ESSAY

Tackling antibiotic resistance

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Abstract | The development and spread of antibiotic resistance in bacteria is a universal threat to both humans and animals that is generally not preventable but can nevertheless be controlled, and it must be tackled in the most effective ways possible. To explore how the problem of antibiotic resistance might best be addressed, a group of 30 scientists from academia and industry gathered at the Banbury Conference Centre in Cold Spring Harbor, New York, USA, from 16 to 18 May 2011. From these discussions there emerged a priority list of steps that need to be taken to resolve this global crisis.

The serious outbreaks of bacterial infection that are increasingly being reported are costly in many respects. When associated with antibiotic resistance, they may become deadly. Recently, the US CDC tracked a multistate outbreak of *Salmonella enterica* subsp. *enterica* serovar Heidelberg infections that were associated with contaminated ground turkey and sickened more than 130 people in 32 different states. Although these bacteria were resistant to several antibiotics, the afflicted could be treated with alternative agents. Some 18 million kilograms of ground turkey product have been recalled to date. In Germany, an epidemic of *Escherichia coli* infections caused by contaminated vegetables affected up to 5,000 people, with more than 50 deaths. Fortunately, antibiotic resistance was not an issue in this case. Looming large over such outbreaks is the emergence and worldwide spread of antibiotic-resistance genes. For example, the New Delhi metallo-β-lactamase-resistance gene (bla_{NDM-1}), which confers resistance to penicillin, cephalosporins and a range of their derivatives, has spread rapidly since first being reported in 2010. bla_{NDM-1} is associated with other resistance determinants and has resulted in increasing mortality in hospitalized patients.

The economic and human cost of antibiotic resistance is already enormous. For instance, in Europe in 2007, the number of infections by multidrug-resistant bacteria was 400,000, and there were 25,000 attributable deaths. The number of extra hospital days was 2.5 million. The expenditure associated with these infections in terms of extra hospital costs and productivity losses exceeded €1.5 billion each year[1]. In the United States, antibiotic-resistant infections are responsible for $20 billion per year in excess health care costs, $35 billion per year in societal costs and 8 million additional hospital days per year[2].

We live in a global economy, and movement of goods and food can have a massive and very rapid impact over a wide area. New, coordinated twenty-first-century approaches to solving this ever-present threat must be developed. We propose that the following priorities for research and intervention be adopted immediately.

Research priorities to control resistance

First and foremost, additional basic information is required to direct strategic efforts towards control of the crisis. Increasing lines of evidence identify the principal reservoirs of resistance genes to be bacteria that live in and on humans and animals, as well as those found in the environment (in soil, water and so on). However there is insufficient information about the conditions and factors that lead to the mobilization, selection and movement of these bacteria into and between animal and human populations.

Key questions for researchers to address therefore include the following: what and where are the crucial stages in the development of clinically important antibiotic resistance for microorganisms in the environment? How can the chain of events be intercepted, and how can this knowledge be used to predict the emergence of new mechanisms of resistance? Can modern diagnostic technology be improved to facilitate more accurate and efficient decision-making in individual point-of-care settings that require rapid action? How can we establish and maintain reliable city-wide, country-wide and worldwide surveillance to ensure the prescription of the most appropriate antibiotics and the treatment (including isolation) of infected people? What role do the dormant persister bacterial cells that are produced by all pathogens have in acting as a potential source of antibiotic-resistant bacteria?

These questions are priorities for preventing the development of antibiotic resistance worldwide. What is more, in order to support the research necessary to track new threats on a global scale, international funding is indispensable. In cases of influenza outbreaks, the WHO and associated agencies have moved rapidly to isolate and eliminate new outbreaks of infection. The same approach should be applied to antibiotic resistance; a new generation of physicians and scientists with modern approaches to diagnostic and predictive medicine needs to be trained.

Urgent actions needed to tackle resistance

It is indisputable that antibiotic resistance is life-threatening in the same sense as cancer, both in the number of cases and the likely outcome; thus, the following actions can and must be taken as a matter of extreme urgency.

Public education. Substantial increases in public education about bacteria and antibiotic resistance are vitally important. The general public must be made aware of the facts concerning the important roles that bacteria have in their lives and well-being, the precious nature of antibiotics and the concomitant importance of using them prudently. This knowledge should be initiated in schools. The e-Bug programme that has been launched as a pan-European effort is a prime example of what can be done to educate children (and their parents) about the necessity for the entire population to take antibiotic use and resistance development personally[3]. Other good examples are the annual Antibiotic Awareness Day in Europe and Canada, and the CDC programme Get Smart: Know When Antibiotics Work in the United States. Total commitment at all levels of the population is the only solution.

Public health, sanitation and quality of life. In some parts of the world a combination of issues seems to create the conditions that disseminate and select resistant bacteria, notably population density, uncontrolled use of antibiotics, a lack of clean water supply, and a lack of proper treatment for sewage and industrial effluent. Local governments must be encouraged and supported to invest in better sanitation infrastructure and tighter prescription regulations to control the rapid evolution of resistance. This is a worldwide, multinational problem and must be treated as such.

New antibiotics. The pharmaceutical industry and health care systems have been battling antibiotic-resistant strains of bacteria for more than 50 years. A continuous supply of new structural classes of antibiotics that are not affected by known or existing mechanisms of resistance is essential. More efforts to make chemical modifications in order to provide antibiotic derivatives that evade known resistance mechanisms are recommended. Who will be responsible for finding and developing such new therapeutics? Given the economics of the development of new antibiotics, profits from 'drugs of last resort' might not justify investment in this area by private pharmaceutical companies alone. Solutions therefore need to include government action in industrialized countries to overcome this 'market failure' by both reducing regulatory barriers to entry and improving the economic incentives for re-engagement by private enterprises. Public–private partnerships taking new antibiotic development forward should be encouraged, particularly for treatment of infections in economically disadvantaged parts of the world.

Old antibiotics. Old and discarded, or even rejected, antibiotics should be re-investigated, repurposed and used as needed. Pharmaceutical companies should provide their stocks for this purpose (retaining rights to other applications). Start-up companies could use this opportunity to generate effective new antibiotic combinations. For example, daptomycin, abandoned by one company for reasons of toxicity, has become a leading treatment for serious Gram-positive infections using a different dosing regimen[4].

Control of antibiotic use. Non-therapeutic use of antibiotics must be discontinued. A total restriction must be enforced on both compounds that are approved for use in humans and the structural derivatives of these compounds that are used as routine feedstocks in animal feed, agriculture and fisheries. At present, more than 50% of the antibiotics produced are employed as animal feeds to promote growth. This practice has been ongoing since the 1950s, despite efforts to prevent such non-prescription use by regulatory authorities such as the United Nations and the WHO. Is there convincing evidence that these supplements are of use when good animal husbandry is common practice? Appropriate treatment for sick animals must, of course, be maintained. Therapeutic use of antibiotics in domestic pets should be by veterinarian prescription only.

Alternatives to antibiotics. The investigation of novel non-antibiotic approaches for the prevention of and protection against infectious diseases should be encouraged, and such approaches must be high-priority research and development projects. These approaches include the use of antibacterial vaccines, phage therapy, immunostimulants, adjuvants, antivirulence therapies, probiotics and their combinations[5]. New and better toxin antidotes are needed for outbreaks of diseases in which antibiotics should not be used. There has been limited success with the development of antibacterial vaccines, a favoured option; this approach deserves more extensive investigation, especially for animal diseases. The use of probiotics is likely to become more important in years to come as microbiological studies of the roles of gastrointestinal bacterial populations (the human microbiome) lead to the identification of those bacterial genera and species that have key roles in human health and disease. Such advances may well lead to the use of bacteria and their products as specific therapeutics[6].

A collaborative approach. It is essential that antibiotic discovery and production be maintained on a scale that is appropriate to our increasing requirements. The Infectious Diseases Society of America (ISDA) has proposed a goal of "10 new antibiotics for 2020" (REF. 7). This will be difficult, given that the industry's search for novel chemical agents acting on new biological targets has become non-productive. However, it is now clear that drug discovery efforts based on natural products have generally focused on readily accessible sources to date[8]. The natural products identified thus far are only the tip of the iceberg in terms of the vast reservoir of bioactive compounds available in nature. For example, in 2008, more than 1,000 novel compounds were isolated from marine microorganisms[9]**.** With such a treasure trove to mine, and with the active involvement and wealth of experience of the established pharmaceutical industry (which was in fact founded on natural-product development in the 1950s–1970s), the IDSA target would be attainable. Without such collaboration, the antibiotic-discovery commitment becomes the responsibility of government agencies, academia and small biotechnology companies, entailing substantial federal investments.

The cost of the undertaking that we propose will be infinitesimally small in comparison to the economic and human cost of doing nothing. The late Joshua Lederberg observed: "barring geno-suicide, human domination is challenged only by pathogenic microbes, for which we are the prey, they are the predators. In natural evolutionary competition there is no guarantee that we will find ourselves the survivors." (REF. 10.) The Banbury participants believe that if the appropriate actions are taken on a worldwide scale, the odds can be changed.

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doi:10.1038/nrmicro2693
Published online 2 November 2011

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Acknowledgements
We thank J.D.W. for initiating and supporting this workshop.

Competing interests statement
The authors declare no competing financial interests.

FURTHER INFORMATION

Julian Davies's homepage: http://www.microbiology.ubc.ca/
Antibiotic Awareness Day in Europe: http://www.antibiotic.ecdc.europa.eu/
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