agricultural, aquacultural and veterinary sectors.⁵ A pricing paradox exists in farming whereby antibiotics, a limited natural resource, cost less than implementing more effective hygiene practices.

Work is also required to develop rapid and cheap point-of-care diagnostics. Microbiological diagnostic tests help to prevent unnecessary antibiotic use and narrow the spectrum of coverage required to treat an infection, but these are often slow and delays in treatment can be associated with higher mortality. Hence, broad-spectrum antibiotic therapy is often used. Development of rapid diagnostics could eliminate this delay, enabling targeted antibiotic or non-antibiotic therapy from the outset.

Drug development

There is also a pressing need to address the drug development pipeline. Whereas we have previously been fortunate enough to have a consistent supply of antibiotics to replace those to which bacteria have become resistant, there has not been a new class of antibiotic developed since 1987.⁶ The microbiology required is complex and all simple classes have been discovered. Furthermore, the current models of payment and reward do not incentivise pharmaceutical companies to invest in the research and development required for antibiotics. Pharmaceutical companies are currently not incentivised to focus on antibiotics as compared to drugs for long-term conditions, such as statins, which are far more profitable. Such drugs for chronic conditions are taken every day for the rest of a patient's life, whereas antibiotics may only be taken for a week once every few years. Furthermore, the need to conserve antibiotics and limit their use contrasts with the reliance on high-volume sales required by pharma to make a profit.

Looking forward

AMR can only be successfully addressed on a global scale: resistant bacteria easily transmit between countries and any mechanism that incentivises the development of new antibiotics will only be effective if applied to the international pharmaceutical market as a whole. We therefore need to galvanise international collaboration to prevent the global spread of AMR: this includes prevention and control, surveillance and monitoring, and stewardship and conservation.

There is a balance to be struck between limiting the availability of antibiotics and ensuring timely treatment for those who need them. Such a balance is difficult to achieve in countries with robust health care systems, but is exponentially more difficult in those with limited facilities. Yet the increasing pattern of resistance shown by Enterobacteriaceae, the leading cause of newborn sepsis in developing countries, demonstrates that resistance is a serious threat in these countries. Concerted global action is required to tackle this problem and, at the same time, ensure equity of access to effective treatments. The development of cheap and rapid diagnostics may be key to ensuring that any antibiotic use is appropriate and accurate. Above all, it is important that work taken forward to combat AMR takes account of the needs of all countries regardless of income or geographical location and that is why a truly global solution is required.

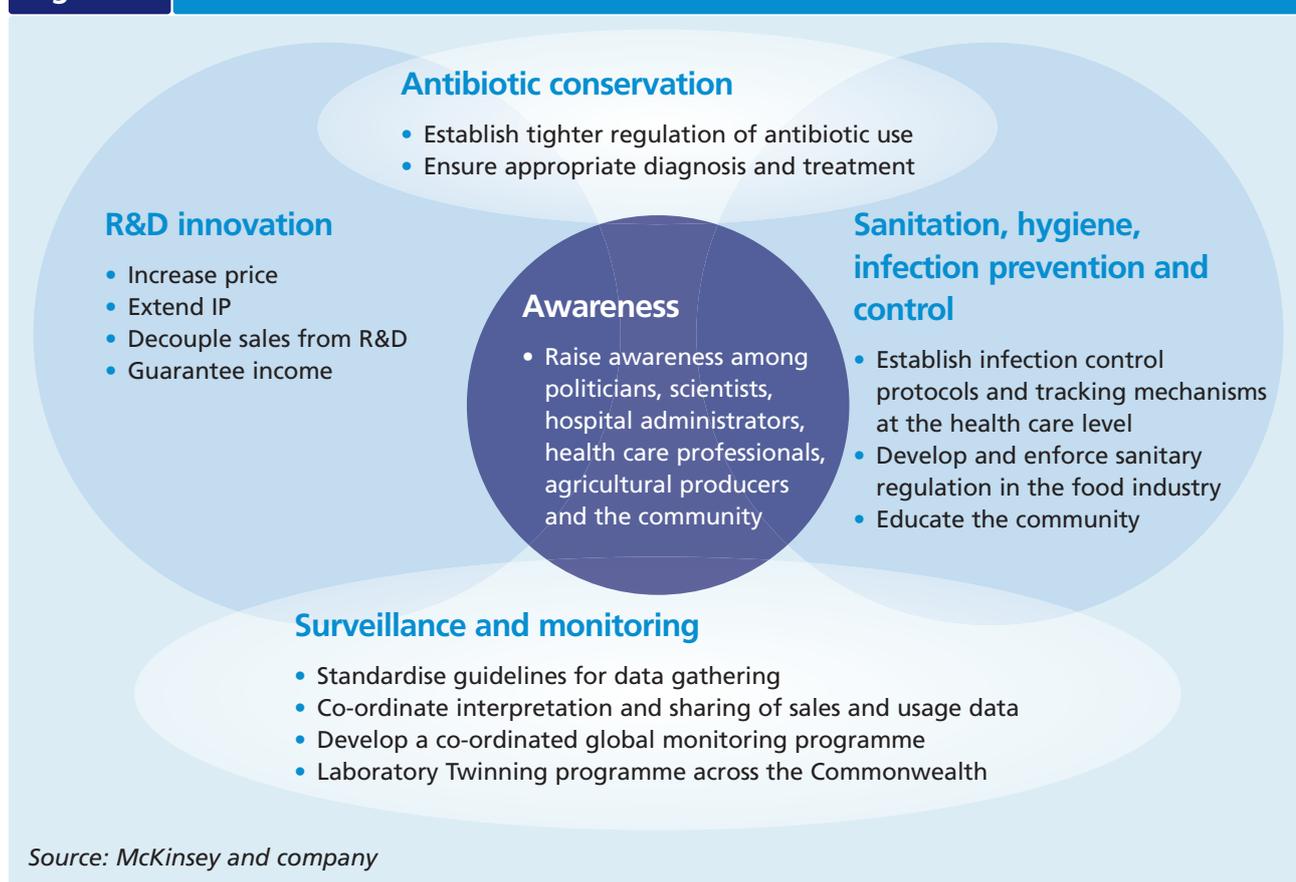
To this end, the World Health Organization (WHO) executive board adopted a resolution on AMR in January 2014 which, if passed at

the World Health Assembly by member states in May 2014, will call for the development of a global action plan to tackle this significant issue as well as committing the WHO to supporting individual countries in developing their own strategies for dealing with AMR. The Commonwealth can also be instrumental here in providing support to countries to develop their laboratories, and surveillance and monitoring systems. We would value input from all Commonwealth countries on this and other aspects of tackling AMR, as the Commonwealth can make a real difference by working together to find solutions to common problems.

Similar action is also needed in the animal arena, in terms of monitoring, surveillance and the enforcement of guidelines regarding the appropriate use of antibiotics. This could be achieved through a resolution passed by the Food and Agriculture Organisation (FAO). There is also a need to further develop the international evidence base regarding AMR; both in terms of the link between animal antibiotic use and human health, and the costs of inaction to society, the economy and our health.

Finally, innovative funding solutions are required to promote research in this field, while removing the incentive for pharmaceutical companies to attempt to maximise sales volume of any newly developed product. New models for innovative financing are therefore required to decouple volume of sales from monetary reward. Such models may be public-private partnerships, advanced purchase agreements or something entirely novel and will likely require collaboration between academia, research funders and not-for-profit organisations. Vitality, economic work to develop such

Figure 2 Call to action



models will need to be done at the global level, as any successful model will need to be standardised across nations.

AMR is of such concern to the UK that it is now on its Department of Health and Department for Environment, Food and Rural Affairs risk register. However, by working together as countries, we believe that we can develop sustainable solutions.

Endnotes

- 1 ECDC (European Center for Disease Control) and EMA (European Medicines Agency), 2009. *The bacterial challenge: time to react*. Stockholm: ECDC.
- 2 i.e. this extra cost is not just due to resistance but is due to having an infection; source: CDC (Centers for Disease Control and Prevention), 2013. *Antibiotic resistance threats in the United States, 2013* [PDF] CDC. Available at: www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf [Accessed 20 March 2014].
- 3 ECDC and EMA op. cit.
- 4 CDC op. cit.
- 5 Based on 2010 figures for the US (9.4 million tonnes, excluding ionophores, used for animals, and 3.3 million tonnes used for humans) from the FDA and IMS Health.
- 6 WEF (World Economic Forum), 2013. *Global Risks 2013, Eighth edition*. Geneva: WEF.

PROFESSOR DAME SALLY DAVIES is Chief Medical Officer for England and Chief Medical Advisor to the UK Government (since 2010), and has led UK delegations to WHO summits and forums since 2004. Her 2011 annual report on infectious diseases focused on AMR and she has since been championing the issue at a national and international level, including as chair of the 2104 AMR forum at the World Innovation Summit for Health in Qatar. Dame Sally is independent advisor to the UK Government on medical matters, with particular responsibilities regarding public health. She is professional head of the department's medical staff and head of the medical civil service. She has been actively involved in National Health Service Research and Development from its establishment having founded the National Institute for Health Research with a budget of £1 billion and retains responsibility in this area. Her own research interests focused on sickle cell disease.

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