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Antimicrobial Resistance Empirical and Statistical Evidence-Base

A report from the Department of Health Antimicrobial Resistance Strategy Analytical Working Group

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Antimicrobial Resistance Empirical and Statistical Evidence-Base

Prepared by the Department of Health Antimicrobial Resistance Strategy Analytical Working Group

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Scope

This is a revision of the original Antimicrobial Resistance Empirical and Statistical Evidence-Base published in December 2014, which provided a broad overview of the current situation of antimicrobial resistance (AMR) in bacteria, and which now includes AMR in both viruses and fungi. Its original aim was to bring together the evidence upon which scenario-based analytical work could be undertaken to assess the impact of emerging AMR in specific pathogens or groups of pathogens, or in particular types of infection or patient groups. The literature on many aspects of AMR is vast and impossible to encapsulate in its entirety in this report.

While aimed at the general reader, some sections of the report are necessarily of a somewhat technical nature, and relevant knowledge will give a better appreciation of the significance of the evidence here.

1. Introduction

Antimicrobials have been at the forefront in the battle to reduce infectious diseases for much of the past century. They are primarily used to treat infectious diseases in humans and animals, but are also of great value in the prevention of infections when used as prophylaxis, such as in the prevention of infections at the site of a surgical incision or in the prevention of *neutropenic* sepsis in patients undergoing chemotherapy treatment for cancer.

Antimicrobial (particularly antibiotic) use has increased to such an extent that resistance to these drugs has emerged and spread too many organisms. Infections with resistant organisms now occur in both community and hospital populations, with the latter accounting for the majority of deaths; it is estimated that more than 25 000 patients die annually in the EU due to multidrug-resistance (MDR) in bacterial infections [1]. It is believed that at some point antimicrobial resistance (AMR) may reach the stage of threatening certain medical procedures by making them too risky to perform.

In a keynote address at the conference on Combating Antimicrobial Resistance: Time for Action held in Copenhagen, Denmark on the 14th March 2012, Dr Margaret Chan, Director-General of the World Health Organization stated "*If current trends continue unabated, the future is easy to predict. Some experts say we are moving back to the pre-antibiotic era. No. This will be a post-antibiotic era. In terms of new replacement antibiotics, the pipeline is virtually dry, especially for Gram-negative bacteria. The cupboard is nearly bare*." "*A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill*." [2]

Gram-negative bacteria, a class of bacteria including Enterobacteriaceae, are of particular concern, as resistance to multiple drugs is now accumulating in these species. While the most serious MDR infections are in healthcare settings, where vulnerable patients are subject to a high antibiotic selective pressure, these resistant bacteria are now also spreading within the community.

The emergence and spread of resistant, particularly MDR, organisms is more concerning now than it has been in the past because it coincides with a decline in the development of novel therapies to take the place of those antimicrobials being rendered ineffective due to this resistance.

The recent European Centre for Disease Prevention and Control/European Medicines Agency (ECDC/EMEA) Joint Technical Report [1] identified that there were 15 systemically-administered antibacterial agents either with a new mechanism of action, or directed against a new bacterial target, but most of them were in early phases of development and were being developed primarily for use against bacteria, such as MRSA, for which treatment options are currently available, although indeed resistance may develop in the future. It was also noted that there was a striking lack of new antimicrobial agents active against MDR Gram-negative bacteria in particular.

Boucher [3] provides a more recent update to the status of development and approval of systemic antibiotics in the United States as of early 2013. Only two new antibiotics had been approved for use since the Infectious Diseases Society of America's 2009 pipeline status report [4], and the number of new antibiotics approved for marketing in the United States continues to decline annually. Only seven drugs were identified in clinical development that could be used in the treatment of infections caused by resistant Gram-negative bacteria.

2. Antimicrobial resistance

The subject of genetic mutations that occur within microorganisms rendering them resistant to antimicrobials is complex. This technical section provides an overview of the mechanisms by which AMR develops, and is included for completeness.

Antibiotics

Different classes of antibiotics possess specific modes of action by which they inhibit the growth or kill bacteria. These include inhibition of bacteria cell wall synthesis, inhibition of protein synthesis, inhibition of DNA synthesis, inhibition of RNA synthesis, competitive inhibition of folic acid synthesis and membrane disorganization. In all cases these effects involve the binding of antibiotics to specific bacterial molecular targets such as enzymes or the organelles. Bacteria can thus become resistant by developing mechanisms to prevent antibiotics binding to their molecular target. The four main methods by which bacteria achieve this are: inactivating or degrading antibiotics, modifying the target site, decreasing cell wall permeability (reducing antibiotic entry into bacterial cells) or active efflux, and metabolic bypass. Bacteria often possess multiple resistance mechanisms making them resistant to several classes of antibacterial agents.

There is a range of mechanisms by which an organism can acquire resistance, the simplest being genetic mutation. Resistant mutants will have a strong survival advantage in the face of antibiotic exposures, giving rise to the often seen association between the total usage of antibacterial agents in a population and the increased proportion of isolates that exhibit resistance to those agents. The indiscriminate and inappropriate use of antibiotics is being tackled by increased awareness of antimicrobial stewardship with the general aim of conserving the effectiveness of currently available antibiotics. Resistance genes can also be transferred between organisms via mobile genetic elements (MGEs) such as plasmids, and transferable resistance is often more important clinically in MDR Gram-negatives than is resistance arising from mutation. There is ample evidence that MGEs are able to transfer resistance mechanisms between genera; for example, Hegstad et al [5] describe MGEs of enterococci being transferred to *Staphylococcus aureu*s. This ability of bacteria to transfer resistance mechanisms provides a major challenge to preventing the emergence of resistance.

Antivirals

Antiviral therapy is frequently used in the setting of intensive immunosuppression, targeted at cytomegalovirus (CMV), herpes simplex virus (HSV), Hepatitis B virus (HBV) and varicella-zoster virus (VZV). The variety of resistance mechanisms that these viruses have acquired are thoroughly documented by Strasfeld and Chou [6].

The use of highly active antiretroviral therapy (HAART) has dramatically reduced the morbidity and mortality from human immunodeficiency virus (HIV) infection. The failure of antiretroviral therapy can result in the emergence of drug resistant forms of HIV. Resistance to the drug classes: nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and integrase inhibitors (INIs), have now appeared through a number of genetic mutations in the targeted viral genes. Detailed descriptions of the current identified mutations are provided at Stanford University HIV Drug Resistance Database [7]

There are two antiviral drugs used to treat seasonal influenza; oseltamivir and zanamivir, with the recommended treatment being dependent upon the circulating stain. Treatment prevents serious infection and lessens the duration of symptomatic illness. Both are neuraminidase (NA)

inhibitors, binding to the virus's NA surface protein and inhibiting enzymatic activity. This prevents flu viruses from spreading from infected cells to other healthy cells. Resistance can emerge through one of numerous mutations in the NA that reduce inhibitor binding efficiency to the enzyme. These mutations differ between type and subtype of influenza virus and in their impact on the two inhibitors, but the most prevalent is an H275Y mutation, known to confer oseltamivir resistance in 2009 H1N1 flu viruses [8].

Treatment of chronic hepatitis C virus (HCV) infections has changed dramatically since the introduction of direct acting antivirals (DAA). The treatments telaprevir and boceprevir have been supplemented by new NS3 protease inhibitors, simeprevir and faldaprevir, a non-nucleoside polymerase inhibitor, sofosbuvir and NS5a replication complex inhibitors daclatasvir and ledipasvir. Used in combination, these have greatly increased the treatment options for chronic HCV with high efficacy and improved safety. Naturally occurring mutations such as the Q80K variant conferring resistance to simeprevir has been observed in proportions ranging from 9%-48% of untreated HCV genotype 1a-infected patients. Resistant variants are detectable in the majority of patients with treatment failure to NS3 protease inhibitor- or NS5a inhibitor-based antiviral therapy. Long-term follow-up studies by population-based sequence analysis have shown the disappearance of resistant variants in the majority of affected patients, with median times to the disappearance of these types of mutations of 4-64 weeks [9].

Antifungals

Despite the development of new antifungal drugs, resistance continues to grow and evolve, and complicates patient management. As with antibacterial agents, in-vitro susceptibility testing is used to select treatments for a given infection. Reliable in-vitro antifungal susceptibility testing has been developed in the USA, the Clinical and Laboratory Standards Institute (CLSI), and in Europe, the European Committee on Antimicrobial Susceptibility Testing (EUCAST). A variety of mechanisms can lead to acquired resistance of *Candida species* to azole drugs, the most common being induction of the efflux pumps encoded by the MDR or CDR genes, and acquisition of point mutations in the gene encoding for the target enzyme (ERG11). Acquired resistance of *Candida species* to echinocandins is typically mediated via acquisition of point mutations in the FKS genes encoding the major subunit of its target enzyme. Antifungal resistance is associated with elevated minimum inhibitory concentrations, poorer clinical outcomes, and breakthrough infections during antifungal treatment and prophylaxis. [10]

3. Antibiotic use

The use of antibiotics in a population is the primary driver of the development of resistant bacteria. However, the factors underlying the development of resistance in pathogens is often more complex than simply using increasing amounts of a certain antibiotic - see section 2. For certain pathogens, resistance to a particular antimicrobial is never seen. For example, group A streptococci have never developed resistance to penicillin; the reasons are unknown.

Over the past few years there has been increased attention on improving the understanding of prescribing data in both the hospital and community settings. The establishment of the English Surveillance Programme for Antibiotic Utilisation and Resistance (ESPAUR) has enabled a co-ordinated approach within England to understanding the prescribing of antimicrobials. This provides a cornerstone for antimicrobial stewardship (AMS) initiatives and the development of prescribing guidance. Prior to ESPAUR there were some sources of data on antimicrobial prescribing and usage but they were often less than ideal. Individual patient level data are rarely readily available, particularly so in the hospital setting.

The ESPAUR report [11], and supplementary materials, provides comprehensive information on antibacterial prescribing and so only a brief précis of the main finding are presented here.

Total antibiotic consumption in England has increased from 21.6 defined daily doses (DDD) per 1 000 inhabitants per day in 2011 to 23.0 DDD per 1 000 inhabitants per day in 2014. Whilst prescribing of many drug classes is increasing, there are decreasing trends over this time period in the consumption of both cephalosporins and quinolones. Indeed for these broad spectrum antibiotics England has the lowest use across the EU member states.

There is also variation between hospital and community prescribing; antibiotic prescriptions in primary care have declined for the last two years. Prescribing in primary care can be measured by the number of prescriptions dispensed, adjusted for the age and sex distributions in the population (STAR-PU). There were 1.18 items per STAR-PU in 2014 compared to 1.23 items per STAR-PU in 2011. However when measured by DDD, prescribing in primary care increased over this time, suggesting that longer courses or higher doses are being used.

Measured by DDD per 1 000 inhabitants, prescribing in hospitals continues to increase, with an 11.7% and 8.5% increase between 2011 and 2014 in inpatients and outpatients, respectively.

Total consumption of key antimicrobial agents in England as measured by DDDs per 1 000 inhabitants per day, and trends over the five years 2010 to 2014 are presented in Figure 1 (adapted from [11]). The predominant antibiotic used in England was penicillins with around 10 DDDs per 1 000 inhabitants per day. Tetracyclines and macrolides are both frequently used with around 4 and 3 DDDs per inhabitant per day, respectively.

The 2011 National Point Prevalence Survey [12] collected information on the antimicrobial usage on a single day for each patient. There were a total number of 25 942 antimicrobial prescriptions in 18 219 patients from a total of 52 443 patients in the survey. This provided an estimate that 34.7% of patients in the survey had been prescribed antimicrobials and, at that time, were prescribed on average 1.42 types of antimicrobial.

Figure 1: Total antibiotic consumption by key agent, expressed as defined daily doses (DDD) per 1 000 inhabitants per day, across England 2010-2014

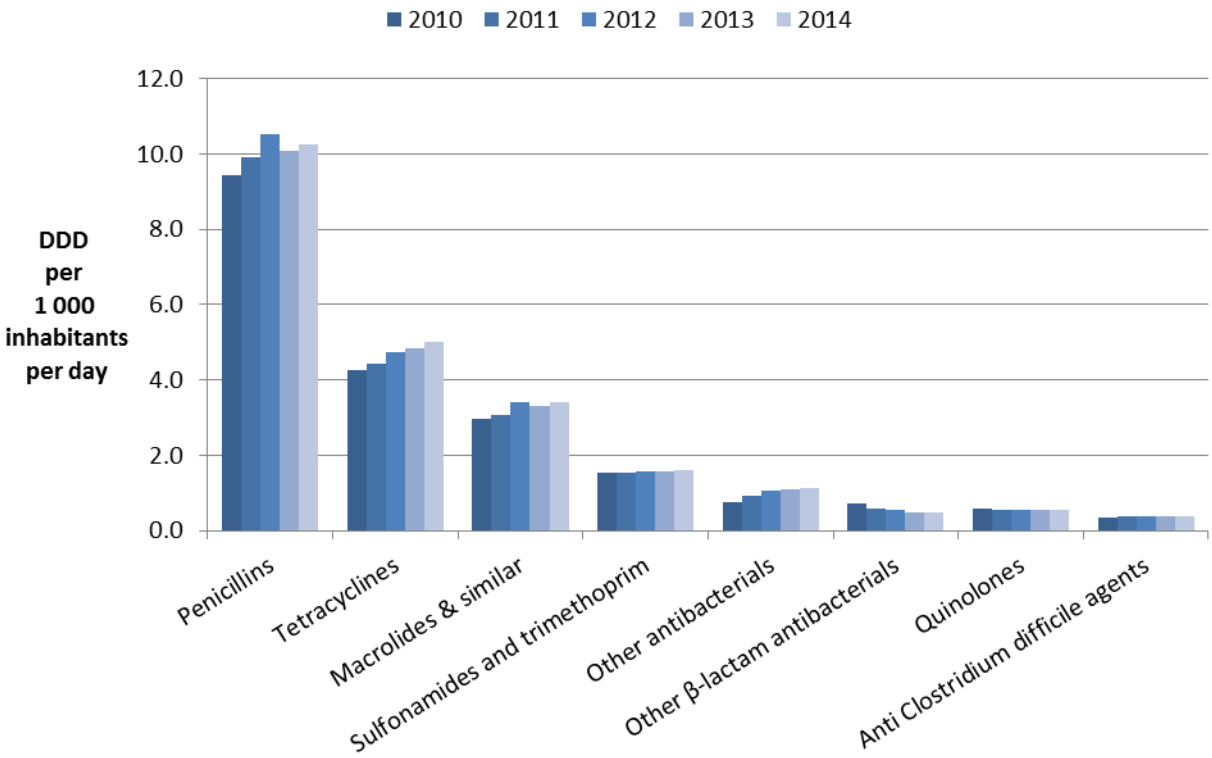


Table 1 adapted from [12] gives the top nine antimicrobials prescribed by intended treatment. For the total number of prescriptions recorded in the survey the observed percentages provide a measure of the use of each antibiotic for treatment, and both surgical and medical prophylaxis. Co-amoxiclav and piperacillin/tazobactam were the most commonly prescribed antimicrobials for treating infections, co-amoxiclav and gentamicin were the most commonly prescribed antimicrobials for surgical prophylaxis, while for medical prophylaxis the most commonly prescribed antimicrobials were co-amoxiclav, gentamicin and trimethoprim.

Table 1: Top nine antimicrobials by treatment intention

Antimicrobial	Treatment of infection No.	Treatment of infection %	Surgical prophylaxis No.	Surgical prophylaxis %	Medical prophylaxis No.	Medical prophylaxis %
Total (all antimicrobials)	**19 411**	**100**	**3 412**	**100**	**2 059**	**100**
Co-amoxiclav	2 674	13.8	703	20.60	107	5.2
Piperacillin/tazobactam	2 111	10.9	54	1.6	44	2.1
Flucloxacillin	1 366	7.0	457	13.4	46	2.2
Gentamicin	815	4.2	583	17.1	126	6.1
Clarithromycin	1 190	6.1	8	0.2	21	1.0
Metronidazole (parenteral)	907	4.7	270	7.9	23	1.1
Amoxicillin	1 062	5.5	50	1.5	31	1.5
Trimethoprim	932	4.8	19	0.6	108	5.2
Meropenem	961	5.0	10	0.3	25	1.2

The increases in the prescribing of carbapenems, co-amoxiclav and piperacillin/tazobactam are undoubtedly increasing the selection pressure on the microbial population and the usual consequences of this are emerging with increasing AMR to these antibiotics.

In addition to the human use of antimicrobials, there is a similar amount used in food producing animals. Consumption of systemic, intramammary and intestinal antibiotics in humans and food producing animals, in 2013, equated to 135 and 55.6 mg per kg of human and animal weight, respectively. The recently published One Health Report [13] provides a comparison of the usage of antibiotics in humans and food producing animals and, for 2013, these data are summarised in Table 2.

Table 2: Total systemic antibiotics prescribed in humans from primary and secondary (ATCJ01, A07AA) and sold for all animal use, i.e. livestock, companion animals and horses (ATCvet QJ01, QJ51, QA07AA), expressed in tonnes active ingredients in the UK, 2013

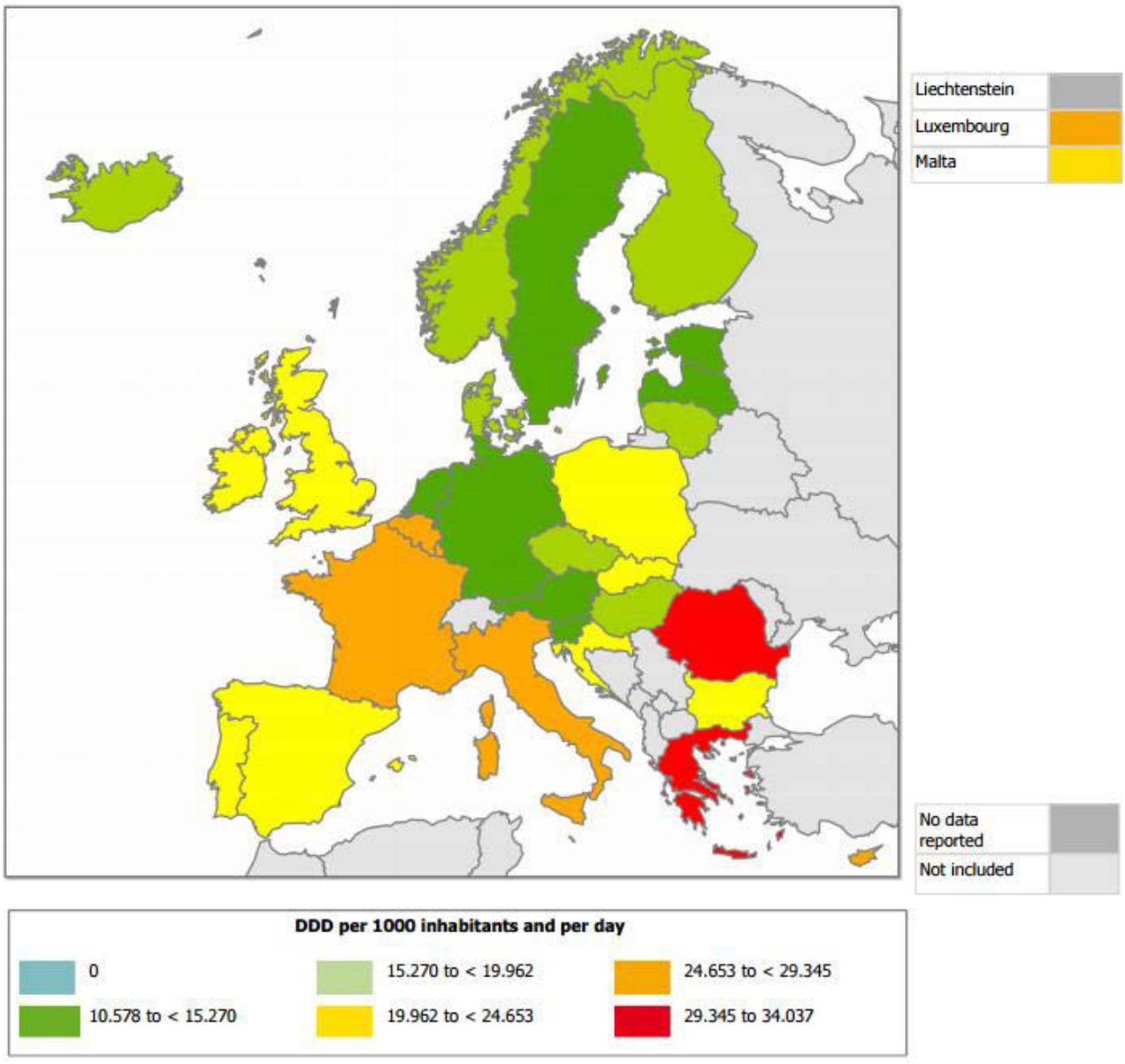
Antibiotic group	Antibiotics prescribed in humans (tonnes active ingredient)	Antibiotics prescribed in humans % of total	Antibiotics sold for animal use (tonnes active ingredient)	Antibiotics sold for animal use % of total
Penicillins	350.1	63.8	90.8	21.7
Tetracyclines	54.6	9.9	182.0	43.5
Macrolides	51.9	9.5	43.0	10.3
Sulfonamides and Trimethoprim	18.3	3.3	60.5	14.5
1st and 2nd generation cephalosporins	17.7	3.2	4.9	1.2
Fluoroquinolones	12.3	2.2	2.6	0.6
Other antibacterials	9.2	1.7	12.6	3.0
Polymyxins	5.1	0.9	0.7	0.2
Monobactams, Carbapenems	3.5	0.6	0.0	0.0
3rd and 4th generation cephalosporins	3.4	0.6	1.2	0.3
Lincosamides	2.4	0.4	13.4	3.2
Glycopeptides	1.6	0.3	0.0	0.0
Aminoglycosides	0.9	0.2	4.3	1.0
Amphenicols	0.1	0.1	2.6	0.6
Other quinolones	0.0	0.0	0.0	0.0
Total (including all other antibiotic groups)	**531.2**	**100**	**418.7**	**100**

While most antibiotic classes are used in both humans and animals, there are no authorised veterinary medicines which contain antibiotics from the monobactam/carbapenem, glycopeptide or ‘other quinolone’ classes in order to minimise the risk of resistance developing. Tetracyclines are the most frequently used antibiotic in food producting animals compared to penicillins in humans.

Antibiotic usage in humans also varies substantially between countries. The European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [14], co-ordinated by the European Centre for Disease Prevention and Control (ECDC), provides comprehensive data on

antimicrobial consumptions across the EU. The most recent available surveillance report [15] contains data up to and including 2012. The overall population-weighted EU/EEA mean consumption was 21.5 DDD per 1 000 inhabitants and per day, and that this has not altered significantly over the past 5 years. However, certain countries showed a significant increase in consumption over the five-year period ending in 2012. Of particular note was that Greece, having the highest figures, showed a considerable decrease in the consumption of antibacterials for systemic use between 2011 and 2012. Figure 2 illustrates consumption figures for Europe in 2014.

Figure 2: Consumption of antibacterials for systemic use (ATC group J01) in the community (primary care sector) in Europe, reporting year 2014



Consumption of antibacterials in the community varied by a factor of 2.8 between the highest consumption (31.9 DDD per 1 000 inhabitants and per day in Greece) and the lowest (11.3 DDD per 1 000 inhabitants and per day in the Netherlands).

The association between antibiotic use and antibiotic resistance

There is a growing literature attempting to quantify the association between antibiotic use and antibiotic resistance. Many of these studies assume that simple selection pressure will lead to

increasing resistance in the face of increasing usage. While this can be demonstrated for certain drug-bug combinations, for others the association, if any, is not so obvious. It is unclear whether it is largely due to methodological issues that some studies fail to find the anticipated association between usage and resistance. For example, there is no agreement regarding how best to measure antibiotic usage in these studies, and what time lag between usage and resistance to use. Bergman et al [37] in a paper exploring the association between antimicrobial usage and resistance in *E. coli* found that most of the associations they studied failed to reach statistical significance. Additionally, rates of resistance often fail to decrease after reductions in use of that relevant antibiotic. In general, there is a lack of understanding of the interactions between host, bacteria and antibiotic that result in the emergence of resistance. It is believed that factors such as the 'clonality' and virulence of the pathogen are likely to play a role.

There are several papers that have failed to find evidence of the associations between antimicrobial resistance in *E. coli* and the use of antibiotics. Only weak associations were found by Livermore et al [38] for resistance to ampicillin and trimethoprim in *E. coli.* Hay et al [39] also found no evidence of an association for amoxicillin and trimethoprim resistance in *E. coli* in urine samples in asymptomatic patients. Kahlmeter et al [40] also found no associations between a range of antibiotics and resistance to these in *E. coli* isolates in patients with community-acquired Urinary Tract Infections (UTIs).

Ecological data are available that allow associations of resistance rates and usage across countries to be investigated. ECDC provides data on (mostly community) consumption of antimicrobials. Figure 3 shows the use of these data for MRSA (meticillin resistant *staphylococcus aureus)* suggesting a fairly strong relationship between consumption of antibacterials for systemic use (ATC group J01) and the degree of resistance reported to ECDC. From this one can estimate the increase in resistance for every additional daily defined dose per 1 000 population as 1.1% (95% confidence interval: 0.6-1.9%).

Figure 3: Relationship between MRSA and community antibiotic consumption of systemic use (Anatomical Therapeutic Chemical group J01) for the 26 countries that provided both figures in 2010

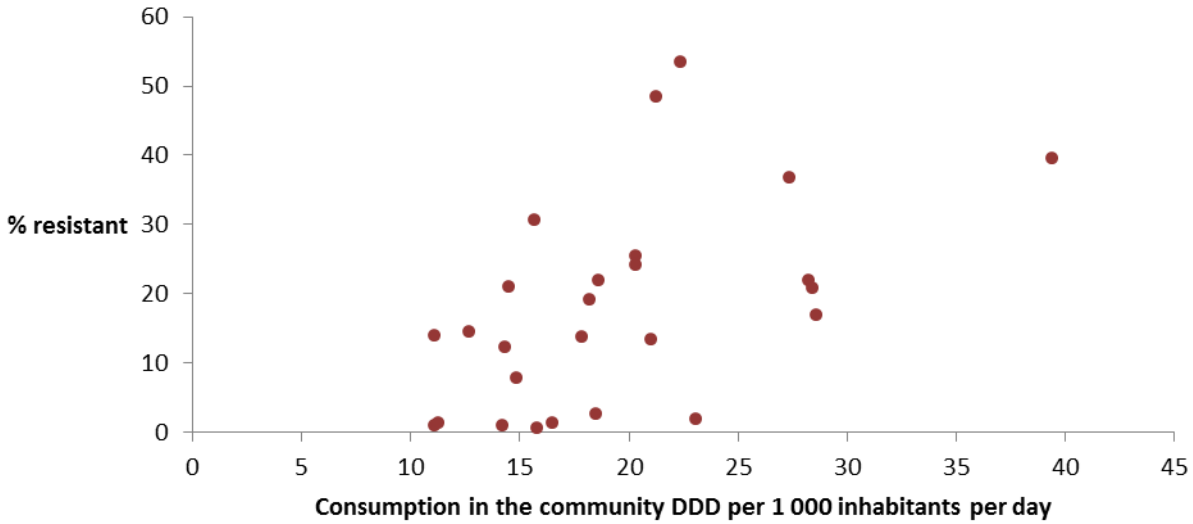


Figure 4 and Figure 5 show the ambiguous evidence for any relationship between the consumption of third-generation cephalosporins and the degree of resistance to them in *Klebsiella pneumoniae* and *E. coli*.

Figure 4: *Klebsiella* pneumoniae resistance to third-generation cephalosporins by countries 2010

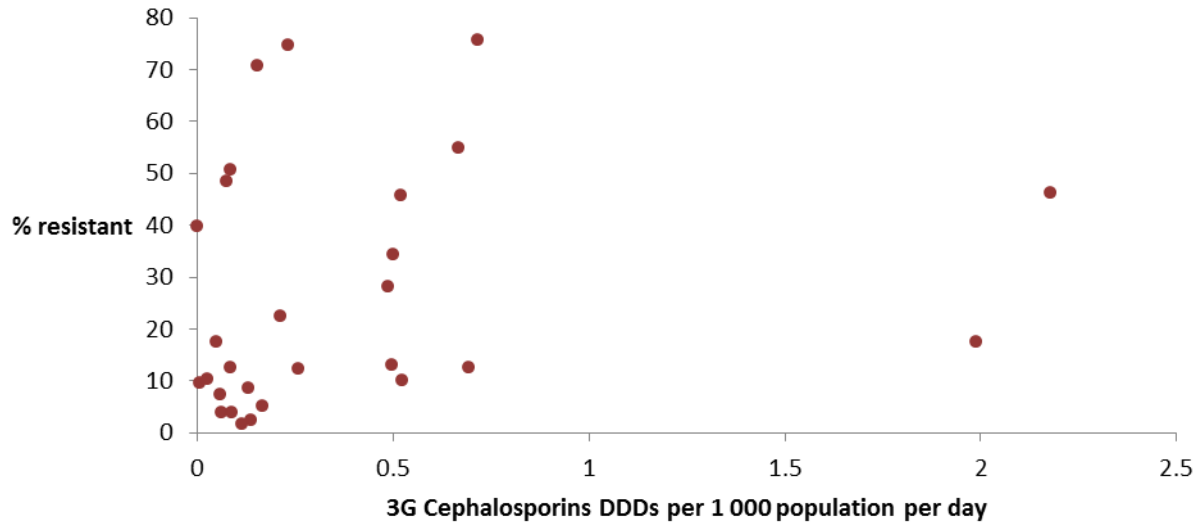
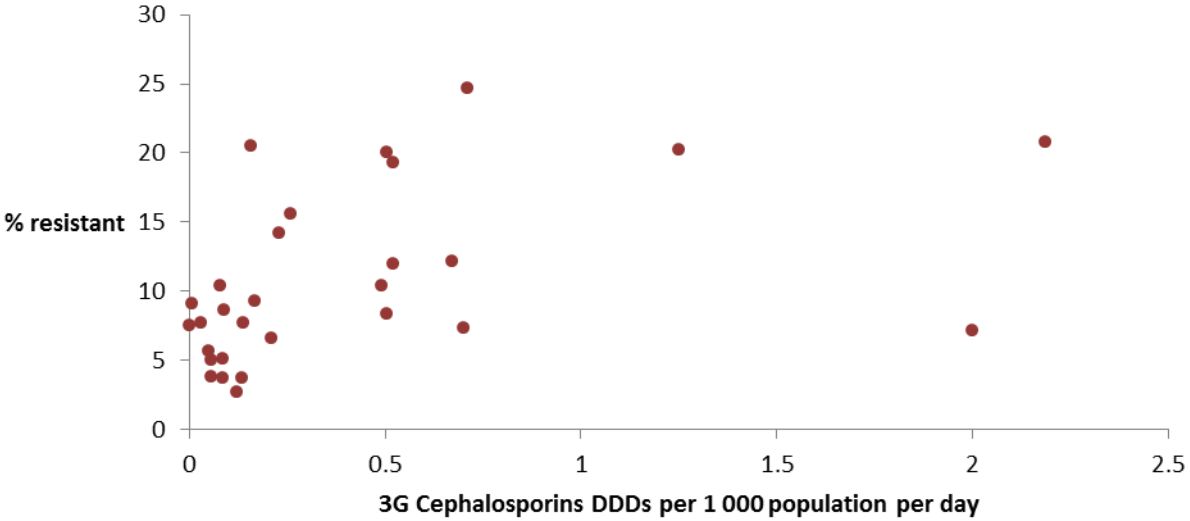


Figure 5: *E. coli* resistance to third-generation cephalosporins by countries 2010

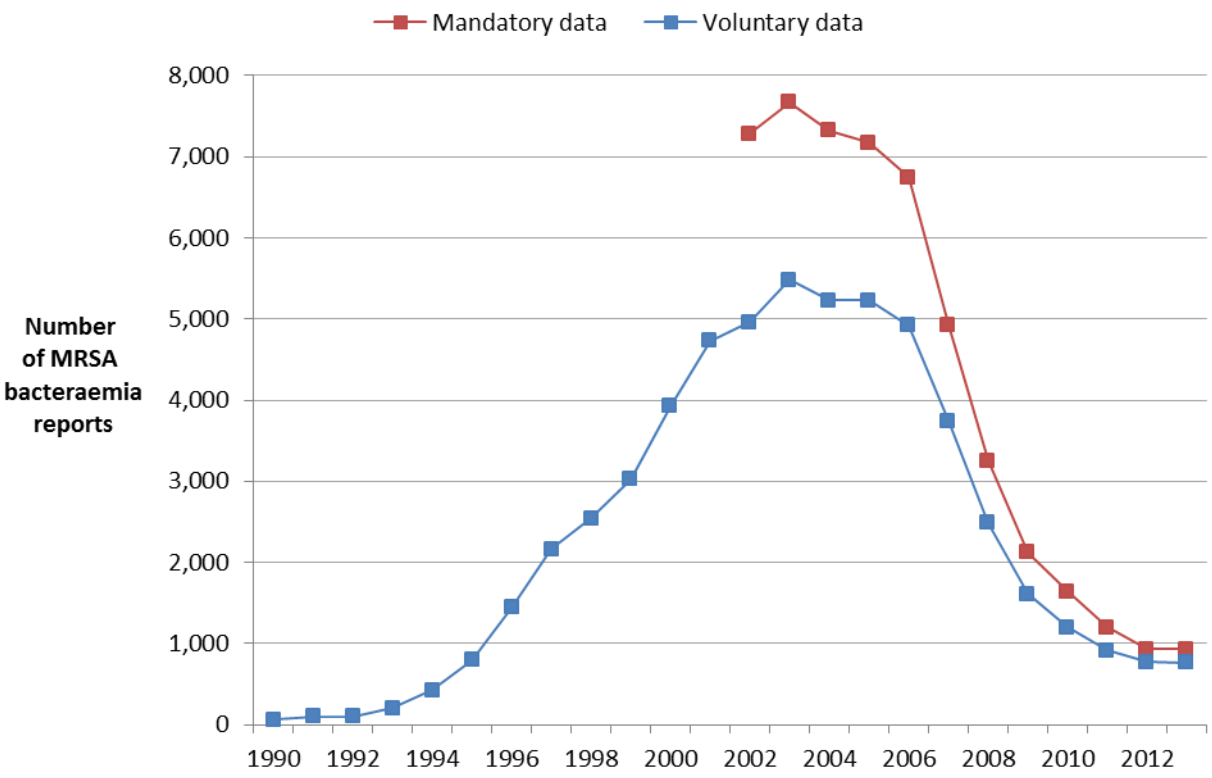


The available evidence and primary analysis presented in this section provide some of the challenges in understanding how increased prescribing can lead to increased resistance. Elucidating the association with the available data is challenging, and a better understanding of the emergence and transmission of resistant pathogens is needed to better preserve the currently effective antibiotics.

4. Current trends in resistance

It is important to remember that 'resistance' is not in itself a disease entity, but it affects many organisms that cause a range of infections. It renders many antimicrobial agents ineffective as treatment options. Available data on the occurrence of AMR are particularly difficult to interpret and are often in short supply, particularly for developing countries. The assessment of emerging resistance and temporal trends in the incidence of AMR are most frequently performed using data from surveillance systems. The number of occurrences of specific AMR reported to surveillance systems are invariably incomplete, because they require laboratory isolation, identification and susceptibility testing of a disease-causing pathogen. This is often not necessary for the clinical management of a patient, and whether a specimen is taken depends upon the nature of the disease, and the clinician's propensity to refer specimens for microbiology. It is usually implicitly assumed that general trends observed in reported isolates reflect those occurring in the wider population of patients and pathogens, although this has rarely been assessed. Figure 6 below (adapted from [16]) compares the mandatory and voluntary meticillin-resistant *S. aureus* (MRSA) bacteraemia reports from English acute trusts each year, and provides support for this assumption.

Figure 6: Comparison of annual reports to mandatory and voluntary MRSA bacteraemia surveillance



Many infections (particularly those occurring in community settings) are treated empirically without any specimens being sent for microbiological investigation. Surveillance data are therefore most complete when they relate to infections for which suitable samples would commonly be referred for microbiology, such as bacteraemia.

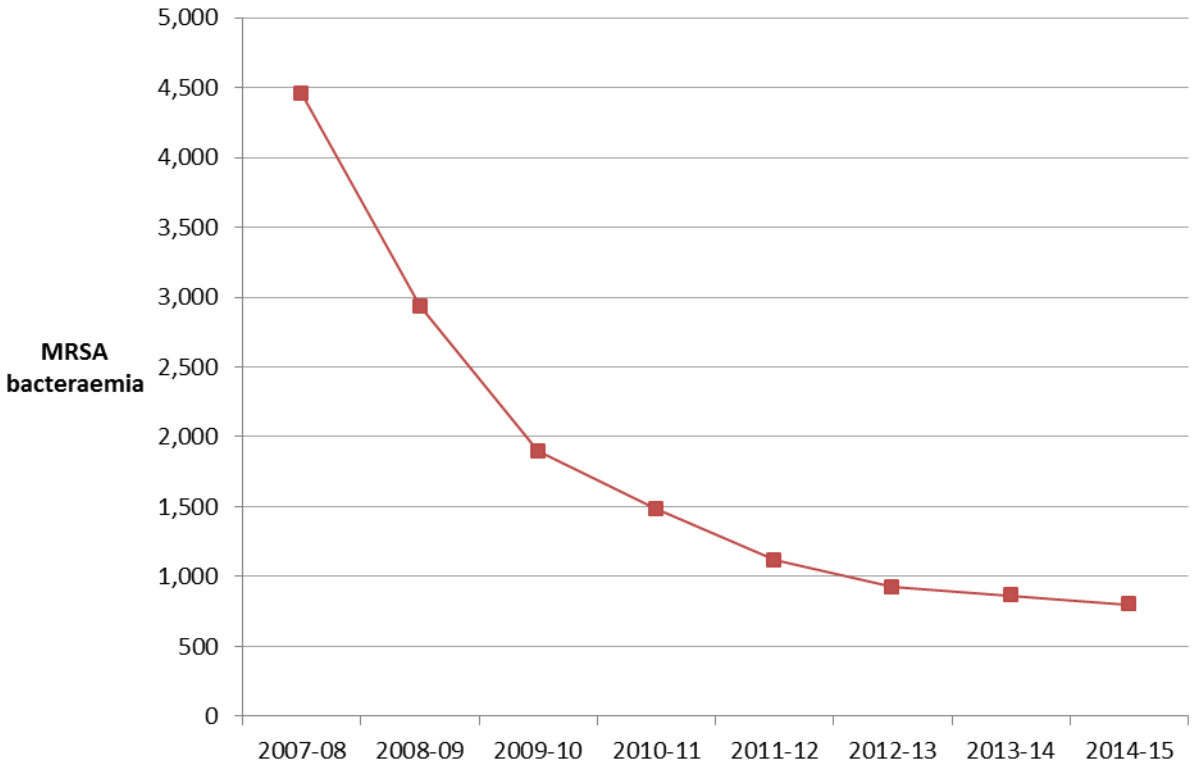
In the remainder of this section some specific examples of current trends are presented. These represent some of the more noteworthy pathogens where AMR has been a problem or is currently considered as an emerging problem.

English perspective

Antibacterial resistance

In England, the observed trends in the numbers of reports of AMR organisms are somewhat heterogeneous. Significant decreases have been seen in the reported occurrence of certain AMR organisms. For example figures from mandatory surveillance show that MRSA bacteraemia reduced by 81% from 4 451 to 862 between 2007/08 and 2012/13. This year on year reduction is shown in Figure 7.

Figure 7: Number of MRSA bacteraemias reported to the DH mandatory surveillance system in each of the past seven financial years



Staphylococcus aureus is also an important causative organism in the development of surgical site infections (SSIs). Reports to the Surgical Site Infection Surveillance System (SSISS) have shown a decreasing trend commencing in 2006/7 when it accounted for 39% of cases, to being the reported pathogen for 16% of cases of inpatient SSIs in 2013/14.

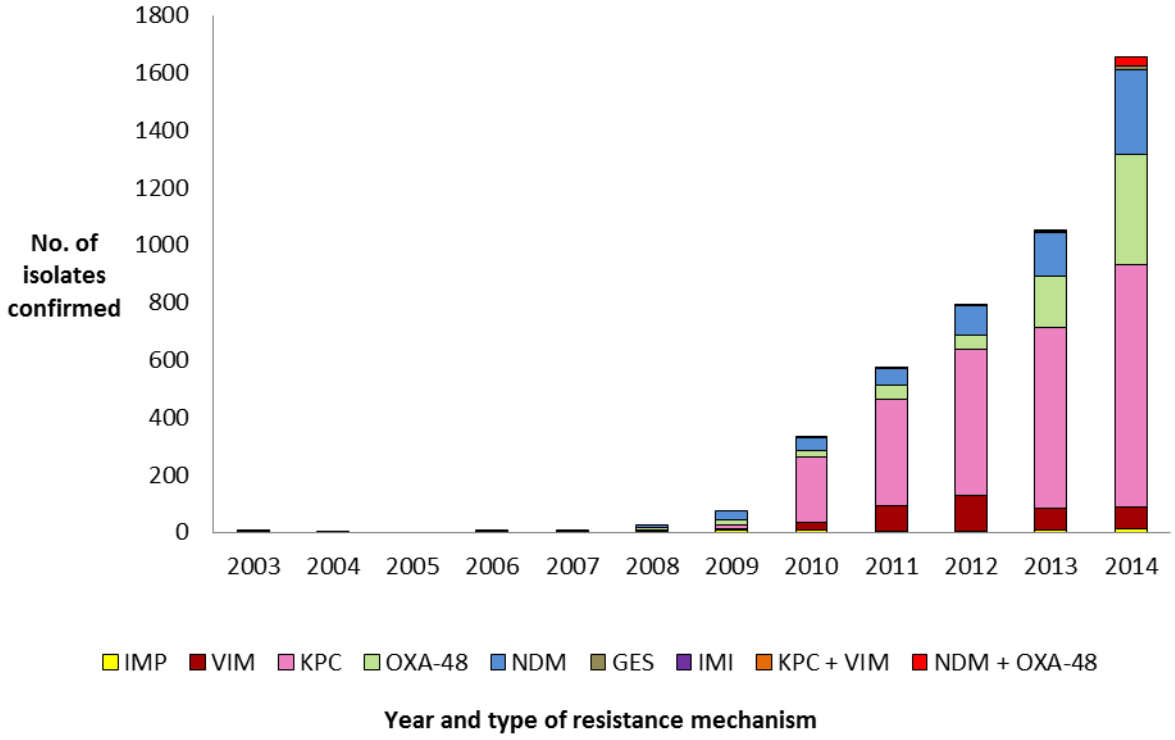
Whilst there has been a reduction in the occurrence of MRSA bacteraemia, increases in isolates of MRSA producing the Panton-Valentine Leukocidin (PVL) toxin have been observed among submissions to PHE's national reference laboratory, with 117 isolates in 2005 increasing to 1 049 isolates in 2010 [17]. MRSA strains producing the PVL toxin have been associated with an increased ability to spread and cause severe infection. A recent study in North London [18] observed a particular PVL-MRSA clone, CC5 which has exhibited a rapid increase, even though the absolute numbers are relatively small. Of further concern, the results of a national study highlighted the emergence of multiply-resistant PVL-MRSA clones causing clinical disease throughout England [19]. However, it is difficult to understand precisely the reasons for the observed trends in PVL-producing MRSA. This could reflect ascertainment bias with increased testing for PVL over recent years or increased PVL-MRSA carriage in the general population.

Extended-spectrum β-Lactamases (ESBLs) are an example of a resistance mechanism that is causing particular concern. These enzymes confer resistance to cephalosporin antibiotics,

which in the past were widely used in many UK hospitals. Worryingly, the British Society for Antimicrobial Chemotherapy (BSAC) bacteraemia surveillance data found that bacteria with ESBLs are commonly multidrug-resistant, with 83% of ESBL-producing *E. coli* exhibiting ciprofloxacin non-susceptibility and 40% gentamicin non-susceptibility [20]. Furthermore, ESBLs are frequently encoded on mobile plasmids, which can transfer this resistance between different strains or even to other species and genera of bacteria. These plasmids often carry other resistance genes, limiting the treatment options for infections caused by ESBL-producing organisms. Data from voluntary laboratory reporting to PHE and from BSAC bacteraemia surveillance showed the rates of non-susceptibility to cephalosporins and quinolones rose amongst *E. coli* and *Klebsiella* spp. until the mid-2000s, but showed a slight decline thereafter. These reversals in trend occurred whilst the incidence of *E. coli* bacteraemia was rising, the incidence of *Klebsiella* bacteraemia was stable and the incidence of *Enterobacter* bacteraemia was falling. This slight decline was not paralleled in EARS-Net data for continental Europe and did not reflect the displacement of a single mechanism of resistance. Rather it coincided with large reductions in hospital cephalosporin and quinolone use, owing to concern about *Clostridium difficile* [21].

Carbapenemase-producing Enterobacteriaceae (CPE) are gram-negative bacteria that are nearly resistant to the last-line carbapenem class of antibiotics and have emerged in the UK over the past decade. There have been reported occurrences in *Klebsiella* spp. (79%), *E. coli* (12%), and *Enterobacter* spp. (7%). These data are based on voluntary referrals made to PHE's national reference laboratory, and indicate an emerging and growing UK problem as shown in Figure 8.

Figure 8: Number of isolates, by year and resistance mechanism, referred from UK hospital microbiology laboratories confirmed as carbapenemase-producing Enterobacteriaceae by AMRHAI reference laboratory



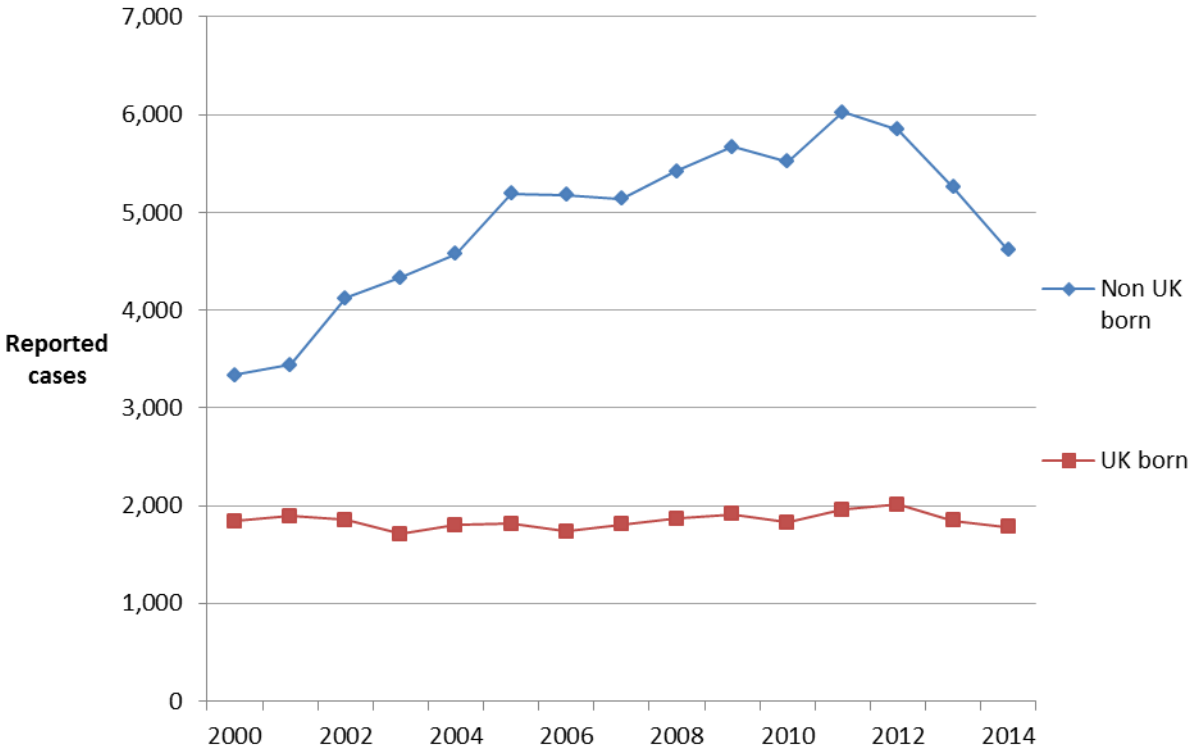
Prior to 2007 the few CPE isolates detected were often imported into the UK, however, the increase in occurrence observed since 2007 has included cases of disease where transmission occurred within the UK. Strains of *E. coli* offer the perfect vehicles for taking these highly

worrying carbapenemases out of hospitals and establishing them in community settings with the potential to impact on primary care.

In response to the growing numbers of CPE isolates, an electronic reporting system for the enhanced surveillance of carbapenem resistance in Gram-negative bacteria has been implemented by Public Health England. The background to this is described in the Health Protection Report published in January 2015 [22].

For tuberculosis (TB), the emergence of strains resistant to first-line antibiotics over the past two decades has been observed. Resistance in TB arises from mutations that are not transferable between strains. The total number of TB cases occurring in those born in the UK has remained reasonably static over the past decade at just under 2 000 cases reported each year as shown in Figure 9 (adapted from [23]). In contrast, reports of TB in those born outside of the UK rose steadily, from 3 329 reports in 2000 to 6 019 in 2011. However, reported cases of these infections have declined over the past few years to 4 610 in 2014 [23].

Figure 9: Tuberculosis case reports for UK and non-UK born individuals, 2000-2014



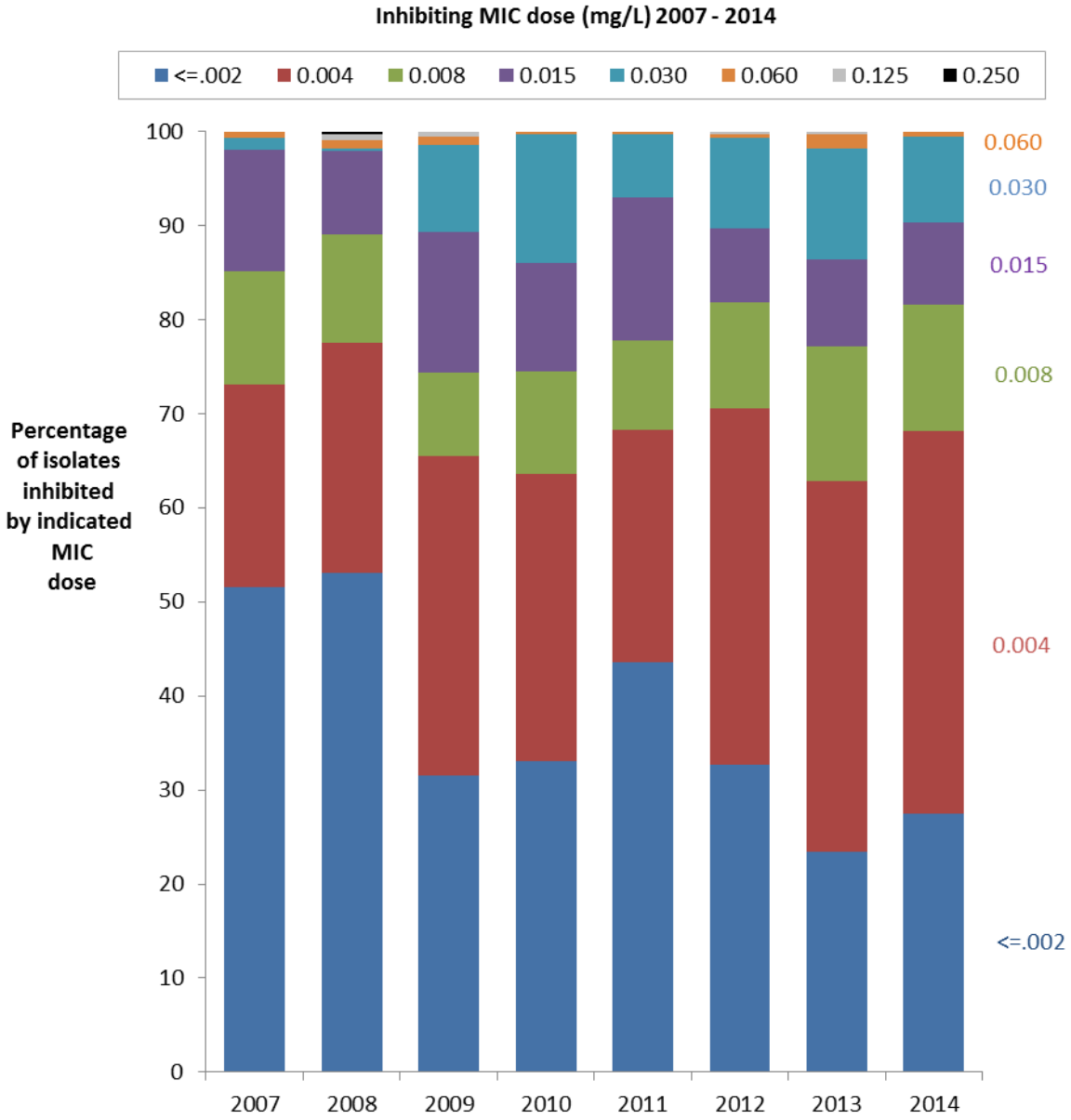
The Tuberculosis in England 2015 report [23] contains comprehensive data on the reports of drug resistant TB, and multidrug-resistant (MDR) TB in particular. The key messages with regard to drug resistance in this report are presented below. Excluding MDR-TB, the proportion of cases with initial resistance to the first-line antibacterial isoniazid has remained fairly stable over the past decade, at around 6%. This initial resistance to isoniazid occurred most frequently in those with a previous history of TB and a high proportion (18%) of cases with resistance had at least one social risk factor. There has been a small decrease since the 2011 peak in the number of initial MDR and rifampicin resistant (RR) TB cases, with 56 (1.4%) in 2014 and 88 (1.8%) in 2011. Of the combined MDR and RR-TB cases 89% were non-UK born, the majority of cases coming from Eastern Europe and the Indian subcontinent, with only six being born in the UK. The numbers of extensively drug-resistant (MDR-TB that responds to even fewer available medicines) TB isolates remain low with three cases reported in 2014 which is similar to the numbers reported over the past six years.

Another disease where resistance has been of concern for a number of years is gonorrhoea. Surveillance in England is performed with a sentinel system: Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP), and voluntary reports to the surveillance system AmSurv, within the Second Generation Surveillance System (SGSS). The 2014 GRASP report [24] provides a comprehensive view of resistance in this pathogen. The key findings were that there were no gonococcal isolates resistant to ceftriaxone, the first-line treatment, reported in GRASP in 2014, and 0.3% of gonococcal isolates routinely tested in primary diagnostic laboratories and reported to SGSS in 2014 were resistant to ceftriaxone. Resistance to azithromycin in GRASP isolates has decreased from 1.6% in 2013 to 1.0% in 2014. Of concern is that in 2015, the Sexually Transmitted Bacterial Reference Unit (STBRU) reference service detected an outbreak of 14 cases of high level azithromycin resistant *N. gonorrhoeae* in heterosexual patients which emerged in Leeds, but with all isolates susceptible to ceftriaxone.

Resistance to cefixime has declined across all sexual orientation sub-groups from 5.1% in 2013 to 1.4% in 2014, with 0.4% of isolates reported in SGSS being resistant to cefixime in 2014. Ciprofloxacin resistance remains high with 37.3% of isolates in GRASP and 29.6% of isolates reported in SGSS resistant in 2014. No isolates in GRASP and 0.4% of isolates reported in SGSS were resistant to spectinomycin in 2014.

The proportion of highly sensitive isolates, organisms whose growth is inhibited by a Minimum Inhibitory Concentration (MIC) of ≤0.002 mg/L, has slightly increased compared to the previous year. However, the 2014 MIC distribution remains higher than was seen from 2007 to 2012 (Figure 10).

Figure 10: Percentage of gonorrhoea inhibited by ceftriaxone Minimum Inhibitory Concentration (MIC) (mg/L); 2007-2014



This figure shows that in 2007 about 52% of gonorrhoea isolates were inhibited by a MIC dose of ceftriaxone of concentration less than .002, whereas by 2014 the figure was only about 27%. In 2007 less than 5% of gonorrhoea isolates were inhibited by a MIC of .03 or greater but this has increased to around 10% in 2014.

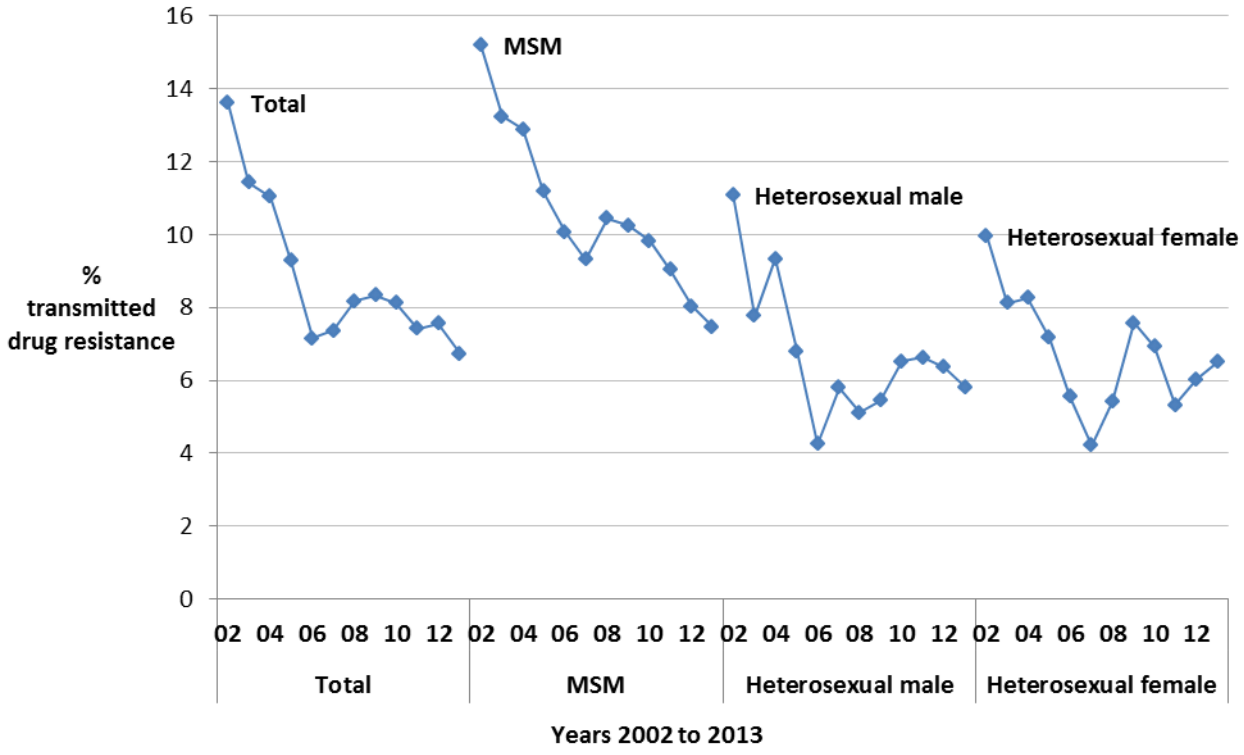
Antiviral resistance

HIV

Increased use of antiretroviral drugs has led to an increase in the incidence of infections that have developed resistance. Virological failure, defined by a viral load criterion, occurring in HIV patients receiving antiretroviral therapy (ART) is often the point at which testing for mechanisms for drug resistance occurs. These individuals can transmit their drug resistant virus to others, an event which is known as transmitted drug-resistance (TDR). TDR is of particular concern as it reduces the options available for first-line treatment.

The total HIV-1 TDR rate estimated from treatment-naïve individuals in the UK has steadily declined from its peak in 2002 at 13.6% (95% confidence interval: 11.3-16.3%) to 6.6% (95% confidence interval: 5.8-7.5%) in 2013 as shown in Figure 11 (adapted from [26]). The prevalence of TDR has always been higher in men who have sex with men (MSM) than heterosexuals. Of the mutations observed in 2013, 3.2%, 3.0%, and 1.6% had one or more mutations associated with the inhibitors NRTI, NNRTI, and PI, respectively. However, most of the recently observed TDR mutations, especially against NRTIs and PIs, are against old drugs no longer used for first-line therapy. These mutations result from sustained transmission among treatment-naïve individuals and have little impact on current recommended first-line therapy [97; 98].

Figure 11: Transmitted Drug-Resistance prevalence trends by risk group 2002 to 2013



The persistence of mutations within individuals has been studied by Castro et al [27]. They studied 313 patients in whom TDR mutations were detected at their first resistance test and who had a subsequent test performed prior to receiving ART. They found that the estimated rate of loss of mutations was 18 (95% confidence interval: 14–23) per 100 person-years of follow-up. (Equivalently one patient with a mutation will on average take 6 years to lose that mutation). However, there was considerable variation in persistence between mutations.

Hepatitis C Virus (HCV)

For HCV there is limited available literature of mutations causing drug resistance, those available being small studies in treatment naive patients. A paper by Beloukas et al [28] provides estimates of the prevalence of the Q80K polymorphism in the HCV NS3 enzyme which reduces susceptibility to novel protease inhibitors. The polymorphism occurred in 44 of 238 subjects (18.5%, 95% confidence interval: 13.6–23.4%), with an estimated prevalence of 27.1% in North West England compared to 14.9% in the South East. Among the 44 subjects with Q80K, four had one additional major NS3 resistance associated mutation, these being V36L and V55A.

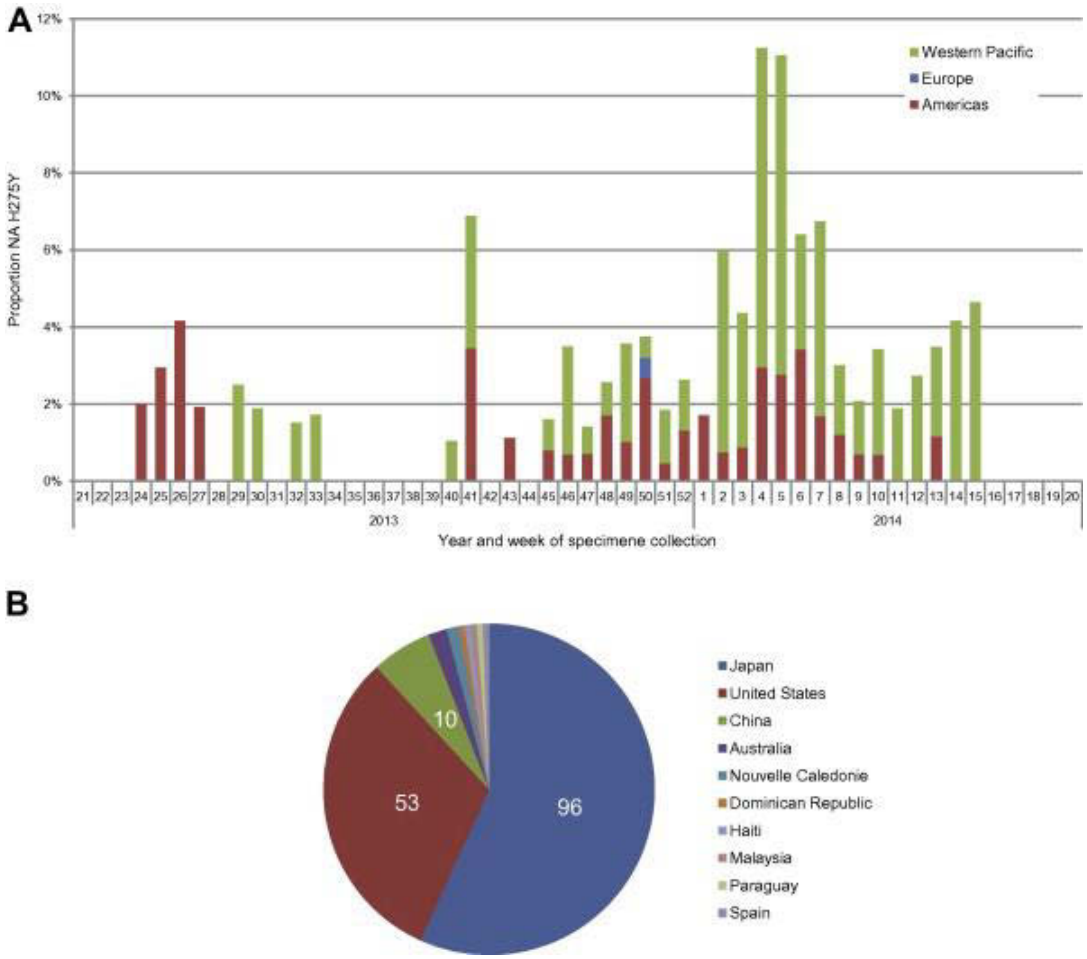
A study by McCormick [29] investigates mutations in the non-structural 5A (NS5A) protein of HCV. This is a multifunctional phosphoprotein involved in regulation of viral replication and virion assembly. NS5A inhibitors targeting domain I of NS5A protein have demonstrated high potency and pan-genotypic antiviral activity, however they possess a low genetic barrier to resistance. The authors found that amino acid substitutions associated with moderate to high level resistance to NS5A inhibitors were detected in 2/42 (5%) HCV-1a, 3/23 (13%) HCV-1b, 4/26 (15%) HCV-2, 1/24 (4%) HCV-3 and 1/23 (4%) HCV-4 infected patients who had not been treated with NS5A inhibitors. They concluded that primary resistance mutations associated with resistance to first generation NS5A inhibitors were observed in all genotypes, albeit at low frequencies.

Influenza

Takashita et al [30] provide a comprehensive view of antiviral resistance to neuraminidase inhibitors (NAIs) used for the treatment and prophylaxis of influenza. The report contains results supplied by four World Health Organization (WHO) Collaborating Centres for Reference and Research on Influenza and one WHO Collaborating Centre for the Surveillance, Epidemiology and Control of Influenza (WHO CCs). A total of 10 641 viruses collected by WHO-recognized National Influenza Centres between May 2013 and May 2014 were examined to determine 50% inhibitory concentration (IC50) data for the NAIs: oseltamivir, zanamivir, peramivir and laninamivir. Approximately 2% (n = 172) showed highly reduced inhibition (HRI) against at least one of the four NAIs, commonly oseltamivir, while 0.3% (n = 32) showed reduced inhibition (RI). Those showing HRI were A(H1N1)pdm09 with NA H275Y (n = 169), A(H3N2) with NA E119V (n = 1), B/Victoria-lineage with NA E117G (n = 1) and B/ Yamagata-lineage with NA H273Y (n = 1). Conversely, approximately 98% of circulating viruses tested during the 2013–2014 period were sensitive to all four NAIs.

Figure 12 (reproduced from [30]) shows the specimen collection timing and geographic distribution of 169 neuraminidase (NA) H275Y containing A(H1N1)pdm09 viruses. Figure 12A is the proportion of the total 5 152 NA H275Y containing A(H1N1)pdm09 viruses tested phenotypic at the WHO CCs by week and region. Figure 12B is the distribution of NA H275Y containing A(H1N1)pdm09 viruses tested phenotypic and genotypic by country.

Figure 12: Specimen collection timing and geographic distribution of 169 neuraminidase (NA) H275Y containing A(H1N1)pdm09 viruses



In 2008, prior to the 2009 A(H1N1) pandemic, the former seasonal H1N1 virus acquired the H275Y mutation associated with oseltamivir and circulated globally, with 100% of H1N1 detections being resistant by early 2009 [93]. A(H1N1)pdm09 viruses with this same mutation have emerged without link to treatment, and caused small outbreaks on several occasions in the past 5 years [94; 95] raising the concern that oseltamivir resistant A(H1N1)pdm09 are transmissible and could circulate more widely.

A previous report [31] of resistance testing to oseltamivir in influenza viruses isolated in the United Kingdom indicated a higher proportion of resistance than found in Europe [30]. This study found around 1% of isolates to be resistant (Table 3).

Table 3: Incidence rates of oseltamivir-resistant influenza A(H1N1)209 virus infection, United Kingdom

Setting	May 09 – Apr 10 Tested	May 09 – Apr 10 Resistant	May 09 – Apr 10 % resistant	May 10 – Jan 11 Tested	May 10 – Jan 11 Resistant	May 10 – Jan 11 % resistant
Community	1 098	0	0.0	364	3	0.8
Hospital	4 489	45	1.0	2 500	24	1.0
Total	**5 587**	**45**	**0.8**	**2 864**	**27**	**0.9**

Antifungal resistance

The first comprehensive analysis of antifungal resistance by PHE was made available at the IDWeek 2015 conference. Previously reporting of invasive mycoses in England has been limited to candidaemia, specific patient subgroups (e.g. neonates) and *ad hoc* reviews. The widespread introduction of antimicrobial susceptibility testing together with new guidelines on testing for resistance to antifungal agents (AF) [32; 33] is increasingly facilitating resistance testing through routine laboratory surveillance.

Table 4: Antifungal susceptibility results of the most frequently reported invasive fungal species; England 2014

Specific Genera	Total	Amphotericin B % tested	Amphotericin B % resistant	Azole % tested	Azole % resistant	Echinocandins % tested	Echinocandins % resistant
Aspergillus	353	3	9	3	0	1	0
Candida	5 211	14	2	19	15	14	2
Cryptococcus	52	33	12	44	22	4	100
Mucor	2	50	0	50	100	0	---
All Genera	**5 684**	**13**	**3**	**17**	**16**	**12**	**3**

The number of reported invasive fungal infections (defined as isolates taken from a normally sterile site) and the proportion identified to species level in the Second Generation Surveillance System (SGSS) increased from 4 869 (57% identified to species level) to 6 231 (59%) between 2010 and 2014. *Candida* spp. (20 745; 88%) was the most commonly reported genus across the five years, followed by *Aspergillus* spp. (1 492; 6%), *Pneumocystis* spp. (495; 2%) and *Cryptococcus* spp. (275; 1%). There has been an increasing number of laboratories reporting AF susceptibility test results over the past five years from 77% in 2010 to 81% in 2014. The proportion of invasive mycoses reported with AF test results has also increased from 10% in 2010 to 17% in 2014. In 2014, the highest number of AF tests were reported for *Candida* spp. (983; 19%), *Cryptococcus* spp. (23; 44%) and *Aspergillus* spp. (11; 3%) isolate reports. Table 4

presents the results of AF testing for invasive fungal isolates reported to SGSS. These results are heavily dominated by testing of *Candida* isolates and for most genera the numbers tested are currently too small to obtain any meaningful understanding of antifungal resistance. Table 5 and

Table **6** show the antifungal susceptibility of isolates from candidaemia and *C. albicans fungaemia* cases in England, Wales and Northern Ireland between 2010 and 2014.

A more detailed analysis of the reported *Candida* spp. is provided in the Health Protection Report weekly [34]. Over the last five years, the proportion of candidaemia reports with susceptibility testing data has increased in England, Wales and Northern Ireland, from 20% in 2010 to 44% in 2014. However the proportions varied geographically, with reporting for one of the five listed antifungal agents ranging from 14% in the Thames Valley region (5/36) to 80% in Cheshire and Merseyside (63/79).

Table 5: Antifungal susceptibility of isolates from candidaemia cases (England, Wales and Northern Ireland); 2010 to 2014

Antifungal agent	2010 No. tested	2010 % res.	2011 No. tested	2011 % res.	2012 No. tested	2012 % res.	2013 No. tested	2013 % res.	2014 No. tested	2014 % res.
Total	**1 712**	**-**	**1 758**	**-**	**1 726**	**-**	**1 712**	**-**	**1 638**	**-**
Amphotericin B	237	1%	377	1%	477	1%	539	1%	557	2%
Caspofungin	138	5%	185	6%	339	3%	474	4%	533	2%
Fluconazole	316	15%	430	18%	568	10%	621	11%	694	14%
Flucytosine	226	5%	326	3%	418	5%	458	3%	472	3%
Voriconazole	264	2%	396	4%	513	3%	564	4%	594	5%

Table 6: Antifungal susceptibility of isolates from *C. albicans* fungaemia cases (England, Wales and Northern Ireland); 2010 to 2014

Antifungal agent	2010 No. tested	2010 % res.	2011 No. tested	2011 % res.	2012 No. tested	2012 % res.	2013 No. tested	2013 % res.	2014 No. tested	2014 % res.
Total	**847**	**-**	**828**	**-**	**807**	**-**	**825**	**-**	**732**	**-**
Amphotericin B	112	<1%	158	<1%	212	<1%	255	1%	244	1%
Caspofungin	56	0%	73	1%	150	<1%	228	0%	230	<1%
Fluconazole	165	1%	189	3%	257	1%	294	2%	312	3%
Flucytosine	111	<1%	18	4%	188	4%	221	2%	210	1%
Voriconazole	126	0%	169	0%	231	<1%	278	<1%	265	1%

International perspective

Resistant pathogens threaten healthcare in every country, every day, and the risk of emergence and spread of the multiplicity of resistant pathogens needs to be continually assessed to minimise this threat. This assessment requires knowledge of how global spread occurs in order to understand how effective control can be maintained. For example, spread can occur by: international travel, inter-hospital transfers both within and between countries, victims from conflict zones and non-human reservoirs such as foodstuffs and animals. The effect of these threats is potentially different depending upon the pathogen, its propensity to colonise, and its mode of transmission.

A recent Nature article [35] describes the emergence and spread of a CPE across the globe. These resistant pathogens have spread to a number of countries over the past decade and it is likely that the vast majority, if not all countries across the globe have Enterobacteriaceae that exhibit resistance to carbapenems. In 2000, laboratory analysis of a *Klebsiella* isolate from a North Carolina hospital from 1996 identified a resistance gene that conferred resistance to carbapenems. By 2007 over 20% of *Klebsiella* isolated from New York hospitals had this particular resistance gene. In 2005 carbapenemase-producing bacteria had spread to Israel from where it spread to other Mediterranean and European countries. In a recent US paper [36] carbapenem resistance was seen in 4% of *E. coli* and over 10% of *K. pneumoniae* isolates associated with certain device-related infections.

The European Antimicrobial Resistance Surveillance Network (EARS-Net) collects data on antimicrobial resistance via a European-wide network of national surveillance systems. From information presented in [1], differences in numbers of resistant isolates across European counties are evident, with the proportion of resistance reported tending to be greater in southern European countries, potentially the result of differences in prescribing practices across Europe. Notable temporal trends include a decline in the proportion of *S. aureus* resistant to methicillin (MRSA) in many EU member states between 2004 and 2007 (and continuing since then), and a steady rise in *E. coli* isolates resistant to third-generation cephalosporins since 2002.

Figure 13: Proportion of Methicillin Resistant *Staphylococcus aureus* (MRSA) isolates in participating countries in 2014

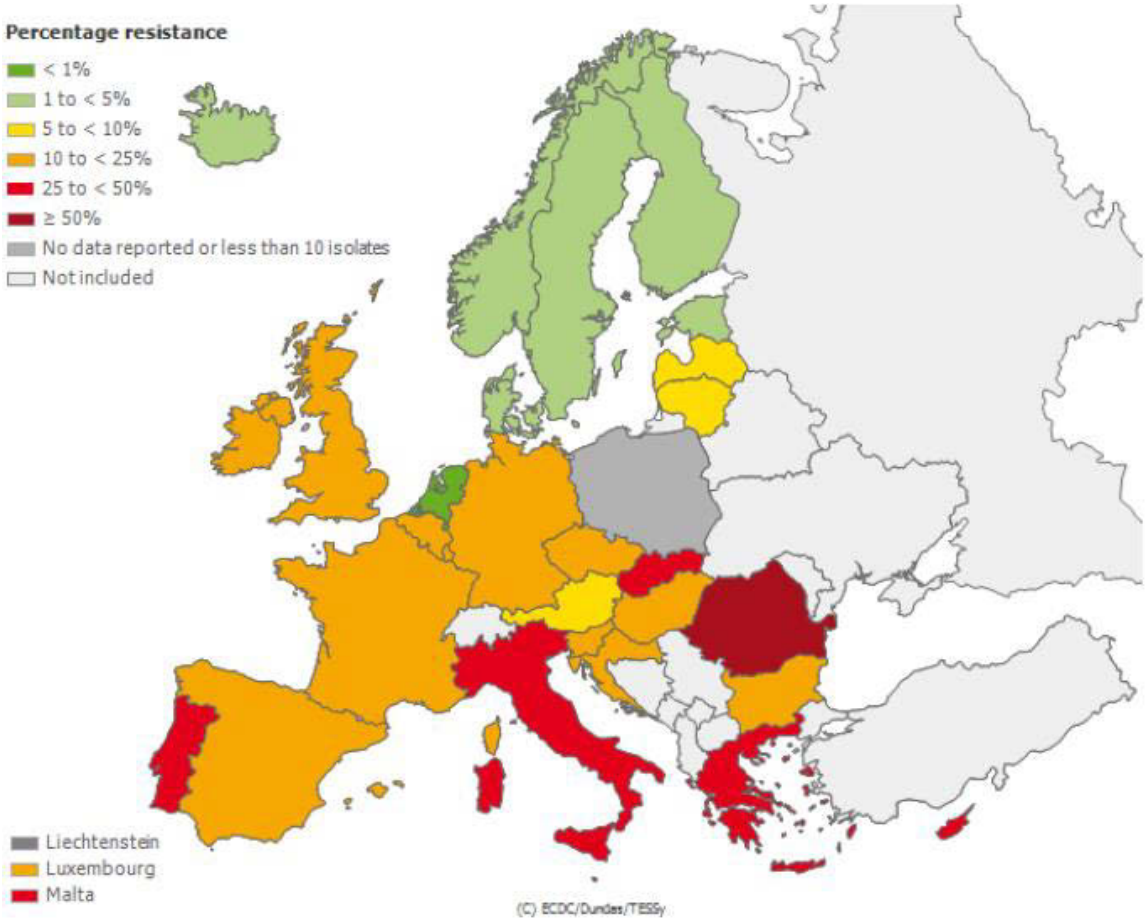


Figure 13 illustrates the variation in the observed proportion of MRSA resistance in specimens tested at laboratories within the EU and reported to ECDC (reproduced from [14]). This enables a comparative analysis of the levels of resistance to chiefly invasive bacteria across countries and time. Figure 13 and Figure 14 provide an illustration for MRSA, comparing the UK with other countries. These figures demonstrate the large variation in meticillin resistance in *S. aureus* observed across the countries of the EU and progress made in the United Kingdom at reducing the incidence of MRSA.

Figure 15 shows the variation across the EU and the growing resistance of *E. coli* to third-generation cephalosporins, with the UK usually lying within the median and upper quartile of the EU countries.

Figure 14 and Figure 15 below show the range of different countries' resistance rates across the years. The median rate across countries within a year is shown with amber bars and the UK values are shown by the red line. The box □ in each year shows the inter-quartile range of the resistance rates. So for each year approximately half the countries have a value within the box, a quarter are above the box and a quarter are below the box.

Figure 14: MRSA resistance rates across Europe 1999 to 2014

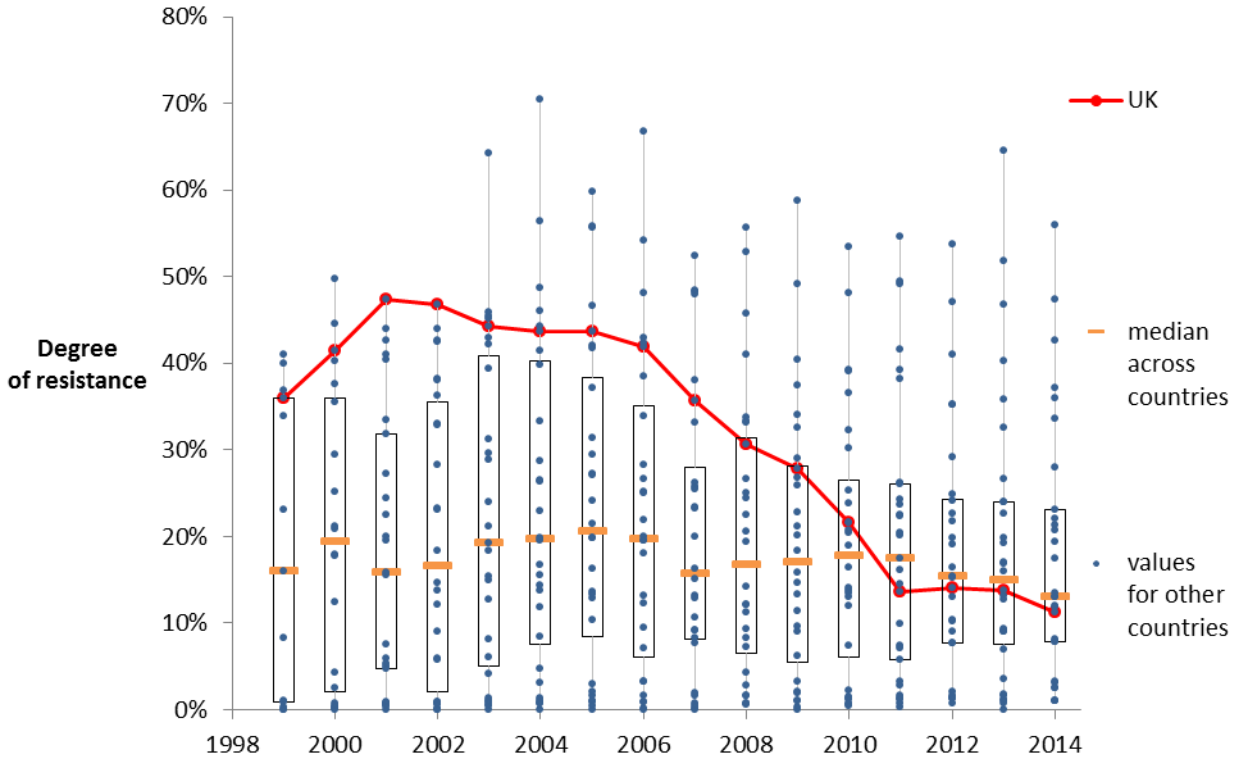


Figure 15: Third-generation cephalosporin resistance rates in *E. coli* across Europe 1999 to 2014

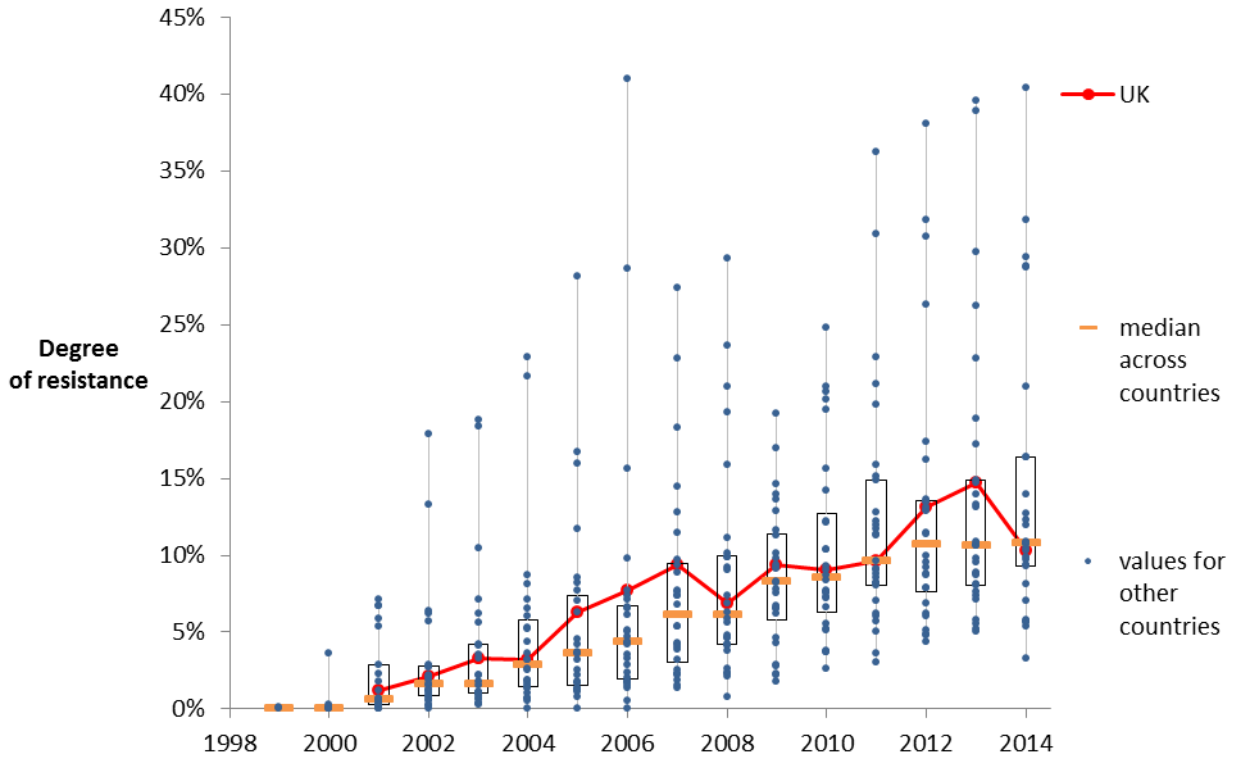
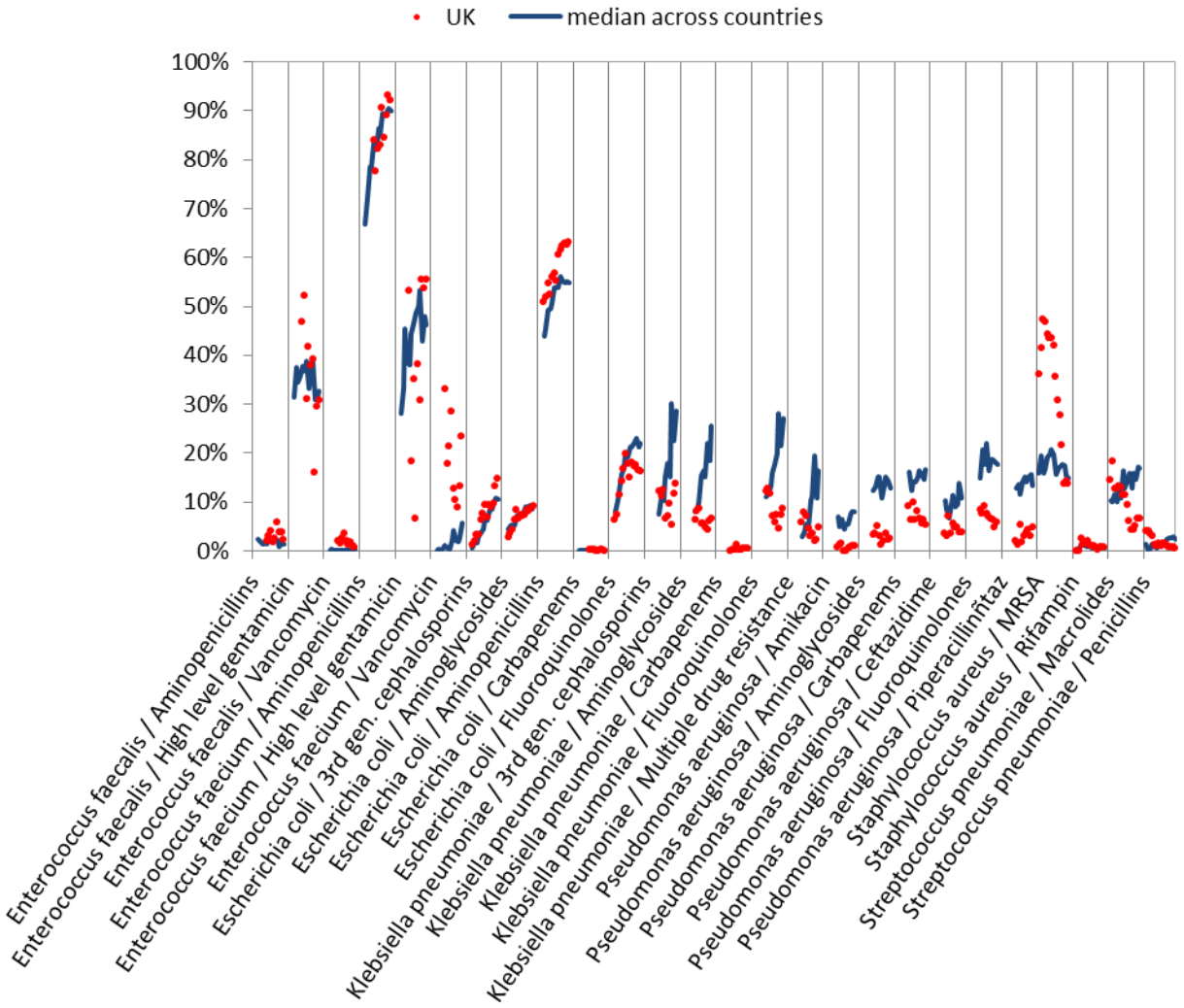


Figure 16 provides a visual summary of the variation in resistance for the UK for 26 drug-bug combinations. For most of them the estimated proportion of resistant isolates in the UK is similar to or below the EU median, with the notable exception of vancomycin resistance in *E. faecium*

where the UK is far above the median and MRSA where in the past the UK was well above the median.

Figure 16: Median Resistance levels across Europe in comparison with the UK for years in which at least 10 countries provided data on the bug drug combination shown 1999 to 2013



5. Burden of infection

The emergence and spread of infections caused by AMR pathogens has to be set in the context of the totality of infections. Certain organisms have a greater propensity to cause infections and these commonly isolated pathogens are of particular concern as they have the potential to cause a large burden of AMR infections.

English perspective

In England, Wales and Northern Ireland, the majority of microbiology laboratories voluntarily report clinically relevant infections to the Second Generation Surveillance System (SGSS). This provides some measure of the relative frequency of disease-causing pathogens. Over the period 1991 to 2011, inclusive, more than 9 million individual bacterial isolates were reported from 3 303 different organism phenotypes. Table 7 is an update from one published in [41] and provides the average weekly counts for the most commonly reported bacterial pathogens, for all specimen types, over the past five years.

Table 7: Mean weekly counts of top 10 most frequently report organisms received by the Second Generation Surveillance System Communicable Disease Reporting; 2011 to 2015, England, Wales and Northern Ireland

Organism name	Mean weekly count
Total (incl. all other organisms)	**39 565**
Chlamydia trachomatis	2 814
Escherichia coli	2 337
Staphylococcus aureus	2 152
Campylobacter sp	1 128
Haemophilus influenzae	1 118
Candida sp	595
Neisseria gonorrhoeae	576
Staphylococcus coagulase negative	543
Pseudomonas aeruginosa	432
Streptococcus pneumoniae	425
Enterococcus sp	380
Trichophyton rubrum	352
Coliform	347
Candida albicans (stellatoidea)	328
Hepatitis C	327

Table 8 is adapted from a recently published manuscript [42] and provides the frequency of reports to the voluntary laboratory reporting system (LabBase2) between March 2007 and May 2012 of selected organisms more likely to cause healthcare associated infections (HCAI). *S. aureus* made up nearly 30% of reported laboratory isolates and *E. coli* just over 20%. However, selective reporting of particular specimen types is likely to result in under-reporting of urinary tract infections where *E. coli* are the most frequent causative pathogen.

Table 8: Frequency of bacterial isolates reported to LabBase2 that are most likely to cause healthcare associated infections between March 2007 and May 2012 (England, Wales and Northern Ireland)

Organism group description	Frequency	%
Staphylococcus aureus	510 600	29.95
Escherichia coli	367 304	21.54
Clostridium difficile	160 157	9.39
Enterococcus spp.	107 624	6.31
Streptococcus pneumoniae	100 221	5.88
Pseudomonas aeruginosa	73 925	4.34
Klebsiella spp.	51 410	3.02
Streptococcus Group B	46 251	2.71
Pseudomonas spp.	43 114	2.53
Mycobacterium spp.	42 288	2.48
Proteus spp.	40 912	2.4
Streptococcus Group A	34 451	2.02
Streptococcus Group C, D, G	26 950	1.58
Enterobacter spp.	23 465	1.38
Streptococcus - other beta haemolytic	21 722	1.27
Serratia spp.	8 978	0.53
Citrobacter spp.	8 415	0.49
Stenotrophomonas spp.	6 243	0.37
Bacillus spp.	4 986	0.29
Morganella spp.	4 441	0.26
Acinetobacter baumannii	2 617	0.15
Burkholderia spp.	1 209	0.07
Total (all organisms)	1 705 126	100

A National Point Prevalence Survey (PPS) was conducted in 2011 [12] to determine the burden of HCAI and antimicrobial usage in acute hospitals in England. A total of 52 443 patients were included, with 3 360 of these having a HCAI, a prevalence of 6.4% compared to 8.2% in 2006. Prevalence was highest in patients in the intensive care units (ICUs) (23.4%) followed by surgical wards (8.0%), as shown in Table 9 (adapted from [12]).

The next PPS survey will be conducted during 2016. Data collection will be undertaken in the latter part of the year with the report on the PPS due to be published in November 2017.

Table 9: Prevalence of healthcare associated infections by ward specialty

Ward/specialty	No. patients	% (95% confidence interval)	No. HCAI	Prevalence % (95% confidence interval)
Total	**52 443**	**100.0**	**3 360**	**6.4 (4.7-8.7)**
ICU	1 351	2.6 (2.3 - 2.8)	316	23.4 (17.3 - 31.8)
Surgery	11 088	21.1 (19.4 - 23.1)	893	8.0 (5.9- 11.0)
Other specialty	1 133	2.2 (2.0 - 2.4)	82	7.2 (4.9 - 10.7)
Paediatrics	2 742	5.2 (4.8 - 5.7)	185	6.7 (4.9 - 9.4)
Combination of specialties	10 639	20.3 (18.6 - 22.1)	614	5.8 (4.2 - 7.9)
Geriatrics	3 845	7.3 (6.7 – 8.0)	218	5.7 (4.1 - 7.9)
Medicine	17 010	32.4 (29.8 - 35.3)	942	5.5 (4.1 - 7.6)
Unknown	291	0.6 (0.5 - 0.6)	13	4.5 (2.4 - 8.36)
Psychiatry	39	<0.1 (0 - 0.1)	<5	-
Obstetrics and gynaecology	4 305	8.2 (7.5 – 9.0)	96	2.2 (1.5 - 3.2)

The most frequent HCAIs detected were respiratory tract, urinary tract and surgical site infections, as shown in Table 10 (adapted from [12]). One obvious limitation of prevalence studies is that many pathogens exhibit seasonality, particularly those affecting the respiratory and gastrointestinal tract. Indeed in the 2006 national prevalence survey 22.8% of all HCAI were gastrointestinal infections. The 2011 survey was performed in September to November, compared to February to May for the 2006 survey. However, the impact of *C. difficile* control measures between the two surveys will also have impacted on the reduction observed in gastrointestinal infections.

Translating these national HCAI prevalence estimates to an overall burden is problematic. In order to estimate the clinical and economic burden of infections in hospitals, it is primarily the outcomes of mortality and additional stay associated with these infections that are of interest and that require quantification [43; 44]. However, such quantification studies tend to be for particular organisms and in single centres, thus necessitating meta-analyses to estimate any statistically significant impact [45; 46]. In addition, there are a number of methodological issues with these methods of estimations.

Table 10: Distribution of healthcare associated infections types from the 2011 Point Prevalence survey [12]

Type of HCAI group	Number	HCAI Prevalence % (95% confidence interval)
Total	**3 506**	**-**
Pneumonia/LRTI	798	1.5 (1.4 - 1.6)
Urinary tract infections	605	1.2 (1.1 - 1.2)
Surgical site infections	551	1.1 (1.0 - 1.1)
Clinical sepsis	367	0.7 (0.6 - 0.8)
Gastrointestinal infections	309	0.6 (0.5 - 0.7)
Bloodstream infections	255	0.5 (0.4 - 0.5)
Unknown	232	0.4 (0.4 - 0.5)
Skin and soft tissue infections	152	0.3 (0.2 - 0.3)
Eye ear nose or mouth infections	98	0.2 (0.2 - 0.2)
Bone and joint infections	50	0.1 (0.1 - 0.1)
Catheter-related infections	26	<0.1 (0.0 - 0.1)
Cardiovascular system infections	24	<0.1 (0.0 - 0.1)
Reproductive tract infections	20	<0.1 (0.0 - 0.1)
Central nervous system infections	19	<0.1 (0.0 - 0.1)

International perspective

The true global burden of healthcare-associated infections (HCAI) remains unknown because of the difficulty in gathering reliable data; many countries lack surveillance systems, especially for monitoring HCAI, and those that have them struggle with the complexities and lack of uniformity associated with diagnosis [47].

The WHO produced a report on the burden of endemic HCAI worldwide in 2011, reporting available data on HCAI endemic burden in high, middle and low income countries and their impact [48]. From this, the following findings can be highlighted: prevalence in hospitalised patients was 7% in developed countries and 10% in developing countries; urinary tract infection is the most frequent HCAI in high-income countries; surgical site infection is the leading infection in settings with limited resources, affecting up to one-third of operated patients which is up to nine times higher than in developed countries; in high-income countries approximately 30% of patients in intensive care units (ICU) are affected by at least one healthcare-associated infection.

6. Burden of resistance

The Burden of Resistance and Disease in European Nations Project (BURDEN), which ran from January 2007 to December 2009, provides information on the burden of disease and the costs attributable to resistant infections caused by antimicrobial pathogens in member states and accession countries of the European Union. Clinical studies carried out as part of BURDEN estimated the impact of antibiotic resistance associated with *S. aureus* and *E. coli*. Specifically, this research estimated the excess bed days and deaths associated with MRSA and strains of *E. coli* resistant to third-generation cephalosporins in 13 European hospitals [49; 50].

Further research using trends established by EARS-Net extrapolated the impact of AMR infection in these clinical studies within specific hospitals to a regional level using nationally reported rates of AMR bacteraemia [51]. For the 31 participating countries overall they estimated that in 2007, 27 711 episodes of MRSA bloodstream infections (BSIs) were associated with 5 503 excess deaths and 255 683 excess hospital days. Similarly, 15 183 episodes of bacteraemia caused by cephalosporin-resistant *E. coli* were associated with 2 712 excess deaths and 120 065 excess hospital days.

These data were used to estimate the trajectories for MRSA and third-generation cephalosporin-resistant *E. coli* prevalence until 2015, using these trajectories the authors suggested that the number of BSIs caused by third-generation cephalosporin-resistant *E. coli* were likely to rapidly increase, outnumbering the number of MRSA BSIs in the near future. In 2014 there were reported 35 646 *E. coli* bacteraemias reported to the mandatory data collection system [99]. For 2014, *E. coli* resistance level to cephalosporin was estimated as 11.6% ([11] web appendix 1). These figures combine to estimate about 4 100 bacteraemias caused by cephalosporin resistant *E. coli*. This figure is 5 times the 784 MRSA bacteraemia for 2014 [99].

Data from NHS England Hospital Trusts

In 2014 there were 107 000 bacteraemia reported by laboratories in England, Wales and Northern Ireland [100]. An estimated 57.5% of these were gram-negative [101]. From the 114 276 bacterial isolates reported in the voluntary system [101], and the 32 196 *E. coli* blood isolates reported in [102] we estimate that 30% of bacterial isolates from blood samples were from *E. coli*. *E. coli* was the most common cause of bloodstream infections in 2014 [11]. Resistance was common with, for example, resistance to third-generation cephalosporins seen in 11-12% of *E. coli* and *Klebsiella* spp ([11] web appendix 1). Resistance to carbapenems is also now being seen, with resistance reported in 11.5% of Pseudomonas ([11] web appendix 1) and for the specific carbapenem, ertapenem, 9% of *Enterobacter* spp [103].

AMR in community-acquired infections

The prevalence of AMR in the community is largely unknown, as the majority of infections seen by GPs are treated empirically. GPs may, on occasion, submit specimens to the hospital laboratory for microbiological investigation, including antibiotic susceptibility testing, but this usually involves patients who have failed one or more courses of antibiotic treatment. Although rates of resistance among bacteria isolated from specimens referred by GPs can be assessed, the rates are likely to be artificially high due to biased referral patterns.

Many of the studies of AMR in the community are focussed on particular groups of at risk individuals such as those in care homes or from a particular ethnic group. The findings, while providing some evidence of reservoirs of AMR in the population, may not apply to the general population. For example, Wickramasinghe [52] studied the community faecal carriage rates of CTX-M ESBL-producing *E. coli* in Birmingham. This study found a prevalence of CTX-M

carriage in the study population of 11.3%. They also found significant differences in carriage between European (8.1%) and the Middle Eastern / South Asian ethnic groups (22.8%), with software used to impute ethnicity from names.

7. Economic burden

The costs and economic impact of infections caused by AMR organisms and the costs and benefits of any successful interventions are challenging to estimate. Basic epidemiological questions surrounding transmission and the efficacy of interventions have yet to be answered robustly, particularly for Gram-negative AMR bacteria, making it difficult to provide useful health economic assessments, given that both sides of the cost-effectiveness equation are uncertain. Direct costs associated with AMR infections are likely to arise through additional length of stay, loss of bed days through ward closures, additional or more costly antibiotic treatment, additional investigations, and health losses (or quality of life) due to hospital stay, infection and mortality.

A number of studies have attempted to estimate the additional cost and resource use of resistant organisms, most commonly through comparison of infections with resistant and susceptible strains. Twenty-five such studies were reported by Smith and Coast [53; 54], where a variety of drug/bug combinations were represented. In addition to these, there were found: one study examining *Pseudomonas aeruginosa* [55]; three examining *E. coli* BSI alone [51; 56; 57]; two studies examining ESBL *Klebsiella* spp. [58; 59]; and five examining mixed species of Enterobacteriaceae including *E. coli*, *Klebsiella* spp., or *Proteus* spp. infections [57; 60-63]. Overall Smith and Coast [53] reported that estimates of the additional cost of resistance varied widely, from less than £3 to more than £20 000 per patient episode in hospital.

There are a number of issues associated with investigating the economics of AMR, and in particular AMR HCAI. A fundamental issue is that estimating the economic burden of resistance requires prevalence estimates (to translate cost per patient episode or per AMR infection to an overall burden), but these are often not as easy to obtain as might be suspected: definitions are often not clear cut, and the bug/drug combinations to be measured are also unclear. Many studies, particularly those using findings from surveillance of AMR, present the *proportions* of resistant pathogens, and while this has some utility, it cannot be easily converted into the *number* of incident or prevalent cases of infections with an AMR pathogen.

Additional length of stay due to infection

As suggested by Graves et al [64], estimating the number of bed-days saved (through preventing infection or not closing wards) and valuing them in monetary terms is a powerful method for describing much of the economic cost (to hospitals) of HCAIs. Quantifying excess hospital stay is essential for assessing how many bed-days might be gained from prevention, and subsequent health economic analyses that inform the allocation of resources to infection control programmes or to get a grasp on the overall burden of resistant organisms [57]. However, there are problems associated with the estimation of additional length of stay and, similarly, with attributable mortality.

Many studies that attempt to estimate the clinical and economic impact of healthcare infections (including those associated with AMR) fail to account appropriately for length of stay and risk of death [65]. This is an extremely important methodological issue that can severely bias estimation of these key economic drivers. Blot et al [66] found that the data on the impact of drug resistance in nosocomial infections were conflicting and depended on the way confounding variables were accounted for. For example, additional length of stay due to infection has been most extensively studied for MRSA yet estimates range from 3-20 days due to differences in accounting for confounders, time-dependent effects and endogeneity.

Alternative modelling and statistical techniques (which account for the time dynamic nature of the process) have been applied to hospital data to quantify additional length of stay or attributable mortality associated with nosocomial pathogens [65; 67-70].

Of note are the studies from the aforementioned BURDEN project [49-51; 71] because they marked an important development in the estimation of the impact of AMR infections as their design and analysis accounted for confounding demographic and health characteristics associated with AMR BSI. Through these studies the total costs attributable to excess hospital stays were estimated to be EUR 44 million for MRSA and EUR 18.1 million for strains of *E. coli* resistant to third-generation cephalosporins.

Underestimating the problem

In the previously mentioned rapid review by Smith and Coast [53], the authors demonstrated that studies typically limited their estimates to the cost of extra treatment of a resistant infection compared with susceptible infection, and that none considered the costs (to society) in a worst case scenario setting where antibiotics are no longer a viable option. The authors suggest that the true extent of the problem of antibiotic resistance remains unrecognised because it '*has fallen victim to evidence-based policy making, which prioritises health problems by economic burden and cost-effectiveness of interventions'*. With current estimates of economic burden failing to consider the cost of the worst case scenario, the true cost of resistance remains a severe underestimate.

International perspective

The ECDC/EMEA Joint Technical Report [1] estimated that in 2007 MDR in bacterial infections in the EU, Norway and Iceland resulted in extra healthcare costs and productivity losses of at least EUR 1.5 billion each year. To arrive at this figure, extra in-hospital costs were estimated at more than EUR 900 million, based on the number of extra hospital days, with outpatient care costs estimated at about EUR 10 million. The productivity losses due to absence from work of infected patients were estimated at more than EUR 150 million, each year, and productivity losses due to patients who died from their infection were estimated at about EUR 450 million each year.

In the US, the Estimates from the Impact of antibiotic resistant bacteria: A report to the U.S. Congress in 1995 [72] estimated the annual additional cost for treating HCAIs caused by six species of AMR bacteria to be at least US $1.87 billion in 2006.

8. Patient outcomes and excess mortality due to infection

There are few reliable studies of the effect on patient outcomes following an infection with an AMR pathogen. A recent letter [73] describes a patient case study where a transrectal ultrasound (TRUS)-guided prostate biopsy was planned. A pre-biopsy rectal swab grew a fluoroquinolone-resistant *E. coli* that was also resistant to penicillins, extended-spectrum cephalosporins, carbapenems, piperacillin / tazobactam, aztreonam, aminoglycosides and trimethoprim/sulfamethoxazole. The limited treatment options had an infection occurred, along with the patient's advanced age and the low-grade nature of his carcinoma led to a decision not to proceed with biopsy. This is an extremely common procedure, with over 1 000 000 such biopsies performed each year in the USA.

A study of uncomplicated urinary tract infections caused by *E. coli* in the community by McNulty et al [74] found that the median time to resolution of symptoms increased from four to seven days in women with a trimethoprim-resistant strain. In this study, approximately 50% of women who reconsulted their GP had a pathogen resistant to the empirical trimethoprim prescription.

A recent study of carbapenem- and multiply-resistant *Acinetobacter baumannii* by Livermore et al [75] reviewed clinical outcomes in relation to antibiotic treatment for 166 consecutive patients infected or colonised with these organisms at 18 London hospitals. Survival rates among infected and colonised patients were similar at 68% and 67%, indicating little attributable mortality. Poorer outcomes were observed among ICU-infected patients and those with pulmonary infection or bacteraemia, whereas unexpectedly trauma patients had significantly better outcomes. There was little association between outcome and therapy with colistin and/or tigecycline except that, among patients with respiratory infection, 12 of 15 treated with intravenous colistin alone had a poor outcome compared with 1 of 8 whose therapy included nebulised colistin.

Estimating deaths attributable to AMR is problematic. Patients most susceptible to AMR infections are often those with co-morbidities. Whether the death was directly attributable to an AMR bacterial infection or other co-existing conditions, complicated by the AMR, is often unclear.

Results from multiple studies have been pooled in meta-analyses to estimate attributable mortality estimates: Cosgrove et al [45] for MRSA and Schwaber & Carmeli [46] for ESBL *E. coli* infection. Three original studies estimated the impact of AMR on mortality (Lautenbach et al [55] de Kraker et al. [51]; Schwaber & Carmeli [46]), of these only the previously described study by de Kraker et al [51] used rigorous statistical analysis of 30-day and in-hospital mortality to estimate the excess risk of mortality due to an AMR infection.

The ECDC/EMEA Joint Technical Report [1] estimated in 2007 that around 25 000 patients die each year in the EU, Norway and Iceland due to MDR in infections caused by five specific bacteria. Given the relative population size of the UK to the whole of Europe, an estimate of 3 000 deaths from AMR in the UK for these bacteria could be extrapolated from this report.

Much of the published literature describes studies performed in specific high-risk patient groups where it is not surprising that most find little attributable mortality. A recent Australian study [76] described a strong association between elevated vancomycin MIC and mortality for MRSA bacteraemia, the estimated odds ratio of mortality being 2.59.

9. Interventions

Interventions against AMR bacteria may aim to reduce the transmission of existing resistant strains, or prevent the development of further resistance. Arguably, hand hygiene has been the primary strategy employed aiming to reduce transmission, and antibiotic stewardship the cornerstone for the slowing or prevention of resistance development.

While many HCAI and AMR infection prevention and control strategies exist (primarily for the hospital setting), evidence of their effectiveness from well conducted trials is lacking. There remains uncertainty over the efficacy of infection control strategies for a number of reasons. Results from trials may be contradictory, and often evaluate different and therefore incomparable, intervention strategies. The effectiveness of strategies may differ between settings, for example by prevalence or specialty, and it is not obvious how findings should be generalized. In addition, often many infection prevention and control interventions are employed at the same time, making it difficult to determine which components are having an effect.

It is extremely rare that interventions are rigorously assessed in clinical trials, and those that have been are for general infection prevention measures not specifically targeted against AMR pathogens. However, while there are few clinical trials of specific interventions against AMR and HCAI, the overall infection prevention and control literature is vast. Selected examples from the published literature, many of which are systematic reviews across the broad range of interventions, are provided in this section.

Antimicrobial stewardship programmes are increasingly being advocated as a means of improving the quality of prescribing [77]. Recent Cochrane reviews evaluating stewardship interventions include: that by Davey et al [78] assessing the evidence for interventions aiming to improve antibiotic prescribing practices for hospital inpatients; the assessment of evidence on prophylactic use of antibiotics to reduce morbidity and mortality in ventilated newborn infants by Inglis et al [79]; and the assessment of antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults in intensive care by Liberati et al [80].

In order to address the need for increased understanding of both antibiotic usage and resistance patterns, the English Surveillance Programme for Antimicrobial Utilization and Resistance (ESPAUR) was established in 2013. The Programme is bringing together antimicrobial surveillance in both primary and secondary care settings, developing quality measures and methods to monitor unintended outcomes of antimicrobial stewardship and behaviour-based interventions.

Hand hygiene as an intervention has been subject to many studies and therefore has a large literature. Stone et al [81] attempted to assess the effect of increased hand hygiene procurement used in NHS trusts in England and Wales, on the observed reduction in MRSA bacteraemia and *C. difficile* infection (CDI), accounting for other interventions. Associations between increased alcohol hand rub and reduced MRSA bacteraemia, and increased liquid soap use and reduced CDI were found. However, there were a number of limitations in this ecological study, particularly the inability to obtain data on mupirocin usage for decolonization of MRSA and antimicrobial prescriptions data, which is clearly associated with CDI. In an assessment of a behavioural intervention to improve hand hygiene compliance, Stone et al [82] found peer group audit and feedback significantly improved compliance, however effects waned towards pre-study levels over time. Both national and international guidance identifies hand hygiene as a key component in the reduction of HCAI [83; 84].

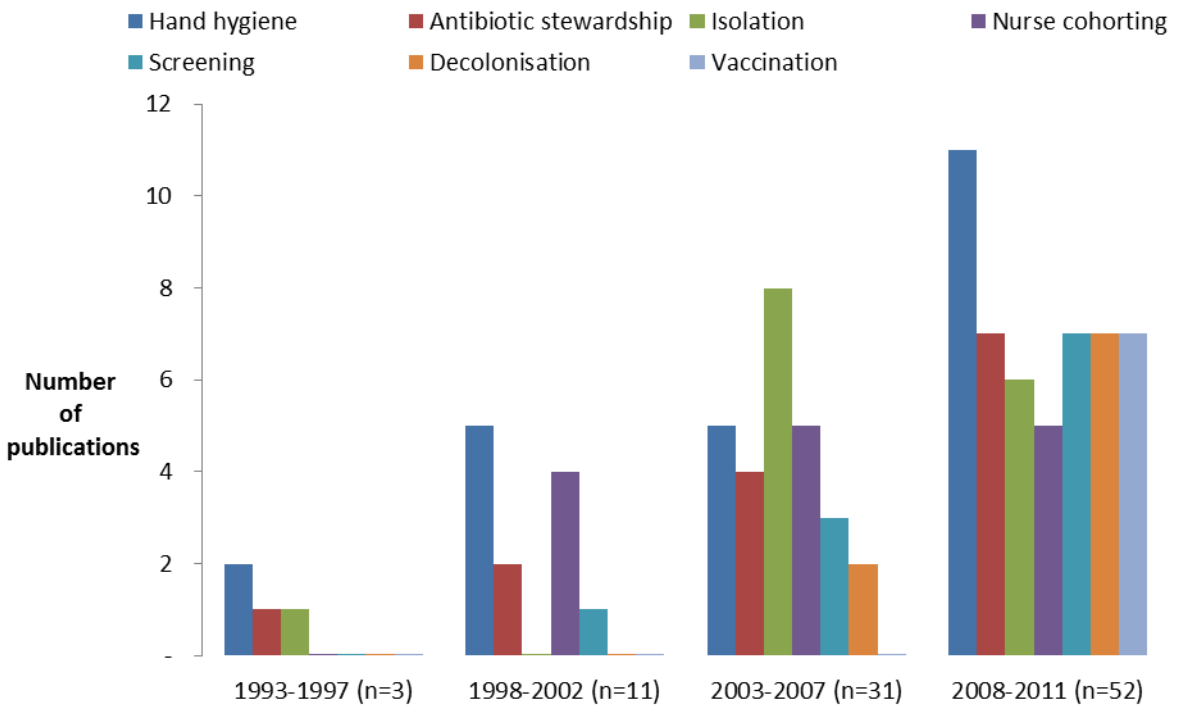
The majority of evidence for the importance of cleaning the healthcare environment in prevention of HCAIs (whether or not resistant) is observational; the systematic review by Dettenkofer et al [85] failed to show lower infection rates associated with routine disinfection.

Primarily due to the problems associated with MRSA over recent years, much of the evidence for intervention effectiveness focuses on staphylococcal infection prevention and control. For example, van Rijen et al [86] reviewed evidence for infection prevention through mupirocin use in nasal carriers. The authors concluded that prophylactic intranasal mupirocin significantly reduced the rate of post-operative *S. aureus* infections among surgical patients who were *S. aureus* carriers. Cooper et al [87] provide a systematic review of isolation measures in the management of MRSA and concluded that insufficient evidence existed to allow the role of isolation measures alone to be assessed.

There is a particular paucity of evidence of the effectiveness of interventions against Gram-negative bacteria, which arguably represent the most worrisome organisms currently [88; 96].

Enterobacteriaceae present a particular problem for control. While suppression of carriage (in the colon) may theoretically both reduce risk of infection for the patient themselves, and also reduce their potential for transmission to others, the beneficial effects of selective decontamination of the digestive tract (SDD) have largely been demonstrated through meta-analyses [89; 90], and would require use of the same decolonizing agents that would be used if therapy was needed e.g. polymyxins. Clearly there are major concerns regarding the non-therapeutic use of this 'absolute last resort' agent. However, in a multi-centre cluster-randomized cross-over trial [91], comparing SDD to oropharyngeal decontamination with antibiotics, absolute reductions in 28-day mortality were 3.5% and 2.9%, respectively, when compared with patients receiving standard care. Moreover, compared with standard care, decontamination was found to be associated with a 10% reduction in total systemic antibiotic use.

Figure 17: Model-based cost-effectiveness evaluations of interventions in the control of healthcare associated infections



Note that some publications did not cite any of the 7 interventions here, and some cited more than one.

In the absence of evidence from clinical trials, mathematical models have been increasingly used to evaluate the effectiveness and cost-effectiveness of infection prevention and control strategies. Between 1993 and 2013 there have been 97 publications utilising model-based cost-effectiveness to evaluate interventions to control HCAI (Figure 17 adapted from [92]). This provides an illustration of the proportionate distribution of the seven most commonly investigated interventions utilising a modelling framework. The number of such studies is steadily increasing over time with over half being performed in the most recent 4 years. Of interest is the fact the early studies concentrated predominately on hand hygiene and antibiotic stewardship, while in recent years similar numbers of studies have been performed across a wide range of interventions.

10. Sources of Data

There is a variety of sources of data from which the incidence and prevalence of infection caused by specific pathogens, the antimicrobial resistance of those pathogens, and the antibiotic prescribing data are available. At national and sub-national levels, PHE collects information on a variety of infectious diseases via a range of surveillance systems. Most of the surveillance systems are pathogen specific and not with the specific objective of understanding the emergence and spread of AMR. There are however, a few generic surveillance systems that do routinely collect antibiotic susceptibility test results. Some of the sources of available data for the study of AMR are listed in Table 11.

Table 11: Examples of available data sources

Sources	Description
England	
Public Health England data sources	
Communicable Disease Reporting (CDR)	This system of reporting by laboratories across England forms the basis of much of PHE's infectious disease surveillance. All laboratories carrying out NHS work should report to the CDR system. Laboratory records are entered onto CoSurv and data is subsequently sent to the Regional Epidemiology Units where it is validated before being submitted to LabBase2 (PHE Colindale).
AmSurv	Antimicrobial sensitivity/resistance bacterial isolates data. Includes both hospital and community samples. Amsurv databases use the AmWeb tool to enable users to obtain descriptive analysis of the collated data.
SGSS	The Second Generation Surveillance System holds both the CDR and AmSurv data sources.
Modular Open Laboratory Information System (MOLIS)	MOLIS is the Laboratory Information Management System (LIMS) at PHE Colindale. This system collects and manages information for all routine reference work.
Data Capture System	Web-based reporting tool for hospitals to report mandatory data, such as MRSA, MSSA, GRE and E. coli bacteraemia, CDI and denominator data.
Surgical Site Infection Surveillance Service	Web-based data entry tool supporting the mandatory and voluntary reporting of SSI.
C. difficile Ribotyping Network	Reference laboratory for *C. difficile* to refer those isolates that meet specific criteria.

Respiratory DataMart System (RDMS)	Laboratory-based virological surveillance system in England. Data collected from routinely tested clinical respiratory samples for a range of respiratory viruses including influenza, respiratory syncytial virus, rhinovirus, parainfluenza, adenovirus and human metapneumovirus from the reference and regional laboratories, and some NHS laboratories in England.
General Practice data sources	
RCGP	Since 1998 - “all consultations”, fully automated, >100 GP practices, covering population of >900 000. Antibiotic resistance surveillance data - National coverage Antibiotic exposure - EPR linked records
Clinical Practice Research Datalink (CPRD)	Primary care data are available online via CPRD GOLD (provides powerful disease and drug coding dictionaries and a fast query tool that DEFINES patient cohorts. An EXTRACT tool then enables, as specified, cuts of the data against a cohort or control group.) Both CPRD GOLD and SILVER will contain the details of all prescriptions, generics and/or branded products issued in primary. Information on formulation, strength and dosing instructions will also be available in both data sources.
EMIS	3 000 practices ‘live’, >39 million patient records Data Extraction Services - Selection of standard patient identifiable, pseudo-anonymised and anonymised extracts if the necessary approvals have been obtained.
The Health Improvement Network (THIN)	Routine practice data. Since 2003, 500+ ‘Vision practices’ have joined. Medical records of 11.1 million patients (3.7M active patients) covering 6.2% of UK population. PATIENT, MEDICAL (diagnoses), THERAPY: all prescriptions along with the date issued, formulation, strength, quantity, and dosing instructions, indication for treatment for all new prescriptions, and events leading to withdrawal of a drug or treatment. ADDITIONAL HEALTH DATA incl. laboratory results. POSTCODE VARIABLE INDICATORS CONSULTATION date, time and duration of consultation, STAFF.
Health and Social Care Information Centre (HSCIC) data sources	
Hospital Episode Statistics	Information on every NHS funded hospital admission and outpatient attendance in England.

General Practices Extraction Services	Information from general practice IT systems, therefore directly from patient records
iView - select, view and extract a range of prescribing data on online system	From April 2013 details of prescribing at CCG level in England, for each section of the BNF for each quarter of the year. Prior to April 2013 (changes to the structure of the NHS) data were available at PCT level. The data has three measures: number of items, net ingredient cost, and actual cost. Does not include: prescriptions written in hospitals/clinics that are dispensed in the community, prescriptions dispensed in hospitals, prescribing by dentists, private prescriptions.
ePACT	Hospital prescribing based on information systems at NHS Prescription Services and on data provided by the commercial company IMS Health. Uses ATC classification.
NHS England data sources	
care.data	Care Episode Statistics Information on every NHS funded hospital admission and outpatient attendance in England.
NHS Prescription Services **ePACT.net**	Access to previous 60mths prescribing data held on NHS Prescription Services' Prescribing Database. ePACT provides data on prescriptions written in primary care / hospitals but dispensed in the community. Updated on a monthly basis, includes: Prescribing totals by prescribers at all BNF levels, Prescribing from non-medical prescribers, Patient list sizes, Average Daily Quantities and Defined Daily Doses, Prescribing On Behalf Of PCT/Practice, Dispensing contractor name and address Prescription Services Portal: standard reports: Indicators and (QIPP) comparators, Measures: Items, ADQs, DDDs, patient weightings.

IMS Health data	IMS Health collects and collates this data on a commercial basis. De-identified patient demographics Drug name Dosing information Whether the prescription is new or a refill The physician's identity and specialty Hospital Pharmacy Audit Index (HPAI) : Based on issues of medicines recorded on hospital pharmacy systems –>IMS Health each month electronically. HPAI monitors usage levels (quantities issued (packs)) by hospitals rather than purchases by Trusts. Uses ATC classification system.
Define / Rx-Info	Developed over 3+yrs. 160 Trusts (135 publishing). Data ownership remains with Trust, Rx-Info = processors. Data sources published to system: all hospital pharmacy systems, FP10 HNC data, Homecare data and outsourced outpatient. Drug use per inpatient bed is possible with granularity allowing analysis down to specialty, prescription type and date filtering
BSAC Bacteraemia Surveillance	Involves 20-25 sentinel clinical laboratories which each collect ten consecutive isolates taken from blood cultures considered to be clinically significant (20 consecutive isolates for S. aureus and E. coli).
Europe	
European Antimicrobial Resistance Surveillance Network (EARS-Net)	Managed by the European Centre for Disease Prevention and Control (ECDC). Participating laboratories send data to the country's data manager where it is uploaded onto The European Surveillance System (TESSy), a web-based system for collection, validation, cleaning, analysis and dissemination of data.
European Reference Laboratory Network for Human Influenza (ERLI-Net)	Managed by the European Centre for Disease Prevention and Control (ECDC). Participating laboratories upload all influenza surveillance data (weekly detections; antigenic and genetic analyses) including antiviral susceptibility data onto The European Surveillance System (TESSy), a web-based system for collection, validation, cleaning, analysis and dissemination of data.

11. Conclusions

This report is intended to provide an overview of the current evidence base in the area of AMR, containing information on relevant data, trends and literature. However, the field is fast-paced with a quickly emerging and developing evidence base therefore, while illustrating the current situation, the report is soon likely to become outdated.

While some forms of resistance such as MRSA have declined in the UK, others have been more difficult to overcome. Antimicrobial stewardship may be one of the key actions required to prevent increasing resistance. Even given effective stewardship, there is still a pressing need for the development of new antimicrobials.

For most pathogens there are currently effective antimicrobials, but a key message is the concern about the growing number of carbapenem resistant pathogens among the enterobacteriaceae family, including types of *E. coli* and *klebsiella.*

References

1. ECDC/EMEA Joint Working Group, 2009. The bacterial challenge: time to react. EMEA/576176, pp.13-42. Available from: http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf (last accessed 03 March 2016)

2. Chan M. Antimicrobial resistance in the European Union and the world. Keynote address, Combating antimicrobial resistance: time for action 14 March 2012. World Health Organization Director-General Programme. World Health Organization. Available from: http://www.who.int/dg/speeches/2012/amr_20120314/en/ (last accessed 03 March 2016)

3. Boucher HW, Talbot GH, Benjamin DK, Bradley J, Guidos RJ, Jones RN, Murray BE, Bonomo RA, Gilbert D, Infectious Diseases Society of America. 10×'20 progress—development of new drugs active against gram-negative bacilli: an update from the Infectious Diseases Society of America. Clinical infectious diseases. 2013 Apr 17:cit152.

4. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clinical Infectious Diseases. 2009 Jan 1; 48(1):1-2.

5. Hegstad K, Mikalsen T, Coque TM, Werner G, Sundsfjord A. Mobile genetic elements and their contribution to the emergence of antimicrobial resistant *Enterococcus faecalis* and *Enterococcus faecium*. Clinical microbiology and infection. 2010 Jun 1; 16(6):541-54.

6. Strasfeld L, Chou S. Antiviral drug resistance: mechanisms and clinical implications. Infectious disease clinics of North America. 2010 Sep 30; 24(3):809-33.

7. PI-Resistance Mutations and Response to New PI-Containing Regimens. Stanford University HIV Drug Resistance Database. Stanford University. Website: http://hivdb.stanford.edu/DR/geno_clinical_review/PI.html (last accessed 03 March 2016)

8. Okomo-Adhiambo M, Fry AM, Su S, Nguyen HT, Elal AA, Negron E, Hand J, Garten RJ, Barnes J, Xiyan X, Villanueva JM. Oseltamivir-resistant influenza A (H1N1) pdm09 viruses, United States, 2013–14. Emerg Infect Dis. 2015 Jan 1; 21:136-41.

9. Schneider MD, Sarrazin C. Antiviral therapy of hepatitis C in 2014: do we need resistance testing? Antiviral research. 2014 May 31; 105:64-71.

10. Pfaller MA. Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment. The American journal of medicine. 2012 Jan 31; 125(1):S3-13.

11. Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) 2010 to 2014: Report 2015. GOV.UK. 2015 November. Available from: https://www.gov.uk/government/publications/english-surveillance-

programme-antimicrobial-utilisation-and-resistance-espaur-report (last accessed 03 March 2016)

12. Health Protection Agency. English National Point Prevalence Survey on Healthcare-associated Infections and Antimicrobial Use, 2011: Preliminary data. GOV.UK. 2012. Available from: https://www.gov.uk/government/publications/healthcare-associated-infections-hcai-point-prevalence-survey-england (last accessed 03 March 2016)
13. HM Government, Public Health England. UK One Health Report: Joint report on human and animal antibiotic use, sales and resistance, 2013. GOV.UK. 2015 Jul. Available from: https://www.gov.uk/government/publications/uk-one-health-report-antibiotics-use-in-humans-and-animals (last accessed 03 March 2016)
14. The European Centre for Disease Prevention and Control (ECDC). European Surveillance of Antimicrobial Consumption Network (ESAC-Net). Website: http://ecdc.europa.eu/en/activities/surveillance/ESAC-Net/Pages/index.aspx (last accessed 03 March 2016)
15. The European Centre for Disease Prevention and Control (ECDC). ECDC Report, Surveillance of antimicrobial consumption in Europe, 2012. ECDC. 2014. Available from: http://ecdc.europa.eu/en/publications/Publications/antimicrobial-consumption-europe-esac-net-2012.pdf (last accessed 03 March 2016)
16. Pearson A, Chronias A, Murray M. Voluntary and mandatory surveillance for methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) bacteraemia in England. Journal of Antimicrobial Chemotherapy. 2009 Sep 1; 64(suppl. 1):i11-7.
17. PVL–*Staphylococcus aureus* infections: an update. Health Protect Report, News Archives Vol. 5 No. 7, 18 Feb 2011. National Archives. Available from: http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/hpr/archives/2011/news0711.htm (last accessed 03 March 2016)
18. Pantelides NM, Rao GG, Charlett A, Kearns AM. Preadmission screening of adults highlights previously unrecognized carriage of Panton-Valentine leukocidin-positive methicillin-resistant *Staphylococcus aureus* in London: a cause for concern? Journal of clinical microbiology. 2012 Oct 1; 50(10):3168-71.
19. Ellington MJ, Ganner M, Warner M, Cookson BD, Kearns AM. Polyclonal multiply antibiotic-resistant methicillin-resistant *Staphylococcus aureus* with Panton–Valentine leucocidin in England. Journal of antimicrobial chemotherapy. 2009 Nov 3:dkp386.
20. Reynolds R. Antimicrobial resistance in the UK and Ireland. Journal of Antimicrobial Chemotherapy. 2009 Sep 1; 64(suppl. 1):i19-23.
21. Livermore DM, Hope R, Reynolds R, Blackburn R, Johnson AP, Woodford N. Declining cephalosporin and fluoroquinolone non-susceptibility among bloodstream Enterobacteriaceae from the UK: links to prescribing change?. Journal of Antimicrobial Chemotherapy. 2013 Jun 13:dkt212.

22. Public Health England. Carbapenem resistance: implementation of an enhanced surveillance system. Health Protection Report Volume 9 Issue 2. 2015 Jan. Available from: https://www.gov.uk/government/publications/health-protection-report-volume-9-2015 (last accessed 03 March 2016)

23. Public Health England. Tuberculosis in England: 2015 report (presenting data to end of 2014). GOV.UK. 2015 Oct. Available from: https://www.gov.uk/government/publications/tuberculosis-in-england-annual-report (last accessed 03 March 2016)

24. Public Health England. Surveillance of antimicrobial resistance in *Neisseria gonorrhoeae:* Key finding of the "gonococcal resistance to antimicrobials surveillance programme" (GRASP) and related surveillance data, 2014. GOV.UK. 2015 Nov. Available from: https://www.gov.uk/government/publications/gonococcal-resistance-to-antimicrobials-surveillance-programme-grasp-report (last accessed 03 March 2016)

25. UK Collaborative Group on HIV Drug Resistance. Time trends in drug resistant HIV-1 infections in the United Kingdom up to 2009: multicentre observational study.

26. Tostevin A, White E, Croxford S, Delpech V, Williams I. Trends in transmitted drug resistance to HIV-1 in the UK since 2010. InHIV MEDICINE 2015 Apr 1 (Vol. 16, pp. 6-6). Available from: http://www.bhiva.org/documents/Conferences/2015Brighton/Presentations/150423/AnnaTostevin.pdf (last accessed 03 March 2016)

27. Castro H, Pillay D, Cane P, Asboe D, Cambiano V, Phillips A, Dunn DT, Aitken C, Webster D, Chadwick D, Churchill D. Persistence of HIV-1 transmitted drug resistance mutations. Journal of Infectious Diseases. 2013 Nov 1; 208(9):1459-63.

28. Beloukas A, King S, Childs K, Papadimitropoulos A, Hopkins M, Atkins M, Agarwal K, Nelson M, Geretti AM. Detection of the NS3 Q80K polymorphism by Sanger and deep sequencing in hepatitis C virus genotype 1a strains in the UK. Clinical Microbiology and Infection. 2015 Nov 30; 21(11):1033-9.

29. McCormick AL, Wang L, Garcia-Diaz A, Macartney MJ, Webster DP, Haque T. Prevalence of baseline polymorphisms for potential resistance to NS5A inhibitors in drug-naive individuals infected with hepatitis C genotypes 1–4. Antiviral therapy. 2014 Mar 12; 20(1):81-5.

30. Takashita E, Meijer A, Lackenby A, Gubareva L, Rebelo-de-Andrade H, Besselaar T, Fry A, Gregory V, Leang SK, Huang W, Lo J. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2013–2014. Antiviral research. 2015 May 31; 117:27-38.

31. Lackenby A, Moran Gilad J, Pebody R, Miah S, Calatayud L, Bolotin S, Vipond I, Muir P, Guiver M, McMenamin J, Reynolds A. Continued emergence and changing

epidemiology of oseltamivir-resistant influenza A (H1N1) 2009 virus, United Kingdom, winter 2010/11. Euro Surveill. 2011 Feb 3; 16(5):19784.

32. Cuenca-Estrella M, Verweij PE, Arendrup MC, Arikan-Akdagli S, Bille J, Donnelly JP, Jensen HE, Lass-Flörl C, Richardson MD, Akova M, Bassetti M. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: diagnostic procedures. Clinical Microbiology and Infection. 2012 Dec 1; 18(s7):9-18.

33. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. Journal of Antimicrobial Chemotherapy. 2013 Dec 29:dkt508.

34. Public Health England. Surveillance of candidaemia in England, Wales and Northern Ireland: 2014. Health Protection Report Volume 9 Issue 33. 2015 Sep. Available from: https://www.gov.uk/government/publications/health-protection-report-volume-9-2015 (last accessed 03 March 2016)

35. McKenna M. Antibiotic resistance: the last resort. Nature. 2013 Jul 25; 499(7459):394.

36. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clinical infectious diseases. 2011 Jul 1; 53(1):60-7.

37. Bergman M, Nyberg ST, Huovinen P, Paakkari P, Hakanen AJ, Finnish Study Group for Antimicrobial Resistance. Association between antimicrobial consumption and resistance in *Escherichia coli*. Antimicrobial agents and chemotherapy. 2009 Mar 1; 53(3):912-7.

38. Livermore DM, Stephens P, Weinberg J, Johnson AP, Gifford T, Northcott D, James D, George RC, Speller DC. Regional variation in ampicillin and trimethoprim resistance in *Escherichia coli* in England from 1990 to 1997, in relation to antibacterial prescribing. Journal of Antimicrobial Chemotherapy. 2000 Sep 1; 46(3):411-22.

39. Hay AD, Thomas M, Montgomery A, Wetherell M, Lovering A, McNulty C, Lewis D, Carron B, Henderson E, MacGowan A. The relationship between primary care antibiotic prescribing and bacterial resistance in adults in the community: a controlled observational study using individual patient data. Journal of Antimicrobial Chemotherapy. 2005 Jul 1; 56(1):146-53.

40. Kahlmeter G, Menday P, Cars O. Non-hospital antimicrobial usage and resistance in community-acquired *Escherichia coli* urinary tract infection. Journal of antimicrobial chemotherapy. 2003 Dec 1; 52(6):1005-10.

41. Enki DG, Noufaily A, Garthwaite PH, Andrews NJ, Charlett A, Lane C, Farrington CP. Automated biosurveillance data from England and Wales, 1991–2011. Emerging infectious diseases. 2013 Jan; 19(1):35.

42. Freeman R, Charlett A, Hopkins S, O'Connell AM, Andrews N, Freed J, Holmes A, Catchpole M. Evaluation of a national microbiological surveillance system to inform automated outbreak detection. Journal of Infection. 2013 Nov 30; 67(5):378-84.

43. Schumacher M, Wangler M, Wolkewitz M, Beyersmann J. Attributable mortality due to nosocomial infections-a simple and useful application of multistate models. Methods of information in medicine. 2007 Jan 1; 46(5):595-600.

44. Girou E, Brun-Buisson C. Morbidity, mortality, and the cost of nosocomial infections in critical care. Current Opinion in Critical Care. 1996 Oct 1; 2(5):347-51.

45. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clinical infectious diseases. 2003 Jan 1; 36(1):53-9.

46. Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum β-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy. 2007 Nov 1; 60(5):913-20.

47. World Health Organization. The burden of health care-associated infection worldwide. World Health Organization Clean Care is Safer Care Programme. World Health Organization. Available from: http://www.who.int/gpsc/country_work/burden_hcai/en/ (last accessed 03 March 2016)

48. World Health Organization. Report on the Burden of Endemic Health Care-Associated Infection Worldwide: Clean Care is Safer Care. World Health Organization Patient Safety. 2011. Available from: http://www.who.int/gpsc/country_work/burden_hcai/en/ (last accessed 03 March 2016)

49. de Kraker ME, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, Icket C, Kalenic S, Horvatic J, Seifert H, Kaasch A. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to *Escherichia coli* resistant to third-generation cephalosporins. Journal of antimicrobial chemotherapy. 2011 Feb 1; 66(2):398-407.

50. de Kraker ME, Wolkewitz M, Davey PG, Grundmann H, BURDEN Study Group. The clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin resistant *Staphylococcus aureus* bloodstream infections. Antimicrobial agents and chemotherapy. 2011 Jan 10.

51. de Kraker ME, Davey PG, Grundmann H, BURDEN Study Group. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. PLoS Med. 2011 Oct 11; 8(10):e1001104.

52. Wickramasinghe NH, Xu L, Eustace A, Shabir S, Saluja T, Hawkey PM. High community faecal carriage rates of CTX-M ESBL-producing *Escherichia coli* in a

specific population group in Birmingham, UK. Journal of antimicrobial chemotherapy. 2012 May 1; 67(5):1108-13.

53. Smith R, Coast J. The true cost of antimicrobial resistance. Bmj. 2013 Mar 11; 346.

54. Smith R, Coast J. The economic burden of antimicrobial resistance. Why it is more serious than current studies suggest. Independent report commissioned and funded by the Department of Health Policy Research Programme Report. 2013. Available from: http://researchonline.lshtm.ac.uk/639028/ (last accessed 03 March 2016)

55. Lautenbach E, Weiner MG, Nachamkin I, Bilker WB, Sheridan A, Fishman NO. Imipenem Resistance Among Pseudomonas aeruginosa Isolates Risk Factors for Infection and Impact of Resistance on Clinical and Economic Outcomes. Infection Control. 2006 Sep 1; 27(09):893-900.

56. Camins BC, Marschall J, De Vader SR, Maker DE, Hoffman MW, Fraser VJ. The clinical impact of fluoroquinolone resistance in patients with E coli bacteremia. Journal of hospital medicine. 2011 Jul 1; 6(6):344-9.

57. Schwaber MJ, Navon-Venezia S, Kaye KS, Ben-Ami R, Schwartz D, Carmeli Y. Clinical and economic impact of bacteremia with extended-spectrum-β-lactamase-producing Enterobacteriaceae. Antimicrobial agents and chemotherapy. 2006 Apr 1; 50(4):1257-62.

58. Piednoir E, Thibon P, Borderan GC, Godde F, Borgey F, Le Coutour X, Parienti JJ. Long-term clinical and economic benefits associated with the management of a nosocomial outbreak resulting from extended-spectrum beta-lactamase-producing Klebsiella pneumoniae. Critical care medicine. 2011 Dec 1; 39(12):2672-7.

59. Stone PW, Gupta A, Loughrey M, Della-Latta P, Cimiotti J, Larson E, Rubenstein D, Saiman L. Attributable costs and length of stay of an extended-spectrum beta-lactamase-producing Klebsiella pneumoniae outbreak in a neonatal intensive care unit. Infection Control & Hospital Epidemiology. 2003 Aug 1; 24(08):601-6.

60. Gardam MA, Burrows LL, Kus JV, Brunton J, Low DE, Conly JM, Humar A. Is surveillance for multidrug-resistant enterobacteriaceae an effective infection control strategy in the absence of an outbreak?. Journal of Infectious Diseases. 2002 Dec 15; 186(12):1754-60.

61. Thouverez M, Talon D, Bertrand X. Control of Enterobacteriaceae producing extended-spectrum beta-lactamase in intensive care units: rectal screening may not be needed in non-epidemic situations. Infection Control & Hospital Epidemiology. 2004 Oct 1; 25(10):838-41.

62. Cheong HS, Ko KS, Kang CI, Chung DR, Peck KR, Song JH. Clinical significance of infections caused by extended-spectrum β-lactamase-producing Enterobacteriaceae blood isolates with inducible AmpC β-lactamase. Microbial Drug Resistance. 2012 Aug 1; 18(4):446-52.

63. Lee SY, Kotapati S, Kuti JL, Nightingale CH, Nicolau DP. Impact of extended-spectrum β-lactamase–producing Escherichia coli and Klebsiella species on clinical outcomes and hospital costs: a matched cohort study. Infection Control. 2006 Nov 1; 27(11):1226-32.

64. Graves N, Harbarth S, Beyersmann J, Barnett A, Halton K, Cooper B. Estimating the cost of health care-associated infections: mind your p's and q's. Clinical infectious diseases. 2010 Apr 1; 50(7):1017-21.

65. De Angelis G, Allignol A, Murthy A, Wolkewitz M, Beyersmann J, Safran E, Schrenzel J, Pittet D, Harbarth S. Multistate modelling to estimate the excess length of stay associated with meticillin-resistant *Staphylococcus aureus* colonisation and infection in surgical patients. Journal of Hospital Infection. 2011 Jun 30; 78(2):86-91.

66. Blot S, Depuydt P, Vandewoude K, De Bacquer D. Measuring the impact of multidrug resistance in nosocomial infection. Current opinion in infectious diseases. 2007 Aug 1; 20(4):391-6.

67. Lambert ML, Suetens C, Savey A, Palomar M, Hiesmayr M, Morales I, Agodi A, Frank U, Mertens K, Schumacher M, Wolkewitz M. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. The Lancet infectious diseases. 2011 Jan 31; 11(1):30-8.

68. Beyersmann J, Gastmeier P, Grundmann H, Bärwolff S, Geffers C, Behnke M, Rüden H, Schumacher M. Use of multistate models to assess prolongation of intensive care unit stay due to nosocomial infection. Infection Control. 2006 May 1; 27(05):493-9.

69. Wolkewitz M, Vonberg RP, Grundmann H, Beyersmann J, Gastmeier P, Bärwolff S, Geffers C, Behnke M, Rüden H, Schumacher M. Risk factors for the development of nosocomial pneumonia and mortality on intensive care units: application of competing risks models. Critical Care. 2008 Apr 2; 12(2):R44.

70. Resche-Rigon M, Azoulay E, Chevret S. Evaluating mortality in intensive care units: contribution of competing risks analyses. Critical Care. 2005 Dec 1; 10(1):R5.

71. Wolkewitz M, Frank U, Philips G, Schumacher M, Davey P, Wilson C, Lawrie-Blum D, Kaier K, Schroeren-Boersch B, Chalkley M, Heather D. Mortality associated with in-hospital bacteraemia caused by Staphylococcus aureus: a multistate analysis with follow-up beyond hospital discharge. Journal of Antimicrobial Chemotherapy. 2011 Feb 1; 66(2):381-6.

72. Congress US. Office of Technology Assessment. Impacts of antibiotic-resistant bacteria. Washington, DC: US Government Printing Office. 1995 Sep. Available from: http://ota.fas.org/reports/9503.pdf (last accessed 03 March 2016)

73. Williamson DA, Freeman JT, Roberts SA, Heffernan H, Dyet K, Paterson DL, Rogers BA, Sidjabat HE, Masters J. Rectal colonization with New Delhi metallo-β-lactamase-

1-producing Escherichia coli prior to transrectal ultrasound (TRUS)-guided prostate biopsy. Journal of Antimicrobial Chemotherapy. 2013 Dec 1; 68(12):2957-9.

74. McNulty CA, Richards J, Livermore DM, Little P, Charlett A, Freeman E, Harvey I, Thomas M. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. Journal of Antimicrobial Chemotherapy. 2006 Nov 1; 58(5):1000-8.

75. Livermore DM, Hill RL, Thomson H, Charlett A, Turton JF, Pike R, Patel BC, Manuel R, Gillespie S, Balakrishnan I, Barrett SP. Antimicrobial treatment and clinical outcome for infections with carbapenem-and multiply-resistant Acinetobacter baumannii around London. International journal of antimicrobial agents. 2010 Jan 31; 35(1):19-24.

76. Holmes NE, Turnidge JD, Munckhof WJ, Robinson JO, Korman TM, O'Sullivan MV, Anderson TL, Roberts SA, Warren SJ, Gao W, Johnson PD. Vancomycin minimum inhibitory concentration, host comorbidities and mortality in Staphylococcus aureus bacteraemia. Clinical Microbiology and Infection. 2013 Dec 1; 19(12):1163-8.

77. Ashiru-Oredope D, Hopkins S. English Surveillance Programme for Antimicrobial Utilization and Resistance Oversight Group. Antimicrobial stewardship: English Surveillance Programme for Antimicrobial Utilization and Resistance (ESPAUR). J Antimicrob Chemother. 2013 Nov; 68(11):2421-3.

78. Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2013 Jan 1; 4(4).

79. Inglis GD, Davies MW. Prophylactic antibiotics to reduce morbidity and mortality in ventilated newborn infants. The Cochrane Library. 2004.

80. D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E, Liberati A. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev. 2009; 4.

81. Stone SP, Fuller C, Savage J, Cookson B, Hayward A, Cooper B, Duckworth G, Michie S, Murray M, Jeanes A, Roberts J. Evaluation of the national Cleanyourhands campaign to reduce Staphylococcus aureus bacteraemia and Clostridium difficile infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. Bmj. 2012; 344.

82. Fuller C, Michie S, Savage J, McAteer J, Besser S, Charlett A, Hayward A, Cookson BD, Cooper BS, Duckworth G, Jeanes A. The Feedback Intervention Trial (FIT)—improving hand-hygiene compliance in UK healthcare workers: a stepped wedge cluster randomised controlled trial. PLoS One. 2012 Oct 23; 7(10):e41617.

83. Boyce JM, Pittet D. Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee

and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. American journal of infection control. 2002 Dec 31; 30(8):S1-46.

84. Pratt RJ, Pellowe C, Loveday HP, Robinson N, Smith GW, Barrett S, Davey P, Harper P, Loveday C, McDougall C, Mulhall A. The epic project: developing national evidence-based guidelines for preventing healthcare associated infections. Phase I: Guidelines for preventing hospital-acquired infections. Department of Health (England). The Journal of hospital infection. 2001 Jan; 47:S3-82.

85. Dettenkofer M, Wenzler S, Amthor S, Antes G, Motschall E, Daschner FD. Does disinfection of environmental surfaces influence nosocomial infection rates? A systematic review. American journal of infection control. 2004 Apr 30; 32(2):84-9.

86. van Rijen M, Bonten M, Wenzel R, Kluytmans J. Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. Cochrane Database Syst Rev. 2008 Jan 1; 4(4).

87. Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, Duckworth G, Lai R, Ebrahim S. Isolation measures in the hospital management of methicillin resistant Staphylococcus aureus (MRSA): systematic review of the literature. Bmj. 2004 Sep 2; 329(7465):533.

88. Tacconelli E, Cataldo MA, Dancer SJ, Angelis G, Falcone M, Frank U, Kahlmeter G, Pan A, Petrosillo N, Rodríguez-Baño J, Singh N. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clinical Microbiology and Infection. 2014 Jan 1; 20(s1):1-55.

89. Silvestri L, Van Saene HK, Milanese M, Gregori D, Gullo A. Selective decontamination of the digestive tract reduces bacterial bloodstream infection and mortality in critically ill patients. Systematic review of randomized, controlled trials. Journal of Hospital Infection. 2007 Mar 31; 65(3):187-203.

90. Daneman N, Sarwar S, Fowler RA, Cuthbertson BH, SuDDICU Canadian Study Group. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. The Lancet infectious diseases. 2013 Apr 30; 13(4):328-41.

91. De Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, Van der Werf TS, Van Der Hoeven JG, Pickkers P, Bogaers-Hofman D, Van Der Meer NJ, Bernards AT. Decontamination of the digestive tract and oropharynx in ICU patients. New England Journal of Medicine. 2009 Jan 1; 360(1):20.

92. van Kleef E, Robotham JV, Jit M, Deeny SR, Edmunds WJ. Modelling the transmission of healthcare associated infections: a systematic review. BMC infectious diseases. 2013 Jun 28; 13(1):294.

93. Meijer A, Lackenby A, Hungnes O, Lina B, Van Der Werf S, Schweiger B, Opp M, Paget J, van de Kassteele J, Hay A, Zambon M. Oseltamivir-resistant influenza virus

A (H1N1), Europe, 2007–08 season. Emerging infectious diseases. 2009 April; 15(4):552-560.

94. Takashita E, Kiso M, Fujisaki S, Yokoyama M, Nakamura K, Shirakura M, Sato H, Odagiri T, Kawaoka Y, Tashiro M. Characterization of a large cluster of influenza A (H1N1) pdm09 viruses cross-resistant to oseltamivir and peramivir during the 2013-2014 influenza season in Japan. Antimicrobial agents and chemotherapy. 2015 May 1; 59(5):2607-17.

95. Hurt AC, Hardie K, Wilson NJ, Deng YM, Osbourn M, Leang SK, Lee RT, Iannello P, Gehrig N, Shaw R, Wark P. Characteristics of a widespread community cluster of H275Y oseltamivir-resistant A (H1N1) pdm09 influenza in Australia. Journal of Infectious Diseases. 2012 Jul 15; 206(2):148-57.

96. Wilson AP, Livermore DM, Otter JA, Warren RE, Jenks P, Enoch DA, Newsholme W, Oppenheim B, Leanord A, McNulty C, Tanner G. Prevention and control of multi-drug-resistant Gram-negative bacteria: recommendations from a Joint Working Party. The Journal of hospital infection. 2016 Jan 4;92:S1-44. Available from: https://dx.doi.org/10.1016/j.jhin.2015.08.007 (last accessed 03 March 2016)

97. Kouyos RD, Günthard HF. The irreversibility of HIV drug resistance. Clinical Infectious Diseases. 2015 May 19:civ400.

98. Mbisa JL, Fearnhill E, Dunn DT, Pillay D, Asboe D, Cane PA, Aitken C, Pozniak A, Cane P, Castro H, Dunn D. Evidence of self-sustaining drug resistant HIV-1 lineages among untreated patients in the United Kingdom. Clinical Infectious Diseases. 2015 May 19:civ393.

99. Public Health England. Quarterly epidemiological commentary: mandatory MRSA, MSSA and *E. coli* bacteraemia, and *C. difficile* infection data (up to October to December 2015). GOV.UK. 2015 Oct. Available from: https://www.gov.uk/government/statistics/mrsa-mssa-and-e-coli-bacteraemia-and-c-difficile-infection-quarterly-epidemiological-commentary (last accessed 03 March 2016)

100. Public Health England. Polymicrobial bacteraemia and fungaemia in England, Wales and Northern Ireland, 2014. Health Protection Report Volume 9 Issue 21. 2015 Jun. Available from: https://www.gov.uk/government/publications/health-protection-report-volume-9-2015 (last accessed 03 March 2016)

101. Public Health England. Uncommon pathogens involved in bacteraemia: England, Wales and Northern Ireland, 2010-2014. Health Protection Report Volume 9 Issue 45. 2015 Dec. Available from: https://www.gov.uk/government/publications/health-protection-report-volume-9-2015 (last accessed 03 March 2016)

102. Public Health England. Voluntary surveillance of *Escherichia coli* bacteraemia in England, Wales and Northern Ireland: 2008-2014. Health Protection Report Volume 9 Issue 23. 2015 Jul. Available from:

https://www.gov.uk/government/publications/health-protection-report-volume-9-2015 (last accessed 03 March 2016)

103. Public Health England. Voluntary surveillance of bacteraemia caused by *Enterobacter spp*., *Serratia spp.* and *Citrobacter spp.* in England, Wales and Northern Ireland: 2010-2014. Health Protection Report Volume 9 Issue 37. 2015 Oct. Available from: https://www.gov.uk/government/publications/health-protection-report-volume-9-2015 (last accessed 03 March 2016)

Additional References

The following references are not cited in the main body of the report but supply additional information and may be of interest to the reader:

- Review on Antimicrobial Resistance: Tackling drug-resistant infections globally. AMR Review. Website: http://amr-review.org/ (last accessed 03 March 2016)

- Robotham JV, Deeny SR, Fuller C, Hopkins S, Cookson B, Stone S. Cost-effectiveness of national mandatory screening of all admissions to English National Health Service hospitals for meticillin-resistant Staphylococcus aureus: a mathematical modelling study. The Lancet Infectious Diseases. 2015 Nov 28.

- Surgical site infections: prevention and treatment. NICE guidelines [CG74]. National Institute for Health and Care Excellence. 2008 Oct. Available from: https://www.nice.org.uk/guidance/cg74 (last accessed 03 March 2016)

- Zingg W, Holmes A, Dettenkofer M, Goetting T, Secci F, Clack L, Allegranzi B, Magiorakos AP, Pittet D. Hospital organisation, management, and structure for prevention of health-care-associated infection: a systematic review and expert consensus. The Lancet Infectious Diseases. 2015 Feb 28;15(2):212-24. Available from: http://ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/guidance-infection-prevention-control/Pages/guidance-organisation-infection-prevention-control.aspx (last accessed 03 March 2016)

- Stone SP. Infection prevention and control: lessons from acute care in England. Available from: http://www.health.org.uk/publication/infection-prevention-and-control-lessons-acute-care-england (last accessed 03 March 2016)

- Schwaber MJ, Lev B, Israeli A, Solter E, Smollan G, Rubinovitch B, Shalit I, Carmeli Y. Containment of a country-wide outbreak of carbapenem-resistant Klebsiella pneumoniae in Israeli hospitals via a nationally implemented intervention. Clinical infectious diseases. 2011 Feb 11:cir025. Available from: https://dx.doi.org/10.1093/cid/cir025 (last accessed 03 March 2016)

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