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Review

Antimicrobial resistance (AMR): significance to food quality and safety

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Abstract

Antibiotic resistance presents a significant challenge to clinical, veterinary, and plant health and is now recognized by the World Health Organization (WHO) as a major emerging problem of global significance. As yet, there have been no successful discoveries of classes of novel antibiotics since 1987. There is an antibiotic discovery void, and it is now widely acknowledged that there is an urgent need for the development of novel antimicrobial agents. For economic reasons, many of the largest pharmaceutical companies have abandoned the antibiotic field, and research conducted by academia was scaled back due to funding cuts following the economic crisis. A post-antibiotic era—in which common infections and minor injuries can kill—far from being an apocalyptic fantasy, is indeed a very real possibility for the 21st century.

Key words: antibiotic; antimicrobial resistance (AMR); antibiotic paradox; antibiotic discovery void.

Introduction

Since the discovery and introduction of antibiotic agents in the early 20th century, their targeted selective toxicity has ensured their widespread use to combat infections. The overuse of antibiotics has now resulted in the emergence of multidrug-resistant pathogens, due to the dispersal of antibiotics into the wider environment, often in sub-lethal concentrations. Antibiotic-resistant bacteria can be transmitted to humans through direct contact with livestock, through the food chain, and the wastewater from farms, hospitals, and pharmaceutical plants.

'The antibiotic paradox' describes the premise that this misuse of antibiotics destroys their curative powers. Antibiotic resistance now presents a significant challenge to clinical, veterinary, and plant health and is now recognized by the World Health Organization (WHO) as a major emerging problem of global significance. With some 80 per cent of the global human population reliant on traditional medicines, much of which is based on plant remedies, global and local research is being undertaken into sourcing novel antimicrobials from native botanical and fungal floras for plant health and biomedical applications. Resources such as higher plants, marine, and terrestrial algae and fungi have not only been historically exploited, but are currently being scouted as potential sources of sustainable alternate natural complimentary therapies.

An Historical Perspective

For all the technological advances humanity has achieved over the preceding few millennia, one of the most important has been our ongoing war against the microbes that surround us in our daily lives. Infectious diseases can and do overwhelm and decimate human populations, as evidenced by the Spanish Flu which followed World War I from 1918 to 1920. This killed somewhere between 50 and 100 million people globally, some 3%–5% of the world's population (Taubenberger and Morens, 2006). Throughout humanity's history of warfare, the overwhelming cause of death has not been wars or military campaigns, but infections, which were much more proficient

at killing than any military strategy. One of the reasons it was so easy for the relatively small Spanish army to subdue millions of people living in South America was the infections such as smallpox, measles, and cholera that came with the invaders (Bianchine and Russo, 1992). To date, humanity has only eradicated a single infectious disease of humans, namely smallpox, caused by the variola virus (WHO, 1988). Writing in 1999, Iwu *et al*. stated that infectious diseases accounted for approximately 50 per cent of all deaths in tropical countries, and that infectious disease mortality rates were actually increasing in developed countries. The increase was attributable to HIV/AIDS and respiratory tract infections, together with an increase in antibiotic resistance in nosocomial and community-acquired infections.

Long before mankind discovered the existence of microbes, our 'war' against them began with vaccination and the pioneering work of Edward Jenner in 1796, when he successfully used pus from cowpox blisters to induce immunity to smallpox. This work was published privately as a text in 1798 (Jenner, 1798). The contemporary understanding of vaccination is the introduction of an antigen (or vaccine) in order to stimulate an individual's immune system and develop immunity to a pathogen via the production of antibodies. Jenner did not understand the close relationship of the two causative agents of cowpox and smallpox, now known to be viruses. The next stage in the development of methods to control microbes came in the 1860s with Joseph Lister's use of sterilization methods and his introduction of antiseptics. Lister pioneered the use of carbolic acid or phenol solution for the sterilization of surgical instruments and direct application to incisions and dressings, which helped turn hospitals from places of high mortality (Lister, 1867). Antiseptics are in common usage today, and all are antimicrobial substances applied directly to the skin or tissue to reduce the possibility of infection. Frequently used antiseptics include alcohol, hydrogen peroxide, iodine, and trichlorophenols (TCP). In 1871, Lister investigated the discovery that urine samples contaminated by moulds did not allow bacterial growth. This was one of the first studies investigating the basic principles of biocontrol and he named the mould responsible as *Penicillium glaucum*.

Within the last century came the first antibiotic, penicillin, discovered by Sir Alexander Fleming, who noted the inhibitory property of a *Penicillium* mould on disease causing staphylococci, in 1928 (Ackerknecht, 1982). This breakthrough was followed by the synthesis of the first sulphonamide drug, Prontosil, by the German biochemist Gerhard Domagk (Domagk, 1935). Prontosil was derived from a synthetic red dye. Its use resulted in a sharp decline in mortality from infections due to Gram-positive cocci, and Domagk was awarded the 1939 Nobel Prize in Physiology or Medicine. Antibiotics (antibacterials) are antimicrobial drugs used to treat or prevent bacterial infections, and are conveniently grouped according to their mechanism of action against bacteria as shown in Table 1. Today, antibiotics are used to treat or prevent bacterial infections in clinical and veterinary situations. Penicillin was developed for use against many bacterial infections, such as scarlet fever (*Streptococcus*). Following the purification of the first penicillin by Florey and Chain, they went on to achieve purification and large-scale production of the first antibiotic, penicillin G, by 1942. Fleming, Florey, and Chain shared the Nobel Prize for Physiology and Medicine in 1945. Penicillin saved the lives of innumerable injured allied soldiers during World War II, as few microbes had been exposed to penicillin before encountering it, and the majority were susceptible to it at that time.

The term antibiotic was credited as being used by Waksman *et al*., in 1947, to include any substance produced by a microorganism that was antagonistic to the growth of other microorganisms in high dilution (Waksman, 1947). In 1944, Waksman and Schatz isolated streptomycin from *Streptomyces griseus* (Schatz *et al*., 1944). Clinically, the role of antibiotics has since expanded from treating serious infections, to preventing infection in surgical and cancer patients, and protecting individuals with compromised immune systems. Antibiotics have also been used in veterinary medicine since they became widely available. An estimated 80 per cent of all antibiotics consumed in the USA are used in the feed of animals intended for human consumption [The Center for Disease Dynamics, Economics and Policy (CDDEP), 2015]. The selective pressures humanity thus placed upon microbial communities by the use of antimicrobials and antibiotics inevitably led to resistance, exactly as Sir Alexander Fleming forecast in an interview after winning the Nobel Prize in 1945 for discovering penicillin: 'The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism'.

Table 1. Antibiotic grouping by mechanism of action.

Mechanism	Class of antibiotic	Selected drug examples
Inhibitors of cell wall synthesis (beta-lactams)	Penicillins	Penicillin G, Methicillin, Ampicillin
	Cephalosporins	Cefalotin, Cefaloxin, Cefotan
	Carbapenems	Ertapenem, Meropenem,
	Monobactams	Aztreonam
	Vancomycin	Vancomycin
	Bacitracin	Bacitracin
Disruptors of cell membranes	Polymyxins	Polymyxin B, Polymyxin E
Nucleic acid synthesis inhibitors	DNA synthesis inhibitors	Nalidixic Acid, Ciprofloxacin
	RNA polymerase inhibitors	Rifampin
Protein synthesis inhibitors	30s subunit—aminoglycosides	Gentamicin, Streptomycin
	Tetracyclines	Tetracycline, Doxycycline
	50s subunit—macrolides	Erythromycin, Clarithromycin
	Chloramphenicol	Chloramphenicol
	Lincosamide	Clindamycin
Folic acid synthesis inhibitors	Sulfonamides/Trimethoprim	Sulfamethoxazole, Trimethoprim
	Pyrimethamine	Pyrimethamine
Mycolic acid synthesis inhibitors	Isoniazid	Isoniazid

Antimicrobial Resistance

Antimicrobial resistance (AMR) is a process in which a microorganism evolves to become either more, or fully resistant to an antimicrobial agent which could previously treat it effectively. Antibiotic resistance, which applies specifically to bacteria and antibiotics in a clinical situation, refers to a microorganism's resistance to an antibiotic, and is a direct result of antibiotic use. AMR is increasing, especially in the context of healthcare-associated infections (HAIs), or nosocomial infections, which are those acquired by hospital patients who were admitted for reasons other than that infection. Such patients have increased reliance on antibiotics, which in turn results in increased drug resistance among common, previously treatable HAIs (Choffness *et al*., 2011), hence the rise of organisms such as vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA). As hospitals and other long-term care facilities use large quantities of antibiotics, they can become reservoirs of resistant pathogens. Other significant issues associated with higher levels of AMR include the increased costs of treatment and raised patient mortality. The US Centers for Disease Control and Prevention (CDC) estimates that antibiotic resistance causes more than 2 million infections and some 23,000 deaths each year in the USA of which 14 000 were attributable to *Clostridium difficile* in 2013. This organism is resistant to most antibiotics and can proliferate in the human intestine after the demise of other antibiotic sensitive species. A further 25 000 deaths a year in Europe were attributed to antibiotic resistance in 2007, with an additional total extra healthcare cost and productivity loss of 1.5 billion Euro (The Bacterial Challenge, 2009). The dates of discovery and introduction of the classes of antibiotics, together with the year when antibiotic resistance to each was first noted, are presented in Table 2, and mechanisms of resistance in Table 3. Resistance due to decreasing antibiotic effectiveness has risen from a minor issue, to a global challenge, and it has been said that we now live in a 'post-antibiotic era'. Keiji Fukuda (Assistant Director-General, Health Security) stated in the Foreword that, 'A post-antibiotic era--in which common infections and minor injuries can kill--far from being an apocalyptic fantasy, is indeed a very real possibility for the 21st century'.

Table 2. Dates of introduction of antibiotic classes and first observation of resistance.

Class of antibiotic	Year of discovery/introduction	Year resistance observed	Activity or target species
Inhibitors of cell wall synthesis			
Penicillins	1928/1938	1945	Broad-spectrum
Vancomycin	1953/1958	1960	Gram-positive bacteria
RNA polymerase inhibitors			
Rifampicin	1957/1958	1962	Gram-positive bacteria
DNA synthesis inhibitors			
Ciprofloxacin	1961/1968	1968	Broad-spectrum
Protein synthesis inhibitors			
30s subunit—aminoglycosides			
Streptomycin	1943/1946	1946	Broad-spectrum
Tetracyclines	1944/1952	1950	Broad-spectrum
50s subunit—macrolides			
Chloramphenicol	1946/1948	1950	Broad-spectrum
Streptogramin B	1963/1998	1964	Gram-positive bacteria

Table 3. Mechanisms of antibacterial resistance.

Basis of resistance	Mechanism	Bacterial proteins/targets responsible	Antibiotic targets
Reduced permeability or uptake	Reduced expression/defective protein	Porins	Beta-Lactams Fluoroquinolones Aminoglycosides Chloramphenicol
Enhanced efflux	Active extrusion	Membrane proteins	All major antibiotics
Enzyme	Hydrolysis	Beta-Lactamases	Beta-Lactams
		Esterase	Macrolide
	Group transfer	Acetyltransferase	Streptogramins Aminoglycosides Chloramphenicol
		Phosphotransferase	Aminoglycosides Macrolides
		Glycosyltransferase	Macrolides
Target modification	Structural alterations/modifications	Penicillin binding proteins	Beta-Lactams
		Cell wall precursors	Vancomycin
		Ribosomal subunits	Streptomycin
	Mutations in genes	RNA polymerase	Rifamycin
	Amino acid substitutions	DNA gyrase/topoisomerase	Quinolones
	Methylation	16S rRNA	Aminoglycosides
	Mutation	23S rRNA	Oxazolidinones
Target protection	Ribosome protection	Ribosome protection proteins	Tetracycline

Antibacterial agents do however leave survivors resistant to that particular agent or antibiotic. Suddenly freed from so many competitors, these survivors reproduce quickly, spread, and colonize. Places associated with scrupulous hygiene, such as hospital wards and operating theatres, are particularly vulnerable. A survey of over 2000 US hospitals in 2009–10 found that some 20 per cent of such hospital-acquired infections involved multidrug-resistant organisms (the so-called 'superbugs') (Sievert *et al*., 2013). By the production of biofilms, bacteria adopt a multicellular behaviour that can facilitate and/or prolong their survival in diverse environmental niches. In hospital settings, the formation of biofilms on vents and medical equipment enables bacteria such as *Pseudomonas aeruginosa* to persist as reservoirs that can readily spread to patients (Kostakioti *et al*., 2011).

Mechanisms of AMR

A significant milestone in our understanding of microbes and their role in infection was the discovery that microbial antibiotic resistance genes themselves are transmissible and promiscuous, so spreading from organism to organism. Bacterial resistance can come about for a number of reasons, classically due to a mutation of the antibiotic-target gene in the bacterial chromosome, or elsewhere following the addition of extra-chromosomal DNA (Ventola, 2015a and 2015b). However, resistance is most commonly associated with the acquisition of extra-chromosomal elements encoding resistance determinants. These elements are acquired from other bacteria in the environment in a number of ways. A transformation event involves the incorporation of free DNA segments into the bacterial chromosome. Transduction involves gene transfer following infection by a defective bacteriophage. The most efficient process, and the one that has the greatest impact on the spread of antibiotic resistance, is via the transfer of plasmids and conjugative transposons during cell-to-cell contact during conjugation (Alekshun and Levy, 2007; Ventola, 2015a). The importance of Horizontal Gene Transfer via conjugation is highlighted in the following reports.

Blanco *et al*. (2016) report that bacterial multidrug efflux pumps are antibiotic resistance determinants present in all microorganisms: efflux pumps are ancient, highly conserved determinants, which have been selected long before the recent use of antibiotics for the therapy of human infections. The role of efflux pumps as relevant antibiotic resistance determinants in bacterial pathogens is likely secondary to other functional roles with reference to bacterial physiology (Blanco *et al*., 2016). However, tetracycline resistance can be encoded by four different determinants residing on plasmids in *Escherichia coli*: plasmid RP1 (class A), plasmid R222 (class B), plasmid R144 (class C), and plasmid RA1 (class D) (McMurry *et al*., 1980).

Shaikh *et al*. (2015) state that transferase enzymes are the most diverse family of resistant enzymes which inactivate antibiotics, including beta-lactams, aminoglycosides, chloramphenicol, and streptogramin A. The mechanism involves chemical substitution, i.e. the addition of chemical groups to the periphery of the antibiotic molecule, which impairs their binding to a target. Polymyxin antibiotic resistance normally involves chromosomal mutation, but an *E. coli* strain, SHP45, possessing colistin resistance that could be transferred to a second strain by a plasmid, MCR-1, was isolated by Liu *et al*. (2016). Leclercq (2002) states that resistance to macrolide (erythromycin) and lincosamide (clindamycin) antibiotics is increasingly reported in clinical isolates of Gram-positive bacteria. There are considered to be three mechanisms of resistance: ribosomal modification, efflux of the antibiotic, and drug inactivation. Plasmid-mediated resistance is not recorded. Resistance to trimethoprim and sulphonamides came about following horizontal spread of resistance genes, expressing drug-insensitive variants of the target enzymes (dihydropteroate synthase for sulphonamide and dihydrofolate reductase for trimethoprim). Two genes, *sul1* and *sul2* expressing dihydropteroate synthases highly resistant to sulphonamide, are carried by transposons and plasmids. Almost 20 different resistance genes expressing drug-insensitive dihydrofolate reductases are spread as cassettes in integrons, transposons, and plasmids (Sköld, 2001). Fluoroquinolone antibiotics (such as nalidixic acid and ciprofloxacin) are broad-spectrum agents used to treat a range of infections. They target DNA gyrase and topoisomerase enzymes which control DNA supercoiling within the cell. Various genes encoding different resistance mechanisms are often found on plasmids, and known as plasmid-mediated quinolone resistance (PMQR) genes, the first one being isolated from a plasmid in a clinical isolate of *Klebsiella pneumoniae* (Redgrave *et al*., 2014). It can be seen that bacteria acquire antibiotic resistance genes most commonly by conjugation, whereby a resistant 'donor' strain can transfer a plasmid to an antibiotic-susceptible recipient in what is termed a horizontal exchange. Plasmids are extra-chromosomal loops of DNA that act as vectors which can carry and transfer antibiotics resistance genes. Such transfer can occur both within members of the same species and also between genera or species. One plasmid with a broad host range is the resistance plasmid RP1, first identified in a clinical strain of *P. aeruginosa*. This plasmid can transfer to most, if not all Gram-negative bacteria (Bennett, 2009) and carries resistance to ampicillin, tetracycline, and kanamycin. Newly resistant cells can then transmit resistance vertically to daughter generations.

AMR bacteria constitute a threat to public health globally. From initially occurring in hospital settings, where organisms with low-level antibiotic resistance were treated with larger antibiotic dosages, given time, highly resistant strains emerged, such as penicillin-resistant *S. aureus* found in hospitals in the 1950s. Initially, the organisms isolated had a single antibiotic resistance, but *Shigella dysenteriae* resistant to tetracycline, chloramphenicol, streptomycin, and sulphonamides was isolated in the late 1950s (Levy, 1982). A notable example is resistance to penicillin among staphylococci, specified by the penicillinase enzyme, which degrades the antibiotic. So, after the surviving pathogenic bacteria adapted to their newly toxic human environment, resistance began to spread rapidly across many species of pathogens, such as between members of the Enterobacteriaceae, where the RP1 plasmid is transmissible between strains of *P. aeruginosa*, *E. coli*, and *Proteus mirabilis*. The sharing of resistance genes and rapid reproduction rate compressed Darwinian evolution, and led to a race between the emergence of resistant pathogens and the human need for miracle cures (Levy, 1982; Ventola, 2015a and 2015b).

The dispersal of AMR bacteria across human communities and globally occurs as for infectious diseases, i.e. by direct contact person to person, from animal to person (by scratches or bites) and vertically from mother to unborn child. In addition, insects such as mosquitoes, midges, fleas, lice, and ticks can act as vectors. The bacterium *Borrelia burgdorferi*, which causes Lyme disease, is transmitted by ticks of the genus *Ixodes*. Certain *Borrelia* strains express resistance to erythromycin (Terekhova *et al*., 2002). Members of the genus *Rickettsia* are obligate intracellular parasitic bacteria that grow directly within the cytoplasm of the eukaryotic host cell. Transmitted by lice of the genus *Pediculus*, *Rickettsia prowazekii* is the causative agent of epidemic typhus. A common site for rickettsial rifampin resistance mutations lies within the *R. prowazekii rpoB* gene, which codes for the β subunit of DNA-dependent RNA polymerase. Mutants which exhibit a single substitution of arginine for lysine at residue 546

carry rifampicin resistance. This mutation falls within a region of the rickettsial protein that corresponds to the rifampin resistance region of *E. coli* (Rachek *et al*., 2000).

Food contamination can allow bacteria to spread to many people from a single source, i.e. *E. coli*, *Salmonella*, or AMR bacteria. Non-typhoidal *Salmonella* spp., *Campylobacter* spp., and *E. coli* 0157 are all listed as causing foodborne illnesses between 2000 and 2008 in a CDC report (www.cdc.gov/foodborneburden). Iweriebor *et al*. (2015a) recorded multiple antibiotic resistances among *E. coli* 0157, in faeces of dairy cattle farms. Finally, AMR bacteria can also be transmitted by indirect contact, where the bacteria persist on an inanimate object, such as a door handle, liable to be touched by many individuals. Perhaps the ultimate form of transmission of AMR bacteria is via recent inventions, particularly global travel by aircraft. More than 1 billion people travel by air each year, and the greatest concern for global health is the ability of an individual with a contagious illness to travel to virtually any part of the world within 24 h. Worth noting was the delay in the spread of influenza by the decrease in air travel, following the attacks of 11 September 2001 (Mangili and Gendreau, 2005; Pavia, 2007). Arcilla *et al*. (2017) reported that the acquisition and spread of *E. coli* and *Klebsiella*, which produce enzymes called extended-spectrum β-lactamases (ESBLs), during and after international travel, were substantial and worrisome. Strains carrying ESBLs are resistant to many penicillin and cephalosporin antibiotics. Travellers to areas with a high risk of acquisition of these strains should be viewed as potential carriers for up to 12 months after return (Arcilla *et al*., 2017).

The Antibiotic Paradox

However, the greatest complicating factor of the modern era has been the widespread and sometimes indiscriminate misuse and overuse of antibiotics. 'The antibiotic paradox' describes the premise that the misuse of antibiotics destroys their curative powers (Polly, 1993; Toner, 2005) or 'How miracle drugs are destroying the miracle' (Levy, 2002). Prescribed initially when there was little option, antibiotics became overprescribed both for medicinal and veterinary use (Mateu and Martin, 2001), so imposing selective pressure on formerly sensitive bacteria to acquire resistance. The ever increasing demand for animal protein and consequential intensification of food animal production has led to greater use of antibiotics, since they were first introduced as growth promoters (Dibner and Richards, 2005; Anonye, 2016). Globally, the livestock sector is divided between developed and developing countries: total meat production tripled between 1980 and 2002, from 45 to 134 million tons. Much of this growth accompanied the rapid economic growth of developing countries, particularly in East Asia, revolving around poultry and pigs. Overall, livestock production and merchandizing in industrialized countries account for 53 per cent of agricultural GDP (Thornton, 2010).

The growth promoter effect of antibiotics was discovered in the 1940s when it was noted that animals fed dried mycelia of *Streptomyces aureofaciens* (containing chlortetracycline residues) improved their growth (Castanon, 2007). These beneficial effects were reported in poultry and swine between 1946 and 1950. The mechanism of action is related to interactions with the animals' intestinal flora (Dibner and Richards, 2005; Niewold, 2007), but by 1951, there were reports of resistance following experimental feeding of turkeys with streptomycin. This was followed by reports of an association of resistance to tetracycline, when growth-promoting levels of this antibiotic were fed to chickens (Dibner and Richards, 2005). Avoparcin is a glycopeptide antibiotic that was widely used in Europe as a feed additive or antibiotic growth promoter (AGP) from the 1970s to 1990s. A similar glycopeptide, vancomycin, became more widely used in the human population from the 1980s (Levine, 2006). In the mid-1990s, as VRE began to emerge, researchers in Denmark were documenting an association between avoparcin use in pigs and poultry with a prevalence of faecal carriage of VRE in animals on exposed farms (Bager *et al*., 1997). Other European research recorded VRE in meat and in faeces of people in the farming community. The issue of VRE contributed to a growing sense of crisis concerning the use of AGPs and to calls for greater scrutiny or restrictions on antimicrobial use in animals, especially AGPs. In 1995, Denmark banned the use of avoparcin as a feed additive, which was followed by the voluntary withdrawal of all AGPs by the pig and poultry industries in Denmark. By 2005, all feed additives containing antibiotics, many of which were in classes used in humans, were banned across Europe (Casewell *et al*., 2003; Keen and Montforts, 2012).

The earliest concerns about the development of antibiotic resistance in human pathogens and recommendations to ban sub-therapeutic use in animal feeds were discussed by Swann, in a report to the UK parliament in 1969 (Swann, 1969). The entry of resistant pathogens to the human food chain, and their subsequent transfer from animal to man by the consumption of contaminated food, is illustrated by *Salmonella enterica*, associated with poultry and poultry meat products. The estimated total cost for non-typhoidal *Salmonella* is in excess of $14 billion per year in the USA alone. Over 40 000 cases of non-typhoidal foodborne salmonellosis are confirmed annually, with an estimated 1 million cases not being reported (Cosby *et al*., 2015). The Food and Agriculture Organization (FAO) Animal Production and Health working paper 'Mapping Supply and Demand for Animal-Source Foods to 2030' reported in 2011 that agricultural production would have to increase by 70 per cent (nearly 100 per cent in developing countries) by 2050 to cope with a 40 per cent increase in global population. This would include an additional billion tonnes of cereals and 200 million tonnes of animal-derived protein, *per annum*, as compared to production in 2005/07. The report notes that there are public health implications of further intensification of livestock production: the rapid spread of infectious diseases (such as the pandemic H1N1 influenza A virus) demonstrating the magnitude of problems arising from the emergence of novel diseases at the animal-human-ecosystems interface (FAO, 2011). In 2010, over 63 000 tons of antibiotics were consumed by livestock globally, a figure which is projected to rise by 67 per cent by 2030, and nearly double in Brazil, Russia, India, China, and South Africa (Van Boeckel *et al*., 2015). Antibiotic-resistant bacteria can be transmitted to humans through direct contact with livestock, through the food chain and the wastewater from farms, hospitals, and pharmaceutical plants. In 2011, the CDC reported that AMR was increasing the economic burden on the entire American healthcare system, to the sum of $20 billion a year in excess costs. An additional $35 billion can be attributed to societal costs, and more than 8 million additional days spent in hospitals.

The Antibiotic Discovery Void

Since the advent of antibiotics, research and development efforts have provided an ongoing stream of novel drugs needed to treat the bacteria that had become resistant to the older antibiotics. However, in 2011, Silver reported that the timeline of dates of discovery of distinct classes of antibiotics showed that there had been no successful discovery of any new *class* since 1987 (Silver, 2011). The latest registered representatives of novel antibacterial classes, linezolid,

daptomycin, and the topical agent retapamulin, were indeed introduced in 2000, 2003, and 2007, respectively, but these chemical classes (oxazolidinones, acid lipopeptides, and pleuromutilins) were first reported (or patented) in 1978, 1987, and 1952, respectively. A timeline of dates of discovery of distinct classes of antibacterials (as opposed to dates of introduction) illustrates that there have been no (as yet) successful discoveries of novel agents since 1987. There is a discovery void of unknown extent rather than a gap (see Table 2). Coates *et al*. (2011) noted that between 1940 and 1962, more than 20 new classes of antibiotics were marketed, and that to return to a situation in which there were enough antibiotics to cope with inevitable ongoing emergence of resistance, governments would have to introduce legislation and provide industry and academia with real incentives. Due to this void pharmaceutical companies have been withdrawing from research in this area, despite the recognition of the continuing need for new antibacterials to combat the rise of resistant organisms (Silver, 2011). According to Ventola writing in 2015, some 15 of the 18 largest pharmaceutical companies have abandoned the antibiotic field. Mergers between pharmaceutical companies substantially reduced the number and diversity of research teams, and research conducted by academia was scaled back due to funding cuts following the economic crisis (Ventola, 2015b).

The reasons why there now exists a void in the development of novel antibiotics are complex. Drugs used to treat chronic illnesses such as diabetes and hypertension offer a much greater potential return on investment for the larger pharmaceutical companies. Research by the pharmaceutical industry ('Big Pharma') is concentrated on drugs likely to make annual global sales in excess of several billion US dollars. In recent years, peak antibiotic sales are in the region of $500 million to US$ 1 billion (World Economic Forum, 2013). On average, pharmaceutical companies spend $5 billion on research and testing for each new drug they bring to the market; some 80 per cent of drugs produced fail in safety and efficacy testing. In the USA, in July 2012, Congress passed the 'Generating Antibiotic Incentives Now (GAIN) Act'. According to the US Food and Drug Administration (USFDA), this act highlighted and listed pathogens with the potential to pose a serious threat to public health, such as *C. difficile* and multidrug-resistant tuberculosis. The GAIN act carried incentives such as granting an additional 5 years exclusivity at the time of product approval for products granted a Qualified Infectious Disease Product (QDIP) designation. There were to be priority reviews for marketing applications for products that carried a QDIP designation, and products granted QDIP designation were to be eligible for fast track designation. The FDA was to review and update at least three guidances per year for the development of antibacterial and antifungal drugs, and publish a guidance on pathogen-focused antibacterial drug development (USFDA, 2013). Other classes of drugs are not beset by resistance issues and would have rapid global coverage, whereas antibiotics would be more restricted, last-resort treatments, resulting in much lower sales. The smaller companies cannot afford the costs of the complex requirements for clinical trials, so compromising the development of potential new agents (Piddock, 2012).

Why Is Developing New Antibiotics Becoming Less Attractive to Big Pharma?

The evidence-base has demonstrated that more and more species and genera of bacteria are becoming more resistance to several existing antibiotics. So, hypothetically, this should generate a demand for the development of new antibiotics to combat these now-resistant bacteria. While this is indeed the case, response from antibiotic manufacturers in Big Pharma has been slow due to the relatively unattractive business scenario that this presents. Figure 1 shows historically the time taken for bacteria to generate resistance

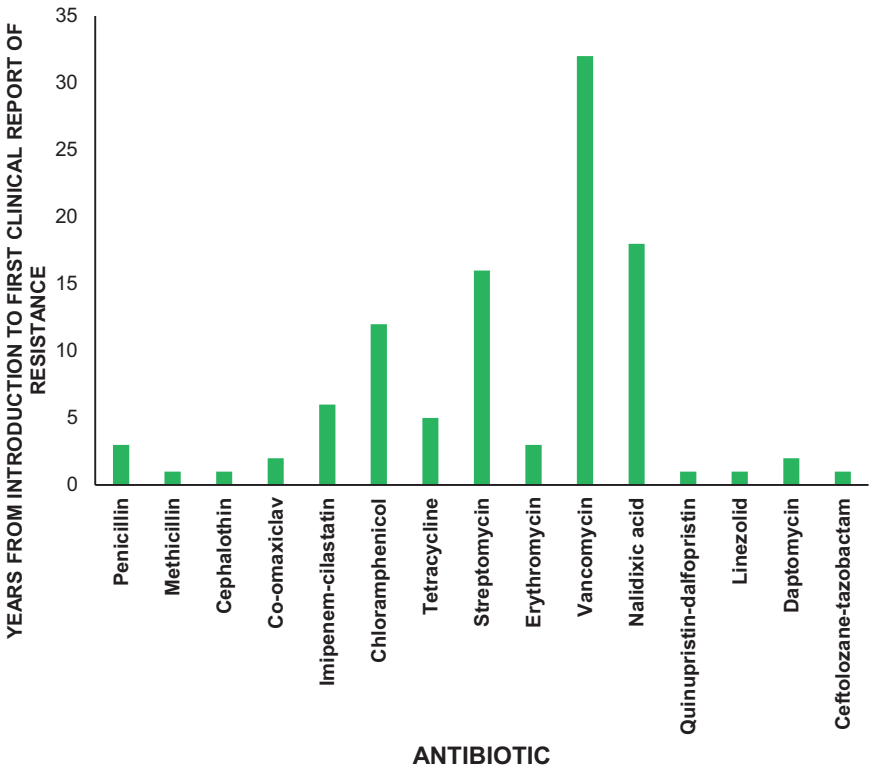

Figure 1. A chart showing time from antibiotic introduction to first report of clinical resistance.

to newly introduced antibiotics. Of the 15 antibiotics listed in Figure 1, the mean duration to resistance is 6.9 years. Given the time taken to develop a new antibiotic through innovation relating to the molecular toxicology screenings and then Phase I, II, and III clinical trials, accompanied by a finite patent life, the addition of biological resistance makes financial investment into novel antibiotics less attractive, even though there is a huge demand in the clinical marketplace.

Conclusion

AMR has now emerged as a global threat to human and veterinary public health. Prudent employment of the existing arsenal of available and licenced antibiotics needs to be emphasized and schemes adopted including antimicrobial stewardship codes of conduct, in order to extend the usefulness and efficacy of such antibiotic agents for generations. New economic incentives need to be developed to encourage investment into novel antibiotics by the pharmaceutical industry, so that society will have effective tools to combat infectious diseases for generations to come.

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Conflict of interest statement

None declared.

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