Preface

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The past few years have seen some alarming headlines in the international press concerning the threat posed to human health by antimicrobial resistance. They include phrases such as—‘a threat to global security’, ‘greatest threats to modern health’ and ‘a future without cures to common community and hospital-acquired infections’.

Concern about the evolution of resistance to widely used anti-infectives is not new. Many editorials and opinion pieces in major scientific journals have drawn attention to the problem over the past few decades [1,2]. In some cases, such as chloroquine resistance in the most severe form of malaria (Plasmodium falciparum), alarm bells have been ringing since the late 1950s when resistant strains emerged in South America and South East Asia. The drug was first manufactured in 1934 but did not become widely used until 1955. It took some time for resistant forms to spread widely, unlike an earlier drug, pyrimethamine, where resistance emerged quickly and spread rapidly. This was due to greater genetic complexity in traits for resistance to chloroquine, in contrast to those conferring resistance to pyrimethamine [3]. More recent examples of the rapid emergence of resistance include HIV-1. In an untreated patient, roughly 100 million new virions are produced each day. Every possible mutation across the RNA viral genome occurs daily, and for monotherapy, selection and concomitant resistance arise rapidly. In practice, treatment failure is prevented by using combination therapy involving three drugs each designed to impact different functions of the viral genome. However, the prevalence of transmitted drug-resistant HIV strains has doubled in low- and middle-income countries in recent years, and multi-drug resistant strains are increasing in frequency [4].

The emergence of resistance is an inevitable consequence of natural selection and it follows a somewhat predictable pattern, represented by an S-shaped curve in resistant trait frequency change over time, starting slowly (and often undetected for many years) and then rising steeply to a plateau. The time scale over which this pattern emerges can vary from a few years to many decades. The time scale and trait frequency at the plateau depend on many factors, including the intensity of drug use, the number of mutations required to confer resistance and the impact of resistance on the overall fitness of the resistant pathogen, by comparison with susceptible strains, in the absence of drug pressure.

The question of how best to slow or even abate the evolution of resistance is a complex issue that depends on the fine detail associated with various biological, epidemiological and drug use processes. These include the population dynamics of within-host pathogen population growth (e.g. the relative growth rates of resistant and sensitive strains, the strength of the host’s immune response) and the pharmacodynamics and pharmacokinetics of the drug–pathogen interaction or interactions. The genetic basis of resistance is of central importance, as are the routes of genetic exchange between organisms (bacteria are very promiscuous in terms of genetic exchange) and the transmission dynamics within and between different patient (and in some cases human and animal) populations.

Much of current international attention on antimicrobial resistance centres on the common bacterial infections acquired in the community or within hospital settings post-surgery. Hundreds of new antibacterial agents have been developed over the past 40 years but relatively few have survived to emerge as effective and widely used therapies. The rate of launch of new antibiotics
has slowed significantly in recent decades (20 new classes of antibiotics were marketed between 1940 and 1962 but since then only two new classes have reached the market [5]), with the pharmaceutical industry increasingly turning to other disease fields such as cancer. The global market for cancer treatments is running at approximately US$90 billion annually, which is to be compared with the current anti-bacterial market of approximately US$38 billion, which operates with high volume and low price, and is dominated by companies producing generics [6]. Innovation in such an environment can be very costly with uncertain returns in the longer term.

The reasons for a decreased rate of discovery of novel antibiotics are many and complex. On the one hand, rapid advances in knowledge about bacterial pathogens, in part, generated by whole genome sequencing, and also by progress in understanding gene function and the factors that determine bacterial virulence, should act to stimulate discovery. However, the promise of new scientific approaches, such as bacterial genomics, high-throughput screening and combinatorial chemistry, has not materialized as envisaged in the discovery of new targets.

Central to current concerns about the decline in new antimicrobial agents is the global rise in bacterial strains resistant to the most commonly used drugs, and increasingly the emergence and spread of multi-drug resistant organisms. The spread of these strains in hospital and community settings is determined by many factors including drug use patterns, patient compliance to prescribed regimens, links to other uses of antimicrobial agents in veterinary and even fish farming contexts, and the growing problem in many emerging economies of counterfeit drugs with suboptimal efficacy. In veterinary practice, antibiotics have been widely used to promote weight gain in livestock. Concern at this practice resulted in the European Union banning the use of antibiotics in animal feeds as growth promoters in 1998. However, the practice still continues in many regions of the world, including the USA.

Advocacy has greatly increased in recent years, arguing for urgent action to reduce (or even reverse) the spread of drug resistant strains of common pathogens. This is to be welcomed, but much less uniformity is apparent in defining practical solutions to this global problem. Fast tracking novel antibiotics with activity against multi-drug resistant strains by the European Medicines Agency and the Food and Drug Administration in the USA is one positive move. Current discussions centre on many issues including the duration of patent protection, increased funding for basic research in this field, improved training for physicians in prescribing antimicrobial drugs, the value of rotational drug use in hospital settings, greatly enhanced national and international surveillance, and strengthening international regulation on drug use in livestock growth promotion.

This volume of papers arose from the current growing concern over the problem of antimicrobial resistance. It represents a collaboration between The Royal Society and The Academy of Medical Science in organizing a joint discussion meeting held at The Royal Society in May 2014.1

The volume consists of papers presented at this meeting plus other commissioned contributions. It covers perspectives on the problem from many different fields including scientific, clinical, public health, veterinary, industry and government. Two papers by Aarestrup [7] and Woolhouse [8] examine the interaction between antimicrobial resistant infections in livestock and humans, and the wider environment. The difficulties in national surveillance, despite the availability of new scientific tools, are discussed by Johnson [9], while the complex world of drug resistance of bacterial populations in the human gut, and genetic transfer within this very large bacterial population, are examined by van Schaik [10]. Epidemiological and population genetic perspectives, based on the study of preventive therapy in hospital settings, are examined in a paper by Kunkel et al. [11], while Mitchell et al. [12] examine the important issue of how antibiotic treatment of pneumococcal carriage populations effects the evolution of vaccine escape mutants. The final two papers present views on research, development and commercialization in the pharmaceutical industry [13], and the task of government in policy formulation to both encourage innovation and reduce the spread of resistance [14].

The diversity of topics covered in this volume well illustrates the complex interplay between many different fields of activity that influence our ability to address this growing threat to human health and the effective treatment of common microbial infections in hospital and community settings.

Endnote

1Royal Society discussion meeting on ‘Antimicrobial resistance—addressing the threat to global health’ held on 22–23 May 2014. Organized in partnership with the Academy of Medical Sciences by Prof. Sir Roy Anderson FMedSci FRS and Prof. Sharon Peacock FMedSci.

References


