A GLOBAL OVERVIEW OF ANTIMICROBIAL RESISTANCE

DAME SALLY DAVIES (TOP), CHIEF MEDICAL OFFICER FOR ENGLAND; CHAIR, UK CLINICAL RESEARCH COLLABORATION AND THE WORLD HEALTH ORGANIZATION SPECIALIST TECHNICAL ADVISORY GROUP ON ANTIMICROBIAL RESISTANCE AND WHO EXECUTIVE BOARD MEMBER; **JOHN WATSON** (MIDDLE), DEPUTY CHIEF MEDICAL OFFICER FOR ENGLAND AND **LAURA SHALLCROSS** (BOTTOM), CLINICAL LECTURER, DEPARTMENT OF INFECTION & POPULATION HEALTH, UNIVERSITY COLLEGE LONDON, UK

Antibiotics, with their ability to save the lives of people with severe infections, have revolutionised medicine in the last 70 years. They now underpin major elements of modern treatments, such as bowel surgery, organ transplantation and cancer therapy, as well as curing most of the bacterial infections that cause common problems such as sore throat. From the start, however, microbes developed resistance to antibiotics (and other antimicrobials active against viruses and fungi) through evolutionary changes. Antibiotic resistance is now a global problem as an increasing proportion of microbes can no longer be treated effectively by readily available antibiotics. Overuse, and inappropriate use, of antibiotics in humans and animals has been the main driver for the development of resistance and this has occurred in countries all around the world.

The threat of antimicrobial resistance can only be tackled through international collaboration and by working across human and animal health sectors. Our global organizations are rising to the challenge with a recent World Health Assembly resolution and a World Health Organization (WHO) Global Action Plan, but we must act now to preserve the benefits to modern medicine that antibiotics have provided, and avoid a return to a pre-antibiotic era.

Microbes have been engaged in an evolutionary battle with the humans and animals they infect since the dawn of time. Every time a new antimicrobial is developed resistance follows, sometimes swiftly, and this occurs for all antimicrobials (anti-bacterial, anti-viral and anti-fungal therapies). Resistant bacteria pose the greatest threat to human health.

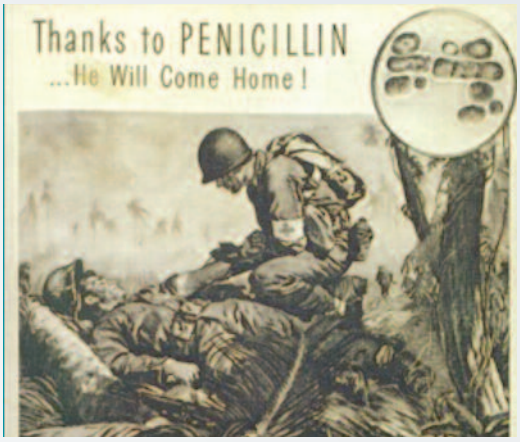
When Alexander Fleming accepted his Nobel Prize for the discovery of penicillin in 1945, he foretold the development of antimicrobial resistance: *(1)*

"I would like to sound one note of warning…It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."

Despite these warnings, from 1943 onwards penicillin was widely marketed as a wonder drug in tablets, syrups and throat lozenges (reference to images). Resistant strains were soon noted in hospitals and by 1950, 60% of the bacterium *Staphylococcus aureus* isolates were resistant to penicillin *(2)*. Soon a familiar pattern emerged: a new drug was introduced and resistance followed, either quickly with the bacterium *Staphylococcus aureus*, or more slowly with *Streptococcus pneumonia* (both common causes of infections). At this time resistance did not pose a serious threat to health because there was a steady supply of new antimicrobials. These drugs were marketed by the pharmaceutical industry and used extensively by health professionals in both human and animal populations, placing selection pressure on bacterial populations and hastening the emergence of drug resistant strains.

Most of the antibiotic classes currently in use were identified in the golden era of antibiotic discovery between 1945 and 1960 and only four new classes have antibiotic have been discovered in the past 50 years *(3)*. With the exception of a few small and medium size biotech enterprises but few larger pharmaceutical companies, there is little work going on to discover new antimicrobials to replace those that are fast becoming ineffective. The technical challenge in developing new antimicrobials is substantial, but the barrier to research and development is economic. Bringing a new drug to market is estimated to cost around one billion US dollars which cannot be recouped at the prices that health systems expect to pay

Figure 1: Examples of early marketing for antibiotics



Source: National World War 2 Museum – New Orleans

Source: Unknown

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for antimicrobials. This issue is complicated further by the public health imperative to hold new antibiotics in reserve for those patients most at risk rather than allowing widespread use that selects the development of resistance.

In recent years the major focus in many countries has been on reducing methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* infections (CDI), because these infections cause substantial morbidity and mortality, primarily amongst patients in hospitals or in long-term care facilities. During this period, the total burden of drug resistant infections has increased, particularly amongst "gram-negative" bacteria such as *E. coli*. Resistance threatens the effectiveness of the carbapenem class of antibiotics, which are widely regarded as the treatment of last resort for severe infections and particularly those caused by gram-negative bacteria. Drug resistance in gonorrhoea, a sexually transmitted infection, has also increased in recent years in England and could become untreatable. In the United States, the Centers for Disease Control and Prevention have updated their empirical treatment guidance for gonorrhoea three times since 2003 because resistant strains have become sufficiently prevalent in the population to compromise the effectiveness of each successive recommended antibiotic regimen *(4)*. Worldwide there is increasing resistance to other antimicrobials such as those used to treat HIV/AIDS, tuberculosis and malaria, impacting heavily on developing countries and increasing morbidity, mortality, the duration of treatment and costs.

The single most important factor driving resistance is antimicrobial use, particularly in humans but also in animals. Antibiotics are among the most commonly prescribed drugs in human medicine and their use continues to rise, partly driven by inappropriate prescriptions for minor viral infections, such as coughs or colds, where they confer no benefit. In some countries, the availability of antibiotics over the counter, falsified and counterfeit drugs and inadequate dosing as a result of prescription of wrong dose, wrong duration or the

Milestone Prizes entail recognition of very early discovery – before the definitive proof of principle of the innovation. These intermediate prizes should be sized so that they would be attractive to academia from applied or fundamental research fields. It would also attract small and medium size enterprises (SMEs), including from LMICs

wrong drug, all select for the development of resistance. In animals, antimicrobials are used to prevent, control and treat disease, and in some countries antibiotics are used as growth promoters. This practice has been banned in Europe and recommended against in the United States. There is still much to be done to ensure appropriate use and conservation (or stewardship) of antimicrobials across both animal and human health sectors.

The human and economic costs of antimicrobial resistance are compelling. Antimicrobial resistance is estimated to cause at least 23,000 deaths per year in the United States and 25,000 deaths per year in Europe *(5,6)*. The economic impact of antimicrobial resistance has been estimated to be 0.4–1.6% of GDP in the United States where antimicrobial resistance has been estimated to cost up to US$ 20 billion in excess direct health-care costs, with additional costs for society for lost productivity as high as US$ 35 billion per year *(5)*.

Individual nations have recognized the importance of antimicrobial resistance as a health issue, but countries have different needs and priorities. In many parts of the world, those with treatable infections lack access to antibiotics, particularly in rural areas. Here the challenge is to improve access without making the drugs so readily available that they can be used inappropriately, the so-called paradox of controlling drug resistance. Counterfeit and substandard drugs pose a threat worldwide but this is a particular issue in developing countries where regulation is lacking in effectiveness, and antibiotics and anti-parasitic agents are the most frequently counterfeited drugs *(7)*.

Some high-income countries have identified the need to take drastic action against antimicrobial resistance. In the United Kingdom, for example, an ambitious strategy to combat antimicrobial resistance was published in 2013 *(8)*, with the goal of slowing the development and spread of antimicrobial resistance by focusing activities around three strategic aims to:

- 1. Improve the knowledge and understanding of antimicrobial resistance;
- 2. Conserve and steward the effectiveness of existing treatments;
- 3. Stimulate the development of new antibiotics, diagnostics and novel therapies.

Antimicrobial resistance – a global problem

Antimicrobial resistance (AMR) is a global problem that cannot be solved by a single country working in isolation. International travel allows people to spread their infections from one country to another, including those with drug resistant infections. An effective response to AMR demands collaboration across international borders and across health professional boundaries, the relevant regulatory agencies and their enforcement arms. Since 1998 there have been a series of World Health Assembly (WHA) resolutions on AMR, paving the way for the 2001 WHO global strategy for the containment of antimicrobial resistance and the 2011 EU AMR strategic action plan. In May 2014 a further WHA resolution on AMR was passed, which builds on previous WHO initiatives but now gives the WHO a mandate to develop a global action plan in 2015, legitimising action by WHO on behalf of member states. Achieving change at the rate required to impact on AMR requires political will and global action, working across the human and animal health sectors through international partnership known as the "One Health" approach.

Different countries have different needs and priorities related to AMR. The draft WHO Global Action Plan has been developed with five strategic objectives which provide member states with the flexibility to set out the priority actions that need to be taken in their country and respond in a step-wise manner to meet both local needs and global priorities. The first objective relates to communication, education and training, to improve awareness and understanding of AMR. The second is to strengthen the knowledge and evidence base through surveillance and research. A further objective is to reduce the incidence of infection through effective hygiene and infection prevention. The final two objectives concern the optimization of antimicrobial use in human and animal health and the development of the economic case for sustainable investment in combatting AMR, taking account of the needs of low- and high-income countries.

Communication, education and training

To reverse the increasing rates of AMR will require major

behavioural change across all swathes of society, from professionals in health and other sectors, governments, organisations, patients and the public. None of this will happen if people are not aware of the harm of misusing antibiotics and dire consequences of not taking action. We must find ways to communicate AMR messages to a wide range of audiences, including social media as well as educational and social marketing tools, as a route for advocacy. We should educate children about infections and antibiotic use and embed AMR and antimicrobial stewardship as a core part of education, training and accreditation for professionals working in human health, veterinary medicine and agriculture.

Surveillance, research and development

The first step in tackling AMR is to understand the burden of disease due to drug resistant infections. This requires active surveillance and research. Hospitals need laboratories that can determine rapidly if patients have an infection, identity the organism and determine the sensitivity and whether there is resistance to antibiotics. This data needs to be collected at local, regional and national level, and then to be collated globally in order to track changes in rates of antibiotic resistance over time and between countries. It is also important to monitor the sales and use of antibiotics, not only from hospitals, but also in the community and their use in the veterinary and agricultural sectors. Present surveillance systems for AMR are fragmented with major gaps in information. Better surveillance will make it possible to better to target resources where they are most needed and monitor the impact of interventions aimed at reducing AMR.

Despite much increased effort over recent years, our understanding of the mechanisms that underlie development of AMR at a molecular, patient and population level remains limited. There is need for much more work including research to develop drugs and new vaccines, and large scale population based studies to evaluate the effectiveness of a range of interventions including those targeted at people's behaviour.

Preventing infection and promoting good hygiene

We must do all we can to prevent infection in the first place. This includes strong public health or hygiene measures such as the separation of potable water from sewage (in countries where this is a problem), and infection control, particularly scrupulous hand-washing in food preparation We need to focus on improving infection control, particularly in hospitals where the majority of serious and difficult to treat infections are treated and where there is widespread opportunity for drug-resistant infections to spread between patients. Vaccination can play a key role in preventing infection, not only in humans but also in veterinary medicine, and is one of the most effective public health interventions.

Optimizing antimicrobial use in humans and animals

We must conserve the antibiotics we have, a process referred to as "stewardship". The right antibiotic should be used at the right dose for the right time period and, if appropriate, in the right combination. We need to stop prescribing antibiotics for viral infections such as coughs and colds where they have no effect. This would be much easier if there were rapid diagnostic technologies to help to target antibiotics to those who really need them. Antibiotics should not be available over-the-counter (as they are in some countries) or over-the-web, but only on prescription from a health practitioner (doctor, veterinarian, dentist, nurse or pharmacist) who follows national guidance informed by the local laboratory surveillance programmes.

Sustainable development

Current levels of investment in infrastructure and resources to tackle AMR are inadequate in most parts of the world, with a clear need for training and capacity building. The costs of remedying this are both significant and long-term and are likely to present a barrier to action, particularly in low-income countries. The development of new drugs and diagnostics is likely to be best addressed by developing new processes to stimulate investment in R&D, such as uncoupling the cost of investment from volume of sales to ensure that new drugs remain effective, are available in high- and low-income countries according to need and are managed within a suitable framework of stewardship.

Conclusions

The threat of antimicrobial resistance is shared by all countries. The challenges in combatting AMR vary from country to country but some priorities for action are common to all. We need to re-double our efforts to ensure effective hygiene and infection control. The antibiotics we have need to be conserved while we reinvigorate research and development to deliver new rapid diagnostics and innovative antimicrobials.

None of this will be possible unless professionals, public and policy-makers understand the threat and agree to work together to solve this problem. Our global organizations are starting to rise to the challenge, with WHO developing a global action plan and supporting countries in developing their own plans. We must keep this high on the political agenda because without concerted action, we risk losing the many

benefits of modern medicine that we have been made possible by antimicrobial agents in the last 70 years.

Dr Laura Shallcross is a Clinical Lecturer in epidemiology and public health, based in the research department of Infection & Population Health at University College London, UK.

Professor John Watson was appointed Deputy Chief Medical Officer for England in 2013. He was previously head of respiratory diseases at Public Health England's Centre for Infectious Disease Surveillance and Control. Professor Watson's main focus is health protection including antimicrobial resistance, immunization and emergency preparedness and response.

Professor Dame Sally Davies was appointed Chief Medical Officer for England in 2010. Previous career highlights include developing the National Institute of Health Research (NIHR). Dame Sally also chairs the UK Clinical Research Collaboration and the World Health Organization Specialist Technical Advisory Group on Antimicrobial Resistance (WHO-STAG) and is on the WHO Executive Board.

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