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Antibiotic Resistance: Modelling the Impact on Mortality and Morbidity

A report by the **Antibiotic Resistance
Working Party**

by Matthew Edwards, Ross Hamilton, Nicola Oliver,
Sheridan Fitzgibbon and Roshane Samarasekera

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1. Introduction

'One sometimes finds what one is not looking for'. Sir Alexander Fleming

Until the 1950s, infectious diseases such as tuberculosis, pneumonia and sepsis constituted the primary cause of mortality amongst the middle aged in the UK. Since the serendipitous discovery of penicillin by Fleming in 1928, the development of mass production techniques, and the subsequent identification of many other antibiotics, we have come to take for granted that all such infections can be successfully treated if diagnosed in time. (The quasi-elimination of infectious disease mortality in the UK and other developed countries also owes a great deal to widespread vaccination programs, in addition to contributions from improved hygiene and sanitation.)

However, over the last (circa) 25 years, the previously rosy horizon has somewhat darkened: bacteria have developed increasingly strong resistance to antibiotics, while at the same time the pharmaceutical industry has not produced any major new antibiotics.

In her foreword to the IFoA's 2016 *Longevity Bulletin* (8) on the subject of Antimicrobial Resistance ('AMR'), Professor Dame Sally Davies, the Chief Medical Officer of England and Wales, wrote:

'The golden age of antibiotics which the world has taken for granted for well over fifty years has ended. Antimicrobial resistance 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; not one major class of proven antibiotics has been discovered since 1987 ...

'We are already seeing the consequences of antimicrobial resistance, 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.

After discussions in the Mortality Research Steering Committee over 2015-16, and a strong display of interest amongst members of the profession attending an evening of talks on the subject of AMR on 24 May 2016, a Working Party was set up (under the Health & Care Board) with the aim of developing a simple modelling framework to help actuaries better quantify plausible AMR impacts.

This paper summarises the Working Party's findings, following our Sessional Paper presentation on 25 February 2019 in Edinburgh, and introduces the simple model developed. The paper and the associated model are aimed at readers / users who have basic familiarity with demographic modelling and related actuarial notation.

It is structured as follows:

1. Introduction
2. Summary
3. Biology
4. Model design
5. Data and parameterisation
6. Results
7. Conclusion
8. Model user guide
9. Weaknesses and limitations
10. Bibliography

While the model seeks to quantify direct impacts of antibacterial resistance, an important consideration is the indirect impact if otherwise 'guaranteed' operations (eg intrusive cardiovascular surgery) become routes to infection and death, or are avoided. This aspect is covered in 3.5.

The paper has been written by the lead members of the Working Party (full listing set out on the front page). However, we would also like to thank Craig Armstrong for his invaluable work on data research and early model development in 2017, and Kez Baskerville-Muscat for her assistance while interning at Willis Towers Watson in further work on data and initial documentation. The Working Party also included Irene Merk and Soumi Sarkar, whom we would like to thank for their support.

2. Summary

2.1 Background

Antimicrobial ('AMR') resistance is the process whereby microbes evolve to become resistant to the action of the drugs used to combat them, rendering those drugs ineffective. This is an umbrella term which includes resistance to antibiotics, antivirals and antifungals. The working party considered which area of AMR to focus its efforts on and decided that, for developed countries in general and the UK in particular, antibiotic resistance ('ABR') is the most relevant in relation to the expected impact on mortality and morbidity.

ABR is the process whereby bacteria become resistant to antibiotics. ABR has grown through a combination of the ability of bacteria to evolve vary rapidly (including a form of 'within generation' evolution) and the misuse of antibiotics (including mass use outside the normal treatment of infectious disease in humans). While ABR has been growing, in the last circa 30 years there has been little progress in discovering any new forms of antibiotic; this is partly because most of the research has historically been on a 'trial and error' basis, rather than fuelled by a detailed understanding of how antibiotics work, and partly owing to pharmaceutical firms' funding and investment return concerns.

2.2 Model Design and Parameterisation

The Working Party's model is a relatively simply multi-state model, with the four states of Healthy, Susceptible (ie the person has an infection that can be treated by antibiotics), Resistant (the person has an infection which is resistant to common antibiotics), and Dead.

The model has been parameterised with regard to *E. coli* only, although the model provides the flexibility and data sources to allow for four other bacteria of particular concern to be modelled. The parameterisation was done using UK data.

2.3 Results

The central result related to an assumption of resistance increasingly linearly, with no change to the infection rate. This leads to an increase in mortality in the 45-64 year age range of +0.01% (multiplicative, not additive) in 20 years, with a cumulative increase over the 20-year period of +0.2%.

Highlighting two of the more extreme scenarios considered in the results section (where the ranges relate to variation of results by age band):

Scenario	Description	Annual Variance (q_x) by 2050	Cumulative Variance in q_x to 2050
4	Current resistance rates double by 2050, no change in current infection rate profile	+0.005%	+0.115% to +0.160%
6	Resistance of 100% reached by 2050, current infection rate doubled	+0.055% to +0.078%	+2.075% to 2.756%

The impact on infant mortality was much higher than that on other age bands.

Although the individual scenario parameter choices were very subjective, the variety of scenarios considered should provide a generally useful range of plausible results.

In addition to the above modelling on direct infectious disease mortality impacts, the Working Party also considered (more approximately) possible impacts of ABR on preventive use of antibiotics (for instance, use of antibiotics as part of cardiovascular surgery). These approximate considerations indicated of the order of several thousand extra deaths might be expected in the UK under high ABR scenarios in circa 20 years.

The Working Party also considered the increased ABR mortality from the model projections with several relevant comparators – in particular, AIDS/HIV-related deaths, deaths relating to adverse drug reactions ('ADR'), and the UK's 'extra deaths' of 2015. In brief:

- ABR deaths under many of the scenarios would be of similar order of magnitude to the number of AIDS/HIV deaths in the 2000-09 decade;
- ADR deaths outweigh ABR deaths under most scenarios by a factor of 5-10;
- The UK's 30,000 'extra deaths' of 2015 (ie deaths greatly in excess of projected figures) dwarf projected extreme ABR deaths by a factor of 50-100.

Section 6.2 contains further details of the above points.

3. Biology

'Some organisms find other organisms impossible to live with'. Harold Edwards¹

3.1 Bacteria and disease

Bacteria are simple single-celled organisms, widely present throughout nature (for instance, they perform important functions in the soil and in the human gut). A small proportion are responsible for various infectious diseases – for instance, tuberculosis and diarrhoea. Mortality from these diseases in particular is low in the developed world, but they represent major causes of death worldwide (eg the Global Burden of Disease² reports respiratory infections and diarrhoea in the top five causes of death in 2017).

Bacteria cause harm through the production of toxins in the body, which may include the release of toxins when the bacteria are destroyed. One problem is that the body's immune system, capable of dealing efficiently with localised infections, in effect 'self-harms' when infections become wide spread (blood-stream infections being an extreme and common case) and the anti-bacterial defences damage the body's tissues.

3.2 Early rise of antibiotics

Although Alexander Fleming is credited with discovering antibiotics, there has been a long history of scientific endeavour relating to the beneficial use of mould. There is evidence that the ancient Egyptians, for example, applied mouldy bread to infected wounds. In 1640, John Parkinson, an apothecary, advocated the use of mould as a treatment.

In 1871 Joseph Lister successfully treated a nurse with an unresponsive infection using a mould-based substance described as penicillium. In 1877, Louis Pasteur observed inhibition of bacterial activity in cultures of anthrax when contaminated with mould. In 1897, Ernest Duchesne applied the protective properties of mould to successfully cure typhoid in animals. In 1920 Belgian scientists Andre Gratia and Sara Dath noted that fungal contamination inhibited the growth of *Staphylococcus aureus*, which they identified as a species of penicillium.

Finally, in 1928 the Scottish biologist, Alexander Fleming, noticed a halo of inhibition of bacterial growth in a staphylococcus culture plate contaminated with a mould identified as penicillium notatum. He subsequently isolated and grew the mould in pure culture, which ultimately led to the successful mass production of penicillin.

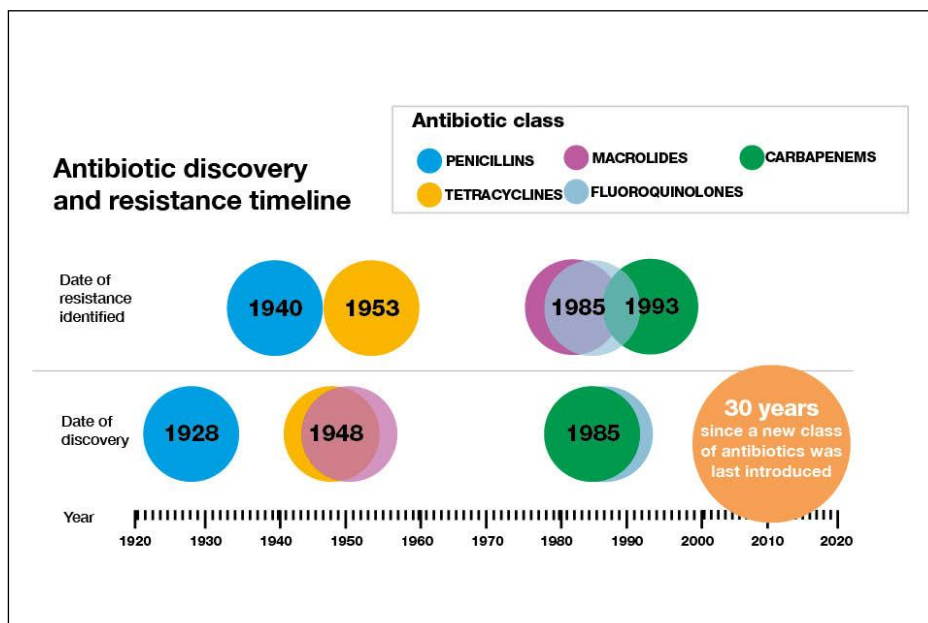
Further antibiotics were discovered largely through intensive programs of trial and error, testing substances found in soil or plants for their success in killing bacteria.

The mechanism by which antibiotics work is by entering the bacterium and then either bactericide – killing the bacterium through lysis, ie splitting the cell's membrane – or bacteriostasis, impeding its reproduction and so allowing the body's immune system to cope, takes place

¹ Edwards is of particular interest as being the first known person to see the potential for large-scale use of antibiotics, orchestrating their use in Royal Army Medical Corps field hospitals in the Italian campaign in 1943 (pre-dating the 1944 D-Day related usage generally referred to in medical histories). Quotation from 1948 edition of 'Recent Advances in Surgery', J&A Churchill Ltd, London.

² <http://www.healthdata.org/policy-report/findings-global-burden-disease-study-2017>

Figure 1. Timeline of modern antibiotic discovery and subsequent resistance according to antibiotic class (Source: Public Health England, 2015a)



3.3 Antibiotic resistance

Bacteria constantly evolve to maintain their viability in the face of the antibiotics used against them. Some bacteria are naturally resistant; new resistances also arise spontaneously by chance mutations and these resistant strains then multiply.

Some resistance mechanisms can be passed from one bacterium to another, spreading resistance between species. Loops of DNA (called plasmids) carry the resistance genes from one bacterium to another. Thus, resistance can propagate within generations as well as down through generations, exacerbating the spread of ABR.

When an antibiotic is given, it kills the sensitive bacteria, but any resistant ones can survive and multiply. The more antibiotics are used (in animals and agriculture as well as in man) the greater will be the selective pressure, favouring resistant strains.

Various modes of antibiotic resistance have been described, including inactivation or modification of the antibiotic, alteration of the antibiotic target site to reduce binding capacity, modification of metabolic pathways of the bacteria, and modification of transport pathways, primarily efflux, which describes the movement of the antibiotic out of the bacteria cell.

Finally, note that antibiotic resistance is 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 1 above shows how quickly resistance has arisen for the five classes of antibiotics included.

3.4 Mitigation

Fundamentally, any effective mitigation program will hinge on combining the development of new antibiotics with heavy reduction in the various mechanisms by which ABR has been growing.

In early 2019, the UK Government published³ the UK's 2019–2024 national action plan to tackle AMR. This sets out the following targets:

- halve healthcare-associated Gram-negative blood stream infections
- reduce the number of specific drug-resistant infections in people by 10% by 2025
- reduce UK antimicrobial use in humans by 15% by 2024
- reduce UK antibiotic use in food-producing animals by 25% between 2016 and 2020 and define new objectives by 2021 for 2025
- be able to report on the percentage of prescriptions supported by a diagnostic test or decision support tool by 2024

Note that there has already been some success with specific campaigns: for instance, action in the UK against *Methicillin Resistant Staphylococcus aureus* (MRSA).

MRSA refers to a group of Gram-negative bacteria (*staphylococcus aureus*) that are widely recognized as being resistant to several antibiotics. MRSA is common in community healthcare settings such as hospitals and care homes. In 2001, the percentage of *S. aureus* blood stream infections ('BSI') that were identified as MRSA was almost 50% in the UK (European Centre for Disease Prevention and Control, 2019). As a result, mandatory MRSA bloodstream reporting was introduced, a target to reduce MRSA BSI by 50% was announced as well as an emphasis on improving infection control measures in hospitals. Patients who were carriers received nasal antibiotic as well as an antiseptic body wash to reduce MRSA carriage.

These measures took several years to really take effect, but as from 2006, the percentage of *S. aureus* isolates reduced dramatically and by 2015 this was around 11% (European Centre for Disease Prevention and Control, 2019). Trends in all case rates of MRSA bacteraemia in England reduced from 8.6 per 100,000 population to 1.5 per 100,000 population (Public Health England, 2019).

Another interesting example relates to the impact of popular pressure, a lever which would be expected to become more significant with the increasing attention paid to trends in social media. In the USA, public concern around the use of antibiotics in chicken farming led the major fast-food firm Chick-Fil-A to announce in 2014 that it would cease using antibiotics for growth-promotion (with a five-year target for elimination); shortly afterwards, other major firms including McDonald's, Subway, Costco and Walmart followed suit⁴.

However, it is impossible to ensure that appropriately 'invincible' antibiotics are produced, partly because of the degree of chance involved in their discovery (some would argue 'creation'), partly because of the financial dynamics of pharmaceutical firms (whose profits depend on the 'for life' prescription of such compounds as statins, as opposed to substances with week-long prescriptions).

³ *Tackling antimicrobial resistance 2019–2024 - The UK's five-year national action plan – HM Government*

⁴ <https://www.scientificamerican.com/article/marlyn-mckennas-book-big-chicken-looks-at-poultrys-effect-on-antibiotic-resistance/>

3.5 Use of antibiotics in prevention

One final thing to raise in this section is the use of antibiotics in a preventive capacity (ie as opposed to use of antibiotics to treat existing bacterial infections). The circumstances where antibiotics are given preventively include, but are not limited to, the following surgical procedures:

- Gastrointestinal surgery
- Cardiac implants including pacemakers and implantable defibrillators
- Cardiac procedures including coronary artery bypass grafts, (CABG) and valve replacements (but not angiography, angioplasty, PCI or stent placement unless the patient is otherwise compromised)
- Joint replacement surgery
- Organ transplant recipients
- Any other surgeries considered 'contaminated' or 'dirty' such as that undertaken for traumatic and penetrating injuries

Additionally, antibiotics are also considered to prevent neutropenic sepsis as a consequence of oncological treatments. More than 350,000 people in the UK were diagnosed with cancer in 2015, 28% of whom received chemotherapy. Patients receiving oncological treatments are up to four times more likely to have a healthcare-associated infection (similar to those in intensive care units) compared to other patients in the hospital and twice as likely to be receiving an antibiotic.

Implications of ABR in Preventive Use

The more antibiotic resistance increases, the more likely it is that such procedures would be affected. The impact could be through an ineffective antibiotic allowing an infection to take hold, or, in a more extreme scenario, the procedures not being carried out at all due to the risk of infection.

The following table provides an overview of the numbers of the surgical procedures undertaken to place an implantable cardiac device that involves prophylactic antibiotic use in the UK.

	England	Wales	NI	Scotland
Population	55m	3m	1.9m	5.4m
ICD/million (n)	94 (5170)	85 (255)	119 (226)	49 (265)
PM/million (n)	621 (34,155)	619 (1857)	432 (821)	NA
CRT/million (n)	201 (11,055)	137 (411)	114 (217)	89 (481)
Total (n)	50,380	2523	1264	746

Table 1. Rates and numbers of cardiac implantable devices, England, Wales, NI and Scotland, 2015/2016 (Source: National Institute of Cardiovascular Outcomes Research [NICOR], 2017)

ICD = Implantable Cardiac Defibrillators PM = Pacemakers CRT = Cardiac Resynchronisation Therapy Devices

In addition, the most up-to-date analysis suggests that just under 17,000 CABGs were carried out in the UK in 2012, 3,388 transcatheter aortic valve replacement (TAVC) procedures in 2016, and 4,187 surgical aortic valve replacement (SAVR) procedures.

Thus around 80,000 patients undergo cardiac surgical procedures that require preventive antibiotics each year in the UK.

4. Model design

4.1 Literature review

One of the triggers for this work was the paper produced by the Review on Antimicrobial Resistance chaired by Jim O'Neill 'Tackling Drug-Resistant Infections Globally: Final Report and Recommendations' and was the starting point for the literature review. The report was informed by two models produced by KPMG and RAND Corporation.

KPMG Model (KPMG LLP, 2014)

The report was prepared by KPMG LLP in the UK, derived from research commissioned by the Wellcome Trust, as part of an independent review into anti-microbial resistance supported by the Department of Health and the Wellcome Trust. The aim of the model was to assess the economic impact of rising AMR globally. The model centred on three bacteria and the related antibiotics and in addition took into account the high rates of mortality caused by Malaria, HIV and Tuberculosis (TB).

Bacteria	Antibiotic
<i>Staphylococcus</i>	Methicillin
<i>Escherichia coli</i>	Third generation cephalosporins
<i>Klebsiella pneumoniae</i>	Third generation cephalosporins

The paper noted that data availability was generally poor and had to supplement this with expert judgement from various countries. Data was sourced from the European Centre for Disease Control (ECDC) with the latest available data up to 2012, and adjustments made where necessary. Infection rates for Malaria, HIV and TB were obtained from the Global Burden of Disease Study.

The effect on life expectancy was quantified through an annual addition to mortality due to AMR set out in Figure 2.

Figure 2. Attributable mortality due to AMR. (Source: (KPMG LLP, 2014)).



The impact to life expectancy was calculated according to the formula set out in Figure 3. Initial life expectancy is calculated as L_i and the additional annual mortality attributable to AMR was calculated in (1) as m_i .

Figure 3. Adjusted life expectancy formula. (Source: (KPMG LLP, 2014)).

$$AdjL_i = [1 + (1 - m_i)^{L_i}] \frac{L_i}{2} \quad (2)$$

The effect on the additional length of hospital stay due to AMR was calculated according to Figure 4.

Figure 4. Short term morbidity calculations. (Source: (KPMG LLP, 2014)).



KPMG produced results on four scenarios:

- An absolute increase in current resistance rates by 40%
- 100% resistance rate applied across all countries
- Double current infection rates for each bacteria, HIV and TB and an absolute increase in current resistance rates by 40%
- Double current infection rates for each bacteria, HIV and TB and an absolute increase in current resistance rates by 100%

RAND Europe model (RAND Europe, 2014)

This study was aimed at stimulating discussions on the economic burden of AMR by building an evidence base for understanding that burden in specific ways:

- Presenting a high-level global estimate of the current economic burden of AMR
- Assessing the potential global economic impact of AMR, under different future scenarios for the burden of AMR from the present year until 2050

The economic cost attributable to AMR was quantified by considering its effects on the supply of effective labour through:

- Increased mortality – which reduces size of working age population
- Increased morbidity – which reduces the effectiveness of the working age population

The scope of the study includes three hospital-acquired infections and three infectious diseases.

Hospital-acquired infection	Infectious disease
<i>Escherichia coli</i> (<i>E. coli</i>)	HIV
<i>Klebsiella pneumoniae</i> (<i>K. pneumoniae</i>)	Tuberculosis
<i>Staphylococcus aureus</i> (<i>S. aureus</i>)	Malaria

The authors developed a theoretical dynamic general equilibrium model using a system of equations to characterise the economic interactions of individual agents, divided into several large regions – eg the 'High' group includes all OECD and EEA countries.

The model then generates long-run GDP and household income projections for the AMR-specific regions, according to changes in AMR levels, which are then compared with a baseline projection of no change to current AMR levels. The impact of the AMR mortality effect fed into a cohort component model that was used to estimate the size of the workforce and the overall population.

The main findings from the report were that the current costs attributable to AMR are not particularly large, but that the estimated future costs of AMR may be material – as much as -1.2% of global GDP annually relative to no resistance (around \$3 trillion per annum), representing a substantial cost to the world economy.

Other models

The literature review was assisted by two systematic reviews of mathematical models of AMR:

- 'A Modeling Framework for the Evolution and Spread of Antibiotic Resistance: Literature Review and Model Categorization' by I. Spicknall et al, 2013 (Spicknall, Foxman, Marrs, & Eisenberg, 2013)

- ‘Send more data: a systematic review of mathematical models of antimicrobial resistances’
Anna Camilla Birkegard et al, 2018 (Birkegård, Halasa, Toft, Folkesson, & Græsbøll, 2018)

Spicknall provides a comprehensive, informative and perceptive overview of the types of model used in this field, categorising models into six forms (where the ‘strains’ below refer to antibiotic sensitive v insensitive bacteria):

- Single Strain – independent strains competing for hosts
- Superinfection – hosts can be infected by more than one strain
- Exclusive infection – hosts can be infected with only one of two possible strains
- Replacement infection – one strain may replace another on reinfection
- Unidirectional conversion – one strain converts to another at a constant rate
- Bidirectional conversion – constant rates of conversion between the two strains.

The authors observe that the appropriate choice of structure depends on the extent to which within-host strain coexistence occurs, replacement infection is possible, and strain conversion is possible; these aspects vary according to the infection being modelled.

Birkegard et al. (Birkegård, Halasa, Toft, Folkesson, & Græsbøll, 2018) provide high-level information on a large number of studies with regard to somewhat more aspects (eg population modelled), although do not provide significant detail on the underlying model structures. They advocate that AMR models should be stochastic, multifactorial and allow appropriately for non-linearity and heterogeneity. Various other criteria are proposed for a satisfactory AMR model. The authors concluded that none of the models within their survey conformed to the TRACE good modelling practice guidelines (Grimm V, 2014) and whilst many mathematical models exist, there is still insufficient knowledge about antibiotic resistance which restricts the development of more appropriate models.

4.2 Criteria for model development

The working party agreed at an early stage to construct a model that met the following criteria:

- *Simplicity* – the model should have the right level of complexity to produce a reasonable answer, but not so complex as to require detailed specialist knowledge
- *Data availability* – the parameters required in the model should correspond to data availability (ie avoiding a later requirement to calibrate parameters for which there is insufficient data)
- *Timeliness* – the model should run quickly

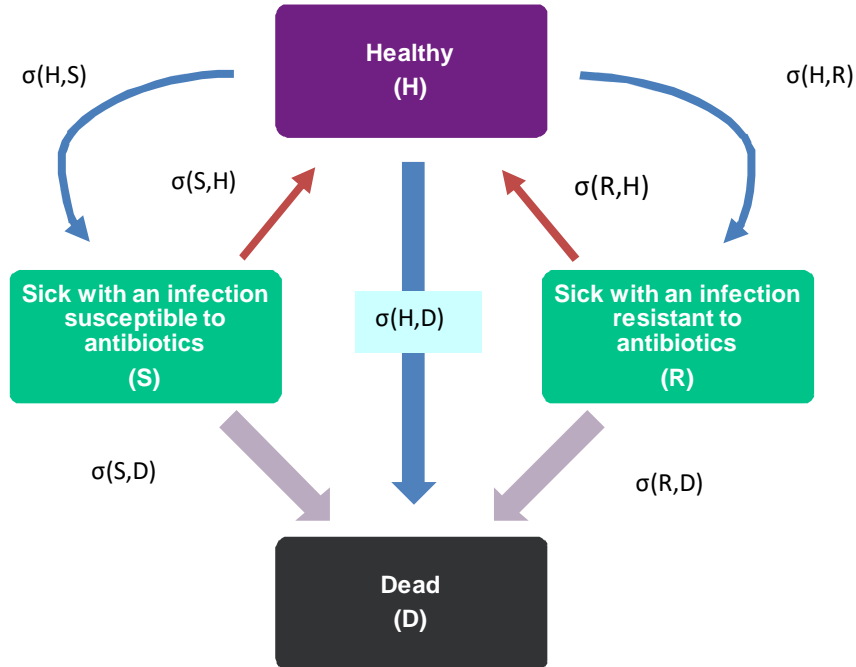
4.3 Model structure

The working party considered the pros, cons and lessons learned from the literature review and applied these to the modelling criteria above. A key area of note from the KPMG/RAND models was data availability. Taking this into account the working party agreed to use a time homogeneous multi-state Markov model with four states, calibrated to data available in the UK (choice of bacteria / infections detailed later), and structured according to Spicknall et al.’s ‘Exclusive infection’ category. The states are:

- 1) Healthy (‘H’) - a person does not have one of the bloodstream infections in-scope
- 2) Susceptible (‘S’) – a person is in hospital and has an in-scope bloodstream infection which is susceptible to the in-scope antibiotics

- 3) Resistant ('R') - a person is in hospital and has an in-scope bloodstream infection which is resistant to the in-scope antibiotics
- 4) Dead ('D')

Figure 5. A schematic of the multistate Markov jump process framework.



Model Assumptions

A Markov chain assumes the process is time-homogeneous ie.

$$\Pr(X_{n+1} = x | X_n = y) = \Pr(X_n = x | X_{n-1} = y) \quad (4)$$

This property of a Markov chain is that of 'memorylessness', so that the probability a random variable changes state during a time step is dependent only on its current state, ie not its history up to that time (or state). In order to satisfy this property, the Markov chain will be modelled in daily time steps over a single year. To assess the effect of changing resistance over longer periods, the model parameters are varied each year.

The model specified above meets the working party objectives by producing the change in the probability of death within a single year and the change in the time spent in the infected states (resistant and susceptible) to inform the impact on mortality and morbidity rates.

Model limitations

The chosen model structure is a significant simplification of the real-world situation, however is considered a practical balance of the working party's objectives. The main limitations of the chosen modelling approach:

- Data availability with sufficient granularity across bacteria / antibiotic, geography, gender, and age (this is discussed further in Section 5)
- In practice the 'memorylessness' feature of a Markov chain may not be appropriate given the length of time a person has an infection is likely to affect their probability of changing state during the next day.

- The model includes a ‘Healthy’ state which incorporates illnesses outside the scope of the bacteria considered. In practice some of these conditions may also be affected by rising resistance rates, for example antibiotics used in a preventative capacity as set out in Section 3.5.
- The model assumes a constant population throughout the projection; however, it is widely accepted the UK has an ageing population structure which could lead to variations in future rates of infection and affect the modelling outputs.
- Hospital treatment efficacy is assumed constant, but an increase in demand on hospitals (in a high ABR scenario) would likely reduce the effectiveness of treatment. Similarly, the risk of becoming infected would also increase in such a situation.
- The model and data used (see Section 5.6) assume that only people with bloodstream infections reported through hospitals will be influenced by ABR. In practice there will be some community-based infection reporting not captured here, and hence a corresponding underestimation of the impact of rising ABR. The working party has taken this approach given the time, data and resources available, but this would be an area where readers (and users of the model) may wish to consider the possible implications.

The final section of the paper provides a fuller exposition of model weaknesses and data limitations, and it is hoped that users of the model will take time to consider them.

4.4 Model scope – bacteria

An important early decision made was the choice of bacteria to model.

The working party decided to model bacteria that were considered to be of particular relevance to current and likely future mortality and morbidity impact in a context of varying levels of antibiotic resistance.

Initially the model was intended to represent a reasonable number of important bacterial strains separately and then combine the impacts in some way (note that, as discussed elsewhere, this approach was simplified). Accordingly, there was a concern to avoid ‘over modelling’ with regard to the number of bacteria included, given the difficulty of accurately allowing for multi-bacterial ‘interactions’.

The working party decided that five would be a broadly sensible number. The five bacteria decided on, with reference to work published by the CDC and similar bodies, were

- *Acinetobacter baumannii* – a bacterium commonly found in soil and water. It can cause a variety of diseases, ranging from pneumonia to serious blood or wound infections, and the symptoms vary depending on the disease. Carbapenem-resistant⁵ *acinetobacter baumannii* is particularly difficult to treat.
- *Escherichia coli* (better known as *E. coli*) – a bacterium that normally lives in the intestines. Some types can cause intestinal infections leading to diarrhoea, abdominal pain and fever.

⁵ Carbapenems play a critically important role in our antibiotic armamentarium. Of the many hundreds of different β -lactams, carbapenems possess the broadest spectrum of activity and greatest potency against Gram-positive and Gram-negative bacteria. As a result, they are often used as “last-line agents” or “antibiotics of last resort” when patients with infections become gravely ill or are suspected of harbouring resistant bacteria.

More severe cases can lead to bloody diarrhoea, dehydration and kidney failure. This study considers third-generation cephalosporin-resistant⁶ *E. coli*.

- *Pseudomonas aeruginosa* – a bacterium commonly found in watery environments in nature and can affect humans, animals and plants. It is a major cause of infection in hospitalised patients, causing localised or systemic damage of immune defences. This study considers carbapenem-resistant *pseudomonas aeruginosa*.
- *Staphylococcus aureus* – a bacterium that can cause disease, particularly if there is an opportunity for the bacteria to enter the body. It can cause mild to life-threatening illnesses such as wound infections, joint infections, pneumonia and blood stream infections. Methicillin resistant *Staphylococcus aureus* (MRSA) is particularly difficult to treat.
- *Streptococcus pneumoniae* – a bacterium that resides asymptotically in healthy carriers. In susceptible individuals with weaker immune systems, however, it may become pathogenic and spread to other locations to cause diseases such as pneumonia, meningitis and septicemia. This study considers penicillin-resistant *streptococcus pneumoniae*.

We are confident that the conditions covered in our work provide a representative picture of the burden of ABR. All five bacteria are recognised as major concerns by the World Health Organisation and have featured prominently in the policy debate surrounding ABR. While *methicillin-resistant S. aureus* (MRSA) might now be considered as a somewhat lesser threat than in recent years, it remains a high-profile health issue. In addition, our inclusion of *E. coli*, i.e. a Gram-negative bacteria, ensures that our approach takes into account types of bacteria that have been described as being of utmost priority (Nicasio et al, 2008; Kollef et al., 2011).

It could be argued that the exclusion of some 'famous' bacteria from the above list will necessarily result in an underestimation of the overall longevity impacts of ABR. However, the working party would reiterate that adding further bacteria introduces extra modelling complexity and extra parameter error (as the above choices have also been made with regard to data availability). As noted above, the impact of such exclusions is expected to be dwarfed by the impact of the very subjective future ABR trends assumed and the relevance of recent data being applied to higher resistance scenarios, where behavioural changes for non-life threatening surgery could have second order impacts on life expectancy.

⁶ Cephalosporins cover a broad range of organisms, are generally well-tolerated, and are easy to administer; thus, these agents are frequently used beta-lactam drugs. Third generation cephalosporin resistance leaves us with only limited options for treating patients with Gram-negative bacteraemia, and carbapenem is considered the treatment of choice.

5. Data and parameterisation

The primary sources of data used within the analysis are:

- Public Health England ('PHE')
- European Anti-Microbial Resistance Surveillance Network (EARS-Net) produced by the European Centre for Disease Control ('ECDC')
- Research papers (with particular regard to data missing from above sources)

5.1 English Surveillance Programme for Antimicrobial Utilisation and Resistance

The English Surveillance Programme for Antimicrobial Utilisation and Resistance ('ESPAUR') has produced five reports in the delivery of the UK Five Year Antimicrobial Resistance Strategy from 2013 to 2018. The table below is a summary of the data produced in the 2018 report (figures are for data collected in 2017), supplemented with mortality data from PHE.

Table 2. ESPAUR Report 2018 (Public Health England, 2018)

Grey rows represent reported infections, overall resistance rates and deaths (to both bacteria that are resistant or susceptible to antibiotics). White rows give additional granularity on resistant rates to key antibiotics identified within this paper.

Pathogen <i>(figures are annual for 2017)</i>	Estimated total number of BSI in England	Proportion resistant	Estimated no. of resistant episodes	Estimated no. of deaths
Escherichia coli (E. coli)	41,287		12,030	5,865
<i>Resistant to third-generation cephalosporins (but not to colistin or carbapenems)</i>		13.0%	5,362	
Acinetobacter spp.	1,001		45	Not available
<i>Resistant to carbapenems (but not to colistin)</i>		3.8%	38	
Pseudomonas spp.	5,133		490	1,116
<i>Resistant to carbapenems (but not to colistin)</i>		7.9%	403	
Staphylococcus aureus	12,750		846	2,547
<i>Resistant to methicillin (mandatory reports)</i>		7.6%	846	
Streptococcus pneumoniae	5,539		73	Not available
<i>Resistant to penicillin (but not to macrolides)</i>		0.7%	40	

5.2 European Antimicrobial Resistance Surveillance Network (EARS-Net)

EARS-Net collects data annually from 30 countries across the EU/EEA according to EUCAST guidelines for the detection of invasive (blood and cerebrospinal fluid) isolates. The data set in the UK is available from 2000 to 2016 split by sub-category as follows:

- Region
- Age groups (0-4, 5-18, 19-64, 65+)
- All in-scope pathogens and the corresponding resistant antibiotic are available

The results used are 'Resistant isolates proportion' which is the proportion of samples with a resistant pathogen to the indicated antibiotic.

Limitations

The following highlights some key limitations and potential sources of bias when using EARS-Net data, although this list is non-exhaustive:

- Population coverage varies across countries, the latest EARS-Net report does not have information on the coverage of the UK. However, the number of laboratories reporting *E. coli* for example has increased from 31 (and 7,369 isolates) in 2014 to 106 (31,579 isolates) in 2017.
- Sampling is present due to data being based exclusively on invasive isolates from blood or cerebrospinal fluid (an isolate is a bacteria that has been isolated from a specimen). EARS-Net notes that the samples (blood or cerebrospinal fluid) may not be representative samples across different bacteria (eg pneumonia may be better represented using an alternative sample such as a saliva swap). This restriction prevents some of the inconsistencies that could arise from differences in clinical case definitions, sampling frames or heterogeneous healthcare utilisation and is therefore the most pragmatic solution.
- Methodology differences may be present in laboratory routines, although the EARS-Net reports indicate that external quality assessments are performed and indicate high data quality.

The working party has considered these limitations and, given the purpose of this study is to investigate UK specific resistance, was comfortable with using the EARS-Net data unadjusted. Other users should consider whether an extension of this study to other countries covered by EARS-Net is appropriate.

5.3 Public Health England Data

PHE produce annual data across the financial year as part of their mandatory surveillance program for key healthcare associated infections ('HCAIs'). Included within this data for in-scope pathogens are the number of reported cases and mortality outcomes for MRSA (2007 – 2018), *E. coli* (2012 – 2018) and *P. aeruginosa* (2017-2018).

The following limitations should be noted:

- PHE data covers England only
- Reports are provided by acute NHS trusts

- The numbers of deaths attributable to a pathogen is taken as the 'all-cause fatality' rate in which a report is classified alongside the pathogen if the person dies within 30 days of an infection report being reported. It is not clear whether death was a direct, indirect or unrelated to the infection, however is a common approach to analysing this type of data. Note that looking at data derived from death certification is similarly problematic due to its subjective nature. Note that there will be likely be some mortality overestimation as a result of bacterial infections being more common in people who are already sick (ie who have a higher mortality rate than the general population).
- Data does not record whether a death is as a result of a resistant or susceptible form of *E. coli* or *P. aeruginosa*

5.4 Research Papers

The data provided by PHE does not have a breakdown of the length of stay in hospital (which can be appropriately attributed to various bacteria) or deaths attributed to resistant and susceptible forms of the pathogen for *E. coli* or *P. aeruginosa*. Therefore additional assumptions are required on any differences in the length of hospital stay ('LoS') and mortality rate differential between the resistant and susceptible forms of the pathogen.

A study by de Kraker and Wolkewitz (M. E. A. de Kraker, 2011) investigated these differences in *E. coli* and found that 32% of those with resistant forms of *E. coli* died within 30 days after enrolment (the date blood cultures were taken), relative to 6% of those with a susceptible form of *E. coli*. In addition, patients with a resistant form stayed in hospital for a mean of 12 days relative to 10 days for those with a susceptible form and had a larger interquartile range of 19 days relative to 11 for susceptible.

The working party did not find any other comparable papers for other in-scope pathogens; however, this does not mean such research does not exist.

5.5 Conclusions from data research

There is good data available for MRSA and *E. coli* resistant to third generation cephalosporins. PHE has started to produce the same level of information on *P. aeruginosa*; however, this is available only for the period 1 April 2017 to 31 March 2018. There is limited data in the required format for both *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*.

As a result, the modelling will focus on data from *E. coli* resistant to third generation cephalosporins and MRSA, with approximate adjustments to consider wider application to other pathogens.

5.6 Parameterisation

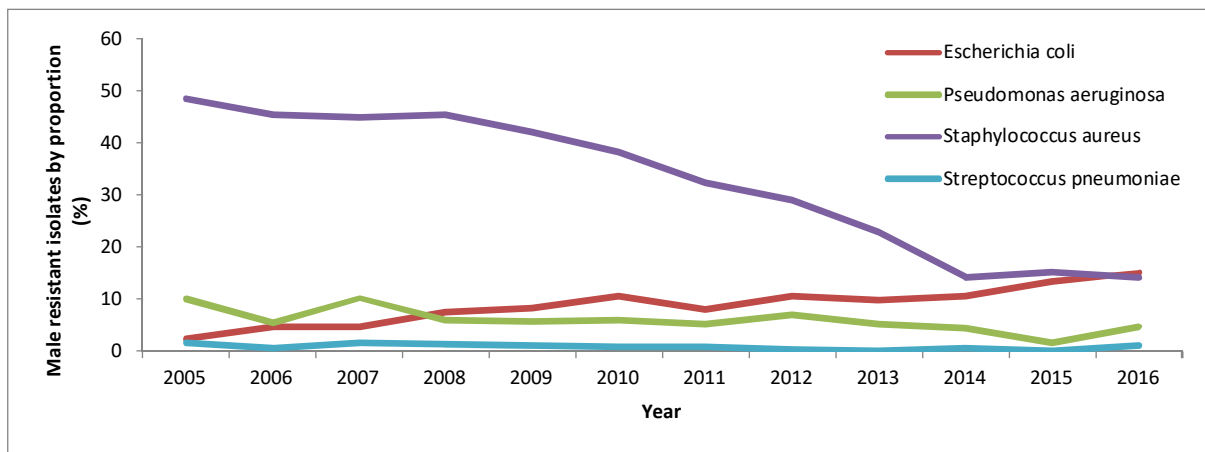
Resistance Analysis

Within the UK the chosen bacteria have exhibited differing profiles of resistance over the past 11 years. The chart below highlights for males that, whilst *E. coli* resistance to third generation cephalosporins has been steadily increasing from around 2% in 2005 to 16% in 2016, other bacterial resistance such as MRSA has reduced from 48% in 2005 to 14% in 2016.

Streptococcus pneumoniae shows low levels of resistance to penicillin and *pseudomonas aeruginosa* resistant to carbapenems indicates no clear pattern of varying resistance. In addition, there was only limited time series data available on EARS-net for *acinetobacter baumannii* resistance to carbapenems.

The graph below shows the resistance trends for the four bacteria (and corresponding antibiotic) being modelled.

Chart 1. Proportion of isolates with bacteria resistant to the specified antibiotic in Section 4.4 for males in the UK (European Centre for Disease Prevention and Control, 2019)

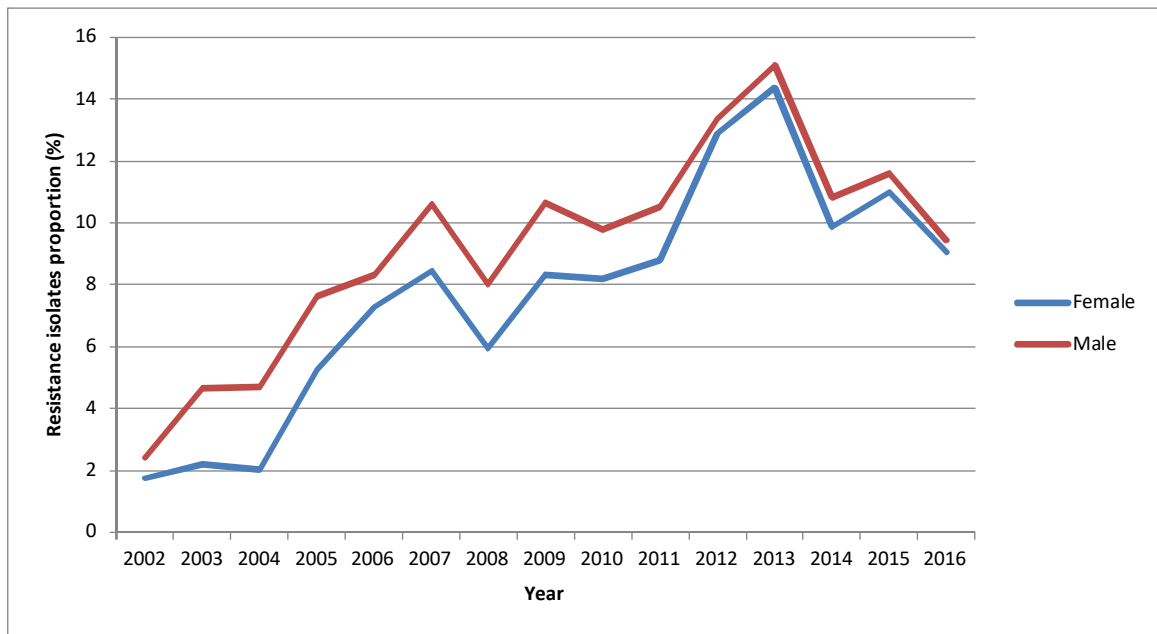


The working party had previously concluded in Section 5.5 to explore *E. coli* and MRSA in more detail. The chart indicates that recent history of *E. coli* and *S. aureus* resistance are following different patterns. In addition, the NHS focus on monitoring and controlling MRSA is likely to have a different future trend to the other bacteria being considered. As a result, the working party has decided to explore *E. coli* in more detail, with an approximate allowance for the other main bacterial strains through an increase of the results in respect of *E. coli*.

Resistance – further details on *E. coli*

The working party has also considered whether any material differences in resistance across different sub-groups of the population: the charts below consider *E. coli* resistance to third generation cephalosporins in more detail.

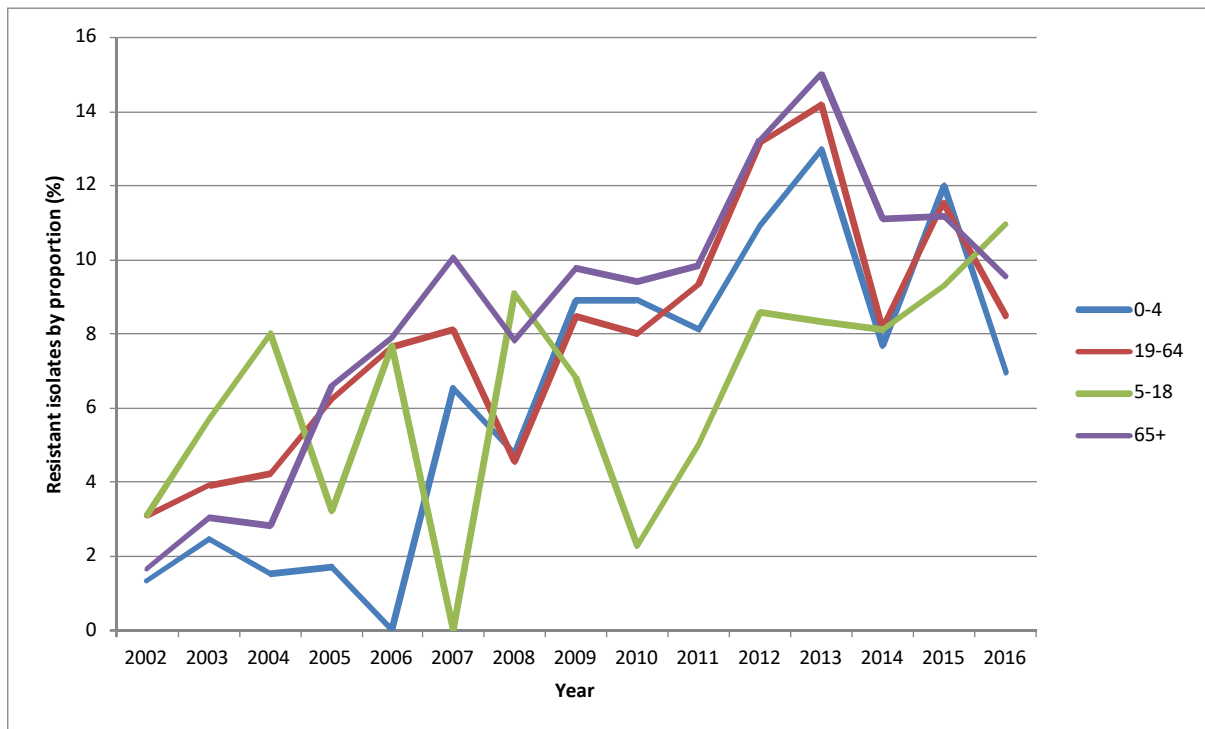
Chart 2. *Proportion of isolates with E. coli resistant to third generation cephalosporins for males and females in the UK (European Centre for Disease Prevention and Control, 2019)*



The chart above shows that females appear to have had a lower level of resistance in earlier years which has now converged to that of males. The overall trend in resistance variation has been similar for the two groups.

The graph below shows variations by age group.

Chart 3. *Proportion of isolates with E. coli resistant to third generation cephalosporins for males and females in the UK split by age group (European Centre for Disease Prevention and Control, 2019)*



There is an increasing trend in resistance for most groups except 5-18 years, where resistance levels are more volatile year-on-year.

Chart 4. Number of reports of *E. coli* in England by age group and year (Public Health England, 2019)

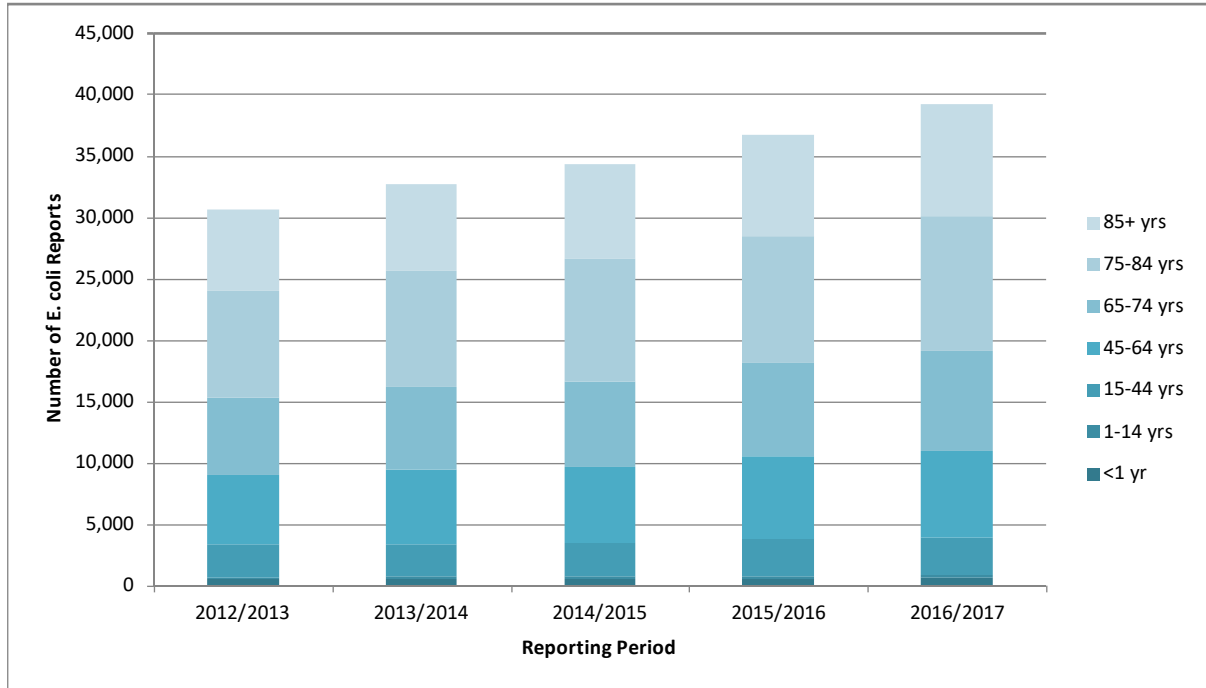
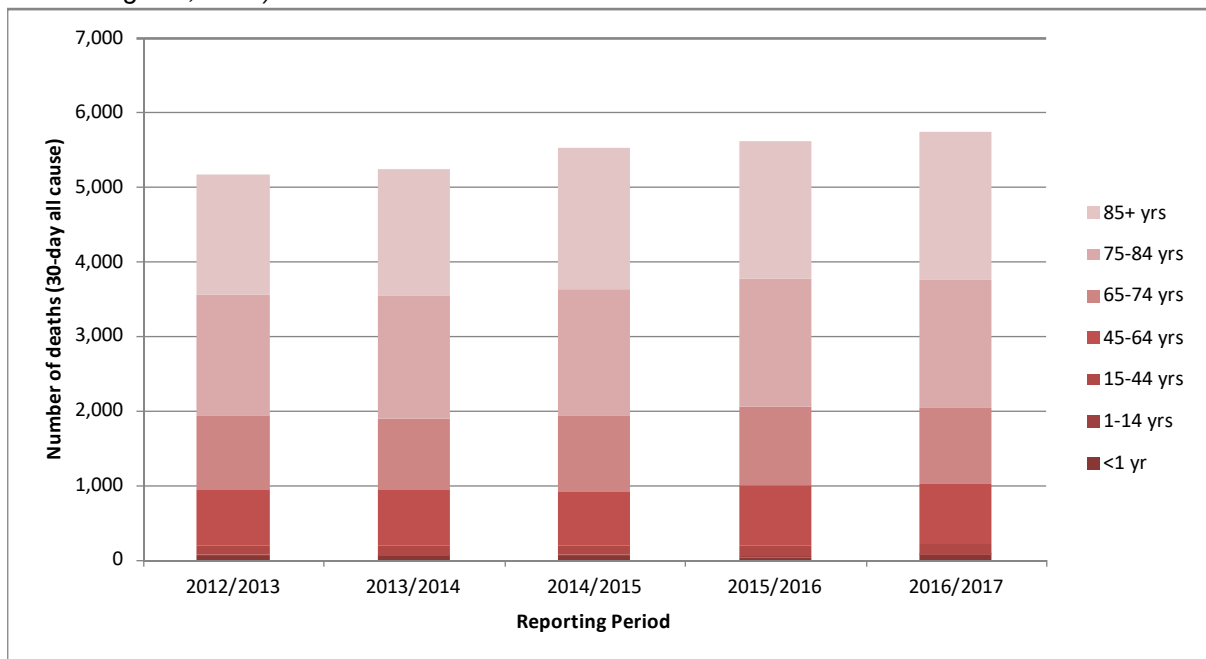


Chart 5. Number of deaths (30-day all cause) due to *E. coli* in England by age group and year (Public Health England, 2019)



Charts 4 illustrate the number of reports with *E. coli* in England since 2012 as part of the PHE's mandatory surveillance programme on healthcare-associated infections. The chart illustrates an increasing number of reports since 2012, with the majority of infections occurring in the 'adult' population (over 15 years old). Chart 5 shows the number of fatalities 30-day all cause fatalities for people with *E. coli*. The data does not indicate whether a fatality was as a result of *E. coli*, only that an *E. coli* infection was reported within 30 days of the person dying.

Other parameters

The most important single parameter in the model is the ratio of mortality for resistant v non-resistant infections.

We have calibrated this ratio at 2.5 which has been informed by research on *E. coli* 'Burden of antimicrobial resistance in European hospitals' (M. E. A. de Kraker, 2011). The study used a 'parallel matched cohort design' where two cohorts of patients were observed over time (July 2007 to June 2008) across thirteen tertiary care centres identified as having representative levels of resistance for their respective country. Both cohorts had *E. coli*; however, one was identified as having a strain susceptible to third generation cephalosporins, whilst the other was resistant to this antibiotic. As a control, the patients were matched to two controls free of *E. coli* based on their length of stay in hospital (+/- 3 days). The results of the study indicated that on average there was a 2.5 times increase in 30-day all-cause mortality (95% confidence interval of 0.9 to 6.8). The working party recognises the limitations of using a potentially outdated study which is aggregated across multiple countries; however, we were unable to find other relevant information to inform the choice of this parameter.

Estimating Transition Intensities – General

One of the properties of using a time-homogeneous Markov model is that transition intensities can be estimated directly from observable data. The data requirements were as follows:

- a) Average population
- b) Total number of deaths
- c) Total number of in-scope infections susceptible to the in-scope antibiotic
- d) Total number of in-scope infections resistant to the in-scope antibiotic
- e) Total number of deaths from in-scope susceptible infections
- f) Total number of deaths from in-scope resistant infections
- g) Days spent in hospital with in-scope susceptible infection
- h) Days spent in hospital with in-scope resistant infections

Estimating Transition Intensities – Details

Transition intensities for a Markov chain have been estimated from observed data as follows:

Table 3. Model parameterisation sources and methodology

Starting state	Ending state	Data source	Methodology
Healthy ('H')	Sick with susceptible bacteria ('S') / Sick with resistant bacteria ('R')	PHE	<p>Total infections of <i>E. coli</i> are available annually over the period 1 April to 31 March for England. Data is available from 2012 to 2017 and split into broad age groups.</p> <p>Within the analysis, reports are apportioned to a calendar year assuming a uniform distribution across the year. A simple average of the available years is then taken to be the level of infections in the starting year (2017).</p> <p>The average level of infections can be scaled across time to illustrate the following factors:</p> <ul style="list-style-type: none"> - incorporate other pathogens

			<p>- allow for a link between resistance and infection rates over time</p> <p>Infection reports are split according to the 'resistance profile' input by the user.</p> <p>Without inputting a scaling factor, the total number of infections remains constant over time. The split between resistant and susceptible infections varies depending on the resistance profile input by the user.</p>
Sick with susceptible bacteria ('S') / Sick with resistant bacteria ('R')	Dead ('D')	PHE	<p>Total deaths due to <i>E. coli</i> are available in the same data set as above. The same approach is taken to split reports across a calendar year and a simple average taken to estimate the number of deaths in 2017 due to <i>E. coli</i>.</p> <p>The user can input a scalar to adjust the starting mortality rate if required.</p> <p>Deaths in the starting year are attributed to resistant and susceptible bacteria by assuming that resistant strains are 2.5 times higher fatality rate than susceptible strains (M. E. A. de Kraker, 2011).</p> <p>Deaths due to susceptible and resistant bacteria are assumed to be proportionate to the number</p> <p>Infection reports are then split according to the 'resistance proportion' input by the user.</p>
Sick with susceptible bacteria ('S') / Sick with resistant bacteria ('R')	Healthy ('H')	N/A	The difference between the number of infections and the number of deaths
Healthy ('H')	Dead ('D')	ONS	Crude mortality rates have been taken as the average deaths over the average population from 2013 to 2016 for England & Wales. The crude death rate is then applied to the average population for England for consistency with the PHE data sets.
Sick with susceptible bacteria ('S')	Sick with susceptible bacteria ('S')	Academic Paper	The expected holding time in state S is estimated using research papers as sufficient data is not available (M. E. A. de Kraker, 2011). The research indicates that the median length of stay in hospital was 10 days for patients with <i>E. coli</i> susceptible to third generation cephalosporins.

			The holding time is calculated as the number of susceptible infections multiplied by the median length of stay.
Sick with resistant bacteria ('R')	Sick with resistant bacteria ('R')	Academic Paper	<p>The expected holding time in state S is estimated using the same research paper as state S (M. E. A. de Kraker, 2011). The research indicates that the median length of stay in hospital was 12 days for patients with <i>E. coli</i> susceptible to third generation cephalosporins.</p> <p>The holding time is calculated as the number of resistant infections multiplied by the median length of stay.</p>
Healthy ('H')	Healthy ('H')	PHE	<p>The expected holding time in state H is estimated as the total population multiplied by the number of days in a year less the holding time in S and R. In addition for people are assumed to die half way through the year and therefore a further reduction is made, resulting in the following:</p> <p><i>(Population – number of deaths x 0.5) x 365 – holding time in S – holding time in R</i></p>

6. Results

6.1 Comparison against typical life insurer catastrophe risk assumptions

A useful point of comparison is with the catastrophe risk in respect of mortality typically allowed for by life insurers and reinsurers. The capital required for this under Solvency II regulations (per the 'Standard Formula') is quantified by assuming a 1.5 per mil mortality shock (eg the result of a pandemic and/or terrorist attack). (For reference, the mortality impact of the 1918 Spanish flu was approximately 5 per mil.)

If we consider the most extreme of the various scenarios analysed in this paper, and calculate the extra ABR-related deaths in 2050 compared with those in the first year of projection, the extra mortality impact is negligible and corresponds to only around 4% of the Standard Formula event. However, if the extra ABR-related deaths are summed up over a long period, the effect becomes non-negligible: the total projected impact over the first 25 years of the projection for the 45-64 year age band, for instance, would correspond to around 40% of the Standard Formula event (for the avoidance of doubt: we compare 25 years of cumulative ABR deaths against one year of Standard Formula-calibrated mortality catastrophe).

6.2 Comparison against other causes of death

There is an almost infinite number of past, current and likely future scenarios and causes of death that our projections can be compared against. Three comparison points that struck the authors as interesting and useful to put the UK situation in perspective were:

- AIDS / HIV-related deaths
- Deaths relating to Adverse Drug Reactions ('ADR')
- The 'extra deaths' of 2015

AIDS/HIV comparison

A recent ONS publication⁷ notes 428 deaths among people with HIV in 2017 (UK). This provides a useful upper bound of the current situation, as not all of those deaths will necessarily relate to HIV. This figure is of the same order of magnitude as the ABR-related deaths projected in the model (precise comparison obviously depending on the scenario and year in question). Equivalent HIV deaths in the 2000-2009 decade averaged around 500 / year⁸, and so the comparison can be considered fairly stable.

ADR comparison

Wu et al. (Wu, et al., 2010) consider various aspects of ADRs in the UK, with particular emphasis on trends. However, if taking just the latest report figures shown (2008-9), there were around 3,500 in-hospital deaths in respect of ADR admissions. Depending on the ABR scenario chosen and the year of comparison, such a number dwarfs ABR-related deaths by a factor of 5-10. (Note that this considers only cases brought into hospital for treatment, not pre-hospital ADR 'sudden death'.)

⁷ Trends in new HIV diagnoses and people receiving HIV-related care in the United Kingdom: data to the end of December 2017

⁸ <http://www.nhshistory.net/aidsdata.pdf>

2015's 'extra deaths'

Actuaries and demographers generally associate 2015 as being a year that saw around 30,000 deaths more than would have been expected based on the experience of previous years (eg Hiam 2017⁹).

As in the above comparison, depending on the scenario and year chosen, such a figure would dwarf ABR-related impacts in any one year by a factor of some 50-100.

6.3 Modelling scenarios and output

The model produces the following outputs for a 34 year period (the apparently strange period length derives from the projection end date of 2050):

- (i) The number of infections in each year
- (ii) The number of deaths in each year
- (iii) The number of days spent in hospital with an infection
- (iv) The probability of dying in the year assuming the person was in the 'healthy' state at the start of the year
- (v) An annual and cumulative variance in (iv)

The working party has produced analysis covering the following scenarios to illustrate how to use the model and to inform the conclusions of this paper:

Table 4. Descriptions of scenarios run for analysis

Scenario	Resistance profile	Infection rate profile	Mortality rate profile
1	Linear extrapolation	No change from input	No change from input
2	Absolute increase in current resistance rates by 40% by 2050	No change from input	No change from input
3	Absolute increase in current resistance rates by 40% by 2050	Double current infection rates	No change from input
4	Absolute increase in current resistance rates by 100% by 2050	No change from input	No change from input
5	Absolute increase in current resistance rates by 100% by 2050	Double current infection rate and increase infection rate annually by 2.5%	No change from input
6	100% resistance in 2050	Double current infection rate	No change from input
7	100% resistance in 2050	Double current infection rate and increase infection rate annually by 2.5%	No change from input

The purpose of the range of scenarios run was to provide a broad spectrum of possible and extreme outcomes to test the model output.

⁹ Hiam L, Dorling D, Harrison D and McKee M. What caused the spike in mortality in England and Wales in January 2015? *J R Soc Med* 2017

6.4 Model output (mortality) scenario 1

The first investigation using available data on *E. coli* and a simple linear extrapolation of resistance over time, other parameters are assumed fixed at levels implied by 2017 data. The probability measure q_x is defined as a person who is in the healthy state at the beginning of the year, dies within 1 year for a given age group. In addition, we have illustrated a plausible impact to life expectancy in 20 years' time with this scenario.

Table 5. Model results scenario 1, all ages

Age Group	Annual Variance (q_x)	Cumulative Variance over 20 years (q_x)	Illustrative impact to life expectancy in 20 years*
<1 yr	+0.02%	+0.365%	N/A
1 – 15 yrs	+0.01%	+0.066%	N/A
15 – 44 yrs	+0.01%	+0.131%	-0.19%
45 – 64 yrs	+0.01%	+0.175%	-0.22%
65 – 74 yrs	+0.01%	+0.196%	-0.24%
75 – 84 yrs	+0.01%	+0.188%	-0.27%
85+ yrs	+0.01%	+0.144%	-0.32%

*Impact of a constant addition to mortality improvements of -0.02% pa in the CMI 17 model using the female National Life Tables 14-16 who is aged X at 31 Dec 2017 compared to a female aged X at 31 Dec 2037

The results indicate that except for those aged less than 1 year old, the annual variance in q_x is relatively small compared to expected future improvements in mortality and overall values of q_x . The reason that infant mortality impacts are significantly greater than other age groups is due to the low level of deaths from other causes which gives greater weight to deaths caused by *E. coli*. However, it should be noted that other data informing the parametrisation such as the length of time spent in hospital may be different to other age groups.

6.5 Model output (mortality) scenarios 2 to 7

The following table sets out the results of scenarios 2 to 7 for age groups over 15 years old. The results illustrate the annual and cumulative variance in q_x by 2050.

Table 6. Model results scenarios 2 to 7 for ages over age 15 years

Scenario	Annual Variance (q_x) by 2050	Cumulative Variance in q_x to 2050
2	+0.002%	+0.047% to +0.064%
3	+0.004%	+0.093% to +0.127%
4	+0.005%	+0.115% to +0.160%
5	+0.114% to +0.166%	+2.914% to +3.870%
6	+0.055% to +0.078%	+2.075% to 2.756%
7	+0.321% to 0.419%	+7.085% to +9.411%

Across the scenarios, older age groups (excluding <1 yrs not shown in table) have a greater impact from rising antibiotic resistance. The reason is likely to be due to the greater proportion of deaths as a result of a bacterial infection, relative to other causes of death. Increasing the rate of infection has a greater impact on q_x than increasing resistance rates by itself. In addition, when incorporating other infections in an approximate manner for example, in scenario 3 by doubling the current infection rate, this has little impact to the annual variance of q_x . This is a result of the model being sensitive to relative changes in infection rates from the starting position.

The different scenarios illustrate how even an extreme resistant shock illustrated in scenario 6 (applied to a wider population of bacteria) cause only a 2% to 3% relative variance to q_x in 2050 from

rates in 2017. However, when applying a link between rising resistance and infection rates (scenario 7) the impact is 3 to 4 times greater.

Infant Mortality

The working party noted that when producing the results there was a much higher relative impact to q_x from antibiotic resistance for those aged under 1 years, relative to adult age groups.

E. coli resistance to third generation cephalosporins within the UK for this age group has increased from around 1% in 2002 to 13% in 2013 (falling down to 7% in 2016 highlighting the significant volatility). Whilst the working party has not found research or data which highlights the relative difference in case fatality rate specific to this age group, a study used within the model (M. E. A. de Kraker, 2011) indicates this to be around 2.5 times and has been for this analysis. Specific age differences may produce a different result to those below if further research concluded this.

To highlight how infant mortality could develop we have illustrated the results under a range of scenarios (in the same order as those above).

Table 7. Model results for infants (under 1 year old), all scenarios

Scenario	Cumulative variance in q_x in 20 years	Cumulative variance in q_x in 2050
1	+0.365%	+0.602%
2	+0.051%	+0.084%
3	+0.100%	+0.165%
4	+0.127%	+0.210%
5	+2.746%	+5.537%
6	+2.486%	+4.102%
7	+6.410%	+13.871%

Scenario (7) has the most extreme parameters out of the scenarios run and illustrates that should infection rates increase and resistance reach 100% in 2050 with a wider scope of bacteria and a link between resistance and infection rates, infant mortality rates could increase by 14%. In absolute terms, infant deaths in 2016 for England & Wales totalled c. 2,700 and an increase of 14% on current levels could lead to an additional 380 infant deaths per year. Whilst this scenario may be considered extreme, it illustrates the potential significant exposure of infants to trends in ABR.

Morbidity

Given the limited available data, impacts to morbidity are inferred from varying the parameter inputs for length of hospital stay and the assumption around a proportionate interaction with the incidence of infection reports (i.e. if infection reports double then the number of bed days doubles; however, in practice higher infection incidence may result in a variable length of stay due to strains on the healthcare system). The relative length of stay input in the model is 1.2 times higher for *E. coli* resistant to third generation cephalosporins (M. E. A. de Kraker, 2011).

The resulting changes in morbidity are illustrated in the following table:

Table 8. Model results for morbidity across all ages and scenarios

Scenario	Increase in no. of bed days per annum in 20 years	Increase in no. of bed days per annum by 2050
1	9,000	15,000
2	1,800	2,900
3	3,500	5,800
4	4,400	7,200
5	493,000	976,000
6	77,500	127,800
7	608,000	1,237,000

Increases in rates of resistance to *E. coli* have a relatively small impact to overall numbers of bed days. For example, in 2016-17 there were around 35m bed days; therefore, in a scenario where resistance to *E. coli* reaches 100% by 2050, this would increase the number of bed days by only around 0.2%. However, increases to infection rates and widening the scope of bacteria covered can have a more material impact. In scenario 5 an increase of 976,000 bed days represents a 2.8% rise from current levels.

Whilst the data and modelling approach to morbidity is done at a high level, these results do indicate how more detailed analysis on the interaction between increasing resistance, infection rates and hospital occupancy could provide valuable information to inform insurers and government on the ABR implications on resourcing or insuring increased stays in hospital.

6.6 Effect of ABR on mortality in respect of preventive use of antibiotics

The above modelling work relates to the effect of ABR on 'direct' infectious mortality (in other words, infectious disease considered as an explicit cause of death). However, as noted in 3.5, there is great concern on the impact of ABR on mortality of patients undergoing (for instance) cardiac surgery

The Working Party also considered, in very approximate form, the possible impacts of ABR on such mortality.

The probability of infection after procedures such as those listed in 3.5 is of the order of 10% (Cove et al. (2012) reports a range of 5-21%¹⁰). So we would expect to see of the order of 10,000 infections. In a high ABR scenario, this would lead to somewhere in the order of 2-3,000 deaths.

Although this represents a material mortality worsening, there is also a degree of double-counting involved (as some of the direct modelling will have picked up infections in patients subsequent to such operations).

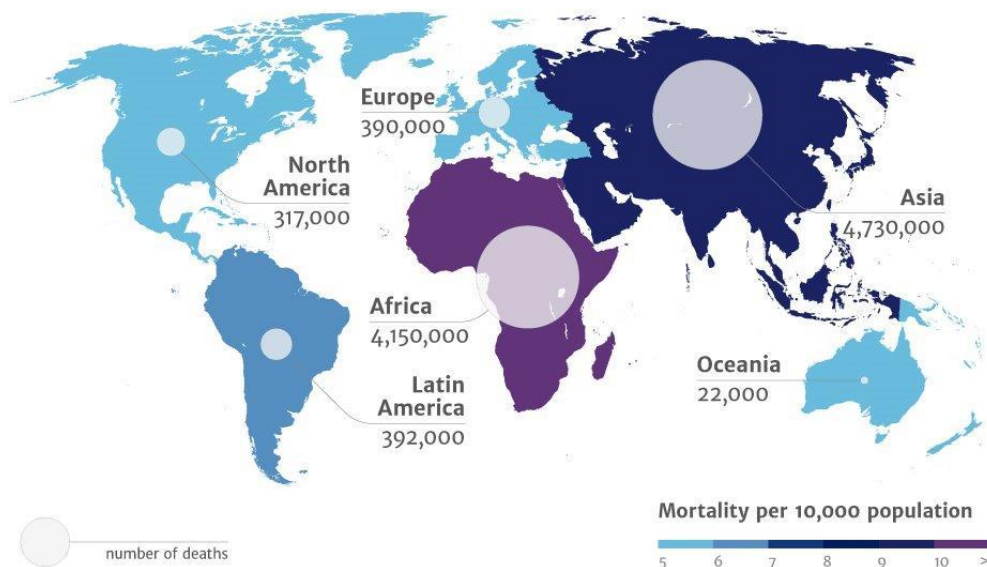
¹⁰ Cove ME, Spelman DW, MacLaren G. Infectious complications of cardiac surgery: a clinical review. *J Cardiothorac Vasc Anesth.* 2012;26(6):1094-100.

7. Conclusions

Within a UK setting (specifically, the available data is considering England), current infection and mortality rates caused by those bacteria in the initial scope of this paper are not material when compared with major causes of death such as cancer and heart disease. The modelling results highlight that only under the most extreme scenario, where resistant rates increase to 100% across a wide range of bacteria and this leads to increasing infection rates, life expectancies could be expected to reduce by around 4% across the adult age groups. In contrast, moderate scenarios (such as scenario 5) could lead to a 1.5% fall in life expectancies across age groups. The primary reason for the model producing this relatively small impact is the relatively few deaths and infection reports experienced in the UK for these types of infection. As a result, large changes to these factors have only a small impact on overall life expectancy; causes of death have much more effect.

The O'Neill Review (Review on Antimicrobial Resistance, 2016) concluded that the global burden from AMR could be significant by 2050 if action were not taken. The outcome of the review was to create a global awareness and action plan for addressing resistance and, as shown in the world map infographic taken from their website ('Review on Antimicrobial Resistance'), the principal world regions contributing to additional deaths would be Asia and Africa. Additional deaths across Europe attributable to AMR were estimated to be 390,000 by 2050; our model (on an extreme scenario) suggests the impact in England would be of an order of magnitude less than this. As an example, a 1% relative increase in mortality across England would lead to less than 10,000¹¹ additional deaths per year attributable to ABR.

Figure 5. World map highlighting the impact of rising AMR by 2050 (Review on Antimicrobial Resistance, 2016)



The impact illustrated by the modelling in this paper is markedly lower than that highlighted in the O'Neill review. The difference relates almost entirely to the influence of infectious disease mortality on

¹¹ Based on 2016 ONS population projections of males and females in England & Wales and projected q_x from NLT (E&W) 14-16 using the CMI 2017 model with core parameters and a long term trend of 1.5% pa

overall mortality in England (and, by extension, the UK and indeed most developed countries) compared with that in third-world countries; this difference can be traced back to material differences in vaccination programmes and general hygiene and sanitation.

However, the working party is not recommending that a different course of action from that advocated by the O'Neill review should be taken in the UK.

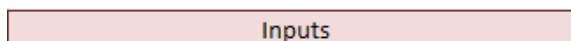
Further research (with corresponding approximate quantifications) into the likely second-order impacts of ABR on treatments such as joint replacement and cardiac implants (v 3.5) would be useful to reach a fuller awareness of the extent of possible future mortality deterioration in the UK, where 'direct' infectious disease mortality is likely to continue to be overshadowed by other causes of death.

In addition, whilst the modelling output does highlight that direct mortality impacts are relatively low, additional pressure on the National Health Service ('NHS') from ABR could be a significant factor. A scenario with very high levels resistance and increasing infection rates would put significant additional pressure on the health system (one scenario highlighted over 1 million additional bed days required). If a rise in resistance is combined with an ageing demographic, this could lead to a severe strain on the level of service the NHS could provide.

8. Model user guide

This paper has been produced alongside a Microsoft Excel spreadsheet which allows the user to adjust the parameters or scenario in order to conduct their own analysis. The workbook requires macros to be enabled in order to run the matrix multiplication functionality. Worksheets have been locked and protected, however there is no password if users wish to see / change the underlying formula.

Input cells are highlighted in light red:



The workbook consists of the following worksheets:

Worksheet Name	Function	Description
Front	Documentation	Sets out information around the TAS compliance of the workbook, users are encouraged to consider the limitations before conducting any analysis.
Input_Scen	Inputs	Allows the user to select the age group, resistance profile and adjust infection / mortality rates over time.
Input_Res	Inputs	Contains the pre-populated resistance profiles used in the working party analysis, alongside a custom entry for users to input their own resistance profile.
Input_Data	Inputs	Contains the population and transition observations as the starting point for the model.
Input_Lists	Inputs	Used to control the naming convention in the workbook, users would not be expected to update this page.
Calc_TransProfile	Calculation	Projects the observations from Input_Data and projects these out over time taking account of the age group, resistance profile and other parameters from the input page. Resistant and susceptible infection / deaths are split out according to the resistance profile and relative mortality impact between resistant and susceptible bacteria.
Calc_TransProb	Calculation	Organises the transition 'observations' over time and calculates daily state transition probabilities.
Calc_Matrix	Calculation	Calculates the 1 year transition matrix from the daily matrix over the period.
Output	Output	Displays the model results.

9. Data sources and limitations

Data Sources

The model comes pre-populated with analysis completed by the working party, however this can be overwritten by the users. Each input is given a unique reference and the following table contains information on how the working party populated this input.

Reference	Source	Details
[Input_Scen_1-5]	N/A	General inputs.
[Input_Scen_6-8]	Research paper (M. E. A. de Kraker, 2011)	Relative mortality rate and length of hospital stay.
[Input_Res]	EARS-Net	Resistance rates based on UK data from 2002 to 2017. A 3-year average (up/down one year) has been taken to smooth annual volatility. Projections begin from 2017 based on the year smoothed rate at 2016.
[Input_Data_1]	ONS	Population estimates have been downloaded from the ONS based on England and represent the mid-point of the calendar year
[Input_Data_2]	ONS	Mortality statistics have been downloaded from the ONS based on England and represent the mid-point of the calendar year.
[Input_Data_3-4]	PHE	Infection reporting and 30-day all-cause mortality rates provided by PHE for England. Data is presented across the financial year (Apr – Mar).
[Input_Lists_1-12]	N/A	General inputs used for data validation drop down lists.

Data Limitations

Limitations for each data source have been set out in Section 5. A further point to note is that the model has been calibrated to use consistent data sets where possible. Given the EARS-net data is across the UK, there is an inconsistency with the remaining data being based on England. In addition, the EARS-net data is provided in less granular age grouping than other sources and has been mapped in a way that is broadly representative (for example +65 yrs has been applied to 65-74 yrs and up, whereas there may be further differences within these categories).

If the user is intending to increase the scope of bacteria by adjusting other parameters (eg infection rates), this should be done with caution and may introduce spurious accuracy. As an example current resistance rates for MRSA are similar to those considered in this paper for *E. coli*; however, the factors driving MRSA resistance (which has been falling for the past 15 years) may be significantly different from those affecting *E. coli* resistance.

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Institute and Faculty of Actuaries

London

7th Floor · Holborn Gate · 326-330 High Holborn · London · WC1V 7PP
Tel: +44 (0) 20 7632 2100 · Fax: +44 (0) 20 7632 2111

Edinburgh

Level 2 · Exchange Crescent · 7 Conference Square · Edinburgh · EH3 8RA
Tel: +44 (0) 131 240 1300 · Fax +44 (0) 131 240 1311

Oxford

1st Floor · Park Central · 40/41 Park End Street · Oxford · OX1 1JD
Tel: +44 (0) 1865 268 200 · Fax: +44 (0) 1865 268 211

Beijing

6/F · Tower 2 · Prosper Centre · 5 Guanghua Road · Chaoyang District · Beijing · China 100020
Tel: +86 (10) 8573 1000

Hong Kong

2202 Tower Two · Lippo Centre · 89 Queensway · Hong Kong
Tel: +11 (0) 852 2147 9418 · Fax: +11 (0) 852 2147 2497

Singapore

163 Tras Street · #07-05 Lian Huat Building · Singapore · 079024
Tel: +65 6717 2955

www.actuaries.org.uk