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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

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Contents

List of Tables and Figures

Tables

Figures

Scope

This report provides a broad overview of the current situation of antimicrobial resistance (AMR) in bacteria. Its primary aim is to bring together the evidence upon which scenario-based analytical work can be undertaken to assess the impact of emerging AMR in specific pathogens, 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 such a report.

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 prevention of *neutropenic* sepsis in patients undergoing chemotherapy treatment for cancer.

Antibiotic use has increased to such an extent that resistance to them has emerged and spread in many organisms. Infections with resistant organisms now occur both in community and hospital populations. However AMR infections in healthcare settings are to which most deaths are related, an estimated 25 000 patients die annually in the EU from an infection with multidrug-resistant (MDR) bacteria [1]. AMR has reached the stage of threatening some 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, 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 combined with a high antibiotic selective pressure, these bacteria are now also spreading in the community.

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

The recent ECDC/EMEA Joint Technical Report [1] identified that there were 15 systemically-administered antibacterial agents 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 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 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 in 2009 [4], and the number of new antibiotics approved for marketing in the United States continues to decline annually. Seven drugs in clinical development for treatment of infections caused by resistant Gram-negative bacteria were identified.

2. Antimicrobial resistance

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 include inactivating or degrading antibiotics, modifying the target site, decreased 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.

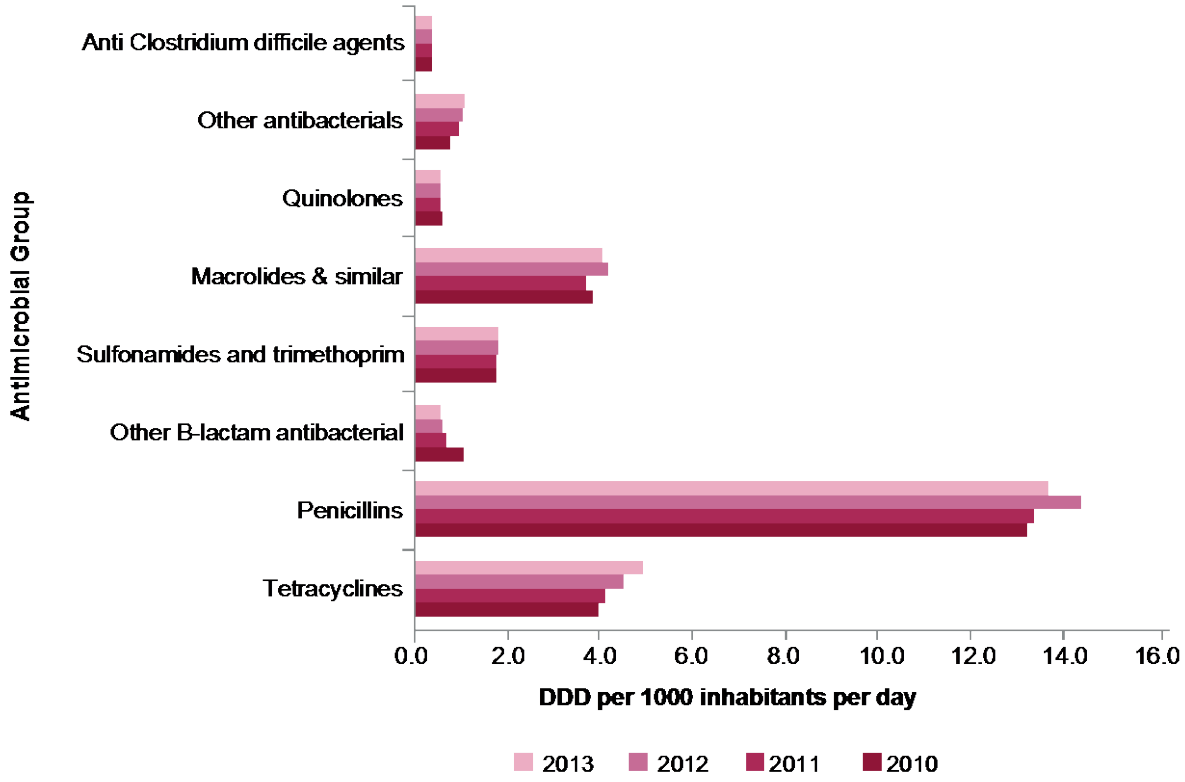
There are a range of mechanisms by which an organism can acquire resistance, the simplest being genetic mutation. Resistant mutants will have a strong survival advantage in the face of antibiotic exposures, giving rise to the often seen association between the total usage of antibacterial agents in a population and the increased proportion of isolates that exhibit resistance to those agents. The indiscriminate and inappropriate use of antibiotics is currently 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 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 a *Staphylococcus aureu*s. This ability of bacteria to transfer resistance mechanisms provides a major challenge to preventing the emergence of resistance.

3. Antibiotic use

The use of antibiotics in a population is the primary driver of the development of resistance. However, the factors underlying the development of resistance in pathogens is often more complex than simply using more 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. While there are some sources of data on antimicrobial prescribing and usage, it is often less than ideal consisting of total numbers of prescriptions or daily defined doses for specific antibiotics by units such as GP practices. Individual patient level data are rarely readily available, particularly so in the hospital setting. Figure 1 provides national antibiotic consumption data showing temporal trends in, and variation between the use of specific antibiotic groups.

Figure 1: Total antibiotic consumption by group*, expressed as DDD per 1000 inhabitants per day, across England, 2010-2013



*Other β-lactam antibacterials include cephalosporins and carbapenems

The volume and trends of antimicrobials prescriptions in England are presented in Figure 1. This figure is reproduced from Figure 3.3 of the English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) Report 2014 [6]. From 2010 to 2013, the predominant antibiotic use in England was penicillins with around 13 DDDs per 1000 inhabitants per day. Tetracyclines and macrolides are both frequently used with around 4 DDDs per inhabitant per day. Both penicillin and macrolide consumption exhibited a general increasing trend over the four years.

The 2011 National Point Prevalence Survey [7] collected information on the antimicrobial usage at the time the patients were surveyed. The total number of antimicrobials prescribed was 25,942 in a total of 18,219 patients. Therefore, 34.7% of the total 52,443 patients were prescribed antimicrobials and those patients on antimicrobials have 1.42 antimicrobials per patient. Table 1 adapted from [7] gives the top 20 antimicrobials prescribed by intended treatment. co-amoxiclav and piperacillin/tazobactam were the most commonly prescribed antimicrobials for treating infections, co-amoxiclav and cefuroxime were the most commonly prescribed antimicrobials for surgical prophylaxis.

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 and increasing AMR to these antibiotics.

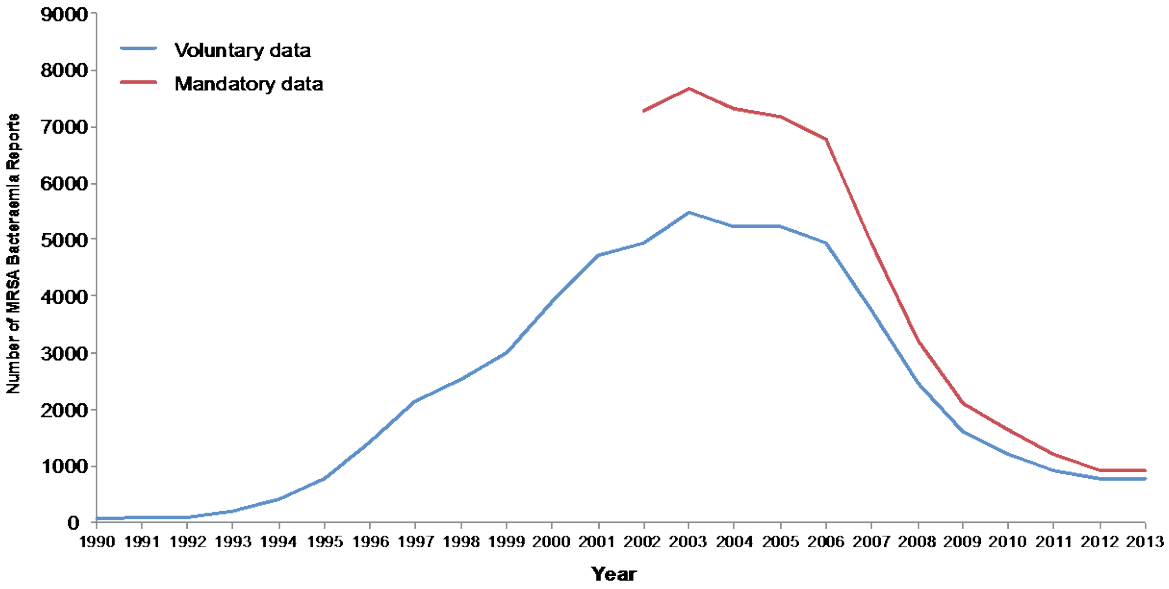
Table 1: Adapted from Table 5-20 [7]: Top 20 antimicrobials by treatment intention

Antimicrobial	*Total*		*Treatment*		*Surgical prophylaxis*		*Medical prophylaxis*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Total	*25942*	*100.0*	*19411*	*100.0*	*3412*	*100.0*	*2059*	*100.0*
Co-amoxiclav	*3579*	*13.8*	*2674*	*13.8*	*703*	*20.60*	*107*	*5.2*
Piperacillin/tazobactam	*2262*	*8.7*	*2111*	*10.9*	*54*	*1.6*	*44*	*2.1*
Flucloxacillin	*1906*	*7.3*	*1366*	*7.0*	*457*	*13.4*	*46*	*2.2*
Gentamicin	*1566*	*6.0*	*815*	*4.2*	*583*	*17.1*	*126*	*6.1*
Clarithromycin	*1245*	*4.8*	*1190*	*6.1*	*8*	*0.2*	*21*	*1.0*
Metronidazole (parenteral)	*1230*	*4.7*	*907*	*4.7*	*270*	*7.9*	*23*	*1.1*
Amoxicillin	*1159*	*4.5*	*1062*	*5.5*	*50*	*1.5*	*31*	*1.5*
Trimethoprim	*1080*	*4.2*	*932*	*4.8*	*19*	*0.6*	*108*	*5.2*
Meropenem	*1021*	*3.9*	*961*	*5.0*	*10*	*0.3*	*25*	*1.2*
Cefuroxime	*895*	*3.5*	*234*	*1.2*	*634*	*18.6*	*20*	*1.0*
Benzylpenicillin	*848*	*3.3*	*686*	*3.5*	*49*	*1.4*	*86*	*4.2*
Metronidazole (oral rectal)	*755*	*2.9*	*619*	*3.2*	*64*	*1.9*	*40*	*1.9*
Ciprofloxacin	*707*	*2.7*	*556*	*2.9*	*38*	*1.1*	*91*	*4.4*
Doxycycline	*631*	*2.4*	*582*	*3.0*	*7*	*0.2*	*21*	*1.0*
Teicoplanin	*612*	*2.4*	*374*	*1.9*	*201*	*5.9*	*20*	*1.0*
Vancomycin (parenteral)	*562*	*2.2*	*508*	*2.6*	*36*	*1.1*	*10*	*0.5*
Fluconazole	*463*	*1.8*	*278*	*1.4*	*14*	*0.4*	*159*	*7.7*
Nitrofurantoin	*348*	*1.3*	*281*	*1.4*	*2*	*0.1*	*57*	*2.8*
Rifampicin	*265*	*1.0*	*255*	*1.3*	*0*	*<0.1*	*4*	*0.2*
Clindamycin	*259*	*1.0*	*239*	*1.2*	*15*	*0.4*	*2*	*0.1*

4. Current trends in resistance

It is important to remember that 'resistance' is not in itself a disease entity, but it affects many organisms causing 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 is 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 trends observed in reported isolates reflect those occurring in the wider population of patients and pathogens, although this has rarely been assessed. Figure 2 below, redrawn and updated from [8], 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 2: Redrawn and updated from [8], comparison of annual reports to mandatory and voluntary MRSA bacteraemia surveillance



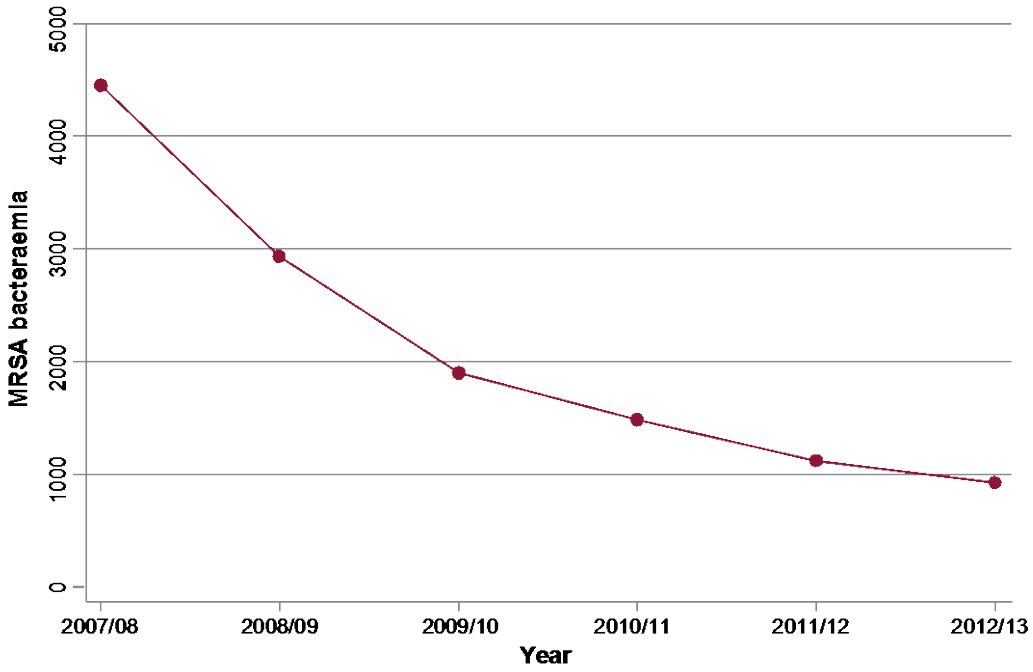
Many infections (particularly those occurring in community settings) are treated empirically without any specimens being sent for microbiological investigation. Surveillance data are therefore most complete when they relate to infections for which suitable samples would commonly be referred for microbiology,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

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, in particular bacteraemia caused by MRSA, the occurrence of which was 4,451 in 2007/08, and which reduced by nearly 80% by 2012/13 where 927 cases were reported to the mandatory surveillance system, this year on year reduction is shown in Figure 3.

Figure 3: Number of MRSA bacteraemias reported to the DH mandatory surveillance system in each of the past six financial years.



The second most frequent pathogen isolated from surgical site infections (SSI) in 2011/12 reported to the Surgical Site Infection Surveillance System (SSISS) was *S. aureus*, causing 349 SSI, which was 24% of all isolates. Of these *S. aureus* isolates, 18% were MRSA; representing a further decrease from the 23% observed in the previous year.

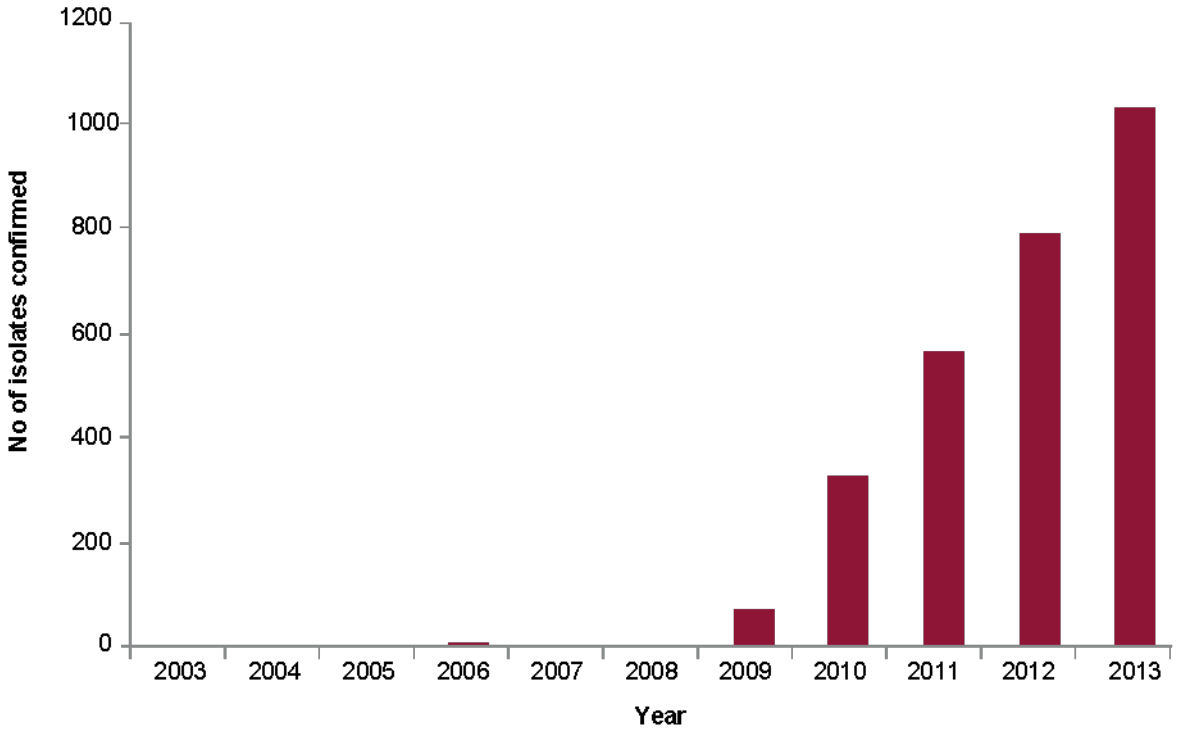
Whilst there has been a reduction in the occurrence of MRSA bacteraemias, increases in isolates of MRSA producing the Panton-Valentine Leukocidin (PVL) toxin have been observed among submissions to PHE's national reference laboratory, with 117 isolated in 2005 increasing to 1049 isolates in 2010 [9]. 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 [10] observed a particular PVL-MRSA clone, CC5 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 [11]. However, it is difficult to understand precisely the reasons for the observed trends in PVL-producing MRSA, which could reflect ascertainment bias with increased testing for PVL over recent years. However, it does beg a question as to whether this increase could reflect 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 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 multi-resistant, with 83% of ESBL-producing *E. coli* exhibiting ciprofloxacin non-susceptibility and 40% gentamicin non-susceptibility [12]. 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. Moreover, 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* bacteraemias was rising, the incidence of *Klebsiella* bacteraemias was stable and the incidence of *Enterobacter* bacteraemias was falling; this trend was not paralleled in EARS-Net data for continental Europe and did not reflect the displacement of single mechanisms. Rather it coincided with large reductions in hospital cephalosporin and quinolone use, owing to concern about *Clostridium difficile* [13].

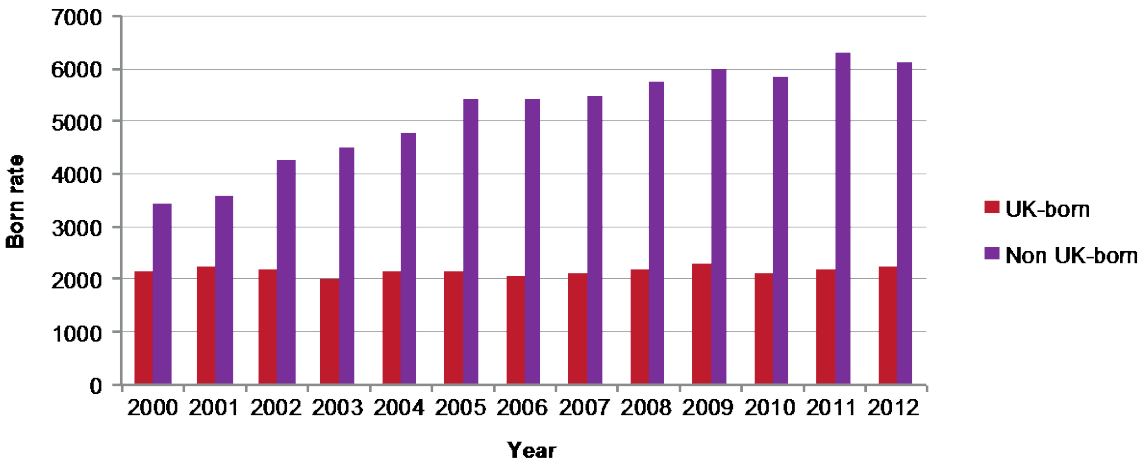
Carbapenemase-producing Enterobacteriaceae (CPE) have emerged in the UK over the past decade, with reported occurrences in *Klebsiella* spp. (79%), *E. coli* (12%), and *Enterobacter* spp. (7%). These data are based on voluntary referrals made to PHE's national reference laboratory, and indicate an emerging and growing UK problem as shown in Figure 4, albeit one that has yet to reach rates that would register on surveillance outputs of, for example, bacteraemia data. 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 potential then to impact on primary care.

Figure 4: Numbers of reports of CPE by year of isolation in the UK



For another infection, 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, which 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 over 2000 cases reported each year as shown in Figure 5. In contrast, reports of TB in those born outside of the UK have risen steadily, from 2358 reports in 2000 to 6287 in 2011 [14]. Only small increases in the proportion of TB isolates that are multi-drug resistant (MDR) have occurred in the UK; the proportion of isoniazid-resistant TB cases increased slightly from 6.4% (311/4840) in 2010 to 7.6% (388/5127), while MDR TB cases increased from 1.3% (65/4846) in 2010 to 1.6% (81/5127) in 2011. Over the last decade, gradual increases in the proportion of MDR TB has amounted to a significant overall upward trend (from 0.9%, 28/3228 cases in 2000 to 1.6% in 2011).

Figure 5: Redrawn from [14]: Tuberculosis case reports, by place of birth, UK, 2000-2012



Another disease where resistance has been of concern for a number of years is gonorrhoea. Variation can be seen in the proportion of *Neisseria gonorrhoeae* isolates in England and Wales, resistant or exhibiting decreased susceptibility to specific antimicrobial agents. Previously reported upward drift in ceftriaxone minimum inhibitory concentrations (MIC) was not evident with an apparent rise in proportion of highly sensitive isolates from the analysis performed in 2011 and 2012 [15]. At present, decreased susceptibility to ceftriaxone (MIC ≥0.125 mg/L) is rare, with just three isolates found in the 2012 sample. Resistance to azithromycin increased slightly in 2012 to 0.7% from 0.5% reported in 2011.

The proportion of isolates exhibiting decreased susceptibility to cefixime at the lower MIC cut-off (≥0.125 mg/L) was 5.6% in 2012, falling from 10.8% in 2011, although slightly higher in London (6.0%) compared with outside London (5.3%). However, at the higher MIC cut-off (≥0.25 mg/L), the proportion increased slightly from 1.3% in 2011 to 2.1% in 2012 (Figure 6).

In addition there was a decline in the proportion of isolates resistant to ciprofloxacin from 34.0% in 2011 to 25.0% in 2012. The prevalence of ciprofloxacin resistance in 2012 was higher in London (29.7%) compared with outside London (20.0%). In contrast tetracycline and penicillin resistance increased to 76.3% and 14.6% from 69.1% and 11.6% respectively, and there were no isolates resistant to spectinomycin in 2012 (Table 2).

Figure 6: Percentage of gonorrhoea cases by cefixime MIC (mg/L) of the causative strain; GRASP 2007-2012. Redrawn from the 2012 GRASP Report [15]

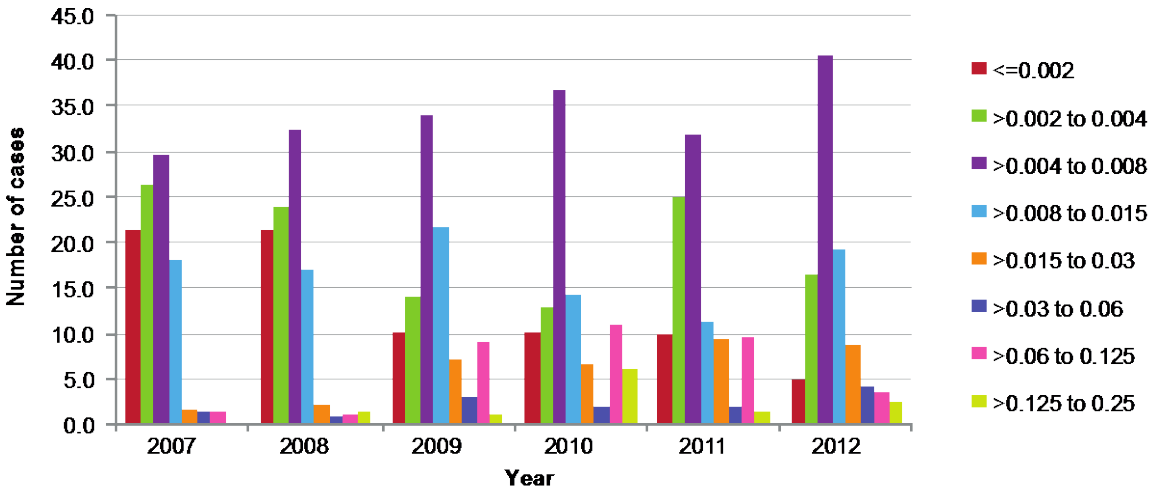


Table 2: Proportions of *N. gonorrhoeae* isolates resistant or showing decreased susceptibility to specific antimicrobials in London and outside London – GRASP 2011-2012. Reproduced from the 2012 GRASP Report [15]

Antimicrobials	2011			2012		
	London % (CI)	Outside London % (CI)	Total % (CI)	London % (CI)	Outside London % (CI)	Total % (CI)
* Cefriaxone (≥ 0.125 mg/L)	0.0 (-,-)	0.0 (-,-)	0.0 (-,-)	0.1 (0.0,1.6)	0.1 (0.0,0.6)	0.2 (0.1,0.7)
Azithromycin (≥ 1mg/L)	0.6 (0.31.5)	0.4 (0.2,1.1)	0.5 (0.3,1.0)	0.4 (0.2,0.9)	1.0 (0.3,3.0)	0.7 (0.3,1.6)
* Cefixime (≥ 0.125 mg/L)	11.9 (8.5,16.4)	9,9 (6.6,14.6)	10.8 (8.3,14.1)	6.0 (4.8,7.4)	5.3 (3.2,8.6)	5.6 (4.4,7.3)
* Cefixime (≥ 0.25 mg/L)	1.9 (1.0,3.5)	0.7 (0.3,1.5)	1.3 (0.7,2.2)	2.5 (1.9,3.3)	1.7 (0.8,3.4)	2.1 (1.5,3.0)
Ciprofloxacin (≥ 1 mg/L)	39.5 (32.5,46.9)	29.0 (2.3,35.3)	34.0 (28.5,40.0)	29.7 (26.6,33.0)	20.0 (14.6,26.6)	25.0 (21.0,29.6)
Spectinomycin (≥ 128 mg/L)	0.0 (-,-)	0.0 (-,-)	0.0 (-,-)	0.0 (-,-)	0.0 (-,-)	0.0 (-,-)
Tetracycline (≥ 2 mg/L)	76.3 (63.3,85.5)	61.9 (50.1,72.4)	69.1 (59.2,77.6)	85.0 (76.4,90.9)	67.6 (56.0,77.4)	76.3 (67.1,83.6)
Penicillin (≥ 1 mg/L or β lactamase +ve)	12.5 (9.7,15.9)	10.8 (7.2,16.1)	11.6 (9.1,14.7)	15.0 (14.1,16.0)	14.1 (10.3,19.0)	14.6 (12.5,16.9)

* decrease sensitivity

This heterogeneous behaviour between organisms highlights the difficulty in any forecasting of future trends. Given that the reasons behind even historical trends are still subject to debate, future forecasts must be treated with caution.

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, 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 [16] describes the emergence and spread of 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 [17] 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.

The variation in the observed proportion resistant of specimens tested at laboratories within the EU is reported to ECDC. This enables a comparative analysis of the levels of resistance to chiefly invasive bacteria across countries and time. Figure 8 above provides an illustration for MRSA, comparing the UK with other countries. This figure demonstrates the large variation in resistance observed across the countries of the EU and progress made in the UK. Figure 9 shows the variation across the EU in growing resistance of E. coli to third-generation cephalosporins.

This figure demonstrates the increasing extent of E. coli resistance to third-generation cephalosporins across Europe, where the UK shows a similar increasing temporal trend, in contrast to the MRSA temporal trend which differed for the UK compared with the EU.

Figure 7: Reproduced from European Antimicrobial Resistance Surveillance Network (EARS-Net) (http://www.ecdc.europa.eu)]. Proportion of meticillin resistant *S. aureus* isolates in participating countries in 2012.

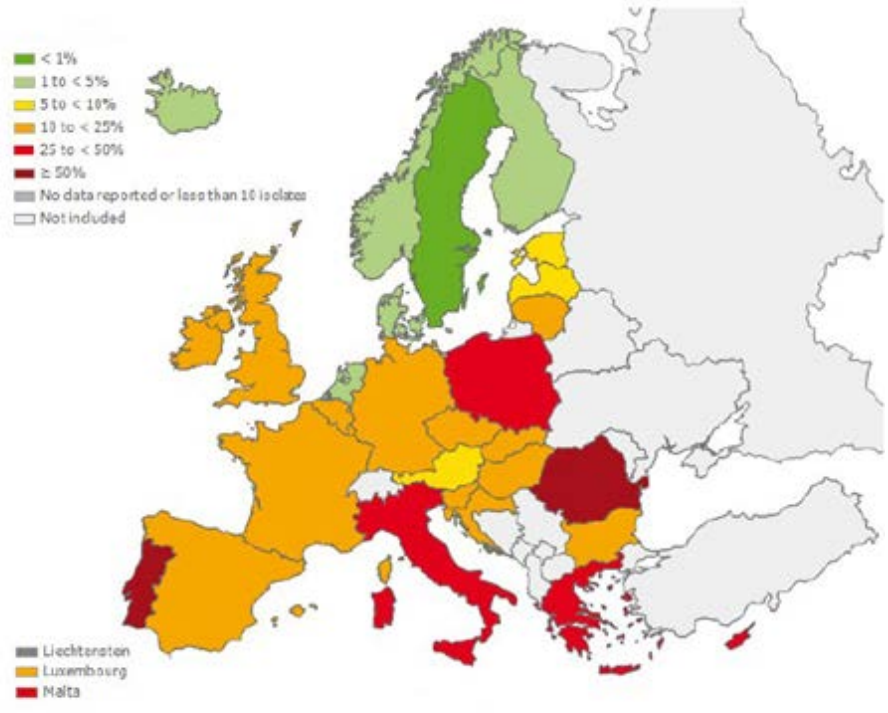


Figure 8: MRSA resistance rates across Europe 1999 to 2012

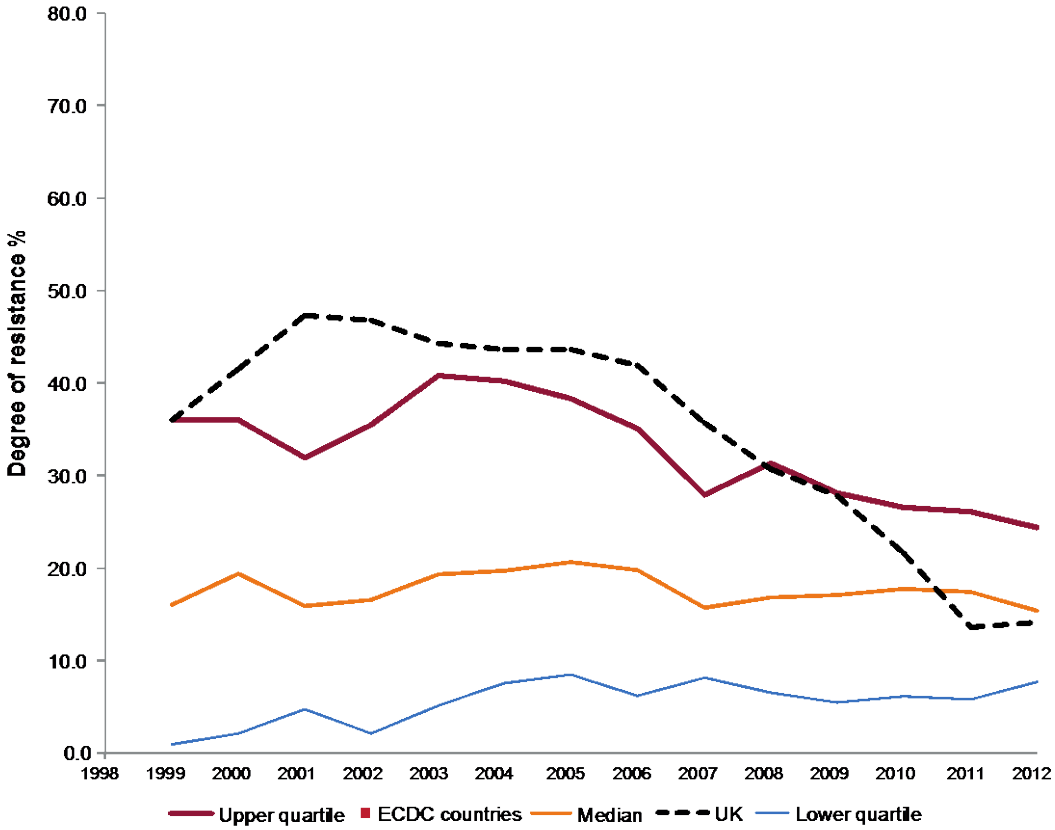


Figure 9: Third-generation cephalosporin resistance rates in *E. coli* across Europe 1999 to 2012

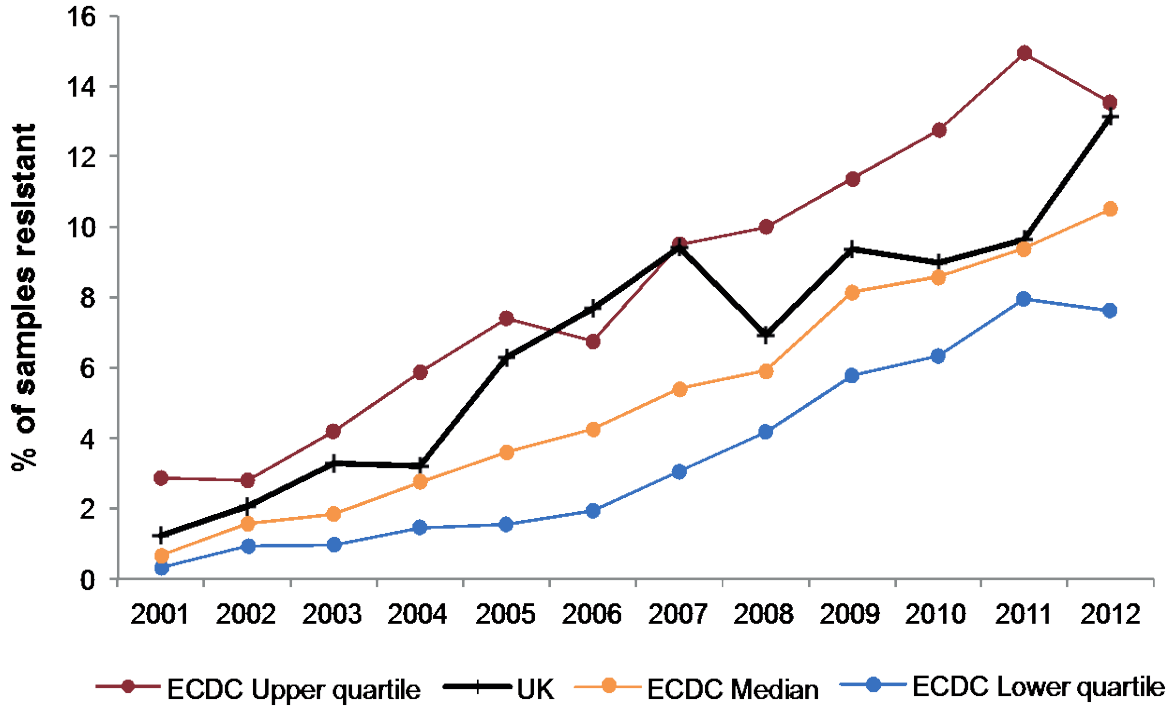
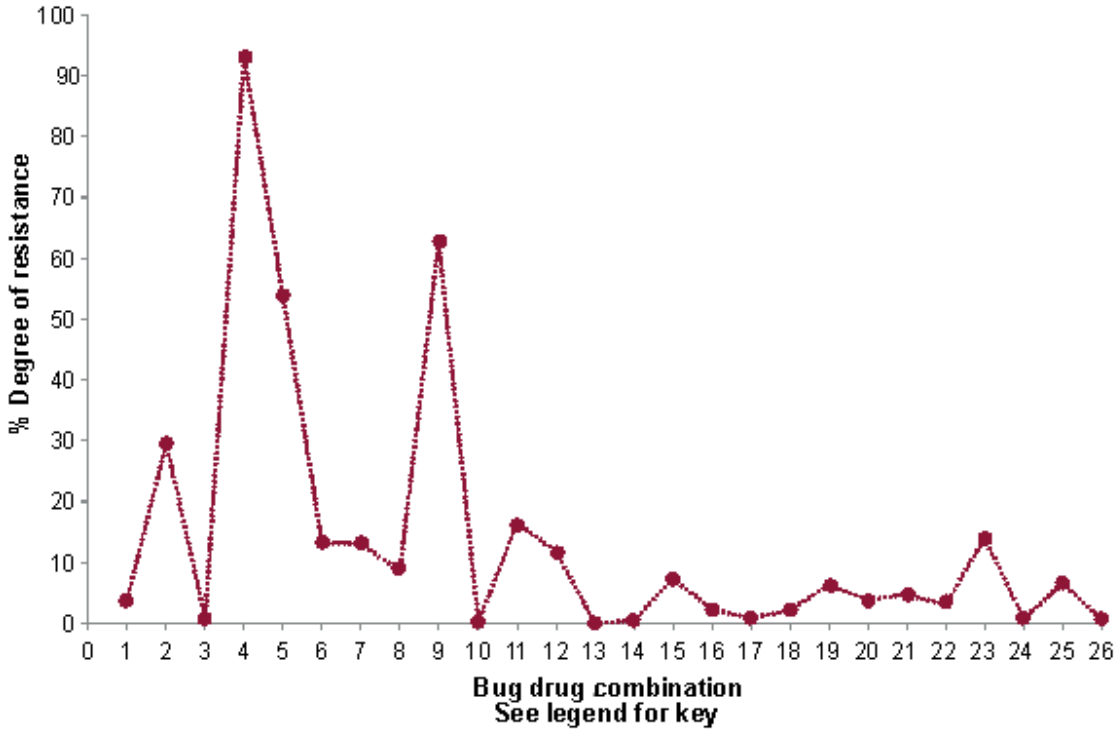


Figure 10: Degree of resistance in the UK reported to ECDC in 2012



Key	infection	Antimicrobial
1	*Enterococcus faecalis*	Aminopenicillins
2	*Enterococcus faecalis*	High-level gentamicin
3	*Enterococcus faecalis*	Vancomycin
4	*Enterococcus faecium*	Aminopenicillin
5	*Enterococcus faecium*	High-level gentamicin
6	*Enterococcus faecium*	Vancomycin
7	*Escherichia coli*	3rd gen cephalosporins
8	*Escherichia coli*	Aminoglycosides
9	*Escherichia coli*	Aminopenicillins
10	*Escherichia coli*	Carbepenems
11	*Escherichia coli*	Fluoroquinolones
12	*Klebsiella pneumoniae*	3rd gen cephalasporins
13	*Klebsiella pneumoniae*	Aminoglycosides
14	*Klebsiella pneumoniae*	Carbepenems
15	*Klebsiella pneumoniae*	Fluoroquinolones
16	*Klebsiella pneumoniae*	Multiple drug resistance
17	*Pseudomonas aeruginosa*	Amikacin
18	*Pseudomonas aeruginosa*	Aminoglycosides
19	*Pseudomonas aeruginosa*	Carbepenems
20	*Pseudomonas aeruginosa*	Ceftazidime
21	*Pseudomonas aeruginosa*	Fluoroquinolones
22	*Pseudomonas aeruginosa*	Piperacillin-tazobactam
23	*Staphylococcus aureus*	Meticillin (MRSA)
24	*Staphylococcus aureus*	Rifampin
25	*Streptococcus pneumoniae*	Macrolides
26	*Streptococcus pneumoniae*	Penicillins

Figure 10 provides a visual summary of the variation in resistance for the UK for 26 drug-bug combinations. The estimated proportion of resistant isolates in the UK is fairly low compared with the other EU countries.

The association between antibiotic use and antibiotic resistance.

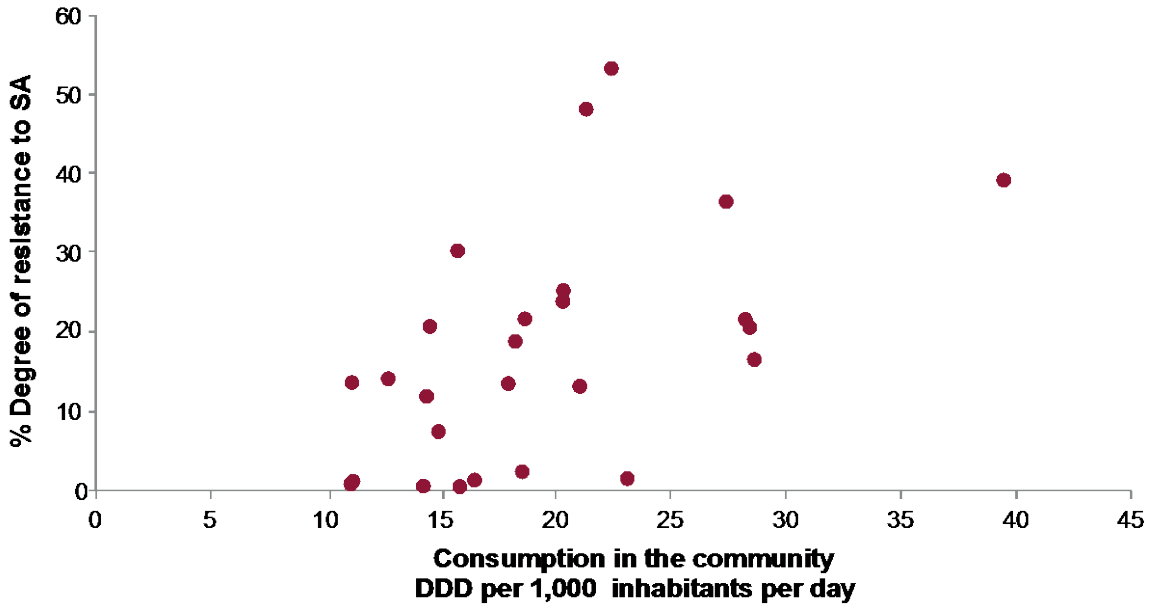
There is a growing literature of studies that attempt to quantify the association between antibiotic use and antibiotic resistance. Many of these studies assume that simple selection pressure will lead to increasing resistance in the face of increasing usage. While this can be demonstrated for certain drug-bug combinations, for others the association, if any, is not so obvious. It is unclear whether methodological issues cause the failure of some studies to find an association between usage and resistance. For example, there is no agreement regarding how best to measure antibiotic usage in these studies, and which lag between usage and resistance to use. Bergman et al [18] in a paper exploring the association between antimicrobial usage and resistance in *E. coli* found that for most of the associations they studied failed to reach statistical significance. Additionally, rates of resistance often fail to decrease after reductions in use of the relevant antibiotic. In general there is a lack of understanding of the interactions between host,

bacteria and the antibiotic that result in the emergence of resistance. 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 [19] for resistance to ampicillin and trimethoprim in *E. coli,* Hay et al [20] also found no evidence of an association for amoxicillin and trimethoprim resistance in *E. coli* in urine samples in asymptomatic patients. Kahlmeter et al [21] also found no associations between a range of antibiotics and resistance to these in *E. coli* isolates in patients with community-acquired UTIs.

Ecological data are available that allow associations of resistance rates and usage across countries. ECDC provides data on (mostly community) consumption of antimicrobials. Figure 11 shows the use of these data for MRSA suggesting a fairly strong relationship between consumption of antibacterials for systemic use (ATC group J01) and the degree of resistance reported to ECDC. One can estimate the increase in resistance for every additional daily defined dose per 1,000 population, this being 1.1% (95% confidence interval 0.6% to1.9%).

Figure 11: 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



Figures 12 and 13 show the poor 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 12: *Klebsiella pneumoniae* resistance to third-generation cephalosporins by countries 2010

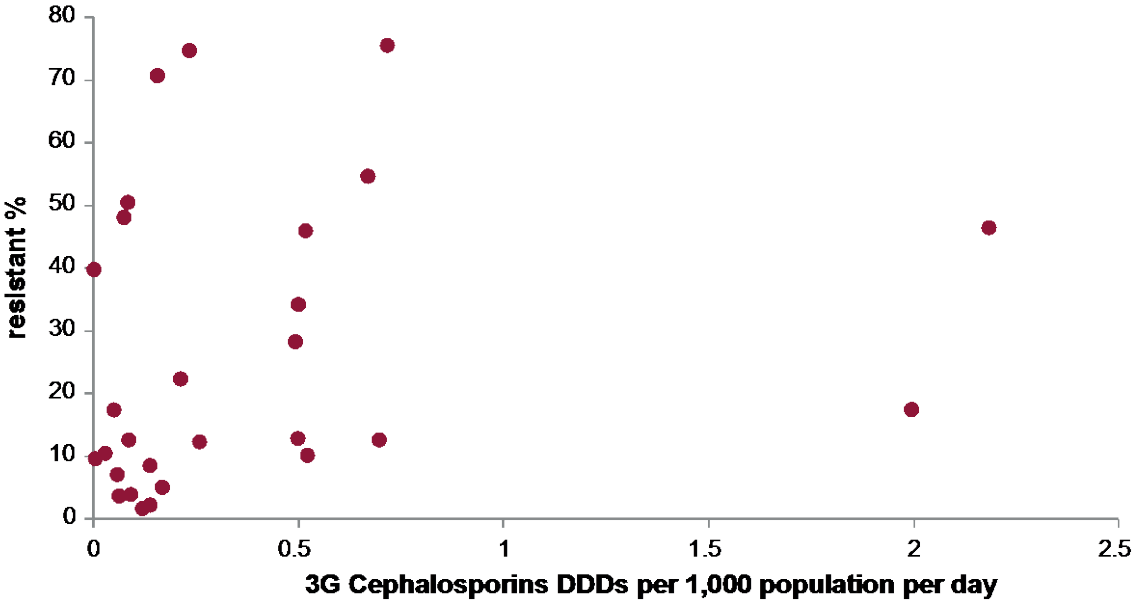
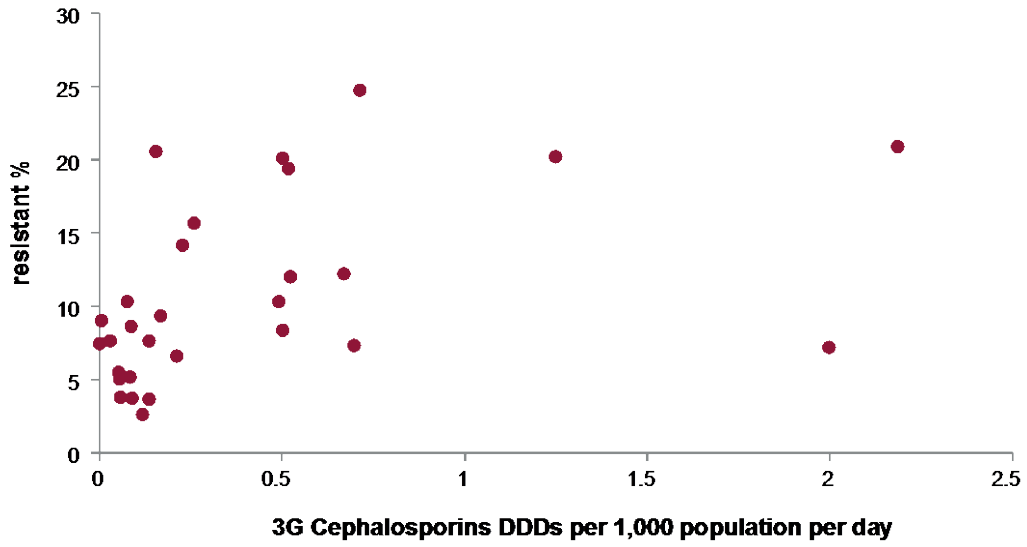


Figure 13: *E. coli* resistance to third-generation cephalosporins by countries 2010



The available evidence and the primary analysis presented provide some of the challenges in understanding how increased prescribing leads 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.

5. Burden of infection

The emergence and spread of infections caused by AMR pathogens has to be set in 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 via the CoSurv system. This provides some measure of the relative frequency of disease-causing pathogens. Over the twenty years 1991 to 2011, inclusive, more than 9 million individual bacterial isolates were reported, from 3,303 different organism/phenotypes. Table 3 is adapted from are recent paper [22] and provides the average weekly counts for the most commonly reported bacterial pathogens, for all specimen types.

Table 3: Mean weekly counts of selected bacteria received by LabBase2, 1991 and 2011.

Organism name	Mean weekly count
Chlamydia trachomatis	1,480
Campylobacter spp.	899
Staphylococcus aureus	764
Clostridium difficile toxin detection	313
Escherichia coli untyped	267
Staphylococcus coagulase negative	167
Pseudomonas aeruginosa	96
Clostridium difficile not stated	81
Streptococcus group B	57
Mycobacterium tuberculosis	54
Enterococcus faecalis	52
Klebsiella pneumoniae	50

Table 4 is adapted from a recently published manuscript [23] 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 4: Frequency of reported isolates on bacteria most likely to cause HCAI to LabBase2 between March 2007 and May 2012.

Organism group description	Frequency	Percent
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
Legionella spp.	887	0.05
Listeria spp.	894	0.05
Providentia spp.	737	0.04
Kluyvera spp.	152	0.01

A National Point Prevalence Survey was conducted in 2011 [7] to determine the burden of HCAI and antimicrobial usage (AMU) 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 5 (adapted from Table 5-7 of the report).

Table 5: Prevalence of HCAI by ward specialty group

Ward/specialty group	No. patients	Percent	No. HCAI	prevalence
	N	% (95% CI)	N	% (95% CI)
Total	52443	100.0	3360	6.4 (4.7-8.7)
ICU	1351	2.6 (2.3 - 2.8)	316	23.4 (17.3 - 31.8)
Surgery	11088	21.1 (19.4 - 23.1)	893	8.0 (5.9- 11.0)
Other specialty	1133	2.2 (2.0 - 2.4)	82	7.2 (4.9 - 10.7)
Paediatrics	2742	5.2 (4.8 - 5.7)	185	6.7 (4.9 - 9.4)
Combination of specialties	10639	20.3 (18.6 - 22.1)	614	5.8 (4.2 - 7.9)
Geriatrics	3845	7.3 (6.7 – 8.0)	218	5.7 (4.1 - 7.9)
Medicine	17010	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	4305	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 6, adapted from Table 5-8 of the prevalence study report. 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.

Table 6: Distribution of HCAI types (by group)

Type of HCAI group	Number	HCAI Prevalence
	N	% (95% CI)
Total	3506	-
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)

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 [24 and 25], however such quantification studies tend to be for particular organisms and in single centres, thus necessitating meta-analyses to estimate any statistically significant impact [26 and 27]. In addition, there a number of methodological issues with these estimations, which are described in later sections.

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 [28].

The WHO produced a report on the burden of endemic HCAI worldwide in 2011 and reported available data on HCAI endemic burden in high-, middle- and low- income countries and their impact worldwide [29]. From this, the following findings can be highlighted: prevalence in hospitalised patients, 7% in developed 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; this 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) provides information on the burden of disease and the costs attributable to infections caused by antimicrobial pathogens in member states and accession countries of the European Union (http://www.eu-burden.info). Clinical studies carried out as part of this project 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 [30 and 31].

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 [32]. For the 31 participating countries overall they estimated that in 2007, 27,711 episodes of MRSA bloodstream infections (BSI) 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 blood stream infections (BSIs) caused by third-generation cephalosporin-resistant *E. coli* were likely to rapidly increase, outnumbering the number of MRSA BSIs in the near future. Indeed there are currently around 3000 bacteraemias caused by cephalosporin resistant *E. coli* per annum in the England, about three times higher than MRSA bacteraemias.

Data from NHS England Hospital Trusts

Approximately 99,000 cases of bacteraemias were reported in adults aged over 18 in the UK between April 2011 and March 2012. Just over half the infections (53%) were caused by Gram-negative bacteria with *E. coli* the most common species (36%). Resistance was common with, for example, resistance to third-generation cephalosporins seen in 9-11% of *E. coli* and *Klebsiella* spp. Resistance to carbapenems is also now being seen, with resistance reported in 9% of *Pseudomonas* and 1% of *Enterobacter* spp.

In comparison with the European BURDEN study findings, results for English NHS Trusts show 1185 reports of MRSA bacteraemia made to the mandatory surveillance system in 2011, and 31,364 *E. coli* bacteraemias (combining mandatory and LabBase2 data). AMR data from LabBase2 suggests that 11% of *E. coli* causing bacteraemias were resistant to third-generation cephalosporins, therefore an expected 3,450 reports of third-generation cephalosporin resistant *E.coli* would be estimated for 2011.

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 [33] 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 infer ethnicity from names.

7. Economic burden

The costs and economic impact of infections caused by AMR organisms and the costs and benefit 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 [34 and 35], where a variety of drug/bug combinations were represented. In addition, we identified one study examining *Pseudomonas aeruginosa* [36], three additional studies examining *E. coli* BSI alone [32; 37; 38], two studies examining ESBL *Klebsiella* spp. [39; 40] and five mixed species of Enterobacteriaceae including *E. coli*, *Klebsiella* spp., or *Proteus* spp. infections [38, 41-44]. Overall Smith and Coast [34] 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), these are often not so 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 [45], 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 [29]. 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 [46]. This is an extremely important methodological issue that can severely bias estimation of these key economic drivers. Blot et al [47], 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 [46; 48-51].

Of note are the studies from the aforementioned BURDEN project [30-32; 52] as 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 [34], the authors demonstrated that studies typically limited their estimates to 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

In Europe, the ECDC/EMEA Joint Technical Report [1] estimated that Infections due to selected MDR bacteria in the EU result in extra healthcare costs and productivity losses of at least EUR 1.5 billion each year; based on the number of extra hospital days, extra in-hospital costs were estimated at more than EUR 900 million in the EU, Iceland and Norway, 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 [532] 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 [54] 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 [55] 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 [56] 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 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.

The ECDC/EMEA Joint Technical Report [1] estimated that currently around 25,000 patients die each year in the European Union from an infection caused by MDR 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 could be extrapolated from this report.

Results from multiple studies have been pooled in meta-analyses to estimate attributable mortality estimates: Cosgrove et al [26] for MRSA and Schwaber & Carmeli [27] for ESBL *E. coli* infection. Three original studies estimated the impact of AMR on mortality (Lautenbach et al [36] de Kracker et al. [32]; Schwaber & Carmeli [27]), of these only the previously described study by de Kraker et al [32] used rigorous statistical analysis of 30-day and in-hospital mortality to calculate the excess risk of mortality due to an AMR infection.

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 [57] 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 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 [58]. Recent Cochrane reviews evaluating stewardship interventions include that by Davey et al [59] 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 [60], and the assessment of antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults in intensive care by Liberati et al [61].

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 will bring together antimicrobial surveillance in both primary and secondary care settings, develop 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 [62] 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* associated diarrhoea (CDAD), accounting for other interventions. Associations between increased alcohol hand rub and reduced MRSA bacteraemia, and increased liquid soap use and reduced CDAD 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 CDAD. In an assessment of a behavioral intervention to improve hand hygiene compliance, Stone et al [63] 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 [64 and 65].

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 [66] failed to show lower infection rates associated with routine disinfection.

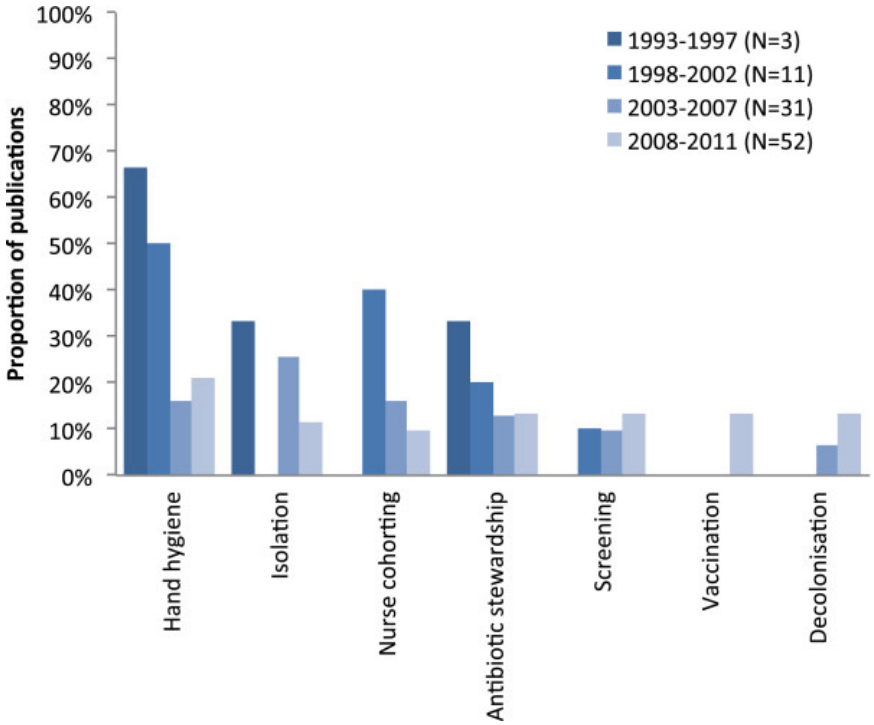
Primarily due to the problems associated with MRSA over recent years, much of the evidence for intervention effectiveness focuses on staphylococcal infection prevention and control. For example, van Rijen et al [67] reviewed evidence for infection prevention through mupirocin use in nasal carriers. The 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 [68] 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 [69].

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 [70; 71], 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 [72], comparing SDD to oropharyngeal decontamination with antibiotics (SOD), 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.

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. Since 1993 there have been 97 publications utilising model-based cost-effectiveness to evaluate interventions to control HCAI (Figure 14 reproduced from van Kleef et al [73])**.** 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.

Figure 14: Model-based cost-effectiveness evaluations of interventions in the control of HCAI



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 is 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 specifically with an 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 7.

Table 7: 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 uses to obtain descriptive analysis of the collated data.
SGSS	The Second Generation Surveillance System will from July 2014 hold 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.
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	3000 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, 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.

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 giving the current picture this is likely to soon become outdated.

References

1. European Centre for Disease prevention and Control/European Medicines Agencies (ECDPC/EMA) ECDC/EMEA Joint Technical report. Stockholm: ECDPC/EMA; 2009. The bacterial challenge: time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents. http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf

2. http://www.who.int/dg/speeches/2012/amr_20120314/en/

3. Boucher HW, Talbot GH, Benjamin DK Jr, Bradley J, Guidos RJ, Jones RN, Murray BE, Bonomo RA, Gilbert D; Infectious Diseases Society of America. 10 x '20 Progress--Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America. Clin Infect Dis. 2013 Jun;56(12):1685-94. doi: 10.1093/cid/cit152. Epub 2013 Apr 17.
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. Clin Infect Dis. 2009 Jan 1; 48(1):1-12.

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. *Clin Microbiol Infect* 2010; 16: 541–554.

6. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) Report 2014 https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

7. English National Point Prevalence Survey on Healthcare-associated Infections and Antimicrobial Use, 2011 http://www.hpa.org.uk/servlet/Satellite?c=HPAweb_C&pagename=HPAwebFile&rendermode=previewnoinsite&cid=1317134304594

8. Pearson A, Chronias A and 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) 64, Suppl. 1, i11 –i17 doi:10.1093/jac/dkp260

9. http://www.hpa.org.uk/hpr/archives/2011/news0711.htm#pvl (accessed 19/03/2014)

10. Pantelides NM, Gopal Rao G, 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? J Clin Microbiol. 2012 Oct; 50(10):3168-71. doi: 10.1128/JCM.01066-12. Epub 2012 Jul 18.

11. Ellington MJ, Ganner M, Warner M, Cookson BD, Kearns AM. Polyclonal multiply antibiotic-resistant methicillin-resistant *Staphylococcus aureus* with Panton-Valentine Leucocidin in England. *J Antimicrob Chemother* 2010; 65:46-50.

12. Reynolds, R. Antimicrobial resistance in the UK and Ireland. *Journal of Antimicrobial Chemotherapy* 2009; 64, Suppl. 1, i19–i23 doi:10.1093/jac/dkp257.

13. Livermore DM, Hope R, Reynolds R, Blackburn R, Johnson AP and Woodford N. Declining cephalosporin and fluoroquinolone non-susceptibility among bloodstream Enterobacteriaceae from the UK: links to prescribing change? *J Antimicrob Chemother* 2013; 68: 2667 –2674 doi:10.1093/jac/dkt212 Advance Access publication 13 June 2013.

14. Tuberculosis in the UK 2013 report: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317139689583 (accessed 19/03/2014)

15. GRASP 2012 Report: Trends in Antimicrobial Resistant Gonorrhoea http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317140152190 (accessed 19/03/2014)

16. McKeena M. The Last Resort. *Nature* 2013 vol 499.

17. Gupta N, Limbago BM, Patel JB and Kallen AJ. Carbapenem-Resistant Enterobacteriaceae: Epidemiology and Prevention. *Clinical Infectious Diseases* 2011;53(1):60–67

18. M. Bergman, S.T. Nyberg, P. Huovinen, P. Paakkari, A.J. Hakanen, and the Finnish Study Group for Antimicrobial Resistance. Association between Antimicrobial Consumption and Resistance in *Escherichia coli*. *Antimicrobial Agents and Chemotherapy*, Mar. 2009, p. 912–917 Vol. 53, No. 3 0066-4804/09/$08.00_0 doi:10.1128/AAC.00856-08
19. Livermore, D. M., P. Stephens, J. Weinberg, A. P. Johnson, T. Gifford, D. Northcott, D. James, R. C. George, and D. C. Speller. 2000. Regional variation in ampicillin and trimethoprim resistance in Escherichia coli in England from 1990 to 1997, in relation to antibacterial prescribing. *J. Antimicrob. Chemother*. 46:411–422.
20. Hay, A. D., M. Thomas, A. Montgomery, M. Wetherell, A. Lovering, C.McNulty, D. Lewis, B. Carron, E. Henderson, and A. MacGowan. 2005. The relationship between primary care antibiotic prescribing and bacterial resistance in adults in the community: a controlled observational study using individual patient data. *J. Antimicrob. Chemother*. 56:146–153.
21. Kahlmeter, G., P. Menday, and O. Cars. 2003. Non-hospital antimicrobial usage and resistance in community-acquired Escherichia coli urinary tract infection. *J. Antimicrob. Chemother*. 52:1005–1010.

22. Enki DG, Noufaily A, Garthwaite PH, Andrews NJ, Charlett A, Lane C, et al. Automated biosurveillance data from England and Wales, 1991–2011 *Emerg Infect Dis* [Internet]. 2013 Jan. http://dx.doi.org/10.3201/eid1901.120493

23. Freeman R, et al., Evaluation of a national microbiological surveillance system to inform automated outbreak detection, J Infect (2013), http://dx.doi.org/10.1016/j.jinf.2013.07.021

24. Schumacher M, Wangler M, Wolkewitz M, Beyersmann J. Attributable mortality due to nosocomial infections. A simple and useful application of multistate models. *Methods Inf Med*. 2007;46(5):595-600.

25. Girou E, Brun-Buisson C. Morbidity, mortality and the cost of nosocomial infections in critical care. *Curr Opin Crit Care* 1996; 2: 347-351

26. Cosgrove, S.E. et al. Comparison of Mortality Associated with Methicillin-Resistant and Methicillin- Susceptible Staphylococcus aureus Bacteremia : A Meta-analysis. *Clinical Infectious Diseases.* 2003 36, 53-59

27. Schwaber, M.J. & Carmeli, Y. Mortality and delay in effective therapy associated with extended spectrum b-lactamase production in Enterobacteriaceae bacteraemia : a systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy.* 2007 60, 913- 920.

28. http://www.who.int/gpsc/country_work/burden_hcai/en/. Accessed 1st July 2014.

29. Allegranzi B, Nejad SB, Castillejos GG, Kilpatrick C, Kelley E, Mathai E; Clean Care is Safer Care Team. Report on the Burden of Endemic Health Care-Associated Infection Worldwide, Geneva, Switzerland: World Health Organization; 2011.

30. de Kraker ME, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, Icket C, Kalenic S, Horvatic J, Seifert H, Kaasch A, Paniara O, Argyropoulou A, Bompola M,Smyth E, Skally M, Raglio A, Dumpis U, Melbarde Kelmere A, Borg M, Xuereb D, Ghita MC, Noble M, Kolman J, Grabljevec S, Turner D, Lansbury L, Grundmann H. 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. *J Antimicrob Chemoth* 2011;**66**:398–407.

31. De Kraker, M.E., Wolkewitz, M. & Davey, P.G. Clinical Impact of Antimicrobial Resistance in European Hospitals : Excess Mortality and Length of Hospital Stay Related to Methicillin-Resistant Staphylococcus aureus Bloodstream Infections. *Society.* 2011 55(4): 1598-1605.

32. De Kraker, M.E., Davey, P.G. & Grundmann, H. Mortality and Hospital Stay Associated with Resistant Staphylococcus aureus and Escherichia coli Bacteremia : Estimating the Burden of Antibiotic Resistance in Europe. *PLoS Medicine.* 2011 8(10):e1100.

33. Nimal H. Wickramasinghe, Li Xu, Andrew Eustace, Sahida Shabir, Tranprit Saluja and Peter M. Hawkey. High community faecal carriage rates of CTX-M ESBL-producing Escherichia coli in a specific population group in Birmingham, UK. *J Antimicrob Chemother* 2012; 67: 1108 –1113 doi:10.1093/jac/dks018

34. Smith R, Coast J. The true cost of antimicrobial resistance. *BMJ* 2013; 346:f1493

35. Smith R, Coast J. The economic burden of antimicrobial resistance. Why it is more serious than current studies suggest. 2013. DH Report. www.lshtm.ac.uk/php/economics/assets/dh_amr_report.pdf. (Accessed 1st July 2014.)

36. Lautenbach E, Weiner MG, Nachamkin I, et al. Imipenem resistance among pseudomonas aeruginosa isolates: risk factors for infection and impact of resistance on clinical and economic outcomes. *Infect Cont Hosp Ep* 2006;27:893–900.

37. Camins BC, Marschall J, DeVader SR, *et al.* The clinical impact of fluoroquinolone resistance in patients with E coli bacteremia. *J Hosp Med* 2011;6:344–9.

38. Schwaber MJ, Navon-venezia S, Kaye KS, *et al.* Clinical and Economic Impact of Bacteremia with Extended-Spectrum Enterobacteriaceae. *Antimicrob Ag Chemoth* 2006;50:1257–62

39. Piednoir E, Thibon P, Borderan G, *et al.* Long-term clinical and economic benefits associated with the management of a nosocomial outbreak resulting from extended- spectrum beta-lactamase-producing. *Crit Care Med* 2011;39.

40. Stone PW, Gupta A, Loughrey M, *et al.* Attributable Costs and Length of Stay of an Extended-Spectrum Beta-Lactamase-Producing Klebsielle Pneumoniae Outbreak in a Neonatal Intensive Care Unit. *Infect Cont Hosp Ep* 2012;24:601–6.

41. Gardam MA, Burrows LL, Kus JV, *et al.* Is Surveillance for Multidrug-Resistant Enterobacteriaceae an Effective Infection Control Strategy in the Absence of an Outbreak? *J Infect Dis* 2002;186:1754–60.

42. 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. *Infect Cont* 2012;25:838–41.

43. Cheong HS, Koo KS, Kang C-I, *et al.* Clinical Significance of Infections Caused by Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae Blood Isolates with Inducible AmpC Beta-Lactamase. *Microb Drug Resist* 2012;18:446–52.

44. Young S, Kotapati S, Kuti JL, *et al.* Impact of Extended-Spectrum b-Lactamase – Producing Escherichia coli and Klebsiella Species on Clinical Outcomes and Hospital Costs□: A Matched Cohort Study. *Infect Cont Hosp Ep* 2006;27:1226–32.

45. 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. Clin Infect Dis. 2010 Apr 1;50(7):1017-21.

46. 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. *J Hosp Infect.* 2011 Jun;78(2):86-91.

47. Blot S, Depuydt P, Vandewoude K, De Bacquer D. Measuring the impact of multidrug resistance in nosocomial infection. *Curr Opin Infect Dis.* 2007 Aug;20(4):391-6.

48. Lambert, M.-laurence et al. 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 11, 30-38.

49. 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. *Infect Control Hosp Epidemiol*. 2006 May;27(5):493-9.

50. 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. *Crit Care*. 2008;12(2):R44

51. Resche-Rigon M, Azoulay E, Chevret S.Evaluating mortality in intensive care units: contribution of competing risks analyses. *Crit Care.* 2006 Feb;10(1):R5.
52. Wolkewitz, M. et al. Mortality associated with in-hospital bacteraemia caused by Staphylococcus aureus : a multistate analysis with follow-up beyond hospital discharge. *Journal of Antimicrobial Chemotherapy.* 2011 66, 3816 - 386

53. U.S. Congress, Office of Technology Assessment, Impacts of Antibiotic-Resistant Bacteria, OTA-H-629 (Washington, DC: U.S.Government Printing Office, September 1995).

54. Deborah A. Williamson, Joshua T. Freeman, Sally A. Roberts, Helen Heffernan, Kristin Dyet, David L. Paterson, Benjamin A. Rogers, Hanna E. Sidjabat and Jonathan Masters. Rectal colonization with New Delhi metallo-b-lactamase-1-producing Escherichia coli prior to transrectal ultrasound (TRUS)-guided prostate biopsy *J Antimicrob Chemother* 2013 doi:10.1093/jac/dkt277 Advance Access publication 3 July 2013

55. C. A. M. McNulty, J. Richards, D. M. Livermore, P. Little, A. Charlett, E. Freeman, I. Harvey and M. Thomas. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. *Journal of Antimicrobial Chemotherapy* (2006) 58, 1000–1008 doi:10.1093/jac/dkl368 Advance Access publication 23 September 2006

56. David M. Livermore, Robert L.R. Hill, Hazel Thomson, André Charlett, Jane F. Turton, Rachel Pike, Bharat C. Patel, Rohini Manuel, Stephen Gillespie, Indran Balakrishnan,Stephen P. Barrett, Nigel Cumberland, Mary Twagira, C-MRAB Study Group. Antimicrobial treatment and clinical outcome for infections with carbapenem and multiply-resistant Acinetobacter baumannii around London. *International Journal of Antimicrobial Agents* 35 (2010) 19–24

57. NE Holmes, JD Turnidge, WJ Munckhof, JO Robinson, TM Korman, MVN O'Sullivan, TL Anderson, SA Roberts, SJC Warren, W Gao, PDR Johnson and BP Howden. Vancomycin minimum inhibitory concentration, host comorbidities and mortality in Staphylococcus aureus bacteraemia. *Clin Microbiol Infect* 2013; 19: 1163–1168 10.1111/1469-0691.12168

58. 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.

59. 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 Apr 30;4:CD003543. doi: 10.1002/14651858.CD003543.pub3.

60. Inglis GD, Jardine LA, Davies MW. Prophylactic antibiotics to reduce morbidity and mortality in ventilated newborn infants. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD004338.

61. Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD000022. doi:10.1002/14651858.CD000022.pub3.

62. SP Stone, C Fuller, J Savage,B Cookson, A Hayward, B Cooper, G Duckworth, S Michie, M Murray, A Jeanes, J Roberts, L Teare, A Charlett. 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:e3005 doi: 10.1136/bmj.e3005

63. Stone S.Fuller C, Michie S, Savage J, McAteer J, Besser S, et al. (2012) The Feedback Intervention Trial (FIT) — Improving Hand-Hygiene Compliance in UK Healthcare Workers: A Stepped Wedge Cluster Randomised Controlled Trial. PLoS ONE 7(10): e41617. doi:10.1371/journal.pone.0041617.

64. Boyce JM, Pittet D. *Guideline for Hand Hygiene in Healthcare Settings: Recommendations of the Healthcare Infection Control Practice Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hygiene Task Force* 2002. p.58

65. Pratt RJ, Pellowe C, Loveday HP, Robinson N, Smith GW, and the epic guideline development team; Barrett S, Davey P, Harper P, Loveday C, McDougall C, Mulhall A, Privett S, Smales C, Taylor L, Weller B, and Wilcox M. The epic Project: Developing National Evidence-based Guidelines for Preventing Healthcare associated Infections. Phase 1: Guidelines for Preventing Hospital-acquired Infections. *J Hosp Infect* 2001; 47(Supplement): S1-S-82.Boyce JM, Pittet D. *Guideline for Hand Hygiene in Healthcare Settings: Recommendations of the Healthcare Infection Control Practice Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hygiene Task Force* 2002. p.58

66. Dettenkofer M, Wenzler S, Amthor S, Antes G, Motschall E, Daschner FD. Does disinfection of environmental surfaces influence nosocomial infection rates? A systematic review. *Am J Infect Control* 2004; 32(2): 84-89.

67. van Rijen M, Bonten M, Wenzel R, Kluytmans J.
Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers.Cochrane Database Syst Rev. 2008 Oct 8;(4):CD006216. doi: 10.1002/14651858.CD006216.pub2.

68. 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 4;329(7465):533.

69. Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, Kahlmeter G, Pan A, Petrosillo N, Rodríguez-Baño J, Singh N, Venditti M, Yokoe DS, Cookson B; European Society of Clinical Microbiology. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect. 2014 Jan;20 Suppl 1:1-55.

70. Silvestri L1, 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. J Hosp Infect. 2007 Mar;65(3):187-203.

71. 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. Lancet Infect Dis. 2013 Apr;13(4):328-41. doi: 10.1016/S1473-3099(12)70322-5. Epub 2013 Jan 25.

72. de Smet AM1, 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, Kuijper EJ, Joore JC, Leverstein-van Hall MA, Bindels AJ, Jansz AR, Wesselink RM, de Jongh BM, Dennesen PJ, van Asselt GJ, te Velde LF, Frenay IH, Kaasjager K, Bosch FH, van Iterson M, Thijsen SF, Kluge GH, Pauw W, de Vries JW, Kaan JA, Arends JP, Aarts LP, Sturm PD, Harinck HI, Voss A, Uijtendaal EV, Blok HE, Thieme Groen ES, Pouw ME, Kalkman CJ, Bonten MJ. Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med. 2009 Jan 1;360(1):20-31. doi: 10.1056/NEJMoa0800394.

73. van Kleef et al. Modelling the transmission of healthcare associated infections: a systematic review. BMC Infectious Diseases 2013 13:294.

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