



# Longevity Bulletin

From the Institute and Faculty of Actuaries



## Antimicrobial resistance

### Clinical implications

How will surgical procedures be affected?

### Longevity

Impact of AMR on longevity improvements

### Economic

How much would be lost?

### Research

30 years since a new class of antibiotics was introduced

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# 1. Introduction by our President

The Institute and Faculty of Actuaries is the only chartered professional body for actuaries in the United Kingdom. It is dedicated to educating, developing and regulating over 28,000 members worldwide and to expand the range of actuarial work beyond its traditional boundaries.

Actuaries have been active in the study of mortality since the earliest days of the profession and it remains an area where the profession can contribute to the quality of public debate and lead in the development of new thinking. Actuarial expertise is used to examine the possible financial, economic, health and resource challenges of demographic change, and understand their impacts. The IFoA continues to embrace the value of collaboration with other professional bodies to rise to the challenges and opportunities facing Government and society.

During the past decade, the threat of antimicrobial resistance has become real and its global dimensions have been increasingly recognised. Meanwhile, an equally alarming decline has occurred in the research and development of new antibiotics to deal with the threat. This edition of the Longevity Bulletin considers potential impacts of antimicrobial resistance on society and demonstrates real collaboration between a number of professions.

I have great pleasure in introducing the eighth issue of the Longevity Bulletin. I would like to thank all the contributors and authors for their thought-provoking and informative articles on the topic of antimicrobial resistance.

We hope that this issue will be read with interest by all those with technical, professional and personal interest in longevity matters.



*Fiona Morrison*

**Fiona Morrison**  
President, Institute and Faculty of Actuaries

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## 2. Foreword by Professor Dame Sally Davies

### Chief Medical Officer for England

The golden age of antibiotics which the world has taken for granted for well over fifty years has ended. Antimicrobial resistance (AMR) has increased alarmingly, accelerated by the overuse of antibiotics in many countries for medicinal and also agricultural purposes. Research into new antibiotics has not matched the evolution of the bacteria themselves; no new major class of proven antibiotics has been brought into clinical use since 1987 (although there are great hopes for last year's development of Teixobactin).

We are already seeing the consequences of AMR, with estimates of around 50,000 deaths per year recently in Europe and the US, due to antibiotic resistant infections, and far greater numbers worldwide. The projected figures are much more worrying. It is quite possible – and perhaps even likely – that the recent era of material mortality improvements will give way to many years of material mortality worsening.

To tackle this problem, we are pursuing a multi-levelled approach in the UK. Action is being taken urgently in a number of areas, from hospital hygiene and animal husbandry to pharma investment and vaccination programs, but to be effective this action needs to be internationally applied.

A good and recent example of such action in the obviously vital area of pharmaceutical research is the January 2016 Declaration by the pharmaceutical, diagnostics and biotechnology industries on Combating Antimicrobial Resistance, launched at the World Economic Forum in Davos, Switzerland. 85 companies and nine industry associations from 18 countries are looking to work with governments to create sustainable market models to allow appropriate investment in the search for new antibiotics.



Actuaries can play an important role by helping to quantify the potential demographic impact facing us under various plausible AMR scenarios and by considering the economic effects of an AMR catastrophe on financial markets, health provision and pension funding.

I am therefore delighted to introduce this issue of the Institute and Faculty of Actuaries' Longevity Bulletin, and hope that the actuarial profession will rise to the challenge of helping with one of the most serious problems we have faced in my working lifetime.

# 3. How antibiotic resistance emerges

Victoria Wells, Professor Laura (JV) Piddock, British Society for Antimicrobial Chemotherapy (BSAC)

## The problem of antibiotic resistance

Antibiotic resistance sits alongside climate change and terrorism on the Global Risk Register. As a growing number of bacteria are able to survive in the presence of antibiotics, it becomes increasingly difficult for doctors to cure patients with infections. Therefore, we run the risk of a post-antibiotic era, where some infections will be fatal if we cannot prevent or treat them. Scientists and other experts are working hard to ensure that this does not happen, but the widespread use of antibiotics in many sectors, including in human and animal medicine and agriculture, is contributing to the growing problem. Wherever antibiotics are used, bacteria that are resistant to them will develop. This is a result of evolution and the ability of bacteria to transfer drug resistance genes between one another. Bacteria that are resistant to antibiotics have an advantage over other drug-susceptible bacteria, and the more antibiotics we use, the greater the selection pressure for drug-resistant bacteria to emerge.

## Bacterial microbiology

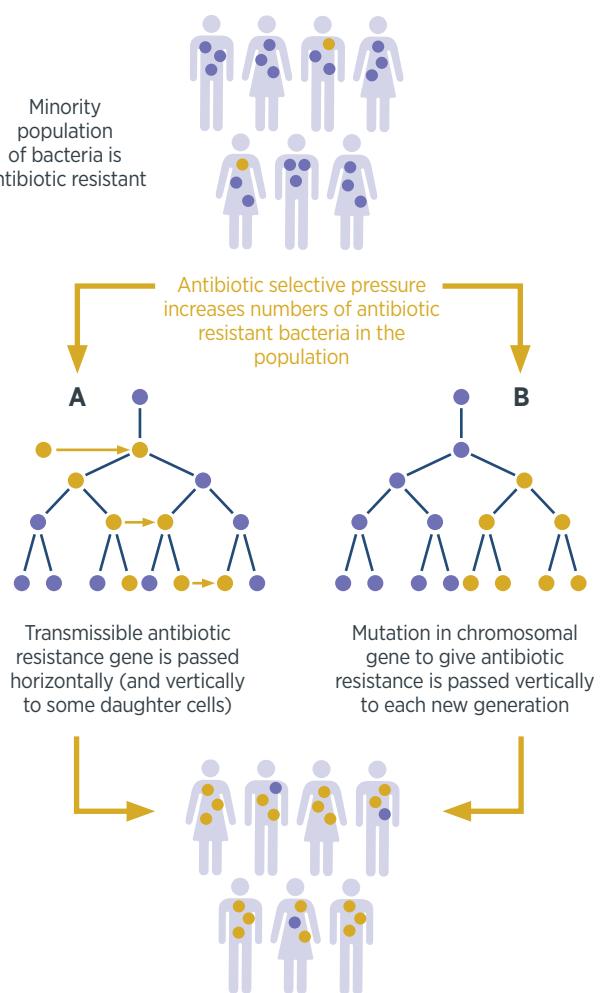
Bacteria are ubiquitous. They are in the soil, on plants, in oceans, on our skin, in our bodies and in our homes. They reproduce through a process called binary fission, whereby one bacterial cell will divide into two new cells, copying their DNA so that each daughter cell contains the same genetic material as the parent. In this way, each individual in a population of bacteria will have similar properties to the original parent cell. They grow and reproduce very quickly; for instance *Escherichia coli* double their numbers every twenty minutes. Mutations occur randomly and some give a benefit to the cell; some of these mutations cause bacteria to develop resistance to one or several types of antibiotic.

## Mechanisms and spread of antibiotic resistance

Antibiotics need to be inside a bacterium to stop it growing or kill it. If a bacterium has developed a way to prevent this, then the antibiotic is ineffective and the bacterium is resistant. Some of these traits include preventing the drug from entering the cell and multi-drug resistance efflux pumps, which eject the drugs out of the cell. Alternatively, bacteria may produce an enzyme that breaks down the drug. There are many different

mutations that can cause many different types of resistance. Depending on the mutation, it may cause bacteria to be resistant to more than one antibiotic, especially if the drugs have similar structures or modes of action. Figure 1 illustrates the spread of antibiotic resistance in populations.

**Figure 1: How antibiotic resistance arises and spreads in bacterial populations**



Produced for Media Planet

In antibiotic-susceptible populations of millions of bacteria, occasionally a few may be drug-resistant. In the presence of an antibiotic, all of the susceptible bacteria die, allowing drug-resistant bacteria to proliferate. These can reach huge numbers within just one day. This is not the only way in which resistance can occur. Some genetic material is stored on small mobile elements within bacterial cells called plasmids. These can be transferred from one bacterium to another. The exchange of plasmids can take place in any environment and even between very distantly related bacteria. In this way, drug resistance can spread between bacterial populations in our bodies, in animals, in water, in our kitchens and everywhere else bacteria exist. The World Health Organization (WHO) estimates that antibiotic-resistant infections kill up to 50,000 people every year in Europe and the United States alone.

## What can be done?

The more often bacteria are exposed to antibiotics the more likely it is that resistant bacteria will have an advantage, allowing them to thrive and spread where others die. This is why overuse and inappropriate use of antibiotics escalates the problem of resistance. Sharing antibiotics or not using the right drug for the infection will not kill the drug-resistant population, but instead will give those with the drug-resistance genes an advantage. Not completing a full course of antibiotics can also leave a small population of bacteria to reproduce. Today, bacteria are resistant to greater numbers of drugs. Some are even pan-resistant, which means that they are resistant to every antibiotic available to treat that infection, even the last-resort therapies. Increased awareness among both healthcare professionals and the public is imperative to changing prescribing and behaviour practices towards more sustainable antibiotic use.

Antibiotic resistance is a natural phenomenon that cannot be stopped. Anywhere that antibiotics are used, drug-resistant bacteria will arise. The more antibiotics are used, the worse the problem will be and so multi-drug resistant, and even pan-resistant, bacterial infections will occur more frequently. Doctors and healthcare professionals around the world are being urged to prescribe antibiotics only when absolutely necessary and only for bacterial infections. This is called good stewardship. Quickly diagnosing the cause of most infections is difficult, but as some can be very serious, doctors urgently need new tests to help them to decide when to use antibiotics and which types to use. This is why the Longitude Prize was launched – to provide a diagnostic test that will work quickly anywhere in the world. Until such a test is available, it is essential that we prevent the spread of infection between people, animals, and the environment. For this reason, it is very important for both people and animals to have clean water and strong public health systems to prevent the spread of infection.

Members of the public can and should practice good stewardship as well. Antibiotics should only be used when absolutely necessary, not for colds or the flu; viruses cause these and antibiotics will not work. Antibiotics should not

be shared and practicing good hygiene will prevent many infections. There are many different types of drug-resistant bacterial infections throughout the world, they are easily transmitted and there are few effective new drugs left to treat them. All non-essential use of these life-saving drugs must be stopped so that they remain effective for as long as possible.

## Further reading:

1. Antibiotic Action <http://antibiotic-action.com/>
2. British Society for Antimicrobial Chemotherapy <http://bsac.org.uk/>
3. Meek, R. W., Vyas, H., & Piddock, L. J. V. (2015) *Nonmedical uses of antibiotics: Time to restrict their use?* PLoS Biology, 13(10), e1002266. <http://doi.org/10.1371/journal.pbio.1002266>
4. Holmes A, Sunsdal A, Steinbakk M, Karkey RA, Guerin P, Moore L, Piddock LJV. (2015) *Sustaining effective antimicrobials: Understanding the mechanisms and the drivers of antimicrobial resistance.* The Lancet 2016 Jan 9;387(10014):176-87. Epub 2015 Nov 18. PMID 26603922
5. Review on Antimicrobial Resistance <http://amr-review.org/>
6. World Health Organisation, Facts about antimicrobial resistance. <http://www.who.int/mediacentre/factsheets/fs194/en/>
7. Joint Programming Initiative on Antimicrobial Resistance <http://www.jpiamr.eu/>
8. Longitude Prize <https://longitudeprize.org/>

## Biographies

**Victoria Wells** is the Science Communications Officer for the BSAC, a UK registered charity, and Antibiotic Action, an independent UK-led global awareness initiative wholly funded by the BSAC.

**Laura Piddock** is Professor of Microbiology and Deputy Director of the Institute of Microbiology & Infection at the University of Birmingham. She is also the BSAC Chair in Public Engagement, and in that capacity is the Director of the public awareness initiative Antibiotic Action.

# 4. Clinical implications of antimicrobial resistance (AMR)

Dr Meghan Perry, Professor Mark Woolhouse, Epidemiology Research Group, University of Edinburgh

AMR has ever-increasing impacts on hospitalisation rates, morbidity and mortality across the globe. This is as a result not only of the increasing incidence of resistant infections but also through the loss of the efficacy of antibiotic prophylaxis used in chemotherapy and many operations and transplants. In 2013 the US Centers for Disease Control and Prevention (CDC), Atlanta, highlighted a number of pathogens associated with serious resistance threats, all of which are a global concern. These pathogens have the potential to cause a broad range of communicable and endogenous infectious diseases as seen in Table 1.

Resistance is fuelled by inappropriate antibiotic use, unnecessarily prolonged antibiotic courses and the use of untargeted antibiotic treatment. Global consumption of antibiotics rose by 36% between 2000 and 2010 (Van Boekel et al., 2014), largely as a result of increased access in the developing economies of Brazil, Russia, India, China and South Africa (Van Boekel et al., 2014).

## How are antibiotics chosen for a given infection?

There are at least 16 classes of antibiotics, each of which have their own spectrum of bacteria against which they are active. When a patient presents with an infection, antibiotics are initially chosen following local antibiotic prescribing guidelines depending on the clinical diagnosis. Treatment guidelines will initially recommend antibiotics that cover disease specific pathogens and take into account local antibiotic susceptibilities. Accurate determination of AMR in clinical isolates by laboratory based susceptibility testing then guides further treatment.

With antibiotic susceptibility results, antibiotics are changed to specifically target the organism identified in the infection. If antibiotic treatment is failing in a patient this is strongly correlated with detection of AMR in the clinical isolate (MacGowan on behalf of the BSAC Working Parties on Resistance Surveillance, 2008).

In the event of a resistant pathogen being identified an antibiotic with a broader spectrum would be required to provide effective antimicrobial chemotherapy.

## Resistant pathogens and initial inadequate antibiotic treatment

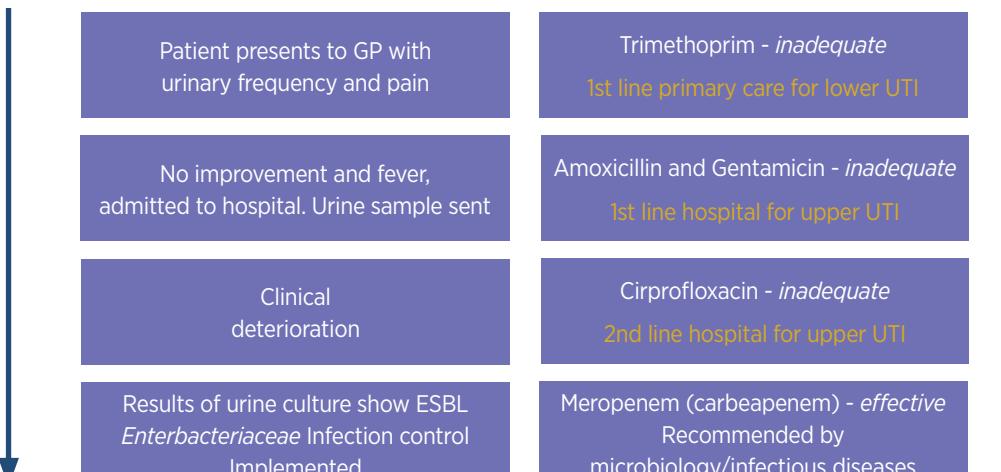
'Initial inadequate antibiotic treatment (IIAT)' is a term developed to refer to the ineffective treatment received by a patient prior to the identification of a resistant organism. A meta-analysis of 16 studies found that IIAT is associated with increased hospital stay and an approximately three-fold increased risk of mortality (summary odds ratio (OR) 3.3 95% CI 2.42 – 4.49) (Raman et al., 2015). Figure 2 represents IIAT in the case of a hypothetical patient presenting with a urinary tract infection (UTI) caused by an 'Extended Spectrum  $\beta$ -lactamase' (ESBL) *Enterobacteriaceae* and illustrates how, through following local guidelines (eg. NHS Lothian, 2016) there can be a delay to effective antibiotic treatment. Inadequate initial therapy could be prevented by identifying 'at risk' patients and through the use of rapid diagnostic testing for resistance (Dortet et al., 2014). The earlier identification of patients with ESBL organisms would decrease nosocomial transmission through appropriate infection control measures.

**Table 1: Common clinical conditions for which antibiotic therapy reduces the risk of mortality and associated resistant pathogens (CDC, 2013)**

<b>Category of condition</b>	<b>Condition</b>	<b>Drug resistant pathogens associated with serious health threats identified by CDC</b>
Communicable diseases	Tuberculosis	<i>Mycobacterium tuberculosis</i>
	Sexually transmitted bacterial infections	<i>Neisseria gonorrhoeae</i>
	Respiratory bacterial infections (especially of the lower respiratory tract)	<i>Pseudomonas aeruginosa</i> , <i>Streptococcus pneumoniae</i> , Methicillin resistant <i>Staphylococcus aureus</i>
	Diarrhoea caused by bacteria	<i>Shigella</i> <i>Clostridium difficile</i> Non-typhoidal <i>Salmonella</i>
	Healthcare associated bacterial infections	Carbapenem resistant <i>Enterbacteriaceae</i> <i>Acinetobacter</i> ESBL producing <i>Enterbacteriaceae</i> Vancomycin resistant <i>Enterococcus</i> <i>Pseudomonas aeruginosa</i> Methicillin resistant <i>Staphylococcus aureus</i> <i>Streptococcus pneumoniae</i>
Endogenous infections	Urinary tract infections	Carbapenem-resistant <i>Enterbacteriaceae</i> <i>Acinetobacter</i> Extended spectrum β-lactamase producing <i>Enterbacteriaceae</i> Vancomycin resistant <i>Enterococcus</i>
	Skin and soft tissue infections	Methicillin resistant <i>Staphylococcus aureus</i>
	Infective endocarditis	Methicillin resistant <i>Staphylococcus aureus</i> Vancomycin resistant <i>Enterococcus</i>
	Sepsis	<i>Salmonella typhi</i> As for 'Healthcare associated bacterial infections'
Prevention of endogenous infection	Burns, wounds Caesarean sections Joint replacements Cancer therapy Organ transplants	

**Figure 2: Hypothetical clinical pathway of a patient with UTI caused by Extended Spectrum Beta-lactamase producing *Enterbacteriaceae*.**  
**Regional primary care and hospital guidelines in yellow text (source NHS Lothian)**

Timeline	Clinical event	ABx prescribed
0hrs	Patient presents to GP with urinary frequency and pain	Trimethoprim - <i>inadequate</i> 1st line primary care for lower UTI
24hrs	No improvement and fever, admitted to hospital. Urine sample sent	Amoxicillin and Gentamicin - <i>inadequate</i> 1st line hospital for upper UTI
48hrs	Clinical deterioration	Ciprofloxacin - <i>inadequate</i> 2nd line hospital for upper UTI
72hrs	Results of urine culture show ESBL <i>Enterbacteriaceae</i> . Infection control Implemented	Meropenem (carbapenem) - <i>effective</i> Recommended by microbiology/infectious diseases



### Carbapenem-resistant *Enterbacteriaceae* (CRE)

This bacteria has caught the media attention because it is resistant to almost all classes of antibiotics and is associated with high mortality rates of 29 to 52% (van Duin et al., 2013). Figure 2 illustrates the pressure on carbapenem use for ESBL infections. Carbapenems (e.g. meropenem) are 'last line' antibiotics which have excellent broad-spectrum cover but whose use risks the development of CRE. Global consumption of carbapenems increased by 45% between 2000 and 2010 reflecting increasing resistance to other antibiotics as well as injudicious use (Van Boekel et al., 2014). Treatment options for CRE are very limited to older antibiotics with significant toxicities. The high mortality rate of patients who have CRE isolated is concerning and Public Health England are focusing on reducing the spread through strict infection control guidelines issued to all acute care trusts (Public Health England, 2014).

### How will surgical procedures and chemotherapy be affected by AMR?

In assessing the impact of AMR on prophylaxis it is useful to look back to the introduction of antibiotics. Prevention of surgical infection relied on antiseptics and aseptic technique until the 1940s when penicillin became available. The use of prophylactic antibiotics perioperatively was immediately realised. When the effect was directly studied in a head to head trial in colonic surgery in the 1960s, patients receiving cephaloridine had post surgical infection rates of 7% compared with 30% in the placebo arm of the trial (Polk and Lopez-Mayor, 1969).

Chemotherapy temporarily destroys the ability of a host's body to produce macrophages, leaving them immunosuppressed and vulnerable to infection. A meta-analysis of randomised control trials conducted between 1973 and 2010 which compared antibiotic prophylaxis to placebo in those undergoing chemotherapy found a significant reduction in all cause mortality risk (risk ratio (RR) 0.66, 95% CI 0.55 to 0.79) and infection related mortality risk (RR 0.61, 95% CI 0.48 to 0.77) (Gafter-Gvili et al., 2012).

Currently, in the US it was estimated, using meta-analysis, that 39% to 51% of pathogens causing surgical site infections and 27% of infections post chemotherapy are resistant to the prophylaxis. A 30% reduction in efficacy of prophylaxis was estimated to lead to 120,000 additional infections and 6,300 additional deaths per year (Teillant et al., 2015).

### Lessons from TB

The story of multidrug resistant and extensively drug resistant *Mycobacterium TB*, occurring predominantly in previously treated patients, leading to complicated chemotherapy regimes and increased healthcare contact is mirrored in many other serious resistance threat pathogens in both communicable and endogenous infections. TB is highly contagious and requires a six-month course of treatment. Since antibiotics were introduced in the past 50 years there has been a gradual increase in cases of multi-drug resistant (MDR) TB that can require up to 2 years of intensive chemotherapy to eradicate with inevitable drug toxicities. In 2014, an estimated 20% of previously treated cases have MDR-TB and 3% of new cases illustrating transmission of resistant organisms. Approximately 10% of these MDR -TB cases have extensively drug resistant (XDR) TB. In 2014 the mortality rate for TB globally was over 15%.

However those with XDR-TB have a 30% mortality rate within a cohort followed since 2012 with rates of up to 47% in South Africa, likely related to HIV co-infection (WHO, 2015).

The rollout of rapid molecular diagnostic tests via the WHO Global TB Programme has enabled drug resistance monitoring in more than 95% of the world's population. More than half of reporting countries are on continuous surveillance and the rest report using epidemiological surveys. This has allowed for early detection of resistance so that patients have been able to receive appropriate treatment. New drugs, e.g. bedaquiline, and repurposing of old drugs has increased the treatment options for MDR and XDR-TB and improved treatment success rates to >75% in 40 of 122 reporting countries (WHO, 2015). This represents a major success for the global response to a specific AMR threat. The response of the WHO to MDR and XDR-TB could be a model for response to other resistance pathogens that pose serious public health threats.

### Measuring the burden of AMR

A 2014 report by the WHO found alarmingly high resistance rates in common bacteria worldwide (WHO, 2015). The report highlighted that AMR is associated with poor clinical outcome and increased use of resources but is likely to underestimate the full extent of the problem as the study was limited to just 7 bacteria and 5 antibiotics. The report also revealed significant gaps in surveillance and a lack of consistency in testing methods.

AMR is a global concern as well as a local one. Drivers such as increased air travel mean that no one country's issues can be viewed in isolation, as illustrated by the rapid international dissemination of the New Delhi metallo- $\beta$ -lactamase (NDM-1) resistance determinant (Biedenbach et al., 2014). The WHO's response to the findings of its report is to implement a global standardized antimicrobial surveillance network that will allow for the measurement of trends and for early identification of problem pathogens (WHO, 2014).

A precise measurement of the clinical burden of detected antimicrobial resistance is complicated by the many potential causes of antimicrobial treatment failure. The outcome of any given infection is a balance of many factors between host, pathogen and antimicrobial agent as seen in Figure 3.

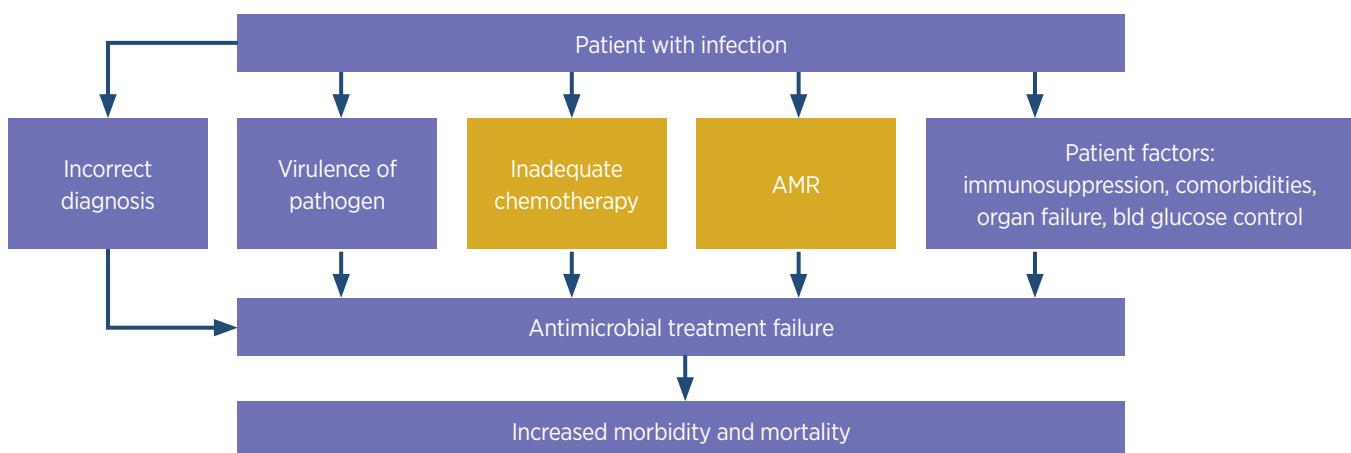
The CDC estimated that AMR was responsible for an excess mortality of 23,000 people per year in the US. However this estimate is not entirely satisfactory as it is not based on data on the frequency and clinical impact of failures of antibiotic therapy attributable to resistance. Studies that estimate IAT (e.g. Raman et al., 2015) provide more epidemiologically sound measures of AMR burden and a global system needs to be developed to record this information routinely to allow for accurate assessment of the clinical burden.

### Clinical response to AMR

Research and development into diagnostics, new drugs and vaccines is essential to combat the effect of AMR. However, to avert disaster now, there needs to be a shift in the public perception and the medical profession's use of antibiotics. The antibiotics that are available currently must be safeguarded through improved stewardship, education, infection control, avoidance of inappropriate treatment and targeted antibiotic therapy when microbiological results are available.

An evaluation of the effect of these principles put into practice in Aberdeen, Scotland compared using a time series model of no intervention, demonstrated a 50% reduction in prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the Grampian region (Lawes et al., 2015). This indicates how much can be achieved through a change in behaviour. NHS England is applying these principles to all resistant pathogens through launching a national incentive-based initiative in 2016 to decrease inappropriate prescribing and gather antimicrobial resistance data (NHS England, 2016). If such measures were to be adopted on a global scale then the rate of AMR development could be significantly decreased and substantial morbidity and mortality averted.

**Figure 3: Antimicrobial treatment failure**



## References:

- Biedenbach, D., Bouchillon, S., Hackel, M., Hoban, D., Kazmierczak, K., Hawser, S., Badal, R. (2014) *Dissemination of NDM Metallo-β-Lactamase genes among clinical isolates of Enterobacteriaceae collected during the SMART Global Surveillance Study from 2008 to 2012*. Antimicrob. Agents Chemother. 59, 826–830. doi:10.1128/AAC.03938-14
- Dortet, L., Poirel, L., Nordmann, P. (2014) *Rapid detection of extended-spectrum-β-lactamase-producing enterobacteriaceae from urine samples by use of the ESBL NDP test*. J. Clin. Microbiol. 52, 3701–3706. doi:10.1128/JCM.01578-14
- Gafter-Gvili, A., Fraser, A., Paul, M., Vidal, L., Lawrie, T.A., van de Wetering, M.D., Kremer, L.C., Leibovici, L. (2012) *Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy*. Cochrane Database Syst. Rev. 1, CD004386. doi:10.1002/14651858.CD004386.pub3
- Lawes, T., Lopez-Lozano, J.-M., Nebot, C.A., Macartney, G., Subbarao-Sharma, R., Dare, C.R., Wares, K.D., Gould, I.M. (2015) *Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated meticillin-resistant *Staphylococcus aureus* infections across a region of Scotland: a non-linear time-series study*. Lancet Infect. Dis. 15, 1438–1449. doi:10.1016/S1473-3099(15)00315-1
- MacGowan, A.P., on behalf of the BSAC Working Parties on Resistance Surveillance. (2008) *Clinical implications of antimicrobial resistance for therapy*. Journal of Antimicrobial Chemotherapy 62, ii105–ii114. doi:10.1093/jac/dkn357
- NHS England. (2016) *NHS England launches national programme to combat antibiotic overusage*. Available at: <https://www.england.nhs.uk/2016/03/antibiotic-overusage/#>
- NHS Lothian. (2016) *Antimicrobial prescribing guidelines*.
- Polk, H.C., Lopez-Mayor, J.F. (1969) *Postoperative wound infection: a prospective study of determinant factors and prevention*. Surgery 66, 97–103.
- Public Health England. (2014) *Carbapenemase-producing Enterobacteriaceae: early detection, management and control toolkit for acute trusts* - Publications - GOV.UK Available at: <https://www.gov.uk/government/publications/carbapenemase-producing-enterobacteriaceae-early-detection-management-and-control-toolkit-for-acute-trusts>
- Raman, G., Avendano, E., Berger, S., Menon, V. (2015) *Appropriate initial antibiotic therapy in hospitalized patients with gram-negative infections: systematic review and meta-analysis*. BMC Infect. Dis. 15, 395. doi:10.1186/s12879-015-1123-5
- Teillant, A., Gandra, S., Barter, D., Morgan, D.J., Laxminarayan, R. (2015) *Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study*. Lancet Infect. Dis. 15, 1429–1437. doi:10.1016/S1473-3099(15)00270-4
- US Centers for Disease Control and Prevention. (2013) *Antibiotic resistance threats in the United States, 2013* Available at: <http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>
- Van Boeckel, T.P., Gandra, S., Ashok, A., Caudron, Q., Grenfell, B.T., Levin, S.A., Laxminarayan, R. (2014) *Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data*. Lancet Infect. Dis. 14, 742–750. doi:10.1016/S1473-3099(14)70780-7
- Van Duin, D., Kaye, K.S., Neuner, E.A., Bonomo, R.A. (2013) *Carbapenem-resistant Enterobacteriaceae: a review of treatment and outcomes*. Diagn. Microbiol. Infect. Dis. 75, 115–120. doi:10.1016/j.diagmicrobio.2012.11.009
- WHO. (2015) *Global tuberculosis report*. Available at: [http://www.who.int/tb/publications/global\\_report/en/](http://www.who.int/tb/publications/global_report/en/) (accessed 3.14.16).
- WHO. (2014) *Antimicrobial resistance: Global report on surveillance*. Available at: [http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf?ua=1) (accessed 3.17.16).

## Biography

**Meghan Perry** is a clinician scientist specialising in infectious diseases. Her clinical work includes antimicrobial stewardship, infection consult rounds, care for inpatients and outpatients with HIV, hepatitis, tuberculosis, community-acquired, hospital-acquired and imported infections. Since she completed a PhD on drug resistance in leishmaniasis her ongoing research work with Professor Mark Woolhouse at the University of Edinburgh focuses on AMR.

**Mark Woolhouse** is a Professor of Infectious Disease Epidemiology at the University of Edinburgh. For his contribution to infectious disease control he was awarded an OBE (2002) and is a Fellow of the Royal Society of Edinburgh (2004) and the Academy of Medical Sciences (2010). He has advised the UK and US governments on emerging infections.

# 5. What you need to know about antibiotic resistance

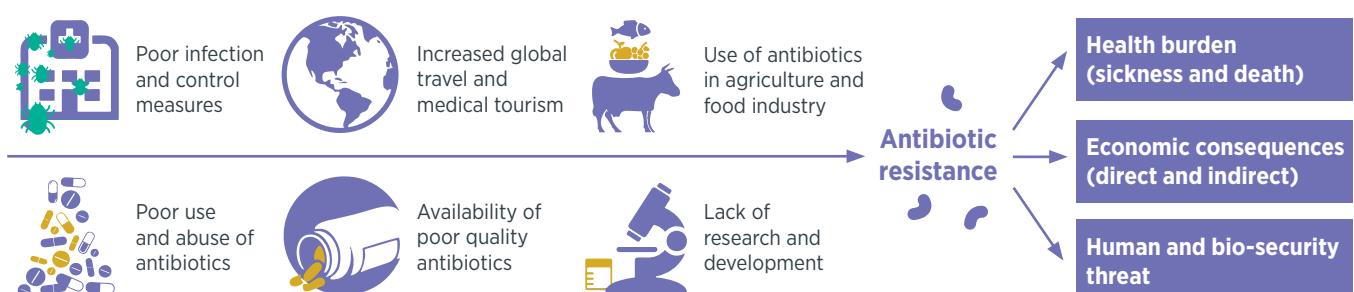
Ivo Holanec, Research Project Manager, Institute and Faculty of Actuaries

Antibiotic resistance occurs when bacteria lose their sensitivity to antibiotics (AMR refers to resistance of viruses fungi, worms, malaria or bacteria). The danger is that life-threatening bacterial infections caused by resistant bacteria can no longer be treated with the antibiotics used today. Yet even minor infections may be rendered major threats if antibiotics lose effectiveness. The UK government considers the threat of antibiotic

resistance as seriously as a flu pandemic or major flooding. Without action to address antibiotic resistance, doctors will lose the ability to treat infections. Routine operations could become deadly in just 20 years.

## The drivers and consequences of antibiotic resistance

As early as 1945, Sir Alexander Fleming, who discovered the first antibiotic penicillin in 1928, had warned during his Nobel Lecture that bacteria may eventually evolve to develop resistance to penicillin and similar drugs (Fleming, 1945).

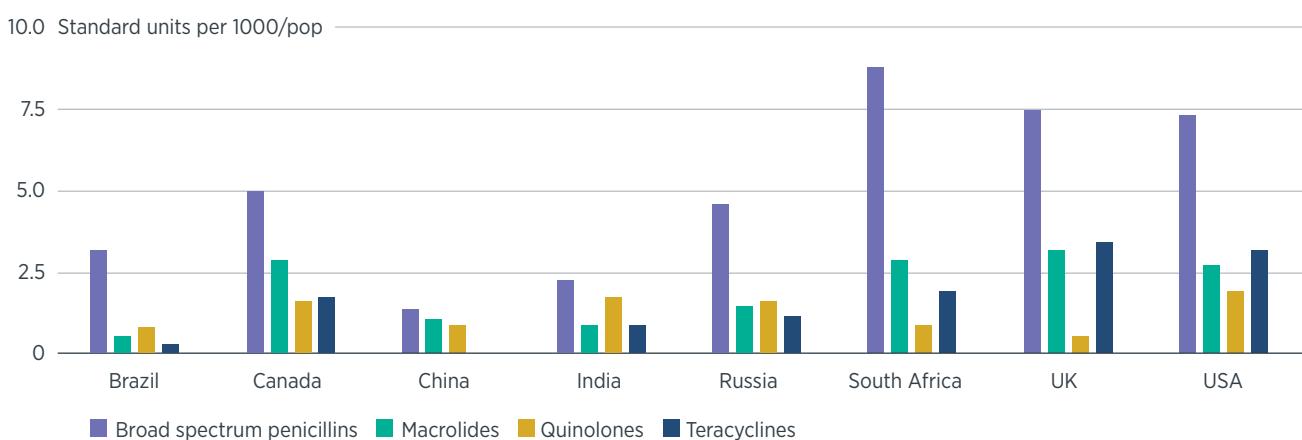


## Antibiotic use in primary care

Global consumption of antibiotics soared by nearly 36% between 2000 and 2010 (Boeckel et al., 2014). Consumption decreased in countries such as Mexico or Chile, however it sharply increased in many low-income and middle-income countries. Figure 4 compares antibiotic use by countries.

In England antibiotic prescribing increased from 21.6 DDD (defined daily dose) per 1,000 inhabitants per day in 2011 to 23 DDD in 2014 (PHE, 2015). There is also a widening deprivation gap where doctors in the most deprived areas are prescribing 20% more antibiotics.

Figure 4: Consumption of antibiotics in 2010 per capita



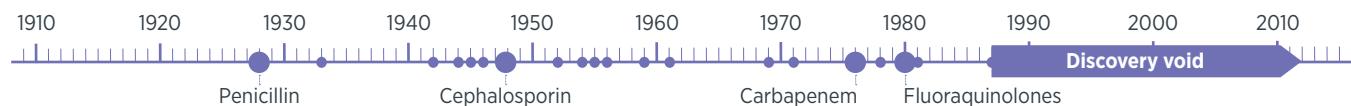
## Antibiotic use in farming

Increasing worldwide demand for meat has led to antibiotic consumption in animals rising by 70% over the past decade (Boeckel et al., 2015). In the UK, nearly 45% of all antibiotics are used in farming as a pharmaceutical crutch to compensate for disease inducing conditions of factory farming (DEFRA, 2013). The total quantities of antibiotic active ingredient in food and non-food animal products are shown in Figure 5.

There is growing evidence that antibiotic use in agriculture promotes resistance in humans. *Salmonella* and *Campylobacter* are clearly linked to antibiotic use in food animals, and food-borne diseases caused by such resistant bacteria are well documented in people (WHO, 2011).

## Antibiotic research and development

Antibiotic resistance is developing faster than new antibiotics are being developed, and finding new antibiotics is becoming increasingly difficult and expensive. Since 1987, no new class of antibiotics has been discovered that is available for treatment of bacterial infections (Mandell et al., 2015).



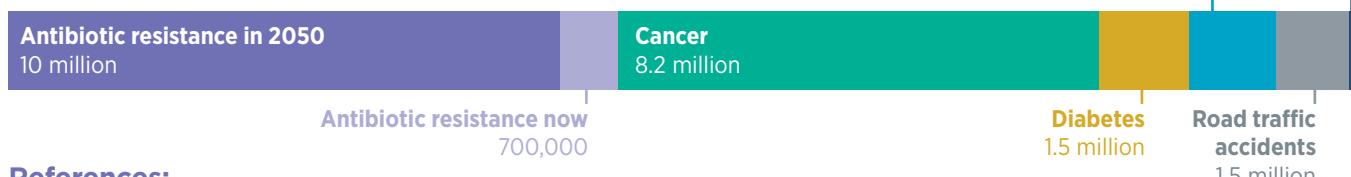
## Economic and human consequences

The human consequences of increased antibiotic resistance are mainly higher mortality in patients with resistant infections, increased length of hospital stays, and higher treatment costs for resistant infections.

In 2050 the deaths attributable to antibiotic resistance would be approximately 10 million per year as seen in Figure 6. Comparison to other major causes of death can be seen in Figure 7.

Deaths from antibiotic resistance would result in a reduction of 2% - 3.5% in GDP, costing the world up to £66 trillion due to lost productivity (O'Neill, 2014).

**Figure 7: Deaths attributable to antibiotic resistance every year compared to other major causes of death**

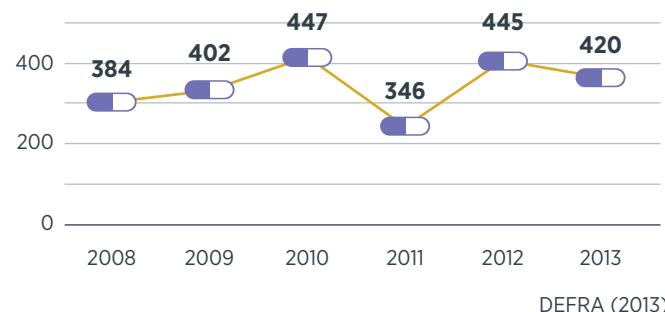


## References:

- Blaser, M. (2011) *Antibiotic overuse: stop the killing of beneficial bacteria*. Nature. 476:393–4. doi:10.1038/476393a.
- CDDEP. (2016) *Resistance map: Antibiotic Use* Available at: <http://resistancemap.cddep.org/resmap/use>
- DEFRA. (2013) *UK veterinary antibiotic resistance and sales surveillance*. UK-VARSS 2013
- Fleming, A. (1945) *Penicillin*. Nobel Lecture
- Mandell, G.L., Bennett, J.E., Dolin, R. (2015) *Principles and practice of infectious diseases*. Elsevier, Eight Edition, Churchill Livingstone
- O'Neill, J. (2014) *Review on antimicrobial resistance - antimicrobial resistance: tackling a crisis for the health and wealth of nations*.
- PEW. (2014) *Tracking the pipeline of antibiotics in development*.
- Van Boeckel, T.P., Gandra, S., Ashok, A. et al. (2014) *Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data*. Lancet Infect. Dis. 14, 742–750. doi:10.1016/S1473-3099(14)70780-7
- Van Boeckel, T.P., Brower, C., Gilbert, M. et al. (2015) *Global trends in antimicrobial use in food animals*. doi:10.1073/pnas.1503141112.
- WHO. (2011) *Tackling antibiotic resistance from a food safety perspective in Europe*.

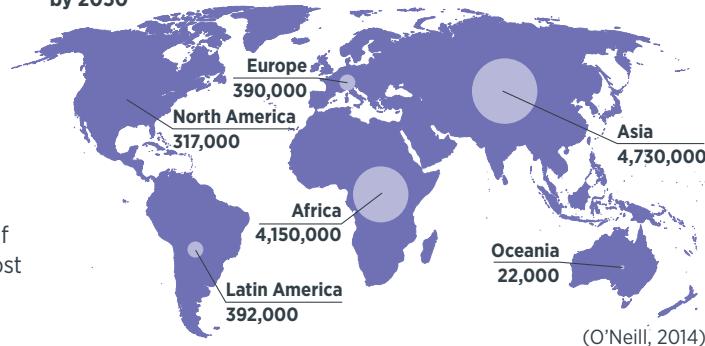
<sup>1</sup> Includes Tetracyclines, Trimethoprim/Sulphonamides,  $\beta$ -lactams, Aminoglycosides, Macrolides and Fluoroquinolones

**Figure 5: UK total veterinary antibiotic use (tonnes of active ingredient)<sup>1</sup>**



Only 3 of the 41 antibiotics currently in development have the potential to act against the majority of the most resistant bacteria. At best, only 1 out of 5 drugs that reach the initial phase of testing in humans will receive approval (PEW, 2014).

**Figure 6: Deaths attributable to antibiotic resistance every year by 2050**



# 6. Antibiotic resistance and longevity improvements

Matthew Edwards, Senior Consultant, Willis Towers Watson

This article provides an overview of the likely impact of antibiotic resistance on longevity improvements, with particular reference to the UK although the general points should be broadly applicable across OECD countries.

## Background

Our current position in the history of medical advances and longevity improvements gives us an unusual and probably unrepeatable perspective. In early 2016, the UK can look back on the last forty or so years and see a generally untroubled pattern of material morality improvements driven largely by lifestyle advances (particularly smoking reduction), improved cardiovascular disease treatment (pharmaceutical and surgical), all aided by large real increases in the NHS budget. Over that period, infectious disease was regarded as a battle won, something from the past (with the exception of HIV/AIDS, which did not ultimately prove to have a significant long-term effect on mortality).

However, if we were to position ourselves instead in the 1970s, our perspective would be completely different. Over the period since 1951, mortality due to CVD had moved little – and likewise as regards the other major causes of death, with one exception. The one major advance was in the field of infectious disease. Age-standardised mortality attributable to infectious disease fell from circa 1 per mille in the 1940s to below 0.1 per mille by 1971 (the figures are similar for men and women) (ONS Health Statistics Quarterly, 2003). For the sake of completeness, one other group that had showed material but much smaller improvements was genitourinary disease.

## Components of the question

What, then, does the future hold, given that antibiotic resistance is ‘no longer a prediction for the future, it is happening right now ... and is putting at risk the ability to treat common infections’? (WHO Fact sheet, 2015)

Part of the problem is that it is hard not to fall into one of two modelling mindsets: that of projecting the past assuming recent trends, perhaps with minor adjustment to parameters; and that of some form of extreme event in line with the 1-in-200 risk-based capital approaches now embedded across insurers.

Neither of these approaches is likely to prove useful: the former can be far too anchored in recent history, while the latter does not help in the context of best estimate outcomes.

A further problem arises from the full nature of the question, ‘What is the impact of AMR on longevity improvements?’ Quantifying this impact is effectively an attempt to solve the equation  $Unknown_1 - Unknown_2 = x$ . If the two are of largely different orders of magnitude, the problem reverts to quantification of the larger unknown. Unfortunately, in this case – as we shall see – both of the unknowns seem to be of broadly similar orders of magnitude.

## Antibiotic resistance projections compared with longevity improvements

A return to infectious disease mortality of the pre-antibiotic era (ie early 1940s) is unlikely. Quite apart from the increasing focus on new antibiotic development and other areas such as hospital hygiene, some of the decline in infectious disease mortality is attributable to improved vaccination programmes, and improved living standards and personal nutrition (e.g. tuberculosis mortality is more severe in the malnourished).

For the purpose of generating some reasonable numbers for comparison, assume that mortality relating to infectious diseases increases to around half of its 1951 level over the next ten years. A return to infectious disease mortality of circa 0.5 per mille by 2025 would correspond to an annual increase in mortality of around 0.2-0.3% in relative terms (depending on age range and gender).

This gives us some indication of a feasible change in mortality over the medium-term future.

What is the point of comparison?

- The CMI’s Working Paper 39 (2009) noted that improvements over the quarter-century 1954-1979 averaged just 0.3% (ages 40-89), and this could be a plausible lower end
- At the higher end, we have the average improvement for males in England and Wales aged 65, 70, 75, and 80 over the 30 year period 1982-2012 of 2.7% per annum

- Somewhere in the middle, Willis Towers Watson has conducted two forms of independent derivation of longevity improvements. One is based on collating the opinions of a panel of medical experts across the main disease groups, and weighting their conclusions using a disease-based mortality model. The other is based on a more general driver-based approach to improvements, quantifying the mortality impact of best estimates of fundamental drivers such as health expenditure, smoking patterns and other societal factors. Both of these approaches have given results of around 1% per annum.

It is evident that the mortality increases from antibiotic resistance could match or even outweigh longevity improvements (higher infectious disease resurgence, lower improvements), while the other combination of lower infectious disease rates and higher improvements still shows a material impact.

### More detailed approaches

What should be the main components of a more detailed approach to modelling the impact of antibiotic resistance? Although the end quantification will always be highly susceptible to parameter error and spurious accuracy, part of the purpose of modelling is to help understand what the primary drivers of the process are, and which are the most significant. A full model would be based on the following two components:

- (1) Causes of death affected by antibiotic resistance  
(by age group and gender, varying by time)
- (2) Resistance of related infections to available antibiotics

These perhaps simple-looking components are themselves complex to model.

For instance, (1) would consist not just of directly acquired infectious diseases but also infections acquired while in hospital for other reasons. Particular areas of concern are post-birth mothers, cancer patients recovering from chemotherapy, and patients recovering from major surgery. The extent to which antibiotic resistance may affect such cases is highly debatable. For instance, regarding hip replacement, an article in the British Medical Journal in 2013 suggested that up to 40% of hip replacement patients would then be subject to 30% fatality from post-operation infection (Smith and Coast, 2013). However, the microbiologist Professor Hugh Pennington regards this as greatly exaggerated, noting that pre-antibiotic amputation fatalities were an order of magnitude lower (Pennington, 2015).

A further complication arises in considering how even the mortality of well-analysed diseases such as TB may be improved by better vaccination programs (part of the strategy for dealing with antibiotic resistance) or worsened by other societal factors – for instance, there is evidence that diabetes is a risk factor for TB, which is clearly problematic given current diabetes prevalence and trends (Dye, 2014).

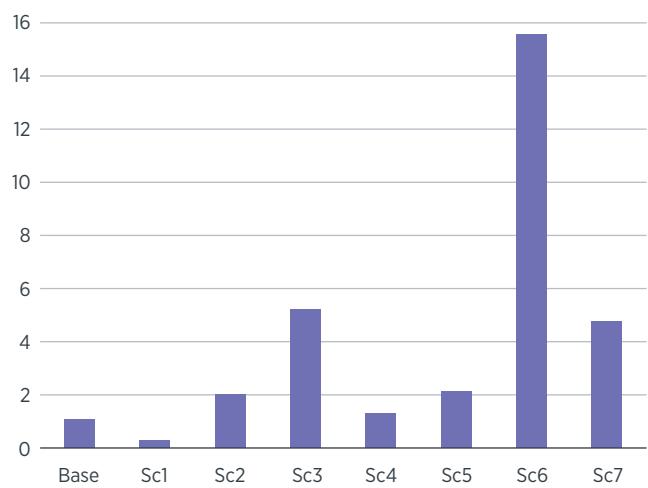
The second component, resistance to available antibiotics, will need to include the assumed release of antibiotics in the future, but also assumptions as to how these will themselves gradually become less effective as bacteria grow resistant to the new drugs. The average time until major pathogenic resistance becomes a problem is around eight years (Schmieder and Edwards, 2012). The parameterisation might also have regard to the fact that some super-resistant strains have greater virulence and increased transmissibility, and hence even the (apparently pessimistic) assumption of a return to past conditions might be optimistic.

In the absence of such a model developed specifically for the UK, we can consider outputs of the model developed by RAND as part of the O'Neill review report (Taylor et al., 2014).

The publication focuses on economic impacts rather than directly on mortality, and there is relatively little detail provided regarding the intermediate mortality calculations passing through the model. However, figures available on the projected working age population loss relative to 0% resistance, by broad zone, allows us to see a mortality increase of around 0.1 per mille per annum over the next 10-20 years.

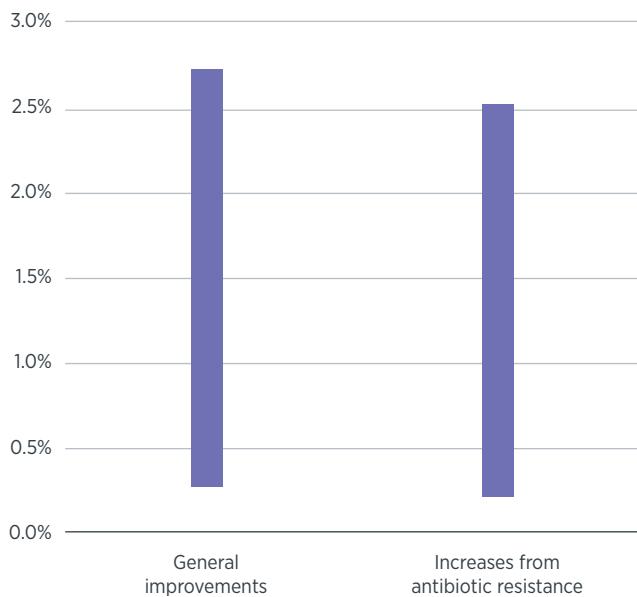
This is based on considering their scenario 4, where around 40% resistance rates are reached in 15 years – for comparison, European TB antibiotic resistance is currently cited in the RAND report at 16% in 2013 per WHO figures. Scenario 4 ranks as the second-most optimistic of the seven scenarios explored (not including the baseline scenario). Figure 8 shows these graphically, with reference to the projected effect by year 20.

**Figure 8: Working age population loss in EU/EEA/OECD countries - million people per year, by year 20**



This represents a mortality increase of circa 2-3% per annum (in relative terms). This result, in conjunction with the previous result of 0.2-0.3% per annum, shows that the impact is likely to be of the same order of magnitude as expected mortality improvements which can be seen in Figure 9.

**Figure 9: Comparison of plausible mortality improvements v mortality deterioration from antibiotic resistance**



## Conclusion

It should be clear from the above that:

- (i) The magnitude of the problem is sufficient to, at best, have a material impact on expected medium term mortality / longevity improvements, and, at worst (a 'plausible' worst rather than a 1-in-200 year extreme event), to largely zeroise or even negate those improvements
- (ii) There is a need for more modelling to be done in a transparent way to allow actuaries to incorporate their own views and to reflect the circumstances of their particular countries, and to use such models to inform both best estimate and stress assumptions.

## References:

- CMI Woking Paper 39. (2009) *A prototype mortality projections model: Part two – detailed analysis*. Available at: <https://www.actuaries.org.uk/documents/cmi-working-paper-39-prototype-mortality-projections-model-part-two-detailed-analysis>
- Dye, C. (2014) *After 2015: infectious diseases in a new era of health and development*. DOI: 10.1098/rstb.2013.0426
- ONS Health Statistics Quarterly. (2003) *Twentieth century mortality trends in England and Wales. Issue 18*. Available at: <https://www.ons.gov.uk/ons/rel/hsq/health-statistics-quarterly/no--18--summer-2003/twentieth-century-mortality-trends-in-england-and-wales.pdf>
- Pennington, H. (2015) *Have bacteria won?* ISBN: 9780745690797
- Schmieder, R., Edwards, R. (2012) *Insights into antibiotic resistance through metagenomic approaches* Future Microbiol. Jan;7(1):73-89. doi: 10.2217/fmb.11.135
- Smith, R., Coast, J. (2013) *The true cost of antimicrobial resistance*. BMJ 2013;346:f1493. Available at: <http://www.bmjjournals.org/content/346/bmj.f1493>

Taylor, J., Hafner, M., Yerushalmi, E., Smith, R., Bellasio, J., Vardavas, R., Bienkowska-Gibbs, T., Rubin, J. (2014) *Estimating the economic costs of antimicrobial resistance: Model and Results*. RAND. Available at: [http://www.rand.org/content/dam/rand/pubs/research\\_reports/RR900/RR911/RAND\\_RR911.pdf](http://www.rand.org/content/dam/rand/pubs/research_reports/RR900/RR911/RAND_RR911.pdf)

WHO Fact sheet. (2015) *Antimicrobial resistance*. Available at: <http://www.who.int/mediacentre/factsheets/fs194/en/>

## Biography

**Matthew Edwards** is the Head of Mortality and Longevity in Willis Towers Watson's life insurance practice. He has a particular interest in disease-based modelling, longer-term driver-based models of longevity, and using the views of medical experts to enhance our understanding of likely mortality trends.

# 7. Economic implications of antibiotic resistance: not all gloom and doom

Professor Cormac Ó Gráda, University College Dublin and CAGE, University of Warwick

## Introduction

Today people in high-income countries can expect to live nearly twice as long as their forebears a century ago. This huge increase in life expectancy at birth ( $e(0)$ ) is due mainly to the eradication or near-eradication of a whole range of potentially fatal infectious diseases. Low-income countries, where infectious diseases still account for nearly half of all deaths, still have a long way to go, but they have been doing better too. Today  $e(0)$  in even the poorest of them is higher than it was anywhere before the revolutions in public health and medicine linked to the findings of Louis Pasteur and Robert Koch.

In demographic terms, these gains are unprecedented. One measure of their impact on human wellbeing is the Human Development Index (HDI), estimated as the geometric mean of measures of income, education, and health relative to an assumed maximum. For example, by assumption, the health measure uses a minimum life expectancy of 20 years and a maximum of 85 years; so its value for a life expectancy of 60 years is  $[60-20]/[85-20]$  or 0.615. Similarly, the income measure is set at a maximum at \$75,000 per capita - for more detail see UNDP 2015. Table 2 compares estimates of HDI and real GDP per capita in Britain in 1870, 1913, 1950, and 2013. While GDP per capita grew more than six-fold between 1870 and 2013, HDI moved proportionally much closer to its

'maximum' value of 1. Note that the contribution of health [ $H$ ], as proxied by  $e(0)$ , to the rise in HDI dwarfed that of literacy [ $L$ ] and income [ $Y$ ] between 1870 and 1950, while income contributed most thereafter. Note too that Britain's HDI value in 1870 would place it well behind, say, Ghana or Zambia today.

The value of a statistical life (VSL) offers a second way of measuring the welfare gains to increased  $e(0)$ . Given that VSL is a measure of the value placed on a marginal change in the likelihood of living longer, it is often estimated by the costs associated with risks taken or avoided (Viscusi, 2014). Its application to poor countries in an earlier era entails an assumption about the appropriate income elasticity, i.e. what is the proportionate change in VSL resulting from a change in income. There is a presumption that the income elasticity of demand [ $\eta$ ] falls as countries get richer so we work with 'high' values of  $\eta$ . To take one historical example, a 'first cut' estimate of the welfare gains from the eradication of malaria in China and India in the 1950s and 1960s implies huge gains. Skipping the arithmetic, the estimated gain from eliminating an annual 0.8 million deaths from malaria in India is 47 per cent of GDP for  $\eta=1$  and a still significant 26 per cent for  $\eta=1.2$ . The same calculation applied to China with  $\eta=1$  yields a welfare gain of 56 per cent of 1950 GDP.

**Table 2: HDI and GDP per capita in Britain, 1870-2013 (Crafts, 2002)** Note: GDP per head is measured using 1990 international Geary-Khamis dollars; education component estimated using years schooling as a proportion of 15 years (assumed to be 3 years in 1870)

Year	HDI	GDP per head	Period	Relative Contribution (percentage of total)		
				$Y$	$H$	$L$
1870	0.476	3,190				
1913	0.628	4,921	1870-1913	14.2	54.1	31.7
1950	0.762	6,939	1913-1950	14.6	63.3	22.1
2013	0.923	23,500	1950-2013	44.0	39.5	16.5

## The cost of AMR: a closer look at tuberculosis (TB)

Today several key antimicrobial drugs are losing their effectiveness, leading several commentators to predict that increasing AMR risks a return to the medical dark ages. Although much of the focus has been on MRSA, the spread of CRE and the recently discovered colistin-resistant *mcr-1*, are the greatest worries now (Dortet et al., 2014; Reardon, 2015).

Here history makes two key points. First, most of the gains in e(O) described above preceded the antibiotic revolution. Before antibiotics, a combination of public action, better living conditions, and preventive medicine led to the eradication of several other infectious diseases—cholera, typhoid fever, measles, diphtheria, and tuberculosis.

Second, the gains in e(O) before antibiotics outweighed those after them. Thus the sudden loss of several antibiotics would not hurl us back into the medical dark ages nor, indeed, would it force us all the way back to the mid-twentieth century, when the age of antibiotics began. That is because factors which helped reduce infectious disease before antibiotics—medical, institutional, and economic—are likely to be much more powerful now.

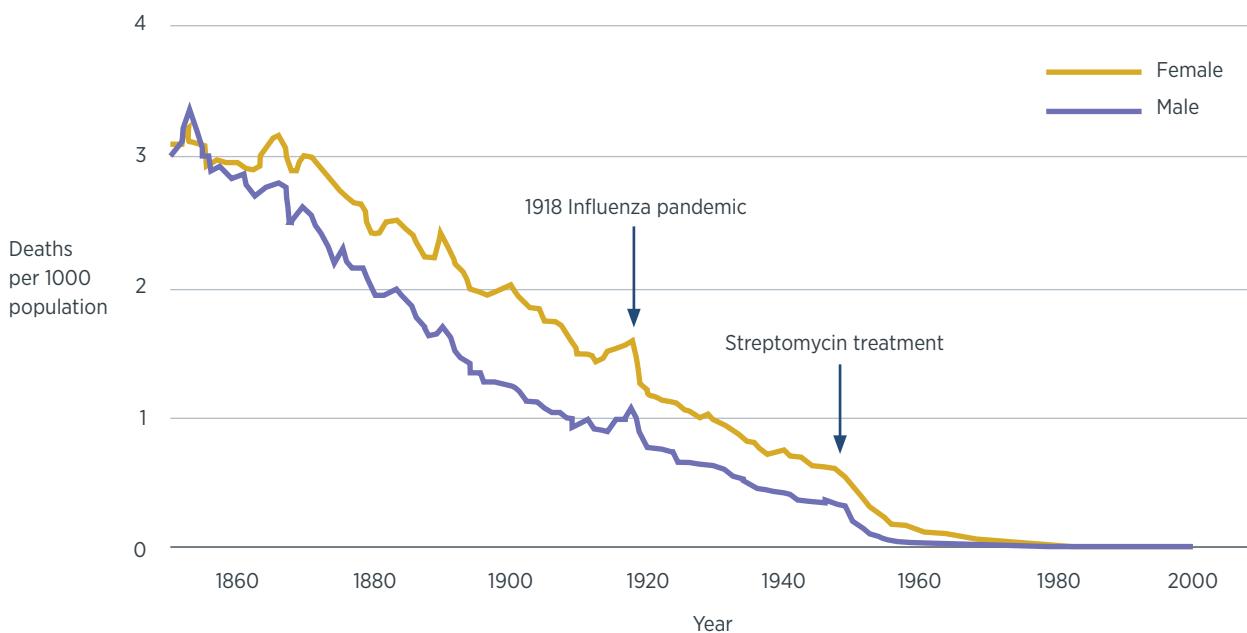
This is not to deny the huge dependence of many modern medical technologies on antibiotics. Without them all kinds of surgery, ranging from interventions against heart disease and cancer to hip and knee joint replacements would become much riskier; many sufferers would die or be forced to leave their conditions untreated.

Although mortality from TB began to decline in England long before the arrival of an effective antibiotic remedy, it took a combination of antibiotics and BCG to eliminate it. This can be seen in Figure 10. TB remains a major killer in low-income countries today, and as multidrug resistant tuberculosis (MDR-TB) becomes more commonplace some of the welfare gains associated with its eradication in high-income countries will be lost unless an alternative remedy is found.

How much would be lost? Hickson (2015) has produced upper and lower bounds of the likely loss for the UK in the event of drugs become ineffective against TB. The former puts a value on the gains from the reductions in TB between 1950 and 2000, thus excluding the gains made in the pre-antibiotic era. Still, the number is big: \$35 billion. But it is very unlikely to be incurred, because the improvements in housing and nutrition that reduced the incidence of TB before 1950 have continued apace. Besides, BCG offers a strong second line of defence against TB. Taking these factors into account reduces the upper bound estimate to a more realistic \$9 billion. The comparison highlights a crucial point about the challenge of AMR. As with MRSA, for many infections prevention and second-line antimicrobials may mitigate the impact of AMR. The real worry is about the small number of cases where this may not apply.

Hickson also produces a lower bound estimate, based on a VSL function to the number of life years burdened with MDR-TB in 2013. It yields an estimate of \$1.9 billion. This refers only to the early phase of AMR, however, when resistance rates are low. Worse case scenarios involve moving closer to the upper bound estimate of \$9 billion as the proportion of drug-resistant cases increases.

Figure 10: TB mortality in England and Wales, age-standardised to the U.K. population in 2000 (Davenport, 2007; ONS, 2003)



## Supply and demand

Antibiotic resistance becomes an issue only when the antimicrobial artillery is not being continuously updated. There is a pervasive sense today that it is not. This technopessimism is based on a sense that all the ‘easy’ discoveries have already been made. Given subsequent advances in cellular and molecular genetics, in bacteriology, and in virology, and the ICT revolution—all far in the future when the first antibiotics emerged and all of which presumably facilitate new discoveries—this may seem somewhat puzzling. A closer look at supply suggests that although the lack of new effective antibiotics is worrisome, technology is not at a standstill. As of December 2015, the U.S. Food and Drugs Administration’s register listed 39 new antibiotic drugs under development ‘with the potential to treat serious bacterial infections’ (Pew Charitable Trusts, 2016). If even a handful of these succeed, they would go some way towards alleviating fears of some forms of AMR for a while (Ó Gráda 2016).

The very large between- and within-country variation in the consumption of antimicrobials suggests a role for public health policy in reducing demand. For example, cutting European consumption to the Dutch level would cut the consumption of antibiotics on the continent by almost half. There is evidence that measures to encourage and curb over-use and over-prescription work, though only temporarily. Other prospects for reducing demand include technologies to inhibit the spread of multidrug resistant organisms (Dortet et al., 2014); personalized medicine; ‘smart’ combination therapies; and the treatment of *C. diff.* infections with faecal transplants or ‘crapsules’. Vaccines, too, offer a potential first line of defence through prevention against the pathogens that cause TB, malaria, hospital-acquired infections, and more.

## Conclusion

The war against microbes is a war against Darwinian evolution: the point is not to win but to stay ahead. In that regard, the threat is probably no more serious now than a decade ago, because in the interim there have been hugely impressive reductions in MRSA resistance and in deaths attributable to *Staph. aureus* and *C. diff.* Awareness of AMR is also much greater, while the new drugs pipeline is now beginning to show more signs of activity than at any point since the 1960s. Growing anxiety about CRE and mcr-1 points to the need for a narrower policy focus on where the threat is greatest (as with the Ebola virus), rather than on the drugs pipeline generally. The situation is worrying and challenging but by no means hopeless.

## References:

- Crafts, N., F., R. (2002) *The Human Development Index, 1870-1999: some revised estimates*. European Review of Economic History 6: 395-405.
- Davenport, R., J. (2007) *Annual deaths by cause, age, and sex in England and Wales, 1848-1900* [dataset]. Economic and Social Data Services (SN5705).
- Davenport, R., J., Hickson, K., Gráda, C.G. (2014) *Health, wellbeing, and antimicrobial resistance: Insights from the past for the present*. Report prepared for the ESRC.
- Dortet, L., Poirel, L., Errera, C., Nordmann, P. (2014) *CarbAcineto NP test for rapid detection of carbapenemase-producing Acinetobacter sp.* Journal of Clinical Microbiology, 52[7]: 2359-2364.
- Gráda, O., C. (2016) *Cast back into the dark ages of medicine? What the past can tell us about the challenge of antimicrobial resistance*. American Journal of Medical Research, 3[1]: 142-73.
- Hickson, K. (2015) *The welfare cost of antimicrobial resistance: tuberculosis as an illustrative example*. University of Warwick, CAGE Working Paper No. 241.
- The Pew Charitable Trusts. (2016) *Antibiotics currently in clinical development*. Available at: <http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development>
- ONS (Office of National Statistics) (2003) *Twentieth Century Mortality: 100 years of Mortality in England and Wales by Age, Sex, year and Underlying Cause*. CD-ROM.
- Reardon, S. (2015) *Spread of antibiotic-resistance gene does not spell bacterial apocalypse – yet*. Nature, 21 December.
- UNDP (United Nations Development Programme). (2015) Human Development Reports: Calculating the Indices. Available at: [hdr.undp.org/en/data](http://hdr.undp.org/en/data)
- Viscusi, W., K. (2014) *The value of individual and societal risks to life and health*, in Mark J. Machina and W. Kip Viscusi, eds. *Handbook of the Economics of Risk and Uncertainty* Amsterdam: Elsevier, pp. 385-452.
- ## Biography
- Cormac Ó Gráda** is Emeritus Professor of Economics at University College Dublin. He has published widely on many aspects of Irish, US, and Jewish economic history. He has served on the editorial board of several professional journals, and is formerly co-editor of the European Review of Economic History.
- ## Acknowledgment
- This article draws on research at Centre for Competitive Advantage in the Global Economy (CAGE), University of Warwick with Romola Davenport and Kerry Hickson.

# 8. Current developments and research in creating new antibiotics

Nicola Oliver, Director, Longevity and Mortality, Medical Intelligence (UK) Ltd

## Introduction

The availability of effective antibiotics in both medical and veterinary practice is essential to prevent and treat infections in humans and animals; the rapid development of bacterial resistance to antibiotics, however, presents a number of challenges and potentially disastrous future scenarios.

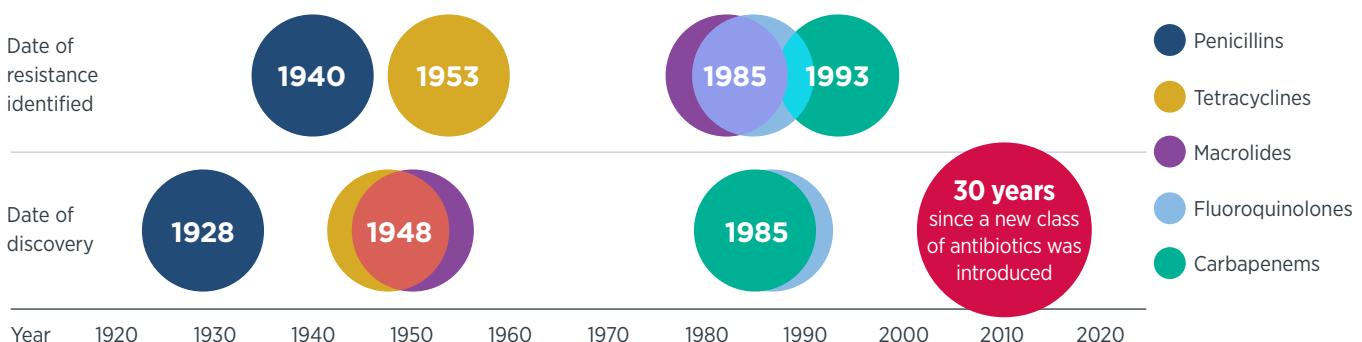
Antibacterial resistance is incidentally by no means a 21st century phenomenon; resistance to penicillin was first identified in 1940 and Alexander Fleming himself predicted the likely hazardous consequence of mass use of antibiotics.

Figure 11 shows a timeline of antibiotic discovery and subsequent resistance according to antibiotic class.

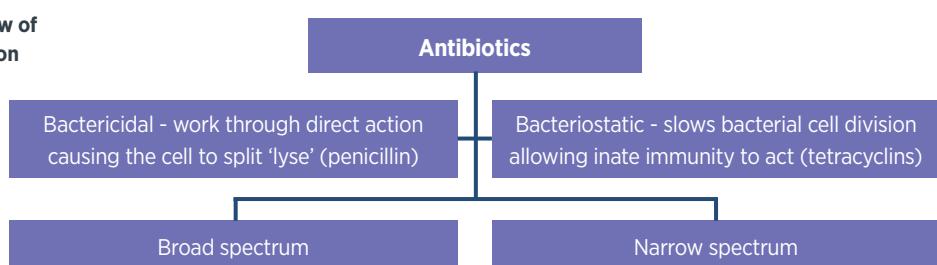
Bacteria constantly evolve to maintain their viability in the face of the antibiotics used against them and this arises simply due to Darwinian evolutional mechanisms. Antibiotic prescribing is undertaken to not only treat suspected bacterial infection, but in some cases, antibiotic prescribing is indicated for prophylaxis particularly intra- and post-operatively.

Antibiotics can be classified by their action; bacteriostatic or bactericidal, and further by their scope; broad or narrow spectrum. Narrow-spectrum antibiotics are specific and act on a molecule in the metabolism of one particular type of bacteria unique to that species, whereas broad spectrum antibiotics act on structures or processes that are common to many different bacteria. Around half of all human antibiotic use is derived from the  $\beta$ -Lactam class, of which penicillin is a member of. Figure 12 displays the classifications.

**Figure 11: Timeline of antibiotic discovery and subsequent resistance (Public Health England, 2015a) displays the classifications**



**Figure 12: An overview of antibiotic classification**



Classifications of bacterial species allow for further tailoring of antibiotic class as features such as Gram status and cell shape are important in determining the type of antibiotic that will be most effective.

The bacteria frequently responsible for bloodstream infections and resistances are displayed in Table 3.

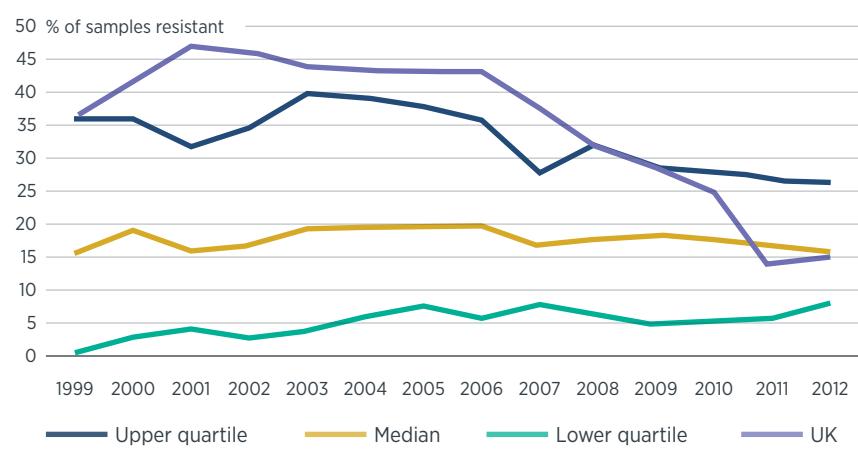
**Table 3: Common pathogens and their level of resistance (ECDC, 2009)**

Bacteria		Resistance used as a marker of multiple resistance to antibiotics
Gram-positive bacteria	Staphylococcus aureus (MRSA)	Methicillin resistance (MRSA) Vancomycin-intermediate resistance and resistance (VISA/VRSA)
		Vancomycin resistance (VRE)
	Streptococcus pneumoniae	Penicillin resistance
Gram-negative bacteria	Enterobacteriaceae	Third-generation cephalosporin resistance Carbapenem resistance
		Third-generation cephalosporin resistance Carbapenem resistance

Figures 13 and 14 display MRSA and 3rd generation cephalosporin-resistant E. coli resistance rates for the UK, ECDC and Europe compared showing upper and lower quartiles.

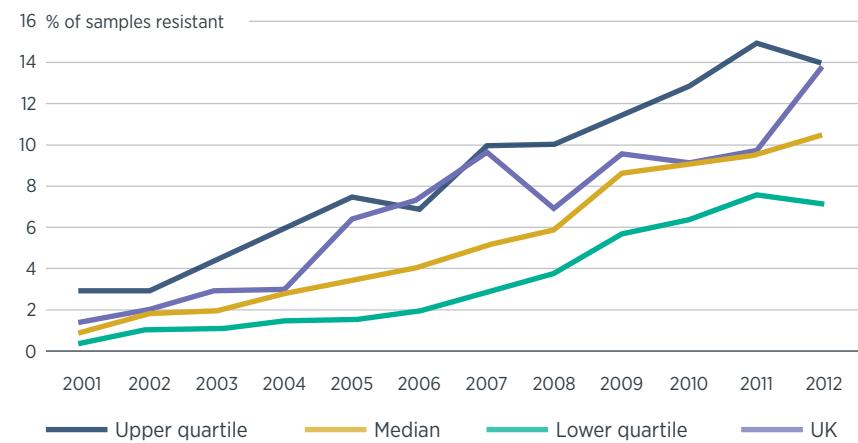
In Figure 13, the degree of MRSA resistance in the UK has been decreasing compared to a relatively stable trend in Europe in general.

**Figure 13: MRSA resistance rates across Europe, showing the UK, 1999 to 2012 (Department of Health, 2015)**



In Figure 14, a marked increase is evident for E. coli resistance in Europe with the UK remaining between the median and upper quartile throughout.

**Figure 14: Third-generation cephalosporin resistance rates in E. coli across Europe, showing the UK, 1999 to 2012 (Department of Health, 2015)**



## Antibiotic development

As of September 2015, an estimated 39 new antibiotics with the potential to treat serious bacterial infections are in clinical development.

There are two new classes of antibiotics:

**Teixobactin** is a small molecule antibiotic that is active against gram-positive bacteria. It appears to belong to a new class of antibiotics, and harms bacteria by binding to important components involved in cell wall construction.

Teixobactin was reported to be potent in vitro against a number of bacteria including those with known antibiotic resistance, and TB. Whilst human clinical trials are yet to be conducted, animal trials have also reported success.

**Brilacidin** is the first of a completely new class of antibiotics called defensin-mimetics which are modelled after natural human immune proteins and therefore may reduce the risk of future bacterial resistance. This drug is in phase 2 stage of clinical trials. Safety and clinical efficacy were demonstrated in a phase 2a clinical trial which involved patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSI).

Table 4 provides a summary of the current status of antibiotic drug discovery, including recently approved compounds, as well as those in the trial process.

Data from the 2015 (Public Health England, 2015b) English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report shows that just 19 antibiotics (belonging to fewer antibiotic classes) currently account for >88% of all prescribing in hospitals and community, and none of these is a recent discovery.

It is suggested that a regular supply of two to four licensed ‘first in class’ compounds per decade would give opportunity to stay ahead of resistance to preceding classes, as long as each new drug is used only as resistance dictates rather than as a potential ‘block-buster’ (HM Government[O'Neill], 2015).

Further analysis by O'Neill also suggests that investment is required in order to develop about 15 licensed antibiotics per decade which should aim to encompass two new broad spectrum classes and two new targeted therapeutic classes every ten years; both of which to address an unmet medical need.

**Table 4: Current status drug development for antibiotics including recently approved compounds. As of September 2015 (O Grada, 2015/PEW charitable trusts, 2015)**

Drug	Year	Status	Target
Tedizolid phosphate	2015	Available	ABSSSI
Dalbavancin	2014	Available (US only)	MRSA
Oritavancin	2015	Approved but not yet launched	MRSA Skin and soft tissue infections (SSTI)
Ceftolozane/ Tazobactam	2015	Available	E. coli and cUTI (complicated urinary tract infection)
Teixobactin	2015	Early stages	MRSA, Mycobacterium and tuberculosis
Ceftazidime-Avibactam	2014	Pre-registration EU/UK	Complicated IAIs (intra-abdominal infections) and UTIs (urinary tract infection)
Delafloxacin	2015	Phase III	ABSSSI
Ervacycline	2015	Phase III	Complicated IAIs (intra-abdominal) and UTIs
Plazomicin	2015	Phase III	cUTI, catheter-related bloodstream infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, complicated intra-abdominal infections, acute pyelonephritis (kidney infection) (some indications specifically target infections caused by Carbapenem-resistant Enterobacteriaceae)
Solithromycin	2015	Phase III	Community-acquired bacterial pneumonia, uncomplicated urogenital gonorrhoea, urethritis
Surotomycin	2015	Phase III	C. difficile-associated diarrhoea
Brilacidin	2015	Phase II	ABSSSI

## Alternative approaches

A number of alternative approaches are being explored and include development of predatory bacteria, antibacterial peptides derived from amphibians and reptiles, phages, (viruses able to attack bacteria), gene-editing to encourage bacterial 'suicide', and the use of metal nano-particles such as copper and silver.

One of these alternatives helping to reduce antibiotic use is outlined in a case study by Matthew Dryden. He explores the significant potential of Surgihoney Reactive Oxygen used as an alternative in wound-healing and infection control applications.

## Conclusion

AMR represents a continuing and potentially increasing area of concern both economically and clinically. Annual excess deaths as a direct result of antibiotic resistance in Europe exceed 25,000 and indications are that the current antibiotic failure rate in the UK of around 15% could rise. Globally, AMR has the potential to reduce GDP by 3.5% and kill an additional 10 million people by 2050.

Coupled with the scarcity of novel antibiotic compounds coming to market, these facts are driving successive governments to issue bleak warnings with regard the potential future burden of antimicrobial resistance and to develop specific policy aimed at reducing unnecessary prescribing as well as increasing attention to infection control both within hospital and the community.

Potential pharmaceutical pipeline developments are few, so perhaps attention now turning toward alternative approaches, along with changes in prescribing policy may be the answer to this disquieting problem.

## References:

- Department of Health. (2015) *Antimicrobial resistance empirical and statistical evidence-base*. A report from the Department of Health Antimicrobial Resistance Strategy Analytical Working Group Available at: <http://www.gov.uk/dh>
- ECDC/EMA. (2009) *The bacterial challenge: time to react*. Stockholm, September 2009 Available at: [http://ecdc.europa.eu/en/publications/Publications/0909\\_TER\\_The\\_Bacterial\\_Challenge\\_Time\\_toReact.pdf](http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_toReact.pdf)
- HM Government. (2014) *Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations*. Chaired by J O'Neill Crown Copyright
- HM Government. (2015) *Securing new drugs for future generations: The pipeline of antibiotics. The review On antimicrobial resistance*. Chaired By Jim O'Neill Crown Copyright
- O'Grada, C. (2015) The challenge of antimicrobial resistance: Lessons from the past for the present and the future global perspectives series: Paper 2 social market foundation/competitive advantage in the global economy. Available at: <http://www.smf.co.uk/publications/the-challenge-of-antimicrobial-resistance-lessons-from-the-past-for-the-present-and-the-future/>
- Public Health England. (2015a) *Guidance - Health matters: antimicrobial resistance*. Available at: <https://www.gov.uk/government/publications/health-matters-antimicrobial-resistance>
- Public Health England. (2015b) *English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) 2010 to 2014* Available at: [https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/477962/ESPAUR\\_Report\\_2015.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477962/ESPAUR_Report_2015.pdf)

## Biography

**Nicola Oliver** is Director and Head of Longevity and Mortality at Medical Intelligence (UK) Ltd, and is responsible for furthering clients understanding of factors driving longevity and mortality risk. She has extensive experience of working within the UK National Health Service in hospital intensive care and in public health. She is a member of the Institute and Faculty of Actuaries, The Royal Society of Medicine and the Royal College of Nursing.

# 9. Case study: Surgihoney Reactive Oxygen (SHRO)

Dr Matthew Dryden MD, FRCPath, FFTM FRCPS, Hampshire Hospitals Trust

Global antibiotic resistance is an unprecedented threat to human health. It will limit the management of many infections in the forthcoming decades, particularly in emerging health economies, where infection control services and antimicrobial stewardship are less developed. This is a case study of one patient's encounter with multi-resistant microbes and one possible solution.

In general, the solutions to the global crisis of antibiotic resistance are logical and are as follows:

1. **Reducing the volume of antibiotic use** and all inappropriate use in human medicine, agriculture and the environment. Currently this is impossible to achieve in the world although efforts are being made at governmental levels.
2. **Discover new antibiotics.** This is proving very slow and may not happen. The investment required is immense and the time to clinical trials and regulatory approval is long. It may be that all the effective classes of antibiotics have already been discovered.
3. **Infection control and antimicrobial stewardship.** These practice standards are very important in preventing transmission of resistant bacteria and reducing selection of new resistant bacteria. They are almost impossible to achieve in developing health economies, although efforts are being made.
4. **New rapid diagnostic tests** to identify when bacterial infection is present to allow the most appropriate use of antibiotics. Some progress is being made in this area but this process is difficult to implement especially when the tests may be more expensive than the antibiotics.
5. **Antibiotic alternatives.** These will not replace antibiotics but may help reduce antibiotic use. Examples of these are bacteriophages, probiotics and antibiotic resistance breaker molecules. A significant development in this field is SHRO which is cheap, simple and can easily be used across the globe in all health economies as an alternative to antibiotics and to reduce the requirement for antibiotics. It is highly antimicrobial even to all known resistant bacteria (Dryden et al., 2014). The vast majority of its antimicrobial action comes from the ability to deliver sustained low levels of reactive

oxygen (RO), or single oxygen atoms, via the formation of hydrogen peroxide for a sustained period. As hydrogen peroxide breaks down it releases reactive oxygen, or single oxygen atoms, which destroys invading microbes (Cooke et al., 2015).

## A patient's story

A retired barrister suffered life threatening necrotising soft tissue infection with multiply resistant bacteria acquired following minor skin trauma while on holiday in India. The wound became inflamed, and pain and spreading infection in the foot required admission to hospital in India. He was started on antibiotics empirically with no cultures taken. There was little improvement and the patient elected to return home.

On the return flight, his foot deteriorated with extending erythema and haemopurulent discharge. On admission to hospital in the UK a diagnosis of necrotising fasciitis was made. He required a prolonged admission for this rare but life-threatening infection, with intravenous antibiotics, surgical debridement and subsequent skin grafting.

Microbiology testing revealed that the bacteria in the infected tissue included a streptococcus (sensitive to antibiotics), a *Staphylococcus aureus* and two strains of coliforms resistant to almost all known antibiotics. One was NDM-1 (New Delhi metallo-beta-lactamase producer) E. Coli. The other antibiotic resistant bacteria was a carbapenemase-producing enterobacter. Not only were these bacteria pathogenic to the patient, but they were present in a hospital environment with the risk of transmission to other patients.

Treatment with SHRO, applied topically to the open infected soft tissue eradicated the multi-resistant bacteria, reducing the bacterial load and biofilm, and promoted healing, while also reducing the risk of transmission to other patients and reducing the requirement for last resort antibiotics. SHRO topical treatment not only helped the healing process but helped with infection control, by eradicating the resistant microbes and, with antimicrobial stewardship, by removing the need to use last resort antibiotics.

## Commentary - SHRO

This patient account illustrates clearly the dangers of antibiotic resistant bacteria. A minor wound can become dangerously infected to threaten limb and life. The multiply resistant bacteria are carried across the globe with the patient and have the potential risk of transmission to other people. The nature of the bacterial resistance makes effective antibiotic therapy difficult and often near impossible. While the infection is not being appropriately treated the infection can progress and can spread to other patients in a hospital environment.

SHRO is a bioengineered (biologically modified) medical honey which produces sustained release of reactive oxygen making it highly antimicrobial (Dryden et al., 2014). It is a significant innovation with a wide range of wound-healing and infection control applications, and is one solution to the problem of global antibiotic resistance. Use of SHRO as a chronic wound dressing has demonstrated wound healing and a reduction in bioburden and wound biofilm (Dryden et al., 2016; Halstead et al., 2016). Chronic wounds are a huge global health burden and a reason for much inappropriate antibiotic use. SHRO can solve this problem (Cooke et al., 2015). SHRO used prophylactically has shown a reduction in surgical site infections (Dryden et al., 2014). Further randomised clinical trials are required (a multi-centre RCT is being set up at present) but SHRO has the potential to be used for all surgery to reduce infection and spare antibiotic use. It has already been tried in a small number of cases to coat deep joint prostheses to prevent infection and biofilm formation (Halstead et al., 2016). SHRO has been successful in clearing multi-drug resistant organisms, including MRSA, and CPE Esch. coli from wounds and vascular line sites (Dryden et al., 2016).

SHRO is a simple treatment which can help towards solving the problem of antibiotic resistance and contributing to antimicrobial stewardship, by reducing the necessity for systemic antibiotic treatment in a number of conditions. RO technology is being developed with other delivery platforms to provide further medical benefits by treating conditions where persistent bacterial colonisation with resistant organisms is a problem: diabetic foot infection, ulcers, chronic sinusitis, bronchiectasis, cystic fibrosis, empyema, recurrent urinary tract infection and more. RO will not replace the need for the discovery of new antibiotics, but with its powerful antimicrobial activity, it can control bacterial growth and biofilm production allowing early healing, preventing further spread of infection and the requirement for antibiotics.

## References:

- Cooke, J., Dryden, M., Patton, T., Brennan, J., Barrett, J. (2015) *The antimicrobial activity of prototype modified honeys that generate reactive oxygen species (ROS) hydrogen peroxide*. BMC research notes; 8:20. Available at: <http://www.biomedcentral.com/1756-0500/8/20>
- Dryden, M., Lockyer, G., Saeed, K., Cooke, J. (2014) *Engineered honey: in vitro antimicrobial activity of a novel topical wound care treatment*. Journal of Global Antimicrobial Resistance. 10.1016/j.jgar.2014.03.006.
- Dryden, M., Dickinson, A., Brooks, J., Hudgell, L., Saeed, K., Cutting, K. (2016) *A multi-centre clinical evaluation of reactive oxygen topical wound gel in 114 wounds*. Journal of Wound Care; 25:140-146.
- Halstead, F.D., Webber, M.A., Rauf, M., Burt, R., Dryden, M., Oppenheim, B.A. (2016) *In vitro activity of an engineered honey, medical-grade honeys, and antimicrobial wound dressings against biofilm-producing clinical bacterial isolates*. Journal of Wound Care; 25:93-102.

## Biography

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# 10. Recent developments and events

## News from the IFoA

### Inaugural research programmes under the IFoA's Actuarial Research Centre



#### Actuarial Research Centre

Institute and Faculty of Actuaries

In August 2015 the IFoA's Research and Thought Leadership Committee (RTLC) published a Call for Research seeking proposals for large scale research programmes which will address some of the major challenges in actuarial science. With 25 submissions received from over 100 institutions, spanning over 20 countries, the IFoA selected three world-class programmes covering:

- The development of a new generation of mortality and morbidity models, with a specific focus on the drivers for mortality and the management of longevity risk, with Heriot-Watt University, partnering with Cass Business School, University of Southampton, Aarhus University in Denmark, University of California Santa Barbara and Longevitas Ltd
- The development of new statistical and actuarial methods in the use of Big Data, in the context of health and wider applications, with the University of East Anglia, with assistance from technical experts within Aviva
- Future pension products that meet customer needs, balancing stability, performance and cost, with Cass Business School and Heriot-Watt University, partnering with Blackrock and Danica Pension

The three programmes, extending over five years, will be run through the IFoA's Actuarial Research Centre (ARC) and will form part of the IFoA's ground-breaking research programme.

You can find more details about these programmes here:  
<http://bit.ly/1RMTCA>

### Research in Longevity Basis Risk

The IFoA and LLMA have announced the appointment of a research team led by Macquarie University to develop a method of assessing basis risk for longevity transactions. Supported by University Waterloo, Australian National University and Mercer Australia, Macquarie University will lead the project to develop a readily-applicable methodology for quantifying the basis risk arising from the use of population-based mortality indices for managing longevity risk.

This is the second phase of the project; phase one was completed at the end of 2014 which led to the development of a methodology that can be used to measure longevity basis risk. This second phase will focus on putting this previous work into practice.

For more details about the Phase 1 and Phase 2 of the project visit: <http://bit.ly/1qEZ8IJ>

### IFoA International Mortality and Longevity Symposium

This international symposium will bring together thought leaders across all the relevant disciplines to discuss the latest thinking on the drivers and future of mortality trends in populations. Whether you are an actuary, modeller, medical scientist, epidemiologist, researcher or other professional, this symposium will provide opportunities to gain new insights and learn new techniques, as well as networking to enhance your professional activity.

Confirmed speakers in 2016 include:

- Dame Karen Dunnell, Chair of Longevity Science Panel
- Matthew Edwards, Senior Consultant, Willis Towers Watson
- Professor Carol Jagger, AXA Professor of Epidemiology of Ageing, Newcastle University
- Paul Johnson, Director, Institute for Fiscal Studies
- Professor Thomas Kirkwood CBE, Associate Dean for Ageing, Newcastle University
- Joseph Lu, Longevity Science Director, Legal & General
- Chris Martin, Clinical Modelling Consultant, Legal & General

- Professor Jay Olshansky, Chief Scientist and Co-Founder, Lapetus Solutions
- Dr Amlan Roy, Managing Director and Head, Global Demographics & Pensions Research, Credit Suisse
- Daniel Ryan, Head R&D: Life, Health and Big Data, Swiss Re
- Professor James W. Vaupel, Founding Director of the Max Planck Institute for Demographic Research and Head of the Laboratories of Survival and Longevity and of Evolutionary Demography

**Venue:** Royal Holloway, University of London in Egham, Surrey, TX20 0EX.

To find out more and book your place visit:

<http://bit.ly/1TDC6ay>

### **Antibiotic Resistance: An Evolving Threat, London**

The IFoA is organizing an evening event in London on Tuesday 24 May that coincides with this edition of Longevity Bulletin. This inter-disciplinary event will outline the scale and impacts of antibiotic resistance, and present ideas on what government, health practitioners, businesses and the actuarial profession can do to address this global problem.

The event will be filmed and available online. To find out more visit: <http://bit.ly/1UK6LEu>

### **Hot Topics in Health and Care: Networking and Drinks, London**

This event will present latest research on the implications for insurers of issues such as new wearable technologies, more advanced cancer diagnostics and the impact of climate change on mortality. It will be of interest to actuaries working in the fields of health and care, and life, and for any other actuaries wishing to learn more about key topics in the health and care market.

This event will take place from 17.00 – 19.00 on 22 June 2016 and booking can be made at: <http://bit.ly/1RR9fee>



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