ANTIMICROBIAL RESISTANCE: A GROWING CRISIS

As this public health threat becomes an increasingly worrying global problem, Yaso Shan explores the need for a coherent and international action plan to minimise infections

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Pictured opposite: coloured scanning electron micrograph of a neutrophil white blood cell engulfing methicillin-resistant *Staphylococcus aureus* bacteria

Abstract

Infectious diseases account for a substantial proportion of deaths worldwide. Much of the progress made recently in treating these infections is now threatened by a growing number of microbes that are becoming resistant to drugs once effective in combating them. The decreasing effectiveness of antimicrobials (antibiotics, antivirals, antifungals and antiparasites) is a growing global public health concern. Multi-drug resistance and gram-negative bacterial resistance are particular concerns. But global taskforce objectives are encouraging, as are guidelines that seek to limit the use and prescribing of antimicrobials, especially antibiotics. Bacteriophage therapy and traditional plant-based medicines offer further scope in tackling what is predicted to be one of the biggest medical challenges of the 21st century.

Keywords
antimicrobial resistance, antimicrobial stewardship, infection control, artemisinin-based combination therapies, bacteriophage therapy, *C difficile*, drug resistance, herbal medicines, infection control, MRSA, multi-drug resistance

THE USE of penicillin during the 1940s was hailed as the medical breakthrough of its generation and brought an end to death from what are now regarded as common illnesses and infections.

Overuse of antibiotics since then (due in part to their inappropriate prescribing and use) has led to resistance to a much-needed treatment option and is having serious ramifications across the world.

The terms 'MRSA', 'superbug' and 'antibiotic resistance' have become familiar. Worryingly, antibiotics are only one group of drugs that microbes are becoming resistant to.

The problem is much broader than bacterial resistance. The overuse of some drugs for a spectrum of infections has resulted in resistance being conferred on drugs that are antiviral, antifungal and antiparasitic. Hence, the collective term 'antimicrobial resistance' (AMR) is widely used to refer to bacterial, viral, fungal and parasitic drug resistance.

AMR is a major and global public health threat, limiting and often negating effective prevention and treatment of an ever-increasing range of infections, such as urinary tract infections (UTIs), pneumonia, bloodstream infections, hospital-acquired infections caused by highly resistant bacteria such as MRSA or multi-drug-resistant gram-negative bacteria, gonorrhoea, HIV, and multi-drug-resistant and extensive drug-resistant tuberculosis (MDR-TB and XDR-TB respectively) (World Health Organization (WHO) 2015).

In parts of the Greater Mekong sub-region, resistance to artemisinin-based combination therapies (ACTs), the best available treatment for falciparum malaria (the most virulent form caused by the *Plasmodium falciparum* parasite), has been detected (WHO 2015). The spread or emergence of multi-drug resistance to ACTs in other regions could jeopardise recent advances in the control of this disease.

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This article aims to examine some of the problems and threats arising from AMR and the strategies of the major global economies in attempting to tackle this emerging healthcare crisis. It will explore some of the newer drugs currently in development and in clinical trials, and the potential of some plant-based options.

The evolutionary programming of microbes dictates that developing drug resistance is an inevitable natural phenomenon. Horizontal transference of drug-resistant genes during microbial replication renders ineffective drugs that were once used against them.

The use and misuse of antimicrobial agents accelerates the emergence of drug-resistant strains (WHO 2015). This is only part of the problem; global travel and trade markets of recent times mean that the causes of resistance in one nation can become a problem worldwide. Issues such as poor infection-control practices, inadequate sanitary conditions and inappropriate food handling, which encourage further spread of AMR, are all applicable to nations across the globe.

Antibiotics

Antibiotic use in farming is a practice established since the 1950s, twinned with the popularity of large-scale intensive farming methods. These drugs are now firmly embedded in the food chain, but public data on antibiotic use in farming and food manufacturing remains poor. The use of antibiotics as growth promoters in animal feed as a means to enhance the growth of livestock, especially pigs, cattle and poultry, was banned in Europe in 2006 as it was deemed non-therapeutic (European Commission 2005). The ban was also an effort to curb overuse and reserve antibiotics for medical use only. There has been a consistent call to make publicly available annual summaries of antimicrobial drug sales and their use in animal feed.

In the UK, antibiotics can only be administered by veterinary prescription and the vet is legally obliged to record it. But there is no centralised collection of this data and gaps in food labelling practices means that in reality, establishing the original source country of some meats in some foods is lacking. Antibiotic-resistant bacteria pass between humans, between animals and between humans and animals in both directions much more frequently than once realised. Copies of antibiotic-resistant genes can also move between bacteria. This exchange can occur in the human gut, so in some cases the bacteria causing infection in humans will not be of farm-animal origin, but the resistance will (Compassion in World Farming 2013).

Campaigners have long called for improved animal husbandry and welfare standards for livestock (for example, improving living conditions by providing ample space, thereby limiting the spread of disease as well as enhancing the quality of life for animals and reducing their stress levels, all of which go towards improving the immunity and wellbeing of animals). The UK Soil Association and the Responsible Use of Medicines in Agriculture Alliance (RUMA) are among a number of organisations that have published guidelines on how best to use antimicrobials in a bid to address the emerging AMR problem (RUMA 2015, Soil Association 2015).

Table 1 Four compelling reasons to tackle antimicrobial resistance

Antimicrobial resistance (AMR) kills (Figure 1)	Infections caused by resistant microbes often fail to respond to standard treatment, resulting in prolonged illness, higher healthcare expenditure and a greater risk of death; for example, meticillin-resistant *Staphylococcus aureus*
AMR hampers the control of infectious diseases	AMR reduces the effectiveness of treatment and patients remain infectious for a longer period, thus increasing the risk of spreading resistant microbes to others; for example, ACT-resistant *Plasmodium falciparum*, MDR-TB
AMR increases the cost of health care	When infections become resistant to first-line drug treatment, more expensive therapies must be used. A longer duration of illness and treatment, often in hospitals, increases healthcare costs as well the economic burden of families and societies
AMR jeopardises healthcare gains to society	Significant advances in healthcare and modern medicines are compromised by AMR. Without effective antimicrobials for prevention and treatment of infections, the success rates of organ transplants, cancer chemotherapy and major surgery are put at risk

(Adapted from WHO 2015)

Consequences of resistance

The combination of irresponsible use and a lack of development of new drugs to combat infection, particularly antibiotics, have resulted in the levels of AMR being witnessed today. Furthermore, AMR threatens many recent medical advances, particularly in the treatment of malaria and HIV.

AMR infections currently claim at least 50,000 lives each year across Europe and the US, with many hundreds of thousands more dying in other areas of the world (Review on Antimicrobial Resistance 2014). Reliable estimates of the true burden of AMR remain scarce. There is considerable

variation globally in the patterns of AMR, with different countries often experiencing different major problems. Parts of Europe are experiencing increasing numbers of patients in intensive care units, haematology units and transplant units who have pan-resistant infections, meaning there is no effective treatment available (Review on Antimicrobial Resistance).

Emerging resistance to treatment for other diseases such as tuberculosis (TB), malaria and HIV has an enormous impact, especially in poorer countries. There were an estimated 480,000 new cases of drug-resistant strains of TB in 2013, of which the majority went untreated (WHO 2015). The spread of resistant strains of malaria is similarly well documented and the development of resistance to antiretroviral therapy for HIV is closely monitored (Review on Antimicrobial Resistance 2014 Table 1 summarises some of the compelling reasons for tackling AMR.

Initial research, based on a broad-brush estimate, shows that a continued rise in resistance by 2050 will lead to ten million people dying each year and a reduction of 2-3% in GDP. It will cost the world up to 100 trillion US dollars (Review on Antimicrobial Resistance 2014). These figures are based only on a subset of drug-resistant bacteria (Table 2) and public health issues because of the lack of readily available data. Tackling AMR must be a global effort; no country can successfully overcome it by acting in isolation.

Global perspective

The report by WHO (2015) on global surveillance of AMR revealed that antibiotic resistance is no longer a prediction for the future – it is happening now.

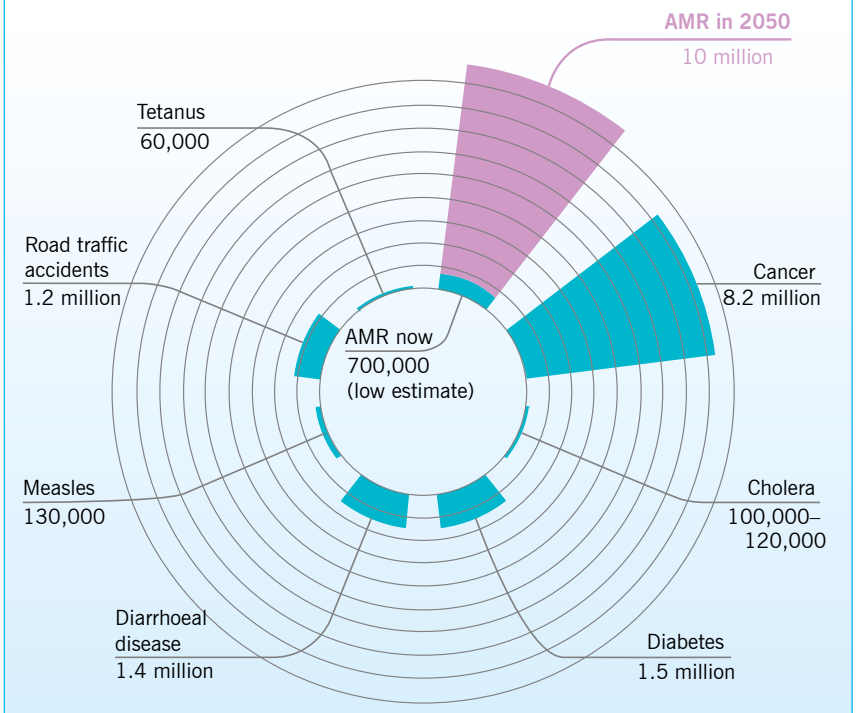
Common infections and minor injuries that have been treatable for decades can once again kill. The five areas of greatest concern are:

- Resistance in bacteria (antibiotic resistance).
- Resistance in TB (MDR-TB and XDR-TB).
- Resistance in malaria (ACT-resistant *Plasmodium falciparum*).
- Resistance in HIV (ART-resistance).
- Resistance in influenza (Influenza A).

The secondary health effects of AMR could signal a return to the dark age of medicine. Prophylactic use of antibiotics reduces the risk of bacterial infections. The areas of modern medicine most at risk of being undermined are:

- Caesarean sections.
- Joint replacements – for example, routine hip-replacement surgery.
- Cancer treatments – for example, chemotherapy.
- Organ transplantations.

Figure 1 **Deaths attributable to AMR every year compared to other major causes of death**



(Taken from Review on Antimicrobial Resistance 2014)

Tackling AMR requires a co-ordinated, effective and consistent global effort. The strategy must address the issues identified and governments must work together with policymakers and the scientific community (industry specialists and academics), in addition to philanthropic organisations with essential funding, to improve the situation. There has been some notable progress in all these areas, but more must be done.

The National Institute for Health and Care Excellence (NICE) published guidance on antibiotic prescribing in summer 2015 to accompany a range of other guidelines specific to selected diseases, such as pneumonia (NICE 2015). The concept of antimicrobial stewardship was developed to support optimal prescribing practices, prevent overuse, misuse and abuse, and to minimise the development of resistance at patient and community levels (NICE 2014).

The current advice from Public Health England's Start Smart – Then Focus (Public Health England 2015) outlines best practice in antimicrobial stewardship in the secondary care setting (NICE 2014). These say that clinical diagnosis and the continuing need for antibiotics should be reviewed within 48 to 72 hours, with five options considered:

- Stop antibiotics if there is no evidence of infection.

- Switch antibiotic formulation from intravenous (IV) to oral.
- Change antibiotic – ideally to a narrower spectrum, but broader if required.
- Continue antibiotics and document next review date.
- Start outpatient parenteral antibiotic therapy.

A survey of antimicrobial stewardship activities in 2014 by the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) revealed the following findings for ten common infections (Public Health England 2014):

- Co-amoxiclav – one of the top-five antibiotics recommended in trust guidelines.
- Cephalosporins and quinolones – recommended in less than 2% of trust guidelines.
- Between 2010 and 2013, co-amoxiclav use increased by 13%.
- Between 2010 and 2013, piperacillin/tazobactum use increased by 46%.
- Between 2010-2013, carbapenems use increased by 31%.

These findings show that despite many English hospital trusts adhering to the recommended antibiotic prescribing guidelines, a greater emphasis is required on implementing and monitoring NICE's guideline on antimicrobial stewardship to reduce unnecessary use of broad-spectrum antibiotics.

What about guidelines of regulatory authorities in other countries? There is either limited public information on specific guidelines per nation and the guidelines are continent-based, or they tend to follow the advice and guidance set by the WHO. In the US, the Food and Drug Administration (FDA) is combating antibiotic resistance through activities that include (FDA 2011):

- Labelling regulations addressing proper use of antibiotics.
- Partnering to promote public awareness.
- Encouraging the development of new antibiotics.

Table 2 Current AMR concerns

Bacteria* that already show concerning resistance levels	Broader public health issues for which resistance is a concern
Klebsiella pneumonia	HIV
Escherichia coli (E coli)	TB
Staphylococcus aureus	Malaria

*Three out of the seven bacterial species that the Word Health Organization highlights as being key AMR concerns

(Adapted from Review on Antimicrobial Resistance 2014)

The overriding strategy of all nations is to improve hygiene and sanitation, break down chains of transmission and implement effective prevention strategies for illness and disease. There is an international governance framework, with the WHO taking the lead to agree between 194 countries a global action plan to tackle AMR, with a draft action plan developed for publication in May 2015 (WHO 2015).

Additionally, the WHO continues to work closely with the World Organisation for Animal Health and the Food and Agriculture Organisation of the UN to promote best practices, including optimal use of antibiotics in both humans and animals to avoid the emergence and spread of antibacterial resistance (WHO 2015).

Given the bleak predictions for treating common infections, it is encouraging to note a number of potential and future treatment options in antimicrobials. These are highlighted in Table 3.

Role of nurses

The WHO (2015) advises that health workers and pharmacists can help tackle resistance by enhancing infection prevention and control in hospitals and clinics, only prescribing and dispensing antibiotics when they are truly needed, and prescribing and dispensing the right antimicrobial drugs to treat the illness. Community nurses are ideally placed to support the implementation of such measures, but can also support other more practical measures to help mitigate the risk of AMR. These include:

- Ensuring optimum nutrition in patients, particularly those who may be typically vulnerable to infection, such as older people and the very young, and considering supplementation (food and/or herbal) to boost immunity where nutritional status is low.
- Advising patients on the benefits of avoiding or managing stress. Stress plays a role in lowering immunity, so managing it may help prevent infection. Cardiovascular exercise to improve physical fitness and relaxation techniques may also enhance general wellbeing and mental health.
- Being instrumental in patient education. Informing and educating patients about basic hygiene practices and what they can do to prevent infection. Also, advising on the need to finish a course of treatment, especially antibiotics (if prescribed).
- Participating in antimicrobial audits and disseminating findings within the care team to support effective communication on current practice and how care can be improved (Royal College of Nursing 2012).

Table 3 Future treatment options in combating infection

New treatment	Comments
Teixobactin	Discovered in a screen of uncultured bacteria, it inhibits bacterial cell-wall synthesis by binding to its important precursors: lipid II and lipid III. No resistance from any mutant strains of *Staphylococcus aureus* and *Mycobacterium tuberculosis* have been observed. This suggests promising strategies for developing antibiotics that are likely to delay or avoid any development of resistance, unlike the current pace of drug resistance, which is relatively rapid (Ling *et al* 2015).
Bacteriophage therapy	Bacteriophages (commonly referred to as phages) are viruses that infect bacteria but not humans. They occur naturally in water, soil and even our gut, existing because of their reliance on bacteria to reproduce (viruses are obligate parasites). Cocktails of phage viruses can kill a bacterial infection in the human body with remarkable accuracy, taking out only the infiltrators and leaving intact healthy populations of 'good' bacteria (Reardon 2014). This is unlike the blunt instrument of antibiotics, which are indiscriminate in their action, leaving the body exposed to opportunistic infections such as thrush (*Candida albicans*). Bacteriophage therapy is not new; it has been widely used in Russia and parts of eastern Europe for nearly a century.
New drugs in clinical trials	In 2010, the Infectious Diseases Society of America (IDSA) established a global initiative to develop ten new antibiotics by 2020. Since then, six new antibiotics have been approved by the FDA for a range of infections in primary and secondary care (IDSA 2015). These drugs address few unmet needs, including treatment for the most urgent threats: *C difficile*, carbapenem-resistant *Enterobacteriaceae* and drug-resistant *Neisseria gonorrhoea* (IDSA 2015). Discovering treatment for gram-negative infections remains paramount (IDSA 2015). A promising new agent Carbavance (meropenem/RPX7009) is currently in Phase 3 trials showing encouraging effectiveness against the most resilient carbapenem-resistant *Enterobactericaceae* (The Medicines Company 2014).
Policy and incentives for drug development	Given the significant cost burden of bringing a new drug to the market and the limited return on investment for antibiotics, it is unsurprising that pharmaceutical companies are reluctant to invest funds in developing new agents in this area of treatment. Nearly all of the large pharmaceutical companies have abandoned their antibiotic research and development programmes. In 2012, President Barack Obama signed into law the Generating Antibiotics Incentives Now (GAIN) Act to help address this economic issue. The act offers a five-year extension on patent life for new antibacterial agents that are designated as qualified infectious disease products (QIDPs), thus increasing their value. The act, along with other legislation, also accelerates the approval process by clearing regulatory hurdles, especially for those drugs that address an urgent unmet need in a limited patient population (Brown 2013).
Revisiting older antimicrobials	Extending the clinical utility of existing agents or those that have fallen out of favour could optimise the pharmacodynamics/effectiveness of older antimicrobials. Adopting novel dosing regimens and considering new combination therapies could combat the most resistant pathogens. Some research suggests that it is possible to re-sensitise bacteria to existing antibiotics by altering their physiology or metabolism, thereby rendering it more susceptible to antibiotics (Pogue *et al* 2011).
Natural alternatives	Nutrition and herbal medicines have formed the backbone of addressing infections in a natural way. Optimum nutritional status is a vital part of remaining infection-free: this might include avoiding processed foods and refined sugars, eating live yoghurts, taking probiotic supplements and consuming prebiotics such as fruits and vegetables. Selected herbal medicines contain a host of effective antimicrobial agents and some modern drugs are refined or modified version of their active constituents (for example, artimisinin for treating malaria is extracted from the *Artemisia annua* herb). Other notable herbs include echinacea (*Echinacea purpurea*), garlic (*Allium sativum*), tree of life (*Thuja occidentalis*), wild indigo (*Baptisia tinctoria*), milkvetch (*Astragalus membranaceous*), damiana (*Turnera diffiusa*) and Siberian ginseng (*Eluetherococcus senticosus*). For milder infections, tea tree oil and clove oil (topical) are useful, as is honey, which has been used traditionally as a prophylactic and for mild infections. There is no evidence to suggest that manuka honey is superior to other honey. Marketing claims made by commercial manufacturers of manuka are not quality controlled and therefore cannot be tested.

Conclusions

AMR is a major and global public health concern. Issues relating to it are complex and inter-related, but a concerted effort to tackle the crisis is vital if nations are to mitigate the inevitable morbidity and possible mortality of common infections that prove unresponsive to current drug treatments. While the outlook appears bleak, governments and regulatory authorities of major economies, along with the WHO, have already started to address AMR.

Poverty alleviation and progress in medicine is at the forefront of this battle, and there are encouraging signs. A coherent, international action that spans drug regulations, investment in infrastructure, and antimicrobial drug use in humans, animals and the environment is urgently needed to keep us safe from avoidable infections.

Find out more

For more information about herbal medicines, visit the websites of the College of Practitioners of Phytotherapy and the National Institute of Medical Herbalists:

- www.phytotherapists.org
- www.nimh.org.uk

Online archive

For related information, visit our online archive and search using the keywords

Conflict of interest
None declared

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