The global rise in antibiotic resistance threatens infection prevention and cure

Dr Bill Love, Founder and Chief Scientific Officer of Destiny Pharma, discusses the rise of antimicrobial resistance (AMR), the antibiotic stewardship required to offset this global threat, and the additional incentivisation initiatives needed to promote innovation, as well as the role of preventative antimicrobial treatments as an important element of this global fight

Financial incentives are seen as necessary in the area of AMR given the lack of a typical return (through significant drug revenues) on the investment needed in such drug development. Revenues have been restricted due to the stewardship policies that limit widespread use of antibiotics, yet the imperative, from a health policy perspective, is for such novel, safe and effective drugs to be available.

Antimicrobial resistance, the need for antibiotic stewardship and its consequences

According to the United States Center for Disease Control and Prevention (CDC), the bacteria responsible for all common infections in the world are becoming resistant to the corresponding antibiotics approved as treatment. Additionally, the US CDC estimates that two million people a year in the US alone acquire an infection while in a hospital, resulting in 90,000 deaths. More than 70% of the bacteria that cause these infections are resistant to at least one of the antibiotics commonly used to treat them.

Worryingly, there are a growing proportion of pathogenic bacteria in hospitals that have become multi-antibiotic-resistant – the so called 'superbugs'. These superbugs are of great concern and blunt the therapeutic benefits of antibiotics, a clearly undesirable effect known as antimicrobial resistance (AMR). AMR is now recognised by most government and international medical bodies and is included as a main agenda item for the United Nations, World Health Organization and the G7/G20 countries.

Consequently, the US CDC and European CDC have had to invent new terms to describe the increasing severity and extent of AMR:

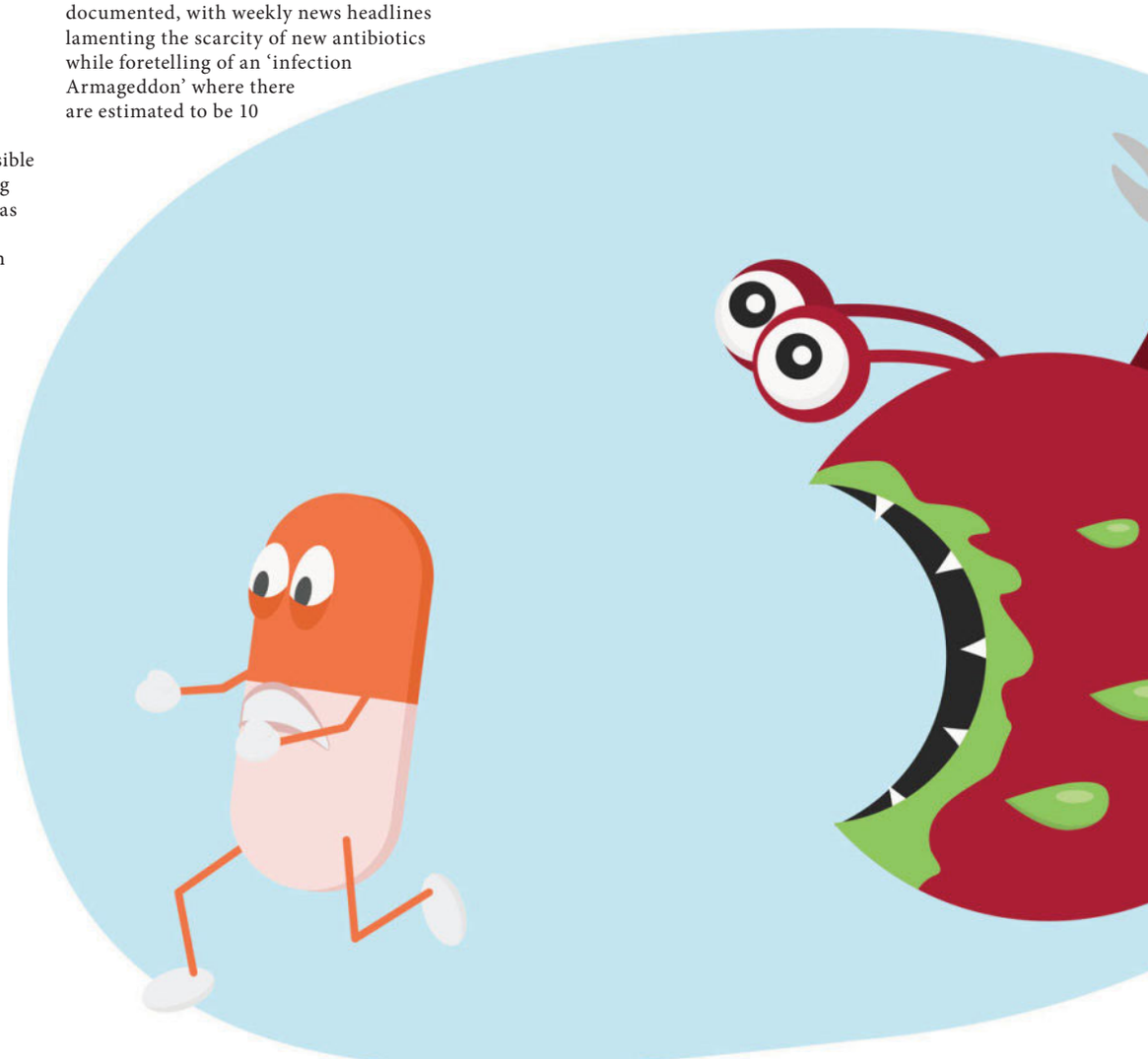
- **Multi-drug resistance (MDR):** bacteria resistant to at least one antibiotic in three or more main pathogenic bacterial categories
- **eXtensive drug resistance (XDR):** bacteria resistant to at least one antibiotic in all but two or fewer pathogenic bacterial categories
- **Pan-drug resistance (PDR):** bacteria resistant to all antibiotics in all pathogenic bacterial categories

With few remaining effective antibiotics, and a shortage of novel antibiotics in global drug pipelines being developed and approved, stewardship of existing antibiotics and the prioritisation of their use for bacterial infection prevention and cure are more important than ever.

The historical context for this situation is well documented, with weekly news headlines lamenting the scarcity of new antibiotics while foretelling of an 'infection Armageddon' where there are estimated to be 10 million AMR deaths per year (more than from cancer) and a $100 trillion global economic cost price tag by 2050. Today, there are just 50 antibiotic/antimicrobial drugs in clinical development, of which just a handful are likely to reach the market, compared to over 1,000 anti-cancer drugs in clinical development.

While there is consensus on the activities needed to address AMR, the funding of such strategies has still to be addressed and is one of the main hurdles to overcome. As antibiotics are taken over a relatively short period of time (typically a few days to weeks), when compared to other medicines, many of which have to be taken every day for the rest of the patient's life, they represent one of the poorest returns on investment of all pharmaceutical classes. Therefore, new payment models which better reflect the societal value of new antibiotics are desperately needed to attract investment.

Current models being considered include market entry rewards, transferable intellectual property vouchers, add-on payments, guaranteed purchase orders and hospital licences. The UK Government's 5- and 20-year plans to tackle AMR were announced at the World Economic Conference in Davos in January 2019 and included a welcome commitment for the National



Institute for Health and Care Excellence (NICE) and NHS England to explore new payment models for antibiotics. The US Government is also contributing to this effort with a number of new incentives, including the Generating Antibiotic Incentives Now (GAIN) Act and the 21st Century Cures Act. These incentives range from extended market exclusivity, faster track to approval and lower regulatory hurdles.

However, much more still needs to be done to address the main issue of pricing and reimbursement (PR) of antibiotics compared to other drug classes. It is incomprehensible that the PR for an anti-cancer drug, which may extend life by a few months, can top $100,000, while an antibiotic, which not only saves a life from a lethal infection but restores the individual to full health, attracts a PR in the region of $1,000.

Another strategy that has been suggested is a 'play or pay' levy on the pharmaceutical industry, many of whose profitable medicines rely on the foundation provided by effective antibiotics. Frustratingly, it is this financial dynamic which is the key hurdle to overcome in order to invigorate this critical arm of the global AMR strategy. If this can be swiftly resolved and the focus of the pharmaceutical industry and investors applied, an expanded pipeline of new anti-bacterial drugs for the future can be secured.

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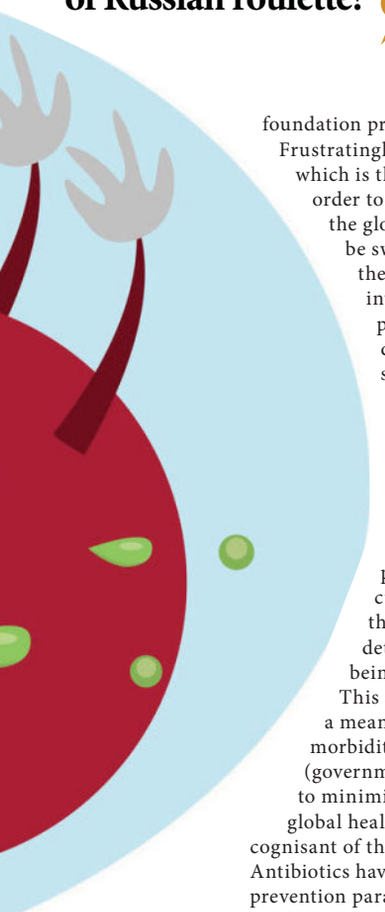

The prevention of post-surgical infections: an area of increasing need and commercial interest

Benjamin Franklin once said about healthcare: "An ounce of prevention is worth a pound of cure". There is no doubt that today this axiom, together with early detection of disease, are increasingly being invoked as guiding principles. This is by healthcare providers as a means of reducing mortality and morbidity, and also by healthcare payors (governmental and private), as a strategy to minimise overall costs of disease as global healthcare systems become more cognisant of their own finite financial resources. Antibiotics have a role in such a disease prevention paradigm.

Whilst not as widely recognised as their main use in curing established bacterial infections in community medicine, antibiotics in hospitals can be utilised for bacterial infection prophylaxis, ahead of, during and for a short period after, surgery. Indeed, without this preventative approach, we would return to a dark age of medicine where mortality from bacterial infection was frequent in this setting and every surgery was a game of Russian roulette!

The bacterium *Staphylococcus aureus* (SA) is one of the world's most common causes of bacterial, post-surgical infection. Including its superbug variant methicillin-resistant (MRSA), this bacterium is a major cause of morbidity and mortality, costing US healthcare alone over $12 billion per year. Patients who carry this bacterium are known to be at a greater risk of a post-surgical infection.

Recent World Health Organization and US surgical infection prevention guidelines have highlighted the value in the suppression of SA in all patients who carry the bacteria ahead of high-risk surgery, which is about a third to half of all patients. Other guidelines, including the United States Agency for Healthcare Research and Quality, recommend a universal preventative treatment of all Intensive Care Unit (ICU) patients upon admission to reduce bacterial infections. Each of these preventative recommendations is based on clinical studies which have shown that the use of an intra-nasal antibiotic (the key location of SA/MRSA colonies), alongside body washes, significantly reduces the bacterial infection rate in these patient groups by some 40-60% – an impressive and valuable reduction. This preventative infection approach is particularly significant given the number of hospital procedures involved, with some 20 million high-risk surgeries (for example, cardiovascular, thoracic, orthopaedic) and five million ICU patients per year in the US alone.

This infection prevention intervention is good news not only for patients, but also for hospitals which are held responsible for such infections that are deemed to be preventable. In fact, safety benchmarks put in place by the Affordable Care Act has led to one in seven US hospitals losing 1% of their Medicare payments due to their failure to reduce hospital-acquired infections, such as those caused by MRSA, with further penalties levied if there is no improvement.

However, these valuable SA/MRSA infection prevention interventions are already threatened before they can begin to deliver their full potential. While a number of large hospital groups are rolling out SA/MRSA suppression regimens, other hospitals with longer experience of the use of antibiotics for this purpose have experienced the rapid emergence of SA/MRSA resistance to such an extent that they have had to halt this intervention and/or seek alternatives. Clearly, the generation and existence of increasing proportions of resistant SA undermine these valuable healthcare infection control interventions.

Non-antibiotic approaches for the suppression of SA/MRSA carriage in surgical patients would be beneficial in allowing the preservation of currently deployed antibiotics, while aiding in the reduction of AMR emergence. Historically, vaccines and mass vaccination for infection/epidemic prevention has been enormously successful, enabling the control and even eradication of some of the world's most serious infectious diseases. Past bacterial vaccine successes include the eradication of smallpox, reduction in the incidence of polio, reduction in illness, disability and death from diphtheria, tetanus, whooping cough, measles, Haemophilus influenza type B and epidemic meningococcal A meningitis.

Vaccination to prevent SA/MRSA post-surgical infection would clearly be an attractive solution. Large pharma companies, realising the attractiveness of this approach, have ploughed hundreds of millions of US dollars into attempts to develop SA/MRSA vaccines but, despite this investment, Sanofi, GSK, MSD and most recently Pfizer have all failed to produce a safe, effective SA/MRSA vaccine; although other vaccine approaches are in clinical development, this is clearly a challenging approach. Undoubtedly, novel approaches are desperately needed to meet this unmet clinical need and provide long-term solutions.

Biotechnology companies have been the engine for innovation in novel anti-infective drug development over the last 30 years in the absence of participation of many bigger pharma companies, and there is a growing awareness that while new antibiotics are needed, the invention and development of fundamentally new anti-infective medicine platforms is critical – particularly those with a focus on novel mechanisms of action and the potential to address AMR by having the ability to retard bacterial resistance emergence. Such platforms would assist in the stewardship of existing antibiotics, reduce AMR bacterial strain emergence, have potency against existing superbug strains, and be utilised in a widespread manner for prevention as well as treatment of infections.

It is this targeted approach that UK-based Destiny Pharma has followed, and the company has developed an anti-bacterial platform, the XF drugs, whose novel bacterial membrane action has been to shown to impede resistance development. The XF drugs are active against all tested global strains of SA/MRSA, and remarkably the bacterium has not been able to generate resistance to XF drug action in extensive repeat exposure studies in which all antibiotics typically fail. The XF drugs therefore represent and offer a potential 'resistance breaker' solution.

In 2019, Destiny Pharma's lead drug candidate, XF-73 (exeporfinium chloride), is entering Phase 2 clinical development in US and European patients for the prevention of SA/MRSA post-surgical infections. This follows a successful Phase 1 trial of XF-73 conducted and funded by the United States National Institute for Allergy & Infectious Diseases (NIAID) in 2016. XF-73 has also been awarded Fast Track and Qualifying Infectious Disease Product (QIDP) status by the US Food and Drug Administration (FDA).

XF-73 has the potential to deliver and sustain the prevention of SA/MRSA post-surgical infections in millions of patients annually. There is also opportunity for allied infection prevention regimens in ICU patents and other groups at high-risk of infection such as dialysis and immune-compromised patients. Due to its unique properties, XF-73 has the potential, unlike antibiotics, to be used in a vaccine-like manner to deliver a cost-effective, long-term SA bacterial infection prevention strategy.

If successful, Destiny Pharma, alongside other companies who are working at developing novel anti-infective treatments, will increase the options available in antibiotic stewardship and avert further bacterial resistance development and thereby aid the global fight against AMR.