Scottish Medicines Consortium

Scottish Antimicrobial Prescribing Group

NHS National Services Scotland

Report on Antimicrobial Use and Resistance in Humans in 2013

Health Protection Scotland

ISD SCOTLAND

Acknowledgements
This report could not have been compiled without antimicrobial resistance data provided by diagnostic and reference laboratories within Scotland and the prescribing team at Information Service Division (ISD) who assisted with analysis of antimicrobial use data. We also extend thanks to the Scottish Microbiology and Virology Network for advice on the development of this programme and their ongoing input into national surveillance of antimicrobial resistance.

Health Protection Scotland (HPS) and Information Services Division (ISD) are divisions of NHS National Services Scotland.

HPS website: http://www.hps.scot.nhs.uk
ISD website: http://www.isdscotland.org/

Published by Health Protection Scotland and Information Services Division

First published January 2015

ISBN: 978-1-873772-46-1

Reference this document as:
Health Protection Scotland and Information Services Division. Report on Antimicrobial Use and Resistance in Humans in 2013. Health Protection Scotland and Information Services Division. 2015 [Report]

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Table of Contents

List of Figures

List of Tables

Executive Summary

This is the sixth annual report that combines information on antimicrobial use and resistance in humans in Scotland.

In 2013, the use of systemic antibacterials in primary care (excluding dental) was 2.09 items/1000/day; 5.4% lower than in 2012 and the largest annual reduction since 2000.

The total use of systemic antibacterials in hospitals was 3.88 DDDs/1000/day; a 1.6% increase from 2012. There has been a continued upward trend since 2009; however, the increase in the rate of prescribing observed in 2013 was lower than in previous years.

From 2012 to 2013, an increase of 2.2% was observed in the use of carbapenems. There has been a continued upward trend in the use of carbapenems since 2009; however, this increase observed in 2013 was lower than in any of the previous three years.

Resistance to carbapenems remained low among Gram-negatives causing bacteraemia with 0.2% of *K. pneumoniae* and none of the *E. coli* isolates being resistant to meropenem. Reports of carbapenemase producing Gram-negative organisms by the AMRHAI Reference Unit also remained stable in 2013-2014, despite a substantial increase in submissions to the reference laboratory.

However, the epidemiological status of carbapenemase producers in Scotland recently changed from 'sporadic' to 'regional spread' following two incidents of local spread reported in 2014. An increase in meropenem resistance was also observed among Scottish *E. coli* urinary isolates (from 0% in 2012 to 0.03% in 2013).

Further development of resistance to carbapenems and spread of carbapenemase producing organisms remains a serious concern in Scotland and across Europe.

There was a 4.5% increase reported in the use of co-amoxiclav in secondary care in 2013 as compared to 2012. This coincided with an increase in resistance to co-amoxiclav among *E. coli* bacteraemias from 18.4% in 2012 to 28.4% in 2013, above that reported in 2009-2011 (range: 23.4%-25.4%).

The use of piperacillin-tazobactam has continued to rise, with a 7.4% increase in 2013 as compared 2012. The resistance (8.6% in 2013) to piperacillin-tazobactam among *E. coli* bacteraemias is of concern due to its frequent clinical use.

The importance of continued efforts to reduce unnecessary antimicrobial use in all healthcare settings to reduce the selective pressure for antimicrobial resistance is highlighted along with specific recommendations in this report.

Introduction

Antimicrobial resistance remains a major public health issue and a threat to the future of health and healthcare. The World Health Organisation has warned of a post-antibiotic era in which common infections and minor injuries can kill. The scale of the threat from antimicrobial resistance and the case for action was set out in the UK Five Year Antimicrobial Resistance Strategy 2013-2018, published in 2013.[1] There are few new antimicrobials in development and conservation of the currently available treatments is vital.

This is the sixth annual report on antimicrobial use and resistance in humans and is intended to underpin the national framework on antimicrobial stewardship co-ordinated by the Scottish Antimicrobial Prescribing Group (SAPG). The report is intended to support NHS boards with planning, implementation and evaluation of interventions to improve antimicrobial use, outcomes for patients with infection, and limit development of antimicrobial resistance.

This report is presented in a different format to the previous reports. The key emerging issues and recent changes in antimicrobial use and resistance patterns are highlighted through short, focussed narratives and graphic illustrations of the key findings. The methods and full dataset on antimicrobial use and resistance is accessible in a data table in an Appendix to this report.

Summary of recommendations

It is recommended that:

- SAPG continue to emphasise the importance of interventions to reduce unnecessary antimicrobial use in primary care to reduce the selective pressure for antimicrobial resistance.
- SAPG continue to implement and monitor hospital based interventions to de-escalate and discontinue treatment when clinically appropriate as part of the broader strategy to reduce population exposure to antibacterials.
- SAPG consider how it can influence appropriate microbiological sampling strategies as part of initiatives to support clinical decision making and de-escalation of initial empirical antibacterial treatment.
- NHS National Services Scotland continue to monitor the use of and resistance to carbapenems and the agents promoted by SAPG as options to spare the use of carbapenems.
- SAPG continue to implement and monitor hospital based interventions to promote alternatives to carbapenems.
- SAPG consider the place in therapy of co-amoxiclav and piperacillin-tazobactam against the background of increases in use in secondary care and resistance among *E. coli* bacteraemias.

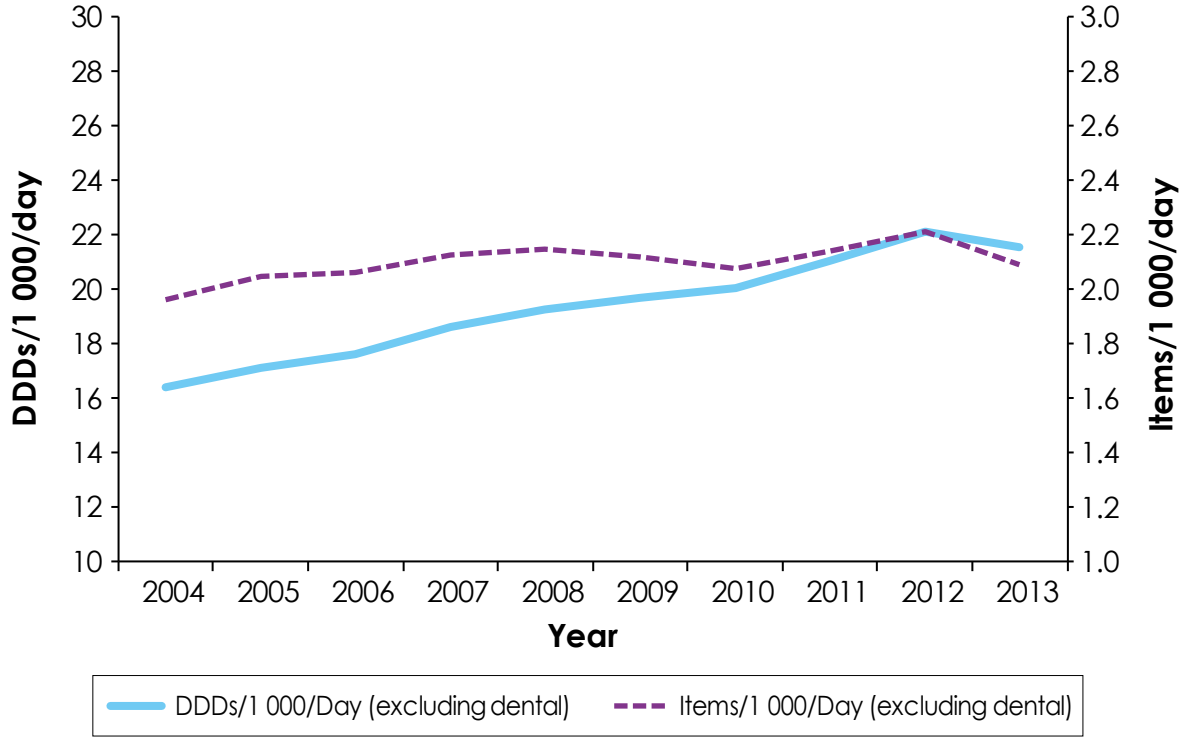
Results

Total use of antibacterials

The development of antimicrobial resistance is a complex evolutionary process, but it is accepted that the driver for the development of resistance is use of antibacterials, and that resistance is greatest where use is greatest. There is evidence from systematic reviews and randomised controlled trials that antibacterials have limited efficacy in treating a large proportion of respiratory tract infections. A key component of the Scottish framework for antimicrobial stewardship in 2013 was the reduction in unnecessary prescribing.

In 2013, the use of systemic antibacterials in primary care (excluding dental) was 2.09 items/1000/day; 5.4% lower than in 2012 (**Figure 1**). This represents a reduction of 224 582 fewer antibacterial items in 2013. This is the largest annual reduction in primary care use of antibacterials since 2000. The rate of antibacterial use in defined daily doses (DDD) decreased in 2013 by 2.5% to 21.57 DDD/1000/day; the first annual reduction since 2004. It is too early to tell whether these reductions have arrested the steady growth in antibacterial use observed over the last ten years.

Figure 1: NHS Scotland: use of antibacterials in primary care, items/1000/day and DDD/1000/day 2004-2013



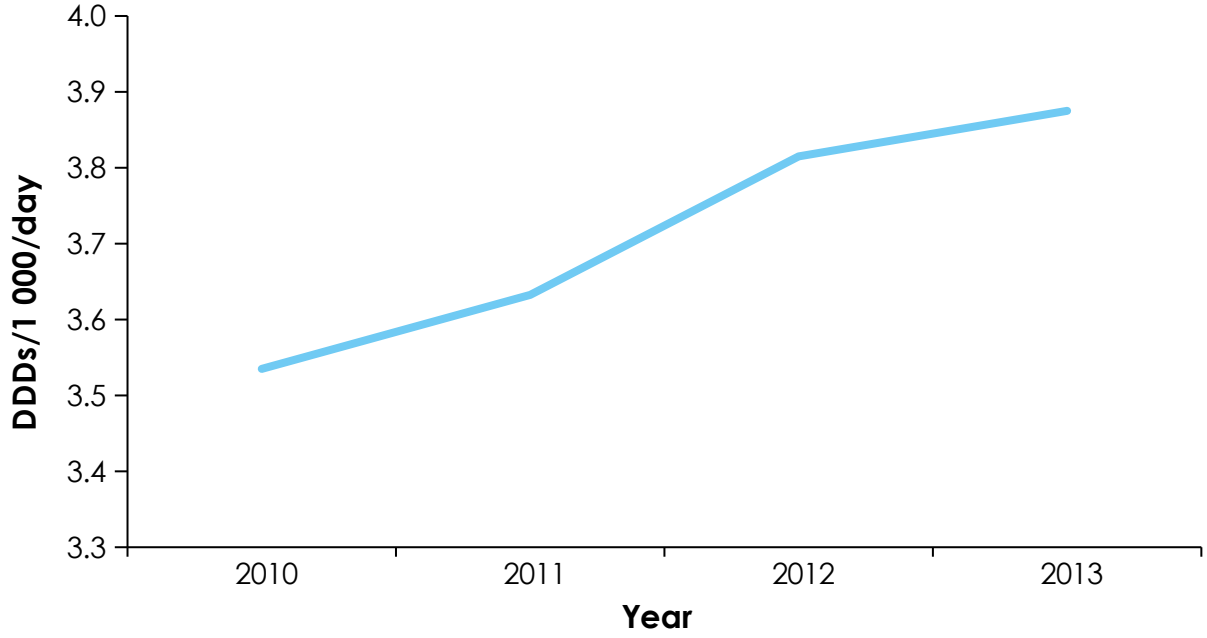
The Scottish Antimicrobial Prescribing Group (SAPG) has given increased prominence in its work programme to initiatives to reduce unnecessary use of antibacterials in primary care. A key action in 2013 was the introduction by the Scottish Government of a Healthcare Associated Infection (HAI) Level Three Quality Indicator on total antibacterial use. This indicator was intended to act as a stimulus to reduce unnecessary antibacterial use. A further key development was the launch in October 2013 of the Scottish Reduction of Antimicrobial Prescribing (ScRAP) programme, developed by SAPG in collaboration with NHS Education for Scotland. This programme is an educational toolkit to help prescribers to reduce unnecessary prescribing of antimicrobials.

Using prescribing data from January to March 2014, one year from the baseline, nine (of 14) NHS boards met the target of having at least 50% of practices at or below the baseline target level or made the minimum acceptable reduction. Overall, 57.5% of Scottish GP practices achieved the level three quality indicator. More details on the indicator results are available in the SAPG Primary Care Prescribing Indicators 2013-14 report.

It is recommended that SAPG build on this initial progress by continuing to emphasise the importance of interventions to reduce unnecessary antimicrobial use in primary care to decrease the selective pressure for antimicrobial resistance.

In 2013, the total use of systemic antibacterials in secondary care was 3.88 DDD/1000/day (**Figure 2**). This was 1.6% higher than in 2012 and, although it continues the upward trend since 2009, the increase in rate of prescribing in 2013 was lower than in previous years. Work is ongoing to analyse how changes in hospital activity, case mix and prescribing guidance may have influenced total use of antibacterials in Scotland.

Figure 2: NHS Scotland: use of antibacterials in secondary care, DDD/1000/day 2010-2013 (13 NHS boards covering 94% of the population)



As part of the national framework for antimicrobial stewardship in Scotland, SAPG has developed, piloted and is implementing prescribing indicators on duration of antibacterial treatment in continuing care wards. The aim of this indicator is to support de-escalation and discontinuation of antibacterial treatment and thereby reduce inappropriately excessive duration of treatment.

It is recommended that SAPG continue to implement and monitor hospital based interventions to de-escalate and discontinue treatment when clinically appropriate as part of the broader strategy to reduce population exposure to antibacterials.

It is important when an infection is suspected that relevant microbiological specimens are taken and submitted for culture and sensitivity testing. As part of initiatives to support clinical decision making, it is important to ensure these test results are reviewed when available to enable de-escalation of initial empirical antibacterial treatment.

It is recommended that SAPG consider how it can influence appropriate microbiological sampling strategies.

Detailed reporting on trends in antimicrobial use is available in the Appendix.

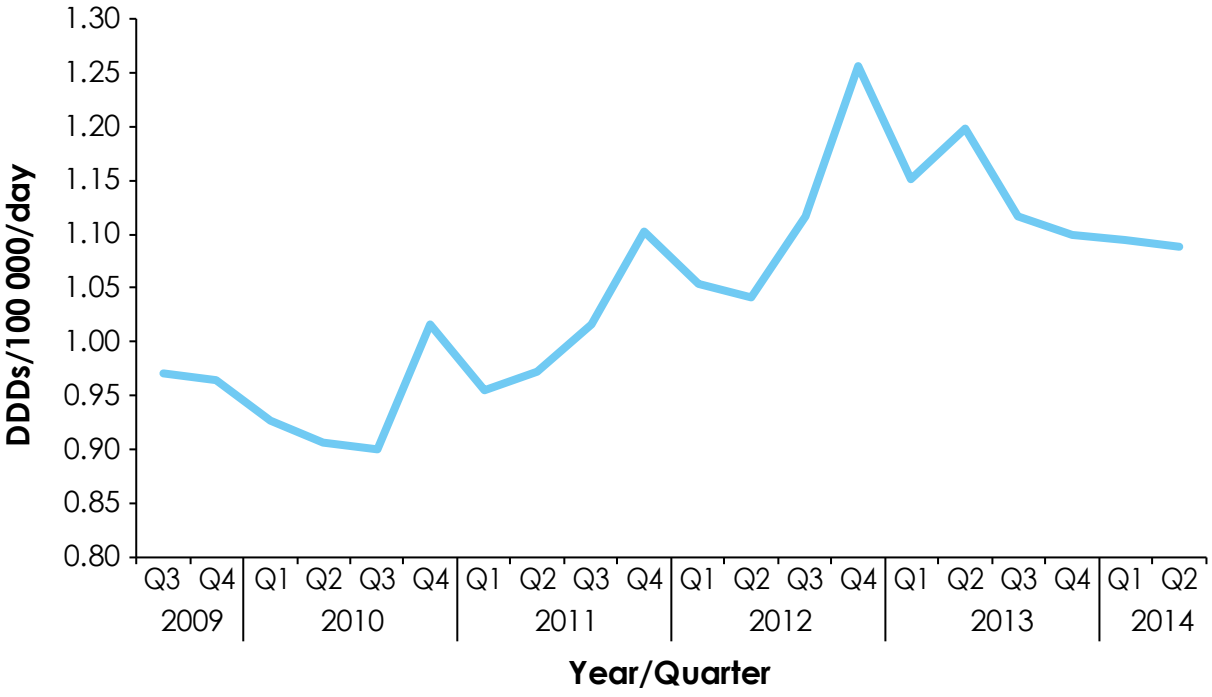
Carbapenem use and the threat from carbapenemase-producing *Enterobacteriaceae*

Carbapenems are used almost exclusively in the hospital setting for the treatment of suspected or confirmed multi-resistant Gram-negative infections. Due to the lack of new antibacterials under development they are considered to be a critically important group of agents whose effectiveness must be preserved. In October 2013, SAPG published guidance for Antimicrobials Management Teams (AMTs) and infection specialists to support clinicians to manage infections caused by Gram-negative bacteria and, specifically, through recommendations for empirical and targeted use of alternative antibacterials, to reduce the use of and thereby preserve the effectiveness of carbapenems.

In 2013, the use of carbapenems was 2.2% higher than in 2012. Although this continues the upward trend observed in previous years the increase in 2013 was lower than in the any of the previous three years. Meropenem accounted for 94.3% of carbapenem use in 2013. **Figure 3** illustrates the use of carbapenems using the most recently available information on a quarterly basis. This shows a steady increase in use up to a peak in quarter four 2012 after which there was a trend toward a reduction in use. It remains to be seen whether this is the start of a sustained reduction in use of carbapenems.

We will continue to monitor the use of carbapenems and the agents promoted by SAPG as options to spare the use of carbapenems in future reports and it is recommended that SAPG continue to implement and monitor hospital based interventions to promote alternatives to carbapenems.

Figure 3: NHS Scotland: use of carbapenems in secondary care, DDD/100 000/ day, Quarter 3 2009 to Quarter 2 2014 (13 NHS boards covering 94% of the population)



In Scotland, a total of 26 carbapenemase producing Gram-negative organisms (including *Enterobacteriaceae* and non-fermenters) were reported from the Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit (Public Health England (PHE)) in 2014, which was at the same level as 2013 (**Figure 4** – for more detailed information see the Appendix). The stable numbers of carbapenemase producers is reassuring especially in the light of a substantial quarterly increase in recent submissions to the AMRHAI Reference Unit for carbapenemase identification and typing as a result of increased awareness among the Scottish diagnostic laboratories. However, there could still be under-ascertainment as no national surveys of referrals patterns and compliance with screening policy have been carried out.

Although spread of *Klebsiella pneumoniae* carbapenemase (KPC)-producing clones of *K. pneumoniae* (ST258) has been reported world-wide, often in association with spread in healthcare settings, this organism was only detected once in Scotland in 2014.

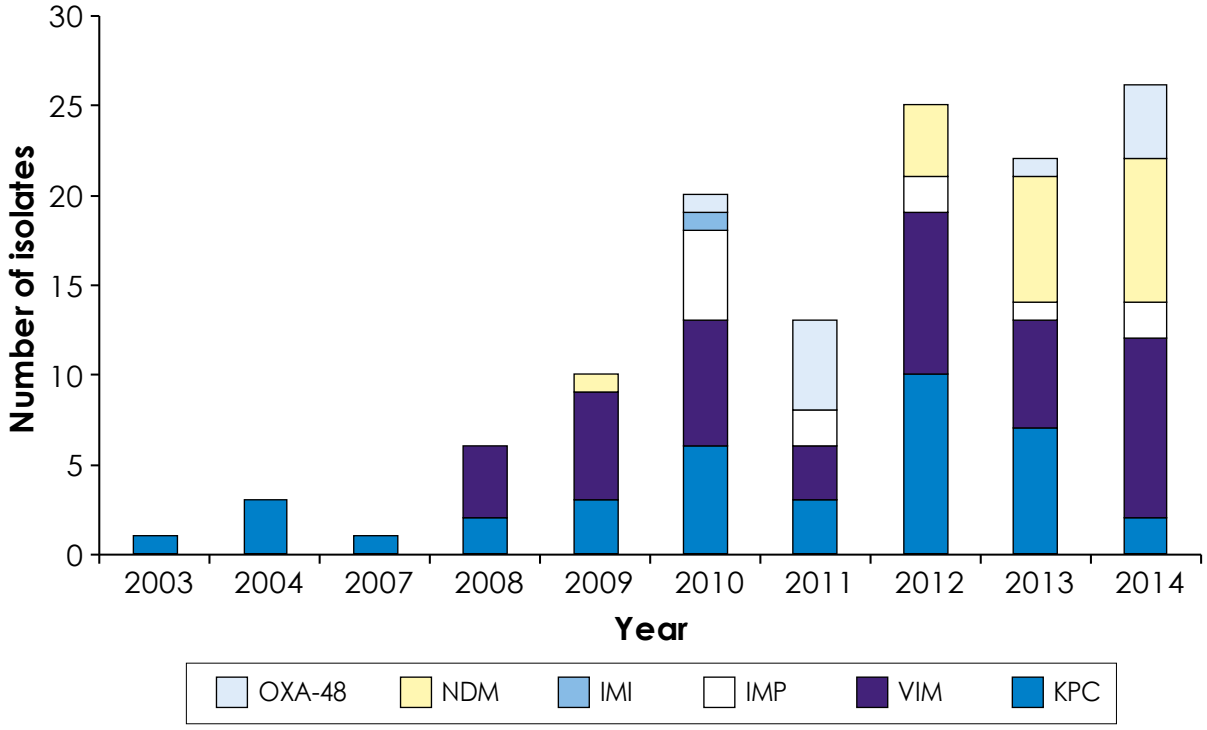
However, New Delhi metallo-lactamase (NDM)-producers were reported on eight occasions in 2014, including *E. coli* (5), *Enterobacter cloacae* complex (1), *K. pneumoniae* (1) and *Proteus mirabilis* (1), with all but two detected in urinary isolates. NDM is disseminated via conjugative plasmids that can be exchanged between different bacterial species often within the Gram-negative gut flora of persons both in the community and healthcare settings, and can therefore spread via multiple routes.

According to previous reports, NDM-producers have been reported more frequently in the UK than in the rest of Europe, but this may partly be due to under-ascertainment in some countries.

Epidemiological stages, ranging from sporadic to endemic spread of carbapenemase producers, are used to compare the spread of carbapenemase producers in European countries.[2] In the previous AMR annual report (for 2012), the spread of carbapenemase producers in Scotland was reported as sporadic. However, two incidents of local spread have now been reported to HPS, which results in Scotland now being reported as a country with 'regional spread' similar to the situation in England.

In 2013, a joint Chief Medical Officer (CMO)/Chief Nursing Officer (CNO)/Chief Pharmacy Officer (CPO) letter (CMO/SGHD (2013)14) highlighted the spread of carbapenemase producers in a number of European countries with some countries moving towards an endemic situation. The letter introduced mandatory screening of patients who have been transferred from a hospital abroad, been hospitalised abroad within the last 12 months or who have previously been positive for carbapenemase producers at any body-site. In addition, NHS boards were required to have an action plan for prevention and control of carbapenemase producers in place in line with the national interim guidance.[3]

Figure 4: Carbapenemase producers reported in Scotland by AMRHAI Reference Unit (PHE)



In recognition of the lack of standardised laboratory testing and laboratory capability to identify and characterise across Europe, the European Survey of Carbapenemase Producing *Enterobacteriaceae* (EUSCAPE) was established with support of the European Centre for Disease Prevention and Control (ECDC).

For a six-month period within 2012/2013, clinical isolates of all types (excluding faecal samples) received for routine diagnostics were screened for potential carbapenemase production (focussing on *E. coli* and *K. pneumoniae* only) followed by subsequent identification of the enzymes by PCR and other methods in line with the EUSCAPE protocol.

The study involved more than 400 hospitals in Europe, including 14 from Scotland from the Greater Glasgow and Edinburgh areas, and the Scottish *Salmonella*, *Shigella* and *Clostridium difficile* Reference Laboratory (SSSCDRL) who functioned as the 'typing centre' for the study. Within the six-month period only, one NDM-producing *E. coli* was identified out of 25 suspect isolates (and 25 controls) in the Scottish part of the study. The epidemiological data obtained are also being analysed at UK and European levels by PHE and the EUSCAPE project group, and it has been agreed to establish a European isolate collection at University Medical Center Groningen (UMCG), the Netherlands, with a view to sequence all isolates from the survey to characterise the relatedness of strains across Europe.

The national laboratory capability to identify and further characterise carbapenemase producers and international collaborations on surveillance and epidemiological surveys are key to controlling the further spread of these resistance mechanisms which occur in a wide range of Gram-negative organisms.

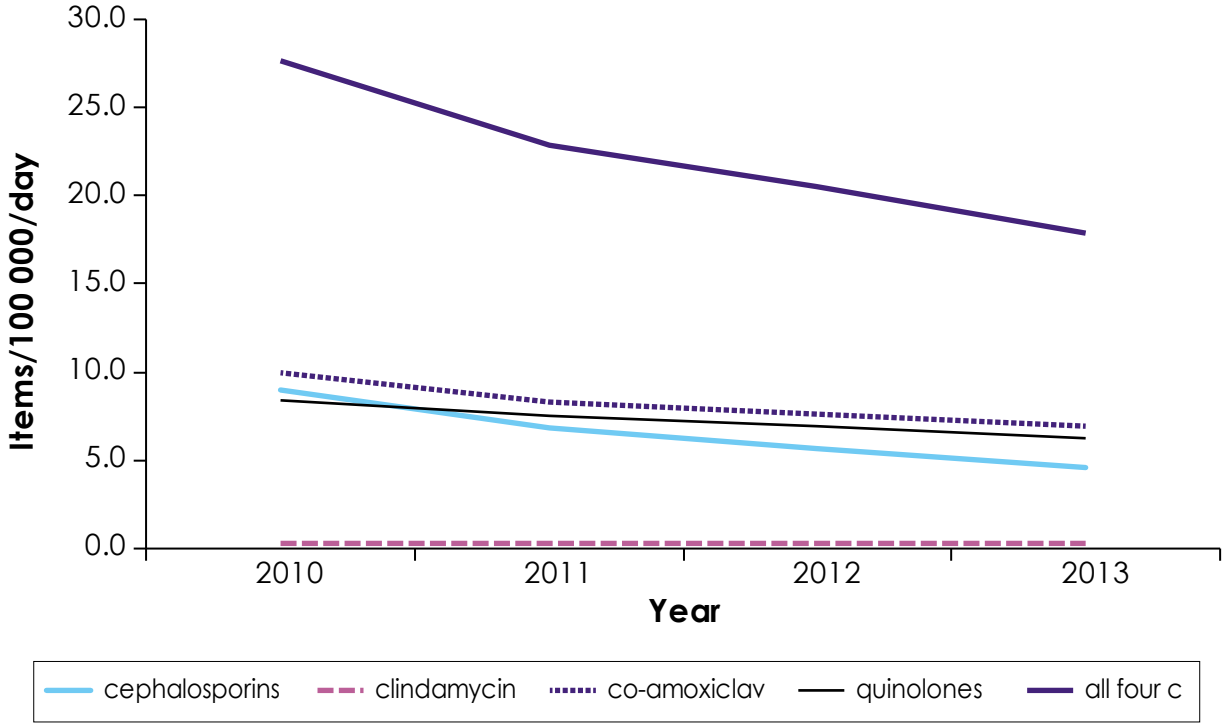
Use of broad-spectrum antibacterials

The initial priority for SAPG following its establishment in 2008 was the development of prescribing policies to improve the quality of prescribing of antibacterials through influencing the choice of antibacterial use for empirical treatment of infection. These policies were intended to promote the use of narrower spectrum agents at the expense of those broader spectrum agents which are associated with a higher risk of *Clostridium difficile* infection (CDI). These agents: co-amoxiclav, clindamycin, fluoroquinolones (mainly ciprofloxacin) and cephalosporin were commonly referred to as '4C' antibacterials.

In 2013, there was a 12.7% reduction in the primary care use of these high-risk antibacterials compared to 2012 (**Figure 5**). There were reductions in use of co-amoxiclav (9.2%), fluoroquinolones (10.1%) and cephalosporins (17.9%), while clindamycin showed no change in 2013. These reductions build on those observed in previous years and reflect the ongoing impact of initiatives on formulary compliance in primary care. This work should continue.

In secondary care a different pattern has emerged. In 2013 there was a 0.3% increase in use of high risk antibacterials. However, it is only when the use of these antibacterials are analysed separately that the full picture is revealed (**Figure 6**). In 2013, the overall increase in use of 4C antibacterials was driven by a 4.5% increase in co-amoxiclav use, whereas there were reductions in the use of cephalosporins (20.0%) and fluoroquinolones (1.3%).

Figure 5: NHS Scotland: use of antibacterials associated with higher risk of CDI, Items/100 000/day, 2010 to 2013, primary care



Resistance among *E. coli* bacteraemias to co-amoxiclav increased from 18.4% in 2012 to 28.4% in 2013, above that reported in 2009-2011 (range: 23.4%-25.4%) (**see also page 12 for caveats related to co-amoxiclav resistance**). This increase in co-amoxiclav resistance coincided with the increased use of co-amoxiclav.

In 2008, when the reduction in CDI was the key priority, it was appropriate to consider these high risk antibacterials as a group to focus improvement activity. However, these antibacterials are not a homogenous group with respect to their risk of CDI [4] or in their place in therapy. The landscape is now different with respect to CDI and AMR. Consideration should be given to the most effective way to feedback information of the use of antibacterials associated with a higher risk of CDI. There is a case for reporting information on these agents separately but there are times when continuing to report cumulative use may be appropriate.

The beta-lactam/beta-lactamase inhibitor combination of piperacillin-tazobactam is a broad-spectrum agent active against a wide range of pathogenic organisms. The use of this combination penicillin continued to rise, with a 7.4% increase in 2013 (**Figure 7**). The resistance (8.6% in 2013) to piperacillin-tazobactam among *E. coli* bacteraemias is of concern due to its frequent clinical use.

Against the background of increases of co-amoxiclav and piperacillin-tazobactam use in secondary care and resistance among *E. coli* bacteraemias, it is recommended that SAPG review prescribing guidance to consider the place in therapy of these antibacterials.

Figure 6: NHS Scotland: use of antibacterials associated with higher risk of CDI, DDD/100 000/day, 2010 to 2013 in secondary care (13 NHS boards covering 94% of the population)

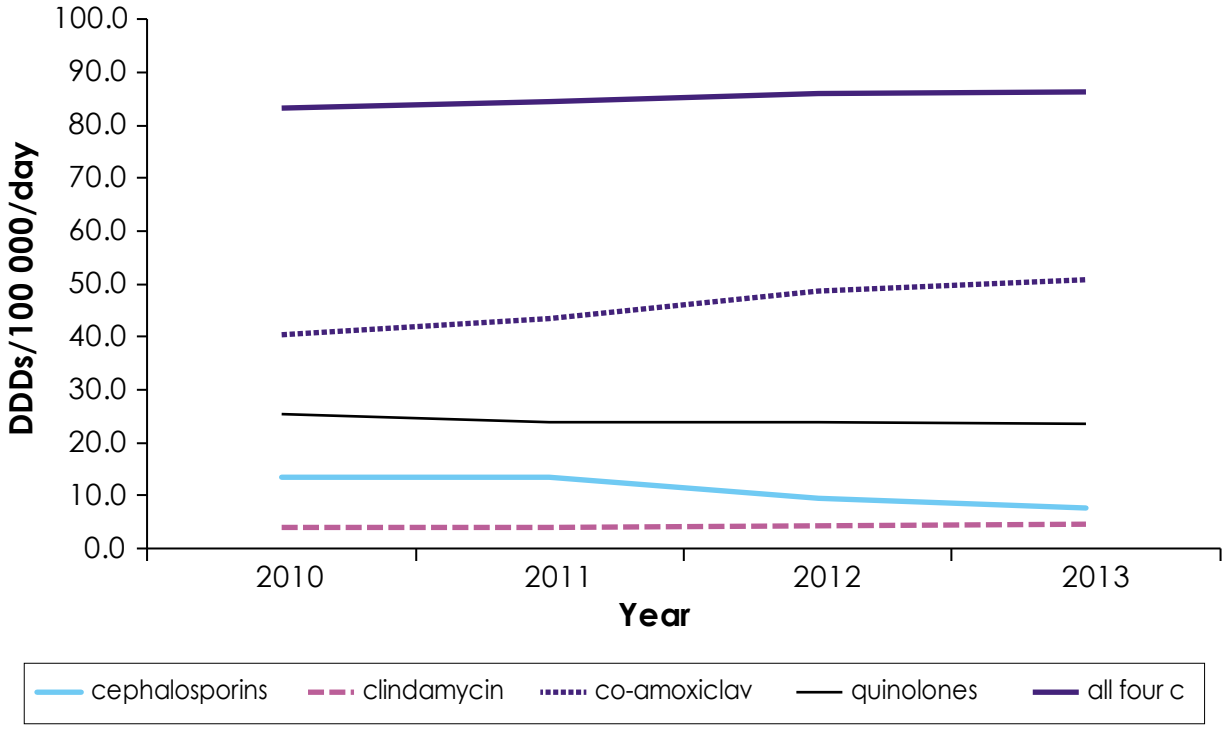
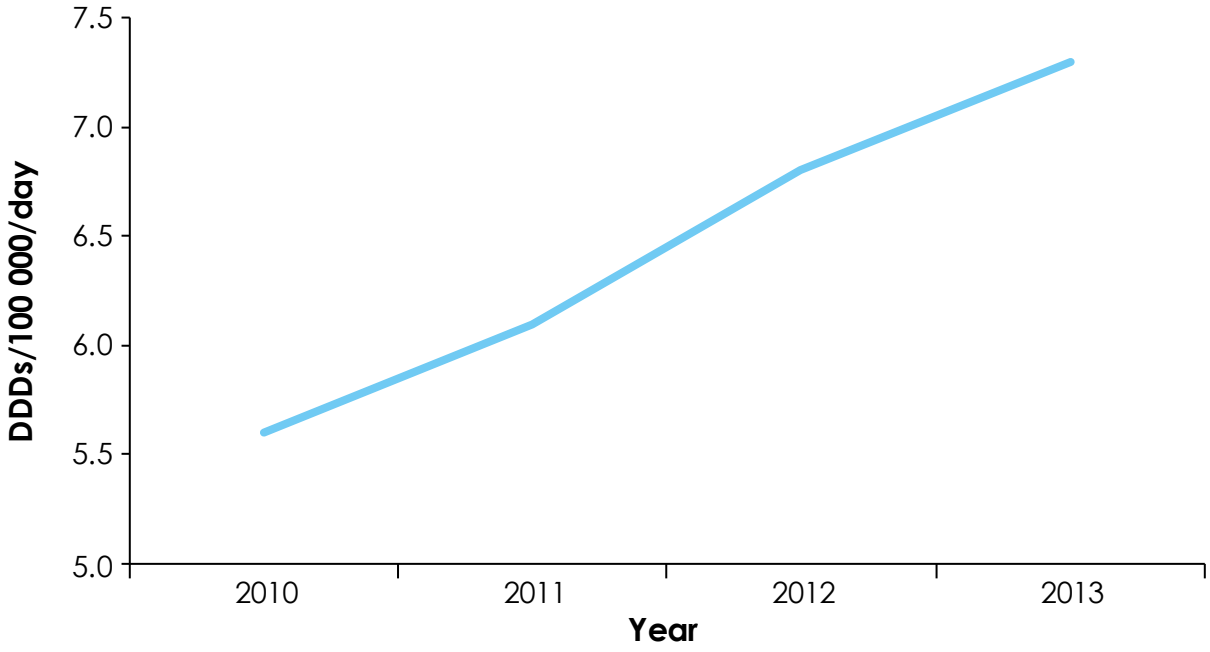


Figure 7: NHS Scotland: use of piperacillin-tazobactam in secondary care, DDD/100 000/day, 2010 to 2013 (13 NHS boards covering 94% of the population)



Detailed reporting on trends in antimicrobials use is available in the Appendix.

Clostridium difficile Infection (CDI)

There was a decrease in Scottish incidence rates of CDI in patients aged ≥65 years in 2013 (34.5 per 100 000 total bed days) compared to 2012 (37.8 per 100 000 total bed days). The incidence rate in the 15-64 years age group was unchanged (35.0 per 100 00 acute bed days).[5]

Cefotaxime resistance decreased in all the major ribotypes found in Scotland with overall resistance decreasing from 89.7% in 2012 (612 isolates tested) to 74.2% in 2013 (484 isolates tested). There were further decreases in resistance to clindamycin and levofloxacin. The decrease in resistance may reflect patterns of prescribing in which the use of cephalosporins, clindamycin and fluoroquinolones have all decreased over 2012 and 2013. The decrease may also be partly explained by the further reduction in the occurrence of ribotypes 001, 027 and 106 which are often resistant to these antibacterials.

Recent studies carried out by HPS have shown that community associated CDI accounts for around 25.7% of all cases in Scotland. Further work linking CDI cases with morbidity, mortality and prescribing data is being carried out to help understand the epidemiology of disease in the community and identify areas for reduction measures. However, the majority of cases remain healthcare-associated and this area should remain the focus for interventions.

Work should continue to drive down unnecessary antibacterial use through good antimicrobial stewardship. It may be useful to determine whether further reductions in CDI could be achieved through improved use of co-amoxiclav, as the prescribing of this antibacterial has increased in secondary care in recent years.

Resistance in Gram-negative bacteria

In 2013, *E. coli* continued to be the most frequent cause of Gram-negative bacteraemia in Scotland (**Table 1**). The incidence rate of *E. coli* bacteraemias increased year on year with an incidence rate of 81 per 100 000 population in 2013 compared to 74 per 100 000 in 2012. This follows an increasing trend in incidence in the period 2009-2012, and an increase in the identification of *E. coli* as the causative organism in HAIs (3.1% in 2005/06 to 12.1% in 2011). Although similar increasing trends in *E. coli* incidence have been reported for England, with variation between regions, the overall rates for Scotland are above that of England.[6]

There has been no concomitant increase in the number of cases of *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* bacteraemias.

Table 1: Number of cases of bacteraemia reported in Scotland between 2010 and 2013

Year	Total	*E. coli*	*K. pneumoniae*	*P. aeruginosa*	*A. baumannii*
2010	4648	3602	715	295	36
2011	4812	3839	697	242	34
2012	4900	3924	718	234	24
2013	5329	4321	688	292	28

Resistance in *Escherichia coli* bacteraemias and urinary tract infections

Resistance to a wide range of important antibacterial classes continue to occur frequently among *E. coli* bacteraemias. This includes resistance against aminopenicillins, cephalosporins, aminoglycosides, trimethoprim, aztreonam and combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides.

The proportion of extended-spectrum beta-lactamase (ESBL) producers among *E. coli* bacteraemias has remained stable since 2010 (**Table 2**). This is reassuring as treatment options are less for ESBL producers and there is the risk of plasmid spread.

Table 2: ESBL producers among *E. coli* and *K. pneumoniae* bacteraemias

Year	*E. coli* (n)	% ESBL	*K. pneumoniae* (n)	% ESBL
2010	3602	7.6	715	8.3
2011	3839	6.5	697	7.0
2012	3924	6.6	718	6.4
2013	4321	6.7	688	6.0

Resistance among *E. coli* bacteraemias remained unchanged between 2012 and 2013 (**Table 3**) to most agents except for resistance to co-amoxiclav, which increased from 18.4% in 2012 to 28.4% in 2013, above that reported in 2009-2011 (range: 23.4%-25.4%). However, it should be noted that due to the change in the breakpoint for co-amoxiclav following the gradual introduction of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and reporting methodology in the Scottish laboratories, the increase in co-amoxiclav should be interpreted with caution.

It should also be noted that co-selection by related antibacterials may have played an important role in co-selection of resistance for co-amoxiclav. There was a temporal association between the increased use of co-amoxiclav in secondary care and increasing co-amoxiclav resistance. Prescribing policies leading to the

restriction of broad-spectrum agents in general (in particular carbapenems), IVOST (IV switch to oral therapy) and de-escalation initiatives may have driven the increased use of co-amoxiclav.

The previous technical issues with determining resistance to piperacillin-tazobactam in VITEK 2 systems have been resolved, and resistance reported for 2013 should be considered as base-line for this agent (see also: http://www.biomerieux-usa.com/upload/connections-augus-2012.pdf). The resistance (8.6% in 2013) to piperacillin-tazobactam among *E. coli* bacteraemias is of concern due to its frequent clinical use. These observations support the recommendation of reviewing the national guidance on the use of co-amoxiclav and piperacillin-tazobactam.

In line with previous years' findings, there were no reports of resistance to meropenem among *E. coli* bacteraemias in 2013. The European Antimicrobial Resistance Surveillance Network (EARS-Net) reported an EU/EEA population-weighted mean percentage for carbapenem resistance of 0.2%, but increasing trends were observed in five countries (Bulgaria, France, Greece, Italy and Spain).

Table 3: Resistance in Gram-negative bacteraemias between 2012 and 2013

Organism	Antibiotic	2012 % resistant (number tested)	2013 % resistant (number tested)	Statistical significance of % change
E. coli	amoxicillin	64.1 (3053)	64.1 (3335)	↔
	aztreonam	7.5 (3117)	7.1 (3650)	↔
	co-amoxiclav	18.4 (3458)	28.4 (3861)	↔
	cefoxitin	3.4 (2727)	3.4 (3419)	↔
	cefuroxime	13.0 (3251)	14.1 (3813)	↔
	ceftriaxone	8.1 (1508)	7.9 (1134)	↔
	cefotaxime	7.2 (2258)	7.9 (3008)	↔
	ceftazidime	6.3 (3254)	5.3 (3437)	↔
	gentamicin	9.1 (3554)	9.1 (3860)	↔
	ciprofloxacin	18.1 (3420)	18.4 (3865)	↔
	meropenem	0.0 (3382)	0.0 (3834)	↔
	piperacillin-tazobactam	6.2 (3109)	8.6 (3826)	↑
	trimethoprim	39.2 (3184)	38.8 (3605)	↔
	ceftriaxone/ ciprofloxacin	6.4 (1484)	6.2 (1134)	↔
	ceftriaxone/gentamicin	3.1 (1507)	2.8 (1133)	↔
	ceftriaxone/ ciprofloxacin/ gentamicin	2.5 (1484)	2.4 (1133)	↔

(Table 3 continued next page)

(Table 3 Contd)

Organism	Antibiotic	2012 % resistant (number tested)	2013 % resistant (number tested)	Statistical significance of % change
K. pneumoniae	aztreonam	7.4 (584)	4.8 (586)	↔
	co-amoxiclav	8.5 (634)	11.4 (622)	↔
	cefoxitin	3.6 (507)	2.6 (536)	↔
	cefuroxime	10.6 (594)	10.7 (609)	↔
	ceftriaxone	8.5 (259)	4.0 (176)	↔
	cefotaxime	6.9 (420)	7.5 (482)	↔
	ceftazidime	6.5 (602)	4.3 (552)	↔
	gentamicin	7.3 (647)	6.6 (622)	↔
	ciprofloxacin	6.5 (626)	6.6 (622)	↔
	meropenem	0.2 (625)	0.2 (616)	↔
	piperacillin-tazobactam	5.3 (617)	7.3 (616)	↔
	trimethoprim	18.4 (592)	21.5 (576)	↔
	ceftriaxone/ ciprofloxacin	5.1 (255)	1.1 (176)	↓
	ceftriaxone/gentamicin	6.2 (259)	2.3 (176)	↔
	ceftriaxone/ ciprofloxacin/ gentamicin	4.3 (255)	1.1 (176)	↔
P. aeruginosa	gentamicin	3.5 (198)	4.0 (251)	↔
	ciprofloxacin	6.6 (197)	4.8 (250)	↔
	meropenem	3.7 (191)	5.3 (245)	↔
	piperacillin-tazobactam	5.6 (179)	10.0 (249)	↔
	trimethoprim	100.0 (3)	100.0 (6)	↔
A. baumanni	ceftazidime	0.0 (13)	0.0 (16)	↔
	gentamicin	5.3 (19)	0.0 (24)	↔
	ciprofloxacin	0.0 (17)	4.2 (24)	↑
	meropenem	5.3 (19)	0.0 (23)	↔
	piperacillin-tazobactam	0.0 (17)	12.5 (16)	↑

Antimicrobial resistance profiles among *E. coli* urine isolates were similar to those observed in *E. coli* bacteraemia (**Table 4**), but while trends were mostly stable in the bacteraemias increasing trends in resistance were observed among the urinary isolates, including increases in resistance to third generation cephalosporins (cefotaxime from 8.2% to 9.6%) and carbapenems (ertapenem from 0.1% to 0.2%, and meropenem from 0% to 0.03%) from 2012 to 2013. The increase in resistance among *E. coli* urinary isolates is of particular concern as this could be an early indication of evolution of resistance in a range of other organisms and isolate types.

Resistance to nitrofurantoin has also increased from 2012 to 2013 (from 4.0% to 4.8%) and resistance to trimethoprim (39.4%) and fluoroquinolones (17.0%) remains high.

Table 4: % Resistance in *E. coli* urinary isolates

Antimicrobial	Comparison between time periods		
	2012 % resistant (number tested)	2013 % resistant (number tested)	Statistical significance of % change
amoxicillin	54.0 (3578)	54.4 (3154)	↔
ampicillin	58.0 (11 740)	58.8 (12 037)	↔
cefotaxime	8.2 (12 281)	9.6 (12 799)	↑
ceftazidime	4.1 (13 846)	4.8 (14 080)	↑
cefuroxime	12.4 (13 841)	16.1 (14 070)	↑
cephalexin	11.2 (13 765)	11.9 (14 040)	↔
ciprofloxacin	17.0 (13 845)	17.0 (14 080)	↔
ertapenem	0.1 (13 459)	0.2 (13 693)	↑
gentamicin	7.1 (13 844)	6.7 (14 079)	↔
meropenem	0.00 (13 840)	0.03 (14 075)	↑
nitrofurantoin	4.0 (13 772)	4.8 (14 045)	↑
tetracycline	31.4 (13 197)	32.2 (14 044)	↔
trimethoprim	38.4 (13 840)	39.4 (14 074)	↔

Resistance in *Klebsiella pneumoniae* bacteraemias and urinary tract infection

Resistance to cephalosporins, aminoglycosides, fluoroquinolones, trimethoprim, and combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides remained stable among *K. pneumoniae* bacteraemias between 2012 and 2013 (**Table 3**).

In comparison with Europe, EARS-Net reported significantly increasing trends for several countries for all of these antibacterials. The EU/EEA population-weighted mean for carbapenem resistance was 8.3%. Meropenem resistance continues to be rare among *K. pneumoniae* bacteraemias in Scotland (a single isolate was reported in 2013).

Since 2009, decreasing trends in resistance among *K. pneumoniae* bacteraemias have been observed for aztreonam, cephalosporins, aminoglycosides, fluoroquinolones, and combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides, though resistance remains high against most of these classes.

Among *K. pneumoniae* urinary isolates there were no significant changes, although resistance to nitrofurantoin (32.1%), trimethoprim (36.0%), the cephalosporins (cefotaxime 13.7%) and fluoroquinolones (ciprofloxacin 10.0%) remains high (**Table 5**).

Table 5: % Resistance in *K. pneumoniae* urinary isolates

Antimicrobial	Comparison between time periods		
	2012 % resistant (number tested)	2013 % resistant (number tested)	Statistical significance of % change
cefotaxime	12.9 (1063)	13.7 (1043)	↔
ceftazidime	10.1 (1194)	9.9 (1134)	↔
cefuroxime	16.7 (1194)	19.3 (1134)	↔
cephalexin	15.4 (1185)	14.9 (1131)	↔
ciprofloxacin	12.3 (1195)	10.0 (1134)	↔
ertapenem	0.8 (1150)	0.5 (1109)	↔
gentamicin	11.7 (1195)	11.4 (1134)	↔
meropenem	0.0 (1195)	0.0 (1134)	↔
nitrofurantoin	32.0 (1060)	32.1 (998)	↔
tetracycline	22.9 (1107)	24.5 (1130)	↔
trimethoprim	32.6 (1195)	36.0 (1134)	↔

Resistance in *Pseudomonas aeruginosa* bacteraemias

Resistance to all commonly used anti-pseudomonal agents was observed among *P. aeruginosa* bacteraemias in Scotland in the period 2009-2013 with stable trends. All resistance proportions compared favourably to those being reported by EARS-Net. The European population-weighted mean resistance for piperacillin-tazobactam was 16.2%, 20.0% for ciprofloxacin, 12.2% for ceftazidime and 17.6% for carbapenems compared to 10%, 4.8%, 4.8% and 5.3% respectively in Scotland (see also **Table 3**).

Resistance in *Acinetobacter baumannii* bacteraemias

Resistance to ciprofloxacin (4.2%) and piperacillin-tazobactam (12.5%) was detected in *Acinetobacter baumannii* bacteraemias in 2013. However, these findings are based on a small number of cases, and may not represent resistance profiles and trends accurately in *A. baumannii* as this organism is more commonly isolated from respiratory tract samples. There was a large variation in the resistance proportions being reported for *Acinetobacter* spp. by EARS-Net (resistance to ciprofloxacin ranged from 0% to 95.0%, however no comparisons were available for piperacillin-tazobactam) (see also **Table 3**).

Resistance in *Haemophilus influenzae*

A total of 42 *Haemophilus influenzae* blood and CSF specimens were reported by reference and diagnostic laboratories in Scotland in 2013. Resistance to ampicillin was reported for two out of five isolates tested (40.0%), which is similar to the proportion of resistant isolates reported in previous years (range 11.1% - 40%). There was no reported resistance to ciprofloxacin or to tetracycline.

Resistance in *Neisseria meningitidis*

A total of 56 *Neisseria meningitidis* blood and CSF specimens were reported by reference and diagnostic laboratories in Scotland in 2013. Resistance to penicillin was reported for two out of 35 isolates tested (5.7%), which is higher than previous years with exception of 2011 (5.7%). No resistance was reported to cefotaxime, ceftriaxone, ciprofloxacin or rifampicin which is similar to reports of low levels of resistance for previous years.

Detailed reporting including trends in resistance is available in the Appendix.

Resistance in Gram-positive bacteria

The total numbers of Gram-positive bacteraemias reported between 2010 and 2013 are listed in **Table 6**.

Table 6: Gram-positive bacteraemias in 2010-2013; number of cases as per EARS-Net definition (adapted)

Year	MRSA (% of all *S. aureus*)	MSSA	*Streptococcus pneumoniae*	*Enterococcus faecalis*	*Enterococcus faecium*
2010	310 (19%)	1317	486	459	251
2011	194 (13%)	1258	446	434	236
2012	173 (13%)	1187	419	419	250
2013	141 (10%)	1327	506	405	261

Resistance in meticillin resistant *Staphylococcus aureus* (MRSA)

bacteraemias

The proportion of MRSA among all *S. aureus* bacteraemias decreased to 10% in 2013 due to extensive efforts to control and eradicate this organism in healthcare settings. This compares favourably to the rest of Europe with EARS-Net reporting a mean of 18.0% and a range of 0% to 64.5%.

In 2013, resistance to key agents including ciprofloxacin, erythromycin, trimethoprim, clindamycin and tetracycline in MRSA remained high though stable compared to 2012 (**Table 7)**. There appears to be a decreasing trend in clindamycin resistance. There have been no reports of resistance to vancomycin in Scotland.

High level resistance to mupirocin among MRSA bacteraemias increased between 2012 and 2013 (from 2.9% to 7.8%), but this increase should be interpreted with caution, as it may be attributable to small numbers with five isolates being reported in 2012 and 11 in 2013. This was accompanied by a more modest increase in high level mupirocin resistance amongst all MRSA isolates tested (including non-bacteraemia isolates, not reported here) at the Scottish MRSA Reference Laboratory (SMRSARL) therefore the significance of the bacteraemia data is uncertain. There remains a concern, however, as mupirocin is used to eradicate MRSA as part of the MRSA screening approach implemented in Scotland during 2011/2012. This is against a backdrop of a reduction in the use of mupirocin in both primary and secondary care.

Three types of mupirocin resistance mechanisms have been described for *S. aureus*. High level resistance, which is generally associated with the acquisition of the plasmid mediated *mupA*, while low level resistance is caused by a mutation in the *ileS* gene, although the clinical significance of the latter is unknown. Increased resistance rates have been associated with extensive mupirocin use. In light of the reported increase in mupirocin resistance it is imperative that that all *S. aureus* isolates suspected of being resistant to mupirocin be referred to the SMRSARL for confirmation. HPS will continue to monitor this situation in conjunction with the SMRSARL, and inform SAPG and key stakeholders should the levels of resistance continue to increase.

Resistance in meticillin sensitive *Staphylococcus aureus* (MSSA) bacteraemias

Susceptibility of MSSA to the majority of antibacterials tested has remained stable since 2009. Resistance to erythromycin and tetracycline remained stable, whereas there were decreasing trends in resistance to ciprofloxacin and trimethoprim.

Table 7: Resistance in Gram-positive bacteraemias between 2012 and 2013

Organism	Antibiotic	2012 % resistant (number tested)	2013 % resistant (number tested)	Statistical significance of % change
MRSA	chloramphenicol	0.6 (173)	0.7 (141)	↔
	ciprofloxacin	89.6 (173)	87.9 (141)	↔
	clindamycin	17.9 (173)	12.1 (141)	↔
	erythromycin	51.4 (173)	58.9 (141)	↔
	fusidic acid	10.4 (173)	11.3 (141)	↔
	gentamicin	6.9 (173)	12.1 (141)	↔
	kanamycin	9.2 (173)	18.4 (141)	↑
	linezolid	0.0 (173)	0.0 (141)	↔
	mupirocin (high level)	2.9 (173)	7.8 (141)	↑
	rifampicin	2.3 (173)	3.5 (141)	↔
	teicoplanin	0.0 (173)	0.0 (141)	↔
	tetracycline	15 (173)	21.3 (141)	↔
	tobramycin	0.0 (173)	0.0 (141)	↔
	trimethoprim	23.7 (173)	33.3 (141)	↔
	vancomycin	0.0 (173)	0.0 (141)	↔
MSSA	chloramphenicol	0.5 (1187)	0.2 (1327)	↔
	ciprofloxacin	4.5 (1187)	3.7 (1327)	↔
	clindamycin	0.8 (1187)	1.8 (1327)	↑
	erythromycin	7.8 (1187)	10.6 (1327)	↑
	fusidic acid	10.6 (1187)	12.9 (1327)	↔
	gentamicin	0.9 (1187)	0.8 (1327)	↔
	kanamycin	2.2 (1187)	1.4 (1327)	↔
	linezolid	0.2 (1187)	0.1 (1327)	↔
	mupirocin (high level)	0.2 (1187)	0.3 (1327)	↔
	rifampicin	0.5 (1187)	0.3 (1327)	↔
	teicoplanin	0.0 (1187)	0.0 (1327)	↔
	tetracycline	6.1 (1187)	7.2 (1327)	↔
	tobramycin	0.0 (1187)	0.0 (1327)	↔
	trimethoprim	4.0 (1187)	2.6 (1327)	↓
	vancomycin	0.0 (1187)	0.0 (1327)	↔
S. pneumoniae	ciprofloxacin	0.0 (399)	1.1 (472)	↑
	erythromycin	6.3 (399)	7.0 (472)	↔
	penicillin	0.3 (399)	0.6 (472)	↔
E. faecalis	vancomycin	0.0 (330)	0.0 (311)	↔
E. faecium	vancomycin	24.4 (209)	20.0 (220)	↔

Resistance in *Streptococcus pneumoniae* bacteraemias

Resistance to penicillin and ciprofloxacin remains very low (0.6% and 1.1%, respectively) whilst resistance to erythromycin is stable compared to 2012 (7.0% vs. 6.3%) (**Table 7**). EARS-Net have reported a range of 1.1% to 40.0% for penicillin non-susceptibility, an EU/EEA mean of 4.9% for fluoroquinolones (no range was reported), and a range of 1.5% to 38.1% for macrolides.

In 2013, the most common Scottish *S. pneumoniae* serotypes isolated from blood isolates were 8, 7F, 22F, 3, 19A, 15A, 33F, 11A, 10A and 6C (in order of decreasing percentage), accounting for 61.1% of all isolates (334/547). Two isolates (serotype 6B) were reported as having combined resistance to penicillin and the macrolides. This serotype is contained within the pneumococcal conjugate vaccine. There is a concern that serotypes not covered by the vaccine may develop resistance to the first line treatment options. In 2013, 20 of 32 isolates (62.5%) of *S. pneumoniae* serotype 15A were reported as being resistant to erythromycin (this serotype is not included in the vaccine). Resistance to erythromycin in this serotype has remained stable since 2011; however, it is important to remain vigilant to any increases in resistance.

We will continue to monitor resistance in *S. pneumoniae* and report any emerging issues to SAPG and key stakeholders.

Resistance in *Enterococcus* spp. bacteraemias

All isolates of *E. faecalis* were susceptible to vancomycin, while 20.0% of *E. faecium* were resistant to vancomycin (**Table 7**). Vancomycin resistance remains high in comparison to the rest of Europe with EARS-Net reporting a mean percentage of 8.9% resistance and a significant increasing trend across the whole of the UK.[7]

One isolate of *E. faecium* was resistant to both vancomycin and linezolid. Following a UK alert, it was advised that laboratories submit all linezolid-resistant enterococci or staphylococci isolates to a relevant national reference laboratory for further characterisation. No enterococcal blood isolates were reported as having combined resistance to vancomycin, linezolid and tigecycline, however this has been reported in non-blood isolates.

Enterococci are an important cause of HAIs and are highly persistent in a hospital setting. They are intrinsically resistant to a broad range of antibacterials and the emergence of combined resistance to vancomycin, linezolid and tigecycline is of concern as it leaves few therapeutic options available.

EARS-Net have reported on the emergence of an important healthcare associated polyclonal complex *E. faecium* $(CC)_{17}$ and also CC_2 and CC_9 in *E. faecalis*. In 2012, a sampling strategy was developed to characterise the molecular epidemiology of vancomycin resistant enterococci in Scottish hospitals. Results are expected to be reported during the first half of 2015.

Detailed reporting including trends in resistance is available in the Appendix.

Developments

The UK Five Year Antimicrobial Resistance Strategy 2013-2018 was published in September 2013.[1] One of the key areas for action is **better access to and use of surveillance data** on antimicrobial use and resistance. In our future reports we will amend the date of publication, format, and content to improve the utility of the information presented.

To provide a more timely publication of the most recent information in line with the wider UK approach, we will work towards bringing forward the date for publication of future reports closer to the period being reported on; e.g. 6-9 months after the end of the year being reported on. The new proposed reporting rhythm will commence with the publication of the AMR information for 2014 being reported by 'mid' 2015.

Through the use of infographics we will improve the communication of the key messages contained in our future reports.

The UK AMR strategy has adopted a 'one health' approach to forge collaboration between human and animal health. Work is underway in Scotland to develop arrangements through the Controlling Antimicrobial Resistance in Scotland (CARS) group to drive forward the surveillance of antimicrobial use and resistance in the veterinary sector. In our future reports we will present more integrated data across these sectors.

The importance of improved data linkage is highlighted in the UK AMR strategy. Improved data linkage has the potential to improve patient outcome, reduce harm from infection and will enable timely and proficient identification of emerging issues such as antimicrobial resistance and unintended consequences. In 2013, work commenced on the development of the NHSScotland Infection Intelligence Platform (IIP). The initial focus within IIP has been the establishment of the technical capability and information governance processes. This work continues but the key focus is now on the delivery of 16 exemplar clinical studies which are intended to demonstrate the benefits of IIP to clinicians. We will summarise the outputs from IIP in future reports.

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