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Antibiotic resistance: what, why, where, when and how?

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Abstract

Background: Antibiotic resistance is a threat to the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi.

Sources of data: Peer-reviewed journal articles, governmental and professional society publications.

Areas of agreement and controversy: There is consensus about the development and spread of antibiotic resistance, the reasons for the development of antibiotic resistance and the clinical impact. There is more debate about the most appropriate way of tackling this increasing problem.

Growing points: This review discusses a number of initiatives (local and global) that are being undertaken to protect the antibiotics we currently have available for use and to encourage the development of newer agents.

Key words: antibiotics, resistance, antibiotic stewardship

Introduction

Antibiotic resistance has been described as one of the greatest global threats of the 21st century.[1] Although it was recognized soon after antibiotics were first introduced, the impact was mitigated initially by the development and use of newer agents. However, very few new classes of antibiotics have been developed since the late 1960s, and development has stalled in recent years.[2] For some organisms, particularly Gram negative bacteria such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and some Enterobacteriaceae (e.g. *Escherichia coli* and *Klebsiella* spp.), there are increasingly extremely limited therapeutic options.[3]

Antibiotics have had a profound positive impact on the management of infectious diseases (e.g. community acquired pneumonia due to *Streptococcus*

pneumoniae), but they have also become an essential component of all aspects of modern healthcare. No advance in medical or surgical practice would remain successful if patients developing infections could not be treated reliably.[4] Developments in chemotherapy for malignancy and organ transplantation make patients more vulnerable to infection, due to immunosuppression. These medical advances would be less meaningful if a patient survived the initial therapy, only to succumb to infection later. Potentially, if antibiotic resistance became more widespread and infection became more difficult to treat, patients might, as just one example, choose to live with their disabilities rather than undergo joint replacement surgery.

Unlike any other class of drugs used in clinical practice, antibiotics act on a third party, the microorganism, rather than just the patient. Microorganisms are transferred readily between individuals, and thus resistance emerging in one patient or the environment can soon affect another. Tackling antibiotic resistance is therefore of great public health importance and must not be underestimated.

Antibiotic resistance is truly a One Health issue and needs to be monitored and controlled not only in human medicine, but also in animal husbandry, agriculture and aquaculture.[4] However, this review will concentrate predominantly on antibiotic use in humans. The term 'antibiotic' is used throughout to mean an agent with activity against microorganisms, rather than the more general term 'antimicrobial'. Also, although antibiotic resistance is important in the treatment of infections due to viruses, fungi and protozoa, this discussion is limited to bacterial infections.

What is antibiotic resistance? What causes it?

Resistance to an antibiotic occurs when a microorganism is able to grow or survive in the presence of a concentration of antibiotic that is usually sufficient to inhibit or kill organisms of the same species. The terms 'susceptible' and 'resistant' relating to antibiotics are usually used in clinical practice to infer the likely success or failure of treatment. Resistance is more likely when the concentration required to inhibit or kill microorganisms exceeds that achievable in a patient.

Microorganisms can be either intrinsically resistant to an antibiotic or develop resistance following exposure to that antibiotic (acquired resistance). Resistance can develop as a result of mutation or direct transfer of genes encoding a resistance mechanism. Transfer of resistance genes can occur by a variety of mechanisms including conjugation (transfer of genes carried on plasmids, which are also known as mobile genetic elements), transformation (direct transfer of naked DNA) or transduction (transfer of similar DNA by bacteriophage).[5] Genetic material, including antibiotic resistance genes, can spread very effectively between bacteria, even those of unrelated species.

The efficiency and rate at which a resistant phenotype spreads within a previously susceptible species are unpredictable. For example, the staphylococcal β-lactamase gene is very successful in *Staphylococcus aureus,* with similar genes in *Haemophilus influenzae* and many Enterobacteriaceae, but they have never spread widely in enterococci. Fortunately, vancomycin resistance genes (e.g. *vanA*) found in enterococci remain rare in *S. aureus*.

Why does antibiotic resistance happen? Why is it important?

Although antibiotic resistance can be considered to be an inevitable consequence of antibiotic use, injudicious use of antibiotics is a major factor facilitating the emergence of resistance worldwide. In many areas, the availability of antibiotics 'over the counter' or via the internet allows the non-prescriber to have free and unrestricted access to these agents. Once resistance has emerged, subsequent dissemination of resistant strains is facilitated by the selection pressure exerted by further antibiotic use, failure to adhere to infection control measures and by poor hygiene (notably in terms of hand hygiene, sanitary conditions and food preparation), which can occur both within and outside healthcare settings.

Antibiotic resistance has significant costs to society in terms of increased mortality, morbidity, use of healthcare resources and time off work. Infections due to resistant microorganisms resulted in 25 000

deaths and cost €1.5 billion per year in hospital and societal costs in one report from the European Union (EU), Iceland and Norway.[6] Another report suggested that nearly 23 000 people die each year as a direct result from infections due to resistant microorganisms acquired in US hospitals, with associated healthcare costs >$20 billion.[7]

Not only does antibiotic resistance have a huge financial impact, but more worryingly, there is major concern about the lack of development of new antibiotics. During the past 25 years, only two new classes of antibiotics have been developed and introduced into clinical practice. These include the oxazolidinones (e.g. linezolid) and lipopeptides (e.g. daptomycin). Many of the other newer antibiotics are modifications of older drugs rather than new classes of agent. Daptomycin was actually discovered several decades ago, but it was not developed commercially because of concern about adverse effects. Both of these new classes of drugs have activity against Gram positive bacteria; new classes of compound with activity against Gram negative bacteria have not been found. This is partly due to failure of new drug discovery, failure to bring potential new agents to market and a restrictive regulatory environment. It has been estimated that it costs in excess of £0.5–£1 billion to develop and market a new antibiotic.[2] The failure rate during development is also higher for antibiotics than for most other drugs, and the returns from antibiotic sales are low compared with other drugs because they are generally only used for short periods of time. In addition, because of concern about resistance, new agents are typically used sparingly and as a last resort. Worldwide, the availability of cheaper generic products potentiates this issue. As a result, developing new antibiotics is unattractive as a business model for the pharmaceutical industry, and many of the larger companies have withdrawn from this market.[2,8]

Where does it happen?

Antibiotic resistance does not only develop in the hospital environment. As healthcare systems have evolved, there has been a blurring of boundaries between traditional healthcare facilities and the community, such that nursing and residential homes are now important reservoirs for resistant organisms in addition to outpatient settings such as dialysis and oncology day units.[9] Modern travel networks have also made it easier for people and the resistant organisms they carry to spread rapidly across and between continents.

Increasing resistance can result from proliferation of the resistant bacterium itself or by transfer of resistance genes from one bacterial species to another. However, the relative importance of these varies with organism and resistant mechanism. The recent increase in resistance to carbapenem antibiotics (e.g. meropenem) is an example of this. The New Delhi metallo-β-lactamase-1 (NDM-1) carbapenemase enzyme found in some Enterobacteriaceae was first detected in 2008 in Sweden from a patient transferred from the Indian subcontinent.[10] Many of the NDM-1-positive patients seen in the UK have also had a recent history of travel to India or Pakistan, or had links with these countries. By 2011, however, it was established that not all patients infected with NDM-1 producing organisms had a history of contact with hospitals or any travel history.[11] Environmental studies have shown that sewage samples and drinking water contained a variety of different organisms harbouring NDM-1 (e.g. *Shigella boydii* and *Vibrio cholerae*) suggesting transfer of mobile resistance elements between species.[12]

Conversely, the spread of *Klebsiella pneumoniae* carbapenemases (KPC) in the USA, Israel and Greece was associated with spread of a single clone of the organism [sequence type (ST); ST258].[13] This single clone is responsible for the recent increase of carbapenemase producing Enterobacteriaceae reported in Greece. Thus, in this example, it is spread of a resistance mechanism within a particularly transmissible variant of a single organism that has led to increasing resistance, rather than rapid transfer of the resistance genes themselves. The spread of various β-lactamase enzymes capable of hydrolyzing cephalosporin antibiotics [such as the CTX-M extended spectrum β-lactamase (ESBL)] within a single clone of *E. coli* (ST131) is another example of this.[14] It was the emergence of these ESBL-producing Enterobacteriaceae that led to increased reliance on carbapenems for effective treatment of infections due to these, and hence an increase in selection pressure for resistance.

Meticillin resistance in *S. aureus* (MRSA) is seen in many different clones of *S. aureus*, and these each have specific geographical associations. For example, epidemic (E)-MRSA-15 and EMRSA-16 were the healthcare-adapted strains of MRSA causing problems in UK hospitals in the 1990s and 2000s but were less frequently seen in the USA, where different strains predominated.

Antimicrobial resistance is related to the amount of antibiotic consumed. Studies from both community and hospital settings have demonstrated this.[15,16] This may explain some of the differences in resistance prevalence between northern and southern European countries. The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) recently examined this issue in England.[17] It reported that

- the total number of patients with bloodstream infections in England increased each year from 2010 to 2013,
- there were an increased number of bloodstream infections where antibiotic resistance was identified,
- antibiotic prescribing had increased year on year,
- the majority (80%) of antibiotic prescribing takes place in the community,
- there is considerable variation in both antibiotic resistance and antibiotic prescribing across England; frequently, areas with high prescribing also have high resistance.

When has it been a success story? When is it still a worry?

There are several examples of successful initiatives to control antibiotic resistance. These initiatives have included infection control programmes to control transmission of resistant organisms, antibiotic stewardship programmes and vaccination programmes.

In the UK, the rise of healthcare-associated infections became a major public concern in the 1990s, such that public and political pressures expedited major reforms in healthcare policy. MRSA bacteraemias peaked in 2002/3 (with 7700 episodes) and fell to 862 in 2013/14 following the introduction of mandatory surveillance and performance targets to reduce them.[18]

Another success story is the introduction of 13-valent conjugate *S. pneumoniae* vaccine. Increasing uptake of the vaccine reduced the number of bacteraemias due to *S. pneumoniae*, which included antibiotic resistant strains.[4]

In the UK, the rates of resistance to cephalosporins and ciprofloxacin in *E. coli* and *Klebsiella* spp. bloodstream infection have fallen since 2008.[19] This may be due to restricted use of these antibiotics as part of antibiotic stewardship initiatives to combat *Clostridium difficile* infection. However, as the use of cephalosporins and fluoroquinolones decreased, the use of carbapenems and β-lactam/β-lactam inhibitor combinations (e.g. co-amoxiclav and piperacillin–tazobactam) has increased. This may have simply moved the selection pressure for the development of resistance from the cephalosporins and fluoroquinolones to these antibiotics instead.

Antibiotic resistance in *Neisseria gonorrhoeae* has increased over the years leading to abandonment of traditional treatment regimens using penicillin, followed by those using ciprofloxacin and other fluoroquinolones.[20] Now, regimens using azithromycin and cefixime are under threat, such that a combination of ceftriaxone and azithromycin is currently recommended for treatment.

The major emerging resistance issue in many countries is among Gram negative bacteria, particularly Enterobacteriaceae, *P. aeruginosa* and *A. baumannii*. Between 2004 and 2008, *E. coli* bacteraemias increased by 33% in England; the species now accounts for >30% of bacteraemias in those aged over 75 years.[21] This continued to increase after mandatory surveillance was introduced in 2011.[4,15] ESBL-producing Enterobacteriaceae used to be predominantly restricted to the hospital setting; these are now increasingly seen in the community setting, including nursing and residential homes.[9,22]

Tuberculosis is another example of a disease caused by an organism that has gradually developed resistance over time. Multidrug-resistant (MDR) tuberculosis (i.e. *Mycobacterium tuberculosis* resistant to at least rifampicin plus isoniazid) emerged in the 1990s, whilst extensively drug resistant [XDR—resistant to isoniazid and rifampicin, any fluoroquinolone, and at least one of the three injectable second-line drugs (amikacin,

capreomycin or kanamycin)] subsequently emerged.[23] Both of these are associated with increased mortality and morbidity, despite prolonged treatment with multiple drug combination regimens.

How do we tackle antibiotic resistance?

Antibiotic resistance is an international concern. Broadly, interventions can be categorized into two main approaches. Firstly, there are strategies aimed at protecting the existing antibiotics and preventing the emergence and spread of further resistance. Then, there are strategies aimed at reinvigorating drug development and bringing new antibiotics to market. Alternatives to current antibiotic therapy also need to be assessed, either through the development of new drug classes or through the use of vaccines or other therapeutic strategies.[24]

A) Strategies to protect antibiotics as a limited resource and prevent the emergence and spread of further resistance

Globally, the resistance problem has been recognized for many years. Although there are many stakeholders in this issue, the World Health Organisation (WHO) has a global overview. The WHO has held meetings, consultations and workshops since 1971. The WHO's first World Health Assembly on antibiotic resistance was held in 1998 where member states were urged to take action. WHO also targets the veterinary and food sectors by publishing booklets on antibiotics for a food safety perspective, running national and sub-regional workshops and creating an advisory group on integrated surveillance. The World Health Assembly may be a forum through which international collaboration can be facilitated.

Most countries have strategies that are based on governance, surveillance, infection prevention and control, regulation, international engagement, communication and research. Effective antibiotic stewardship is required globally, together with better diagnostic tests to identify or rule out infection quickly.

Several international groups and societies have been established to tackle antibiotic resistance. One of the most prominent is Action on Antibiotic Resistance (ReAct), an independent international organization funded by the Swedish International Development Cooperation Agency.[25] It aims to raise awareness and stimulate action on antibiotic resistance. One example of an international awareness campaign is European Antibiotic Awareness Day, held annually on 18 November since 2008 under the auspices of the European Centre for Disease Control (ECDC).

In 2009, the British Society of Antibiotic Chemotherapy (BSAC) convened a working party to consider issues relating to the lack of antibiotic discovery and development.[2] This became known as 'The Urgent Need' or 'TUN' report. It suggested increased funding to support antibiotic research and development and promoted the establishment of a BSAC Chair of Public Engagement in order to increase the public and political awareness of antibiotic resistance and promote dialogue. This has been taken forward under the banner of 'Antibiotic Action,' a UK led global initiative to ensure that we have effective antibiotics in the future. Initiatives with similar aims have been established in the USA under the auspices of the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America (IDSA).[26]

In India, the Chennai Declaration aimed to tackle the challenge of antibiotic resistance in a developing nation.[27] Until this, the authors of the declaration claimed that there were no functioning national antibiotic policies and no national policy to contain antimicrobial resistance in India. There were no restrictions in purchasing antibiotics and no standardized infection control practices. The first meeting laid out a roadmap for tackling antibiotic resistance. It managed to create awareness among policymakers and the highest authorities on the need of effective antibiotic policies in India.

In Asia, the Asian Network for Surveillance of Resistant Pathogens (ANSORP) acts as a centre for research collaboration of infectious diseases and antibiotic resistance. More than 100 hospitals in 14 countries participate. The Australian Antimicrobial Resistance Prevention and Containment Steering Group have set out strategies and mandated Standard 3 of the National Safety and Quality Health Service (NSQHS) Standards 'Preventing and Controlling Healthcare Associated Infection' in all Australian

hospitals.[28] The Central Asian and European Surveillance on Antibiotic Resistance (CEASAR) is a collaboration initiated in 2012.

The first UK strategy against antimicrobial resistance was published over a decade ago and aimed to improve antibiotic prescribing practice and increase funding for drug discovery programmes and research. Some have argued that its impact was limited. In 2013, the Department of Health in England launched a new Five Year Antibiotic Resistance Strategy (2015–2018).[29] It was published as part of a One Health programme, which aimed to address antibiotic resistance in humans, animals, agriculture and the wider environment. Its main objectives were to improve the knowledge and understanding of antibiotic resistance, to conserve and steward the effectiveness of current antibiotics and stimulate the development of new agents, diagnostics and novel therapies. In the strategy and her annual report, published in February 2013, the Chief Medical Officer in England recommended that antibiotic resistance be placed on the national risk register. Seven key priorities were outlined:

1. Optimizing prescribing practices (i.e. antimicrobial stewardship),
2. Improving infection prevention and control,
3. Raising awareness and changing behaviour,
4. Improving the evidence base through research,
5. Development of new drugs/vaccines/other diagnostics and treatments,
6. Improving evidence base through surveillance,
7. Strengthening the UK and international collaboration.

Optimizing antibiotic prescribing has been targeted in both community and hospital settings. Antibiotic stewardship programmes aim to ensure the effective treatment of patients with infection whilst minimizing collateral damage from antimicrobial use.[30] They do this by optimizing antimicrobial selection, dosing, the route and duration of therapy to maximize clinical cure or prevention of infection while limiting unintended consequences (e.g. emergence of resistance, adverse drug events and costs). Education, audit, guidelines and policies, IV to oral conversion and appropriate de-escalation are all potential elements. These interventions to reduce excessive antibiotic prescribing in hospital inpatients can reduce antimicrobial resistance, hospital-acquired infections and can improve clinical outcomes.[31]

Antibiotic cycling or rotating (i.e. the scheduled alternation of various classes of antibiotics) has also been studied, although its benefit is still debated. The goal of antibiotic cycling or rotation is a sustainable decline or stabilization in antimicrobial resistance through successive, prospective alterations in antibiotic selection pressures that prevent the selection of specific resistance mechanisms. Abel Zur Wiesch et al. (2014) recently performed a meta-analysis of 46 clinical studies addressing the effect of cycling on nosocomial infections; 11 met their selection criteria.[32] They concluded that cycling may be useful in some circumstances, though too long cycling periods could be detrimental.

In the UK, a number of tools are available to support antimicrobial stewardship in primary care. They include '*Target Antibiotics Responsibly, Guidance and Educational Tool*' (TARGET), available on the Royal College of General Practitioners website. Another is the '*Stemming the Tide of Antibiotic Resistance*' (STAR), an educational programme that includes resources for clinicians to share during public consultation. In 2007, the Health Protection Agency established a multiagency collaboration to improve antimicrobial prescribing in primary care. From this, epidemiological data collections and primary care-directed guidelines were produced (e.g. antibiotic and diagnostic guidance on urinary tract infection). The 'Start smart then focus' programme is an antibiotic stewardship initiative from the UK directed at secondary care. This programme was introduced in England in 2011 but was updated in 2015 as an evidence-based toolkit for hospitals and explains the importance of antimicrobial stewardship for treatment and prophylaxis.[33]

New techniques have been developed to aid the diagnosis of infection and/or resistance earlier than conventional culture and sensitivity testing. Biomarkers such as C reactive protein (CRP) or procalcitonin can potentially reduce unnecessary antibiotic use.[34] Molecular methods such as polymerase chain reaction (PCR) have allowed earlier detection of MRSA strains and also rifampicin resistance in *M. tuberculosis*.[35]

Multiplex gene detection PCR assays and next-generation sequencing are other methods that are being utilized to achieve earlier detection of antibiotic resistance.[36] Identification of cultured bacteria through mass spectrometry (e.g. by Matrix-Assisted Laser Desorption Ionization Time of Flight (MALDI-ToF)) has reduced the time to identification of organisms compared with conventional biochemical means. Automated susceptibility testing also has the potential to deliver results more quickly.[36]

B) Reinvigorating drug development pathways and bringing new antibiotics into market

The need for new antibiotics was illustrated in the TUN report.[2] Among the aspects that need addressing is the failure of new drug discovery (described above). In addition, increasing levels of bureaucracy and lack of clarity within regulatory frameworks and variation in the clinical trials process in different countries hinder the development of new agents. Several antimicrobials have failed to reach the market at this final hurdle. Lack of international harmonization, continual changes to processes and ineffective pathways for dialogue between organizations, industry and regulators are all significant deterrents to the research and development of new antibiotics.

However, it is clear that there is now political engagement with this issue and many initiatives are now ongoing around the world. In 2003, the IDSA launched the 'Bad Bugs, No Drugs' campaign with recommendations to Congress, the Food & Drug Administration and the National Institute for Allergies & Infectious Diseases.[26] In 2009, the EU, under the presidency of the Swedish Government, launched the 'Innovative Incentives for Effective Antibacterials' programme.[28] In 2010, the IDSA produced a report entitled 'The 10 × 20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020'.[8] This initiative aspires to develop 10 new antibiotic agents by 2020.

A number of novel approaches to reinvigorate antibiotic development have been proposed.[2,8] One area being widely discussed in the concept of 'delinking', where the pharmaceutical company revenue from antibiotics is not directly dependent on absolute sales of these agents. Public–private partnerships could be set up to mitigate the up-front costs of drug discovery. Pathogen-targeted approaches could be developed to optimize efficacy against a single pathogen/resistance mechanism. Orphan drug legislation could help address the issue of needing large numbers of patients in clinical trials, thus shortening the length of a trial. Other examples laid out in the English Chief Medical Officer's Annual Report to foster research and development of new drugs include research-related tax incentives, patent buyouts, health impact funds and funding of translational research.[4]

The WHO held a summit in 2011 entitled 'No action today, no cure tomorrow'.[37] In Europe, the 'New Drugs 4 Bad Bugs' initiative is a series of programmes that were set up by the Innovative Medicines Initiative (IMI) in the EU and was designed to directly address some of the scientific challenges associated with antibacterial drug discovery and development.[38] One element of this is the DRIVE-AB programme, which aims to produce and review economic models for the various ways that funding of antibiotic drug development could be undertaken.

In the USA, the Generating Antibiotics Incentives Now (GAIN) Act was enacted in 2012. This provided a pay-out at the end of the development process with 5 years of guaranteed market exclusivity and priority review for antibiotics that target certain qualifying pathogens. The President's Council of Advisors on Science and Technology (PCAST) reported about antimicrobial resistance in September 2014[39] and, in the UK, the Prime Minister asked Dr Jim O'Neill, an economist, to chair a review of the economic impact of antibiotic resistance and consider possible solutions. It is due to produce a final report in 2016, but the initial findings have been published and include a proposal to set up a global antimicrobial resistance innovation fund to boost the number of early research ideas, ensuring that existing drugs are used appropriately, improving the use of diagnostics wherever they can make a difference, attracting and retaining a high-calibre skills base and modernizing the surveillance of drug resistance globally.[40]

Conclusion

The relentless rise in antibiotic resistance is a major public health concern, which will need to be acted upon now. We might not be able to stop antibiotic resistance or, in many cases, reverse the trend to ever-increasing resistance, but we certainly need to contain the speed to which this is happening. No single action or initiative by a single country would be able to achieve this. It requires participation and support from all levels; political, medical, veterinary, agricultural, environmental, academic, industry and the general public. It is clear that there is political engagement with this issue and many different bodies are considering potential options to tackle it. However, it remains to be seen if activities can be sufficiently coordinated worldwide to effect a change in the situation.

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