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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 must be tackled in the most effective ways possible. To explore how the problem of antibiotic resistance might best be addressed, a group of thirty scientists from academia and industry gathered at the Banbury Conference Centre in Cold Spring Harbor, New York, May 16-18, 2011. From these discussions 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 Center for Disease Control tracked multistate *Salmonella* Heidelberg infections associated with contaminated ground turkey that sickened more than 130 people in 32 different states. Although resistant to several antibiotics, the afflicted could be treated with alternative agents. Some 18 million kilos of ground turkey product have been recalled to date. In Germany, an epidemic of *E. coli* infections due to contaminated vegetables affected up to 5000 people with more than 50 deaths. Fortunately antibiotic resistance was not an issue in this case. Looming large over such catastrophies is the constant development and worldwide spread of antibiotic genes. For example, since first being reported in 2010, the New Delhi metallo ß-lactamase gene (NDM-1) confers resistance to a variety of penicillin/cephalosporins and their derivatives. It 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 with 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 (Ref 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 each year (REF 2).

We live in a global economy and movement of goods and food can have a massive impact over a wide area very rapidly. New, coordinated 21st 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 for controlling antibiotic resistance

First and foremost, additional basic information is required in order 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 (soil, water, etc). However there is insufficient information on the conditions and factors that lead to their mobilization, selection and movement into and between animal and human populations.

The key questions for researchers to address are therefore:

- What and where are the critical stages in the process of development of clinically significant antibiotic resistance from microbes in the environment and how can the chain of events be intercepted?
- When reliable information on the above is available, will it enable the prediction of the emergence of new mechanisms of resistance? If so, what actions should be taken?
- Modern diagnostic technology is critical for accurate and efficient use of antibiotics. Can the methodology be improved to facilitate decision-making in individual, point-of-care settings requiring rapid action?
- Containment of outbreaks of antibiotic resistance is dependent on an early warning system. The establishment and maintenance of reliable city-wide, country-wide and international surveillance is essential to ensure the prescription of the most appropriate antibiotics and treatment (including isolation) of infected people. How can such a world-wide network be created?
- Dormant persister bacterial cells are produced by all pathogens and may serve as a potential source of antibiotic-resistant bacteria, although further studies are required to define the correlation. Better understanding of persisters and ways to eliminate them is needed.

These questions are priorities for the prevention of antibiotic resistance development worldwide; in order to support the research necessary to track new threats on a global scale, international funding is indispensable. In cases of influenza outbreaks, 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 physician/scientists with modern approaches to diagnostic/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 numbers of cases and likely outcome; thus the following actions can and must be taken as matters of extreme urgency.

Public education

Significant increases in public education about bacteria and antibiotic resistance are vitally important. The general public must be made aware of the facts concerning the critical roles that bacteria play 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) of the necessity for the

entire population to take antibiotic use and resistance development personally (Ref 3). Other good examples are the annual *Antibiotic Awareness Day* in Europe and Canada (Ref 4) and the CDC program "Get Smart: Know When Antibiotics Work" in the United States (Ref 5). 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 appear to create the conditions that disseminate and select resistant bacteria, notably population density, uncontrolled use of antibiotics, lack of clean water supply and a lack of proper sewage and industrial effluent treatment. 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 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 new antibiotic development, 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, re-purposed 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 regime (REF 6).

Control of antibiotic use

Non-therapeutic use of antibiotics must be discontinued. A total restriction on both human-approved compounds and their structural derivatives as routine feedstocks in animal feed, agriculture, or fisheries must be enforced. At the present time 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 UN and 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 prevention of and protection against infectious diseases should be encouraged and must be high-priority research and development projects. Among others, these include the development of vaccines, phage therapy, immunostimulants, adjuvants, anti-virulence therapies, probiotics and their combinations (REF 7). New and better toxin antidotes are needed for outbreaks of diseases where 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 play key roles in human health and disease. Such advances may well lead to the use of bacteria and their products as specific therapeutics (REF 8).

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 has proposed a goal of “10 new antibiotics for 2020” (Ref 9). This will be difficult, given that industry’s search for novel chemical agents acting on new biological targets has become non-productive. However, it is now clear that natural-product drug discovery efforts to date have generally focused on readily accessible sources (Ref 10). These are only the tip of the iceberg in terms of the vast reservoir of bioactive compounds available in nature. For example, in 2008, over 1000 novel compounds were isolated from marine micro-organisms (Ref 11)**.** With such a treasure trove to mine and the active involvement and wealth of experience of the established pharmaceutical industry (which was in fact founded on natural product development in the 1950s – 70s) the IDSA target would be attainable. Without such collaboration, the antibiotic discovery commitment becomes the responsibility of government agencies, academia and small biotech companies, entailing significant 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 that “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 12). The Banbury participants believe that if the appropriate actions are taken on a worldwide scale, the odds can be changed.

Acknowledgments

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