Antibiotic resistance:

As leaders gather at the UN General Assembly to fight antimicrobial resistance – only the fourth time in UN history that a health topic has been discussed at this level – **Marc Mendelson** and **Ramanan Laxminarayan** explain why the issue is so important

In 1899, a report published in the *Athens-Clarke County Weekly Banner* described the case of CW Jones whose foot was cut by a blade of grass. In this pre-antibiotic era, his foot had to be amputated to prevent the spread of an infection. Twenty-nine years later, Fleming discovered penicillin, since when millions of lives have been saved using antibiotics.

However, only 75 years after that fortuitous discovery, a man with a severely fractured ankle and secondary infection of the joint was admitted to a hospital in Cape Town in July 2016. Having received multiple courses of antibiotics to try to control the infection, he grew a bacterium from a bone biopsy that was resistant to the last line of antibiotics. Just as in the case of Jones, the man's foot had to be amputated to control the infection.

The scenario of untreatable bacterial infection, or those that are susceptible only to the last line of antibiotics, is now commonplace across the globe, and heralds a change in modern medicine as we know it. Antibiotics are vital to maintain health; not only to treat bacteria causing pneumonia, meningitis, gonorrhoea, urinary tract infections and a long list of other common infections, but also as prophylaxis to prevent infections in persons whose immune systems are compromised, such as those living with HIV or receiving a transplant, and to prevent surgical wounds becoming infected at the time of operation.

Smith and Coast estimate that without antibiotics, just under half of patients who undergo a total hip replacement would develop a post-operative infection in the new joint, and about one third who developed such an infection would die. Although estimates of the number of additional deaths from loss of antibiotics as surgical site infection prophylaxis for total hip replacement in the US were lower in modelling reported by Teillant and colleagues,

The need for an international response

with markedly increased odds of death the decision to have a total hip replacement – even if you really needed one – would be far more difficult to make. Similarly, chemotherapy used to treat cancer causes the body's normal defence mechanisms against bacteria to be suppressed. If a patient with cancer is carrying a highly resistant bacterium to which no antibiotic is available, then giving chemotherapy to that person would carry an extremely high risk that an infection with that bacterium would develop and be fatal. These cases exemplify how great a game-changer the loss of antibiotics to treat bacterial infections will be.

It seems counterintuitive that taking an antibiotic can itself encourage the development of resistance to that antibiotic. Most antibiotics have been isolated from soil bacteria and fungi, and are chemicals that are produced by these microorganisms to attack other bacteria. Just as with any example of natural selection, some bacteria have a survival advantage and possess the capability to resist such an attack. Furthermore, the majority of genes that code for the different resistance mechanisms are carried on plasmids (circular pieces of DNA), which can be transferred from bacteria to bacteria of the same, or different species. Hence, antibiotic resistance in bacteria can either be naturally occurring or acquired. Humans share a symbiotic relationship with around 100 trillion bacteria and other microorganisms that live on epithelial linings of our gut, respiratory tract, skin and other body surfaces. These microorganisms play vital roles in the development of our immune system, digestion of food and vitamin metabolism, and provide a virtual barrier to more pathogenic microorganisms, outcompeting them by their sheer number.

When we take an antibiotic, bacteria sensitive to the action of that antibiotic will be killed, but those that are able to resist will be selected out. Given the right circumstances, the resistant strains will replicate and become the dominant species. Those that colonise body linings such as skin are transferrable to other people, which is a danger, particularly in hospitals where sick patients are in abundance. Alternatively, it may cause an infection in that person, which would then need to be treated with a 'higher-level' antibiotic that remains ▶

▶ sensitive to the resistant bacteria. And so the cycle continues, with more and more selection of increasingly resistant bacteria until there is no antibiotic left that can overcome the multi-drug resistant infection. It follows therefore, that the more antibiotics are used, the more resistant bacteria will be selected out, and an increasing number of antibiotics will be unavailable to treat common infections.

Quite simply, the increase in bacterial resistance has been driven by our misuse and overuse of antibiotics. Antibiotics are only active against bacteria and a small number of other microorganisms, but have no action against viruses. However, for decades, doctors have been misusing antibiotics to treat viruses such as those that cause the common cold, and for a host of conditions from fever to body aches against which an antibiotic has no effect other than to cause harm from side effects or selection of resistance.

The drivers of misuse and overuse include poor education of prescribers and the public, lack of available diagnostic tests that fuels diagnostic uncertainty, entry into the market of falsified or substandard antibiotics and, in a number of countries such as India, access to antibiotics without prescription over the counter from pharmacies, non-pharmacy stores and street sellers.

In exactly the same manner as in humans, bacteria in animals can become resistant to antibiotics. Globally, around 80 per cent of all antibiotics are used in animals, mostly in feed animals to promote growth and reduce the time delay to market, or for metaphylaxis (mass medication of a group of animals to prevent infection). A small percentage is used for treatment of sick animals.

The increasing resistance of bacteria in animals is well documented, and the recent identification of a new plasmid-mediated resistance mechanism rendering the common bacterium E. coli resistant to colistin in poultry on the farm, chicken meat in the abattoir and on shop shelves, and in humans admitted to hospital with infection, confirms the passage of bacterial resistance to antibiotics from farm to fork.

Overall antibiotic consumption

What remains unclear, and is a cause of much debate, is the degree to which development of bacterial resistance in animals is driving the problem of bacterial resistance in humans. The problem is yet more complex, with bacteria-carrying resistance genes entering the environment through farm slurry, antibiotic manufacturing facilities discharging antibiotics directly into the environment from run-offs, and antibiotics being used in aquaculture entering the waters. Even some paints used for ships' hulls and harbour walls are impregnated with antibiotics to stop barnacle attachment. Hence, overall antibiotic consumption is far greater than what is used for prevention and treatment in humans.

If the overuse and misuse of antibiotics are not reversed, not only will our ability to practise medicine radically change, but modelling suggests that by 2050, the death rate from drug-resistant infections will have risen from the current 700,000 deaths a year, to over 10 million deaths per annum, dwarfing deaths from cancer and other common medical conditions.

The hammer blow will be felt most keenly in low and middle income countries (LMIC) in Africa and Asia, where 90 per cent of deaths will occur. Economically, we would see in excess of $100 (€89) trillion wiped off global GDP.

Arguably, antibiotic resistance represents our greatest current public health crisis. To react, it must be viewed in the same way as climate change, as antibiotics are global public goods that lie: "Within a shared-resource system where individual users acting independently according to their own self-interest behave contrary to the common good of all users by depleting that resource through their collective action." In other words, this global crisis demands an international response with no bystanders.

Over the last three years, much has been done to start addressing the issues. A tripartite alliance has been formed between the World Health Organization (WHO), the World Organisation for Animal Health and the Food and Agriculture Organisation of the United Nations to help drive the international response. In May 2015, the 68th World Health Assembly adopted the Global Action Plan for Antimicrobial Resistance (AMR), mandating each member state to develop a national action plan for AMR by May 2017.

A common approach centres around: Surveillance (bacterial resistance and consumption of antibiotics); stewardship (optimising antibiotic use); and infection prevention, overseen by a national governance structure, and underpinned by education, public awareness, and R&D of new antibiotics, vaccines and diagnostics. The tripartite alliance is supported by work packages of the Global Health Security Agenda, drawing in international expertise to address crosscutting issues of One Health, global stewardship frameworks and support of key surveillance platforms.

At country level, technical assistance is provided to member states by the tripartite alliance and organisations such as the Global Antibiotic Resistance Partnership and ReAct – Action on Antibiotic Resistance, that have formed global networks for concerted action on AMR and provide in-country support to develop action.

The required international response and funding models to tackle AMR have been most successfully articulated by the Review on Antimicrobial Resistance chaired by Jim O'Neill. Three sets of actions are proposed: A sustained global public awareness campaign estimated to require $40-100 (€35-89) million per annum; new models of antibiotic R&D; and actions to reduce consumption of antimicrobials.

In terms of antibiotic R&D, the global community needs antibiotics that have activity against resistant bacteria, which at present still comprise a small percentage of the total burden of bacterial infection. However, the current pharmaceutical business model of profit linked to volume of sales runs contrary to this desired aim. A number of de-linkage models have been proposed by *The O'Neill Report*, The Chatham House Working Group, and DRIVE-AB.

A One Health approach to building antimicrobial resistance National Action Plans in middle and low income countries

Wilton Park in the UK recently held a meeting focused on the National Action Plans (NAPs) which WHO member countries are drafting to tackle antimicrobial resistance (AMR).

It brought together representatives from countries in middle and low income economic settings, who are leading the development and implementation of their NAPs, sharing their experiences so far and learning from one another. NAPs should embrace a 'one health' approach to combating AMR by addressing all relevant sectors: Agriculture; livestock; and human health. They should also consider the importance of incentives for the development of new treatments and the stewardship of existing drugs.

The event built on the recent resolutions agreed by the WHO, FAO and The World Organisation for Animal Health to tackle AMR. It followed the Science Summit organised by the Wellcome Trust in April 2016, providing a scientific basis for NAPs development. The discussions also took into account the findings from the independent AMR Review, led by Lord O'Neill. CRJ *hopes to provide more details of this event, either in our blogs or in a future edition.*

■ *www.wiltonpark.org.uk.*

One such model based on market-entry rewards is gaining credence. It would provide a series of payments to the developer in return for an oversight body ensuring that consumption was being directed by public health policy and priced at a cost that enables global access.

Currently, more children under the age of five die from lack of access to antibiotics for pneumonia, than do those from antibiotic-resistant infections. Although the tipping point may soon be reached and the cause of mortality reversed in favour of resistance, access to assured quality antibiotics to all who need them is a fundamental human right, and under the current linkage model, has been compromised for decades. The proposed de-linkage models with stewardship oversight aims to reverse this inequity.

Recent accelerator initiatives such as the Global Antibiotic Research and Development Partnership set up by the WHO and Drugs for Neglected Diseases Initiative, and Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), a public-private partnership between US Government agencies, UK-based funding and research groups, signify critical new funds and a welcome step towards the development of new antibiotic R&D strategies.

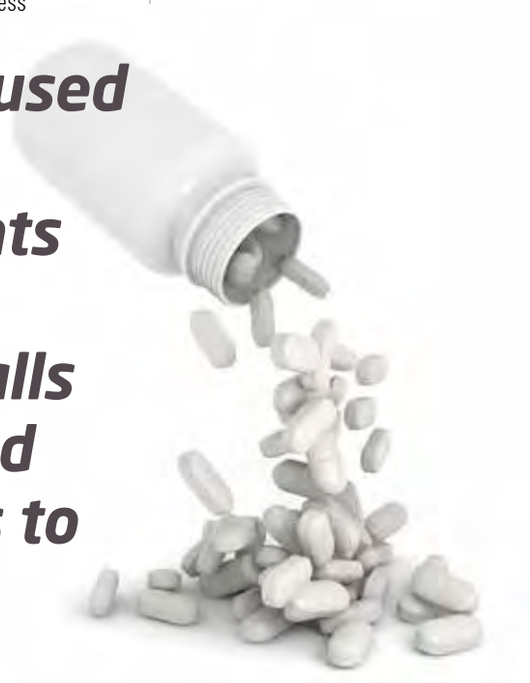
However, the benefit of such financial investment is unlikely to be felt in the short to medium term. Indeed, bringing a new antibiotic to market currently takes many years. Hence action to conserve existing antibiotics needs to be taken with greater urgency. It requires a combination of interventions, primary among which is to address infection prevention to reduce the need for antibiotics in the first place. LMICs are commonly without clean water and adequate sanitation, which if put in place, are estimated to reduce diarrhoeal illness by up to 60 per cent and therefore also reducing unnecessary antibiotic use. Similarly, increasing access to vaccination to prevent pneumonia and other illnesses in humans reduces the need for antibiotics, and preventing infection in animals reared for food by increased vaccination levels positively affects food security and antibiotic consumption levels. Improving means of preventing infection in feed animals is one of a number of important interventions towards reducing the need for animal growth promoters and metaphylaxis.

Research and development of alternative strategies to antibiotics such as antibodies, phage therapy, and probiotics among others, could reduce the burden of need for antibiotics, as could the introduction of new diagnostics at point of care, which can differentiate a bacterial infection from other causes of the illness. Lastly, improved surveillance of antibiotic resistance in humans and animals, supporting the rollout of the WHO Global Antibiotic Resistance Surveillance System, as well as increased surveillance of consumption and drug quality, are fundamental areas of knowledge to enable optimisation of antibiotic prescribing and to direct stewardship programmes to areas of greatest need.

In September 2016, The UN Assembly High-Level Meeting of Heads of State will discuss sustainable access to effective antimicrobials. This meeting provides the chance to establish a High-Level Co-ordinating Mechanism (HLCM), which could drive many of the interventions discussed here at a high level. HLCM functions would include driving the global access debate and raising awareness of the antibiotic resistance crisis, setting up a global co-ordination and monitoring platform, establishing enforceable targets for monitoring and evaluation, and co-ordination of multisectoral action.

This historic meeting represents a unique opportunity for the world to respond in unison to the One Health threat of antibiotic resistance, and ensure the continued benefit of antibiotics, that we have come to take for granted. C•RJ

Antibiotics are used in aquaculture. Even some paints for ships' hulls and harbour walls are impregnated with antibiotics to stop barnacles



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