

## Swamping our defences: the rising tide of antibiotic resistance

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### Introduction

Several health authorities have recently issued stark warnings that we are on the threshold of a post-antibiotic era (CMO, 2011; CDC, 2013; WHO, 2014). The loss of these antibiotic drugs would be a severe public health setback, taking humanity back to a time when patients succumbed from infections now routinely treated. Antibiotic resistance also puts at risk key attainments of modern medicine, such as intensive care medicine, transplant surgery and chemotherapy for cancer, which are all reliant on antibiotics. Antibiotic resistant infections already exact a severe toll: an estimated 23,000 persons die from resistant bacterial infections in the United States, with associated treatment costs of US\$20 billion (CDC, 2013). A high percentage of bacteria that cause common infections – such as urinary tract infections, pneumonia, and bloodstream infections – show resistance in all areas of the world (WHO, 2014).

Despite the documentation of the rapid rise of resistant bacterial strains worldwide, the full extent of the problem has arguably not been fully recognized and understood by policy makers, the health establishment, and the public. To date, this emerging global healthcare crisis has received less attention than other threats, such as HIV/AIDS. Crucially, maintaining antibiotics in the arsenal of modern medicine will depend on the actions of many actors, from parents not demanding antibiotics for their children's routine coughs, to changes in livestock raising, and re-focussing drug development.

### Scientific debate

The resistance of bacteria to antibiotic drugs occurs naturally, when an error in the process of replication bestows resistance on a micro-organism. The application of antibiotics kills the weak organisms but bestows an advantage on the mutated strains of the bacteria that have developed resistance. The resistance genes are then passed on to their offspring. Over-use and incorrect use of antibiotics multiplies the

probability of resistant bacteria arising. Another way bacteria acquire resistance is horizontally, that is from other bacteria. Resistance genes are highly transmissible and can jump from one bacterium to another. Interestingly, research shows that bacteria from a range of environments have developed resistance, doing so quite independently of human intervention, and most likely to fend off the antibiotic chemistry of competing organisms (Nesme et al, 2014).

Although the emergence of resistance to antibiotic agents is a natural process, its spread has been hastened by a number of practices. Over-use and inappropriate use, e.g. for viral infections such as colds and the flu, is one problem; it is estimated that in the United States up to half of antibiotic use in humans is unnecessary and inappropriate (CDC, 2013). If resistance is a natural and expected consequence, it follows that antibiotics ought to be deployed like a scarce and possibly finite resource. This is especially true of broad spectrum drugs, those that are effective against a broad number of bacteria, and which are thus especially valuable. However, for human use, antibiotics have been the subject of poor use and prescription practices; controls over the drugs vary widely by country, with a special concern being the availability of antibiotic drugs without prescription. At the same time, while this undoubtedly contributes to the emergence of resistance, this must be weighed against the issues of access to medicines in regions with a shortage of doctors. In hospitals poor infection control contributes to the spread of resistant strains, although relatively simple and cost-effective measures can dramatically improve patient outcomes (Pronovost & Vohr, 2011).

A particular concern is the use of antibiotics in animal husbandry for growth promotion and prophylactic purposes. By some estimates, up to 80 per cent of antibiotics by weight sold in the United States were used in livestock production,

including drugs with importance for human health (Philpott, 2011; FDA, 2014). Low doses of antibiotics, given to large numbers of animals in concentrated areas, as is the case for modern feedlots, favours the development of resistant strains of bacteria (Marshall & Levy, 2011). A growing area of concern is the use of antibiotics in the aquaculture industry (Cabello, 2006). Based on concerns over the emergence of resistance, the use of antibiotics for growth promotion was first prohibited in several European countries, followed by an EU-wide ban in 1999. Historically, the US has taken a more permissive approach, with the recent voluntary guidelines to curb non-therapeutic use of antibiotics (PCAST, 2014; FDA, 2013).

Due to the complexities of gene exchange, it has been difficult to establish direct evidence linking resistance in animals to that in humans (Marshall & Levy, 2011; Laximinarayan et al, 2013). What is transmitted are not resistant bacteria themselves, but rather the highly mobile genetic elements encoding for resistance. Strong circumstantial evidence is available suggesting that resistance genes circulate between people, animals and the environment (Laximinarayan et al, 2013).

Unlike drugs for chronic conditions, such as diabetes, antibiotics are normally taken only in short courses, but still face the same development costs (upwards of US\$1.2 billion for new therapeutics) thus diminishing the incentives for pharmaceutical companies (DiMasi & Grabowski, 2007). In fact, based on the standard economics of new drug development, in order to recoup development costs, the hypothetical price charged for a course of a new antibiotic could be in the tens of thousands of dollars (PCAST, 2014). Coupled with the difficulty in identifying new agents, this has led to a situation where very few new antibiotic drugs are in development. Efforts are underway to incentivize the discovery of new antibacterial drugs, including through guaranteeing an additional five years of market exclusivity in the US for drugs targeting certain pathogens (PCAST, 2014).

While in the past, the emphasis was on drugs acting against a broad range of harmful bacteria – broad spectrum antibiotics – the reality of the rapid evolution of drug resistance means that this model may no longer be viable (Laximinarayan et al, 2013). Instead, a more productive focus could be on antibiotic drugs targeted at a narrower range of susceptible organisms. Rapid diagnostic tests at the point of care will be needed to facilitate treatment with such antibiotics, as will education of clinicians, who are reliant on broad spectrum drugs to treat infections where the precise causative organism is not known.

In addition to new antibiotics, alternative treatment approaches include compounds that aid or amplify the effect of antibiotics, so-called adjuvants, which target bacterial resistance mechanisms, as well as compounds that reduce the virulence of pathogens, for instance by inhibiting the secretion of toxins (Laximinarayan et al, 2013). Another alternative involves the use of bacteriophages – viruses that invade and kill bacteria – a form of treatment in use before the advent of antibiotics (Golkar, 2014). The use of bacteriophages – so-called phage therapy – is effective against antibiotic resistant bacterial infections because it is not susceptible to the usual resistance mechanisms; however, it must be narrowly targeted, with specific phages killing specific bacteria (Reardon, 2014).

#### **Issues for consideration**

The following are among the issues suggested for further consideration by policy-makers:

- Enhance global and national surveillance of antibiotic resistance and strengthen mechanisms for reporting and information sharing.
- Promote careful stewardship of antibiotics as a public good through more rational prescription practices and education of clinicians and the public about the causes and risks of antibiotic resistance.
- Promote a shift from routine use of broad spectrum antibiotics towards targeted treatment.
- Accelerate the development and deployment of clinically useful rapid diagnostic tests.

- Accelerate the development and supplementary treatment options. deployment of alternative and

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