NHS National Services Scotland

Scottish Antimicrobial Prescribing Group (SAPG)

Report on Antimicrobial Use and Resistance in Humans in 2009

Health Protection Scotland

ISD Scotland

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List of Abbreviations

AMR	Antimicrobial resistance
AMT	Antimicrobial management team
ARMRL	Antibiotic Resistance Monitoring and Reference Laboratory
AST	Antimicrobial susceptibility testing
ATC	Anatomical Therapeutic Chemical
CDI	*Clostridium difficile* infection
CHI	Community Health Index
CLSI	Clinical and Laboratory Standards Institute
DDD	Defined daily dose
EARS-Net	European Antimicrobial Resistance Surveillance Network (formerly EARSS)
EARSS	European Antimicrobial Resistance Surveillance System
EMEA	European Medicines Agency
ECDC	European Centre for Disease Prevention and Control
ECOSS	Electronic Communication of Surveillance in Scotland
ESBL	Extended spectrum beta-lactamase
HMUD	Hospital Medicines Utilisation Database
HPS	Health Protection Scotland (NHS National Services Scotland)
ISD	Information Services Division (NHS National Services Scotland)
KPC	*Klebsiella pneumoniae* carbapenemase
MDR	multidrug resistant
MIC	Minimum inhibitory concentration
MRSA	Meticillin resistant *Staphylococcus aureus*
MSSA	Meticillin sensitive *Staphylococcus aureus*
NDM-1	New Delhi beta-lactamase (type 1)
NHS	National Health Service
NORM	Norwegian Resistance Monitoring System
NORM-Vet	Norwegian Resistance Monitoring System - Veterinary
OCBD	Occupied bed days
PCR	Polymerase chain reaction
PDR	pandrug-resistant/resistant to all approved antimicrobial agents
PRISMS	Prescribing Information System for Scotland

SAPG	Scottish Antimicrobial Prescribing Group
ScotMARAP	Scottish Management of Antimicrobial Resistance Action Plan
SMC	Scottish Medicines Consortium
SHLMPRL	Scottish Haemophilus, Legionella, Meningococcus and Pneumococcus Reference Laboratory
SMRSARL	Scottish MRSA Reference Laboratory
SSSCDRL	Scottish Salmonella, Shigella and Clostridium difficile Reference Laboratory
STRAMA	Swedish Strategic Programme Against Antibiotic Resistance
SWEDRES	Swedish report on antimicrobial resistance
UK	United Kingdom
VIM	Verona integron-encoded metallo-beta-lactamase
WHO	World Health Organisation
XDR	extensively drug resistant

Executive summary

Antimicrobial resistance is recognised as a major threat to public health and patient safety. It reduces the available treatment options for infection and is associated with increased morbidity and mortality due to the failure of the empirical antimicrobial therapy. It is accepted that the way in which antimicrobials are used, sometimes inappropriately, will increase the risk of antimicrobial resistance developing.

This is the second annual report from the Scottish Antimicrobial Prescribing Group (SAPG), published by Health Protection Scotland (HPS)/Information Services Division (ISD) of NHS National Services Scotland that combines information on antimicrobial use and resistance in humans in Scotland. The information presented is intended to support National Health Service (NHS) Boards in their long-term strategic planning, implementation and evaluation of antimicrobial use as part of the wider strategy of preventing, treating and controlling the spread of infections.

The information presented in this report is 12 months in arrears to enable comparisons with other national datasets issued elsewhere in the UK and Europe (national information on antimicrobial use in primary care has already been made available to all NHS Boards). We believe comparisons with information from other countries helps identify how and where attention should be focused in containing and reducing antimicrobial resistance.

The information contained in the report covers the period to the end of 2009, the first full year following the establishment of SAPG in 2008. This allows initial assessment of SAPG interventions aimed at improving the quality of antimicrobial prescribing. In particular this report should be of relevance to Antimicrobial Management Teams (AMTs), Infection Control Teams (ICTs) and microbiologists.

Use of antimicrobials

This report presents information on the use of systemic antibacterials within primary care in Scotland. The primary measure used in the report is the number of prescription items for antibacterials. To enable international comparison with Scottish data, use of antibacterials is also presented using Defined Daily Doses. In 2009 the overall use of systemic antibacterials, expressed as number of items per 1000 population per day (items/1000/day) was 1.6% lower than in 2008 and is equivalent to 44,500 fewer prescriptions in 2009 than in 2008. This is the first annual reduction since 2004.

SAPG aimed to restrict the use of co-amoxiclav, fluoroquinolones and cephalosporins, known to increase the risk of Clostridium difficile infection (CDI) through national guidance to support the development of NHS Board prescribing policies.

This report illustrates that progress has been made toward restricting use of these antibacterials. Specifically the use (expressed as items/1000/day) of penicillin combinations (co-amoxiclav) in 2009 was 14.7% lower than in 2008. This represents the largest annual reduction since 1999. Use of fluoroquinolones in 2009 was 7.1% lower than in 2008, the first annual reduction in the number of prescriptions for fluoroquinolones since 2002. There was also a 21.2% reduction in the use of cephalosporins in 2009 compared to 2008.

The use of first-line antibacterials promoted in SAPG Management of Infection Guidance for Primary Care increased by 4.9% in 2009 compared to 2008. The Scottish Government Health Directorate has set a target that seasonal variation in the use of fluoroquinolones should be no greater than 5% higher in the winter compared with the preceding summer. In 2009 this target has been met at national level for the first time.

These changes in the use of antibacterials in 2009 compared to 2008 may provide an early indication that SAPG working with AMTs is having a positive impact on the quality of prescribing in primary care in Scotland. In 2009 there was a 42% reduction in the rate of CDI in patients aged 65 years or over compared with 2008. There is a temporal association between reduction of CDI and reduction in the use of antibacterials that are reported to have an increased risk of CDI which could suggest improved quality of prescribing may explain at least part of the reduction.

In 2009 Scotland took part in the European Surveillance of Antimicrobial Consumption (ESAC) point prevalence survey (PPS) of antimicrobial use in hospitals. SAPG co-ordinated the participation of 31 Scottish hospitals. The results demonstrated there was a lower use of antimicrobials associated with a high risk of CDI and a greater use of narrow spectrum antibacterials in Scotland compared to participating European hospitals. A number of areas for improvement including: recording the reason for antimicrobial use in individual's medical records; compliance with local prescribing policies and use of antimicrobials for surgical prophylaxis were identified and are being taken forward across Scotland by SAPG in collaboration with AMTs.

The Hospital Medicines Utilisation Database (HMUD) will become available in Scotland from 2010. HMUD will make accessible standardised information on hospital use and will support national and local surveillance of antimicrobial use in hospitals in Scotland

Antimicrobial resistance

This report presents information on patterns of antimicrobial resistance for key organisms causing bacteraemias in humans, including *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Enterococcus* spp.

The antimicrobial susceptibility (AST) data which cover 2009 were collected and analysed in line with the EARS-net protocol (the European Antimicrobial Resistance Surveillance Network) and compared to corresponding data from 2008. In addition AST-data on *Acinetobacter baumannii* are presented in this report.

Overall there has been a large increase in reporting of Gram-negative bacteraemias from 2008 to 2009 as electronic reporting from diagnostic laboratories to HPS was fully implemented during this period. Given that reporting of bacteraemias to HPS was incomplete prior to 2009, we are not able to comment on whether there has been a true increase in the number of Gram-negative cases in this period.

Resistance to nearly all clinically important classes of antibiotics, including aminopenicillins, second and third generation cephalosporins, fluoroquinolones and aminoglycosides were observed among the Gram-negative bacteraemia isolates.

No major increases in resistance (to the antibiotics tested) were observed among the key Gram-negative organisms (*E. coli*, *K. pneumoniae*, *P. aeruginosa*) when comparing 2009 with 2008. In contrast, resistance to third generation cephalosporins in *E. coli* decreased significantly in this period. The stabilisation of resistance development seen in Scotland in 2009 is unusual. In the 10-year period in which resistance in Gram-negatives has been monitored throughout hospitals in Europe, resistance trends have mostly been going up. It is interesting to speculate whether the effective restriction of cephalosporins in Scotland could be associated with the containment/decrease in resistance. Recent studies from Europe and the US have demonstrated that the association between antimicrobial use and resistance is very hard to verify by "simple statistical models" (Sande-Bruinsma *et al*., 2008, Bergman *et al*, 2009, Bosso *et al.*, 2010).

One exception to the general downward/stable trend was a minor increase in resistance to aminoglycosides in *E. coli* which rose from 7.3% in 2008 to 8.2% in 2009 (a non-significant change, $p>0.05$). Resistance to gentamicin is of particular concern and will be followed closely as this antibiotic is used increasingly in hospitals following the restriction in cephalosporin use.

A further positive result was that combined resistance to third generation cephalosporins and either fluoroquinolones or aminoglycosides decreased significantly in *E. coli* and *P. aeruginosa* ($p<0.05$). Although resistance trends among the Gram-negatives are stable or decreasing for some antibiotics (and combinations of those), a different picture emerged when we analysed the data in line with the recent European expert proposal on standardisation of terminology of multidrug resistance. In total 16.6% of *E. coli* and 10.3% of *K. pneumoniae* isolates from 2009 could be categorised as multidrug resistant (MDR), defined as resistant to at least 3 categories of antimicrobials with different mechanisms of actions. In a small number of isolates of *E. coli* and *K. pneumoniae* resistance was detected in up to 8 antimicrobial categories. As not all isolates were tested against antibiotics of all categories these figures could be under-estimates of the true occurrence of multidrug resistance.

These findings are worrying, as a recent publication reported frequent identifications of carbapenemase producing *Enterobacteriaceae* (from the UK, India and Pakistan) which are extensively resistant to most available antibiotics (Kumarasamy, 2010). The European Centre for Disease Prevention and Control (ECDC) have in 2010 recognised carbapenemase producing *Enterobacteriaceae* as a significant risk for public health in Europe and worldwide as treatment options for these infections are very limited.

Resistance among Gram-positive isolates remain less of a concern overall in Scotland and there were few changes in resistance proportions from 2008 to 2009. With the exception of MRSA, resistance remains low in the Gram-positives. One exception to this is the increase in resistance of *Enterococcus faecium* to vancomycin. Resistance has increased from 17% in 2008 to 28% in 2009. This surveillance programme is in its infancy and so it is difficult to be certain that this is a true increase. Nonetheless, vancomycin resistance in this organism continues to be a concern due to the fact that the resistance mechanism can be transferred to other pathogens (including MRSA).

Despite promising trends in some areas antimicrobial resistance remains a serious cause for concern, new mechanisms of resistance are being reported, particularly the emergence of carbapenemases. It is essential that the efforts in improving the quality of antimicrobial prescribing and monitoring of antimicrobial resistance continue. Changes in prescribing practice will alter selection pressures on the microbial flora leading to new patterns of resistance. Complacency could have serious consequences for the control and treatment of infectious diseases.

Introduction

Emerging antimicrobial resistance (AMR) is recognised as a worldwide public health threat. It reduces the available treatment options for infections and is associated with increased mortality, morbidity and healthcare costs due to the failure of empirical antimicrobial therapy. The importance of containing antimicrobial resistance in the European Union was emphasised in Council Conclusions on Antimicrobial Resistance adopted by EU health ministers in June 2008 (Monnet and Kristinsson, 2008).

The European Centre for Disease Prevention and Control (ECDC) has established the Programme on Antimicrobial Resistance (AMR) and Healthcare Associated Infections as one of seven key programmes to address infectious disease within the European Union. The key aims of this programme are to minimise the use of antibiotics and prevent the spread of resistant strains between individuals.

Of particular concern is the emerging threat of multidrug resistant organisms such as the carbapenemase producing *K. pneumoniae* and *E. coli* that are being increasingly reported from around the world. In the absence of novel agents to treat infections caused by these organisms it is incumbent on all of those involved in healthcare to minimise the risk of emergence and spread of these organisms.

Within this context the Scottish Government published the Scottish Management of Antimicrobial Resistance Action Plan (ScotMARAP) in 2008. A key action of this plan was the formation of the multidisciplinary network, the Scottish Antimicrobial Prescribing Group (SAPG), which aims to coordinate national efforts to improve the quality of antimicrobial prescribing, contain antimicrobial resistance and enhance infection management in all healthcare settings through the implementation of a national 'antimicrobial stewardship programme. The Scottish antimicrobial stewardship programme brings together key activities including guidance on antimicrobial prescribing, surveillance of antimicrobial use and resistance and infection management, and links with other national programmes on infection control to contain the emergence of antimicrobial resistance.

The national antimicrobial stewardship programme supports the delivery of the quality ambitions set out in the Healthcare 'Quality Strategy for NHS Scotland', which 'aims to deliver the highest quality healthcare services to people in Scotland' through effective clinical treatment and support to everyone with the least possible harmful variation at all times (Scottish Government, May 2010).

Alongside good infection control measures, rational use of antimicrobials also plays a key role in minimising the risk of *Clostridium difficile* infection (CDI). The Scottish surveillance programme for antimicrobial use and resistance complements the Scottish 'CDI reduction programme' co-ordinated by HPS. A successful outcome of this programme will be a reduction in the use of antimicrobial agents, early identification and containment of multidrug resistant organisms, particularly in the healthcare setting, and a sustained reduction in cases of CDI. Alongside this, there must be continuous monitoring of the impact of changes in antimicrobial prescribing that may have 'unintended consequences' that go beyond new selection pressures for resistance. Preliminary work has begun to develop systems for identifying unintended consequences through special studies and use of existing national datasets. This will be developed further in the coming year.

This is the second annual report bringing together antimicrobial resistance and usage data alongside national trends in CDI. The information presented is intended to support NHS Boards in their long-term strategic planning, implementation and evaluation of antimicrobial use as part of the wider strategy for preventing, treating and controlling the spread of infections.

Whilst the resistance datasets available for 2009 remain limited (partly due to the complexities involved in implementing automated data transfer), the data in this report is more complete than in the first annual the report (which covered 2008) with all diagnostic laboratories now reporting to HPS through ECOSS, although not all NHS Boards are yet reporting the full antimicrobial susceptibility datasets required.

Even with this caveat there are some interesting comparisons with 2008, and whilst it is too early to comment on resistance trends, the implementation of antimicrobial stewardship across Scotland appear to have some impact on both antimicrobial use and resistance. It is important, that within the context of the Quality Strategy for NHS Scotland and the health and welfare of the Scottish population, that these efforts continue particularly in the absence of new antimicrobial agents to treat the emerging resistant pathogens.

Chapter 1 - Antimicrobial Use

Background

A major driver for the development of antimicrobial resistance is the way in which antimicrobials are used, and misused. The surveillance of use of antimicrobial is important to understand the developing patterns of resistance and to monitor the impact of strategies that aim to improve antimicrobial stewardship in Scotland.

The Scottish Antimicrobial Prescribing Group (SAPG) was established in 2008. It aims to co-ordinate national antimicrobial stewardship to improve the quality of prescribing and treatment of infection in Scotland.

This second annual report of antimicrobial use and resistance presents information for 2009, the first full year following the establishment of SAPG. This enables the initial impact of SAPG interventions to improve the quality of antimicrobial prescribing in the primary care setting in Scotland to begin to be assessed.

The term antimicrobial covers antibacterial, antiviral and antimycotic (antifungal) agents. In this chapter we present information on use of systemic antibacterials in humans in primary care at a national level in Scotland. A summary of a national point prevalence survey of use of antimicrobials in Scottish hospitals is also presented. Other national information developments on antimicrobial use are outlined in the future developments section.

Methods

Data source - primary care

In Scotland all antibacterials for systemic use are classed as Prescription Only Medicines. This means that they can only be supplied in accordance with a prescription given by a doctor, dentist or other authorised prescriber.

Information on the use of antibacterials in primary care has been obtained from a database of all NHS prescriptions dispensed in the community in Scotland maintained by Information Services Division (ISD) of NHS National Services Scotland (NSS). The information is supplied to ISD by Practitioner Services Division of NSS who is responsible for the processing and pricing of all prescriptions dispensed in Scotland.

Data in this report is from prescriptions written by GPs, dentists and other non-medical prescribers and those written in hospitals but dispensed in the community.

Data presentation

The data on antibacterial use is based on the Anatomical Therapeutic Chemical (ATC) classification. This is the internationally recognised classification system to identify the therapeutic ingredient of all medicines for human use. Antibacterials for systemic use fall into ATC group J01. For further details on the ATC system please see WHO Collaborating Centre for drug statistics methodology website at http://www.whocc.no/atcddd/

The primary measure of antibacterial use in Scotland presented in this report is the number of items. This depicts the number of times an antibacterial appears on a prescription.

To enable international comparison with Scottish data, use of antibacterials is also presented using Defined Daily Doses (DDD). The DDD is the internationally recognised technical unit of measurement of medicine consumption. DDDs are recommended by the World Health Organisation (WHO) as the standard to allow comparative use of medicines over time and between different locations. The DDD is the assumed average maintenance dose per day for a medicine used in its main indication in adults. In general, the DDDs for antibacterials are based on their use in moderately severe infections. However, some antibacterials are only used in severe infections and their DDDs are assigned accordingly. For further details on DDD methodology please see WHO Collaborating Centre for drug statistics methodology website at http://www.whocc.no/atcddd/

The normal convention is to present information on use of antibacterials expressed as number of items per 1000 population in Scotland per day (items/1000/day) and total DDD per 1000 population per day (DDD/1000/day). This allows comparison of usage over time.

Time period

All data in this report is presented by calendar year except seasonal variation of fluoroquinolone antibacterials and the primary care prescribing indicators which are presented by financial year (April to March).

Results

Primary Care

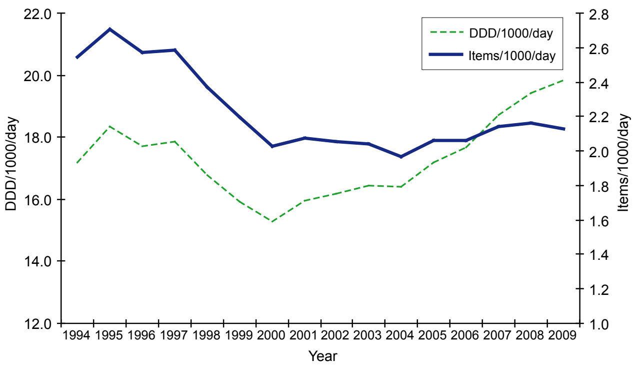
In 2009 SAPG adopted the Health Protection Agency (HPA) Management of Infection Guidance for Primary Care. It was disseminated to AMTs to support development of local prescribing policies for first line empirical treatment of infections commonly encountered in a primary care setting in Scotland. This evidence based guidance provided advice for prescribers on the drug, dose and duration of antibacterials in specific infections. The guidance aims to restrict the use of antibacterials such as co-amoxiclav, fluoroquinolones, and cephalosporins that are associated with a higher risk of CDI and to promote the use of narrow spectrum antibacterials to minimise the emergence of bacterial resistance in the community.

Overall use of antibacterials

In 2009 the overall use of systemic antibacterials in the primary care setting in Scotland was 2.1 items/1000/day. This was 1.6% lower than in 2008 and is equivalent to 44,500 fewer prescriptions in 2009 than in 2008. Figure 1 shows the overall use of antibacterials over a 15 year period since 1994. This shows that for the first time since 2004 there has been a small annual reduction in the number of prescription items for antibacterials. It remains to be seen whether this small reduction is the start of a trend. When use of antibacterials is expressed as number of DDD/1000/day a different pattern emerges. The overall use in 2009 was 19.8 DDD/1000/day. This is 2.2% higher than in 2008.

The implementation of the SAPG Management of Infection Guidance for Primary Care has supported changes to clinical practice that have resulted in higher doses of commonly used antibacterials being prescribed. The differing direction of annual change in antibacterial use expressed at items/1000/day and DDD/1000/day between

Figure 1: NHS Scotland: use of antibacterials in primary care 1994 – 2009



2008 and 2009 may in part be explained by the higher doses recommended in the newly approved guidance. This move toward larger doses, in line with evidenced based practice, is welcome but it is contributing to the increase in antimicrobial use expressed as DDD/1000/day.

The small annual reduction in 2009 in the number of antibacterial items prescribed may be an early indication of the positive impact SAPG and AMTs are having on antimicrobial use in Scotland.

Choice of antibacterial

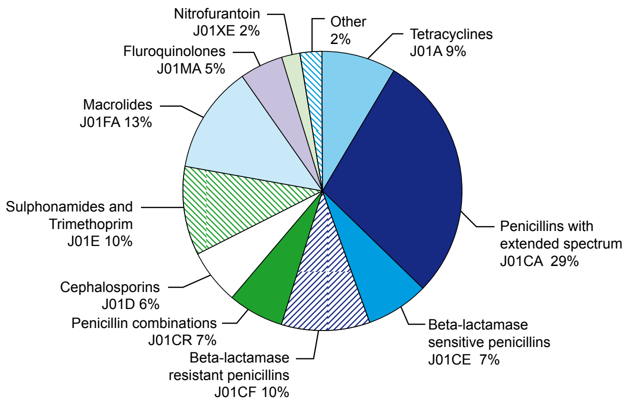
Ten most commonly used antibacterials

Table 1 presents the ten most commonly used antibacterials that account for 87% of all antibacterial use in 2009. Of the ten most commonly used in 2009, seven are recommended in the SAPG Management of Infection Guidance for Primary Care.

Use of antibacterials by group

Antibacterials are divided into a number of different groups (e.g. penicillins) on the basis of their chemical structure and spectrum of activity against different organisms. The distribution of the different groups of antibacterials used in 2009 is shown in Figure 2. The two most frequently used groups are penicillins with extended spectrum (mainly amoxicillin) which represented 29% of total use in primary care and macrolides which accounted for 13%.

Figure 2: NHS Scotland: use of antibacterials in primary care, items/1000/day percent of total items/1000/day in 2009



Other frequently used groups were beta-lactamase resistant penicillins, mainly flucloxacillin (10%), sulphonamides and trimethoprim (10%), beta-lactamase sensitive penicillins, mainly phenoxymethylpenicillin (7%) and penicillin combinations including co-amoxiclav (7%). Overall, penicillins (J01C) accounted for 53% of total antibacterial use in 2009.

Table 2 presents the change in use of antibacterials for each of these groups in 2009 compared to 2008. This shows that in 2009 there was a reduction in the antibacterial groups associated with increased risk of CDI (penicillin combinations (co-amoxiclav), fluoroquinolones and cephalosporins).

Tetracyclines

Tetracyclines are long established antibacterials with a narrow spectrum of activity that have a broad range of indications in primary care. The SAPG Management of Infection Guidance for Primary Care recommends doxycycline as a treatment for exacerbations of chronic bronchitis, chronic obstructive pulmonary disease or acute sinusitis. In 2009 the use of doxycycline, expressed as items/1000/day in the primary care setting in Scotland was 17% higher than in 2008. When use is expressed as DDD/1000/day the increase in 2009 compared to 2008 was 9%.

Penicillins with extended spectrum

In 2009 amoxicillin accounted for virtually all use of penicillins with extended spectrum. SAPG recommends amoxicillin as a first line treatment for many commonly

Table 1: NHS Scotland: use of antibacterials in primary care - top 10 in 2009

Antibacterial	Anatomical Therapeutic Classification Group	Number of items	% total Antibacterial use
All antibacterials		4,040,080	100
Amoxicillin*	Penicillins with extended spectrum	1,160,917	29
Flucloxacillin*	Beta-lactamase resistant penicillins	410,581	10
Trimethoprim*	Trimethoprim and derivatives	406,188	10
Phenoxymethylpenicillin*	Beta-lactamase sensitive penicillins	289,551	7
Co-amoxiclav	Penicillin combinations	257,906	6
Erythromycin*	Macrolides	255,236	6
Clarithromycin*	Macrolides	224,807	6
Cefalexin	First generation cephalopsorins	215,475	5
Ciprofloxacin	Fluoroquinolones	186,009	5
Doxycycline*	Tetracyclines	114,100	3

* recommended in SAPG Management of Infection Guidance for Primary Care as first line agents

Table 2: NHS Scotland: use of antibacterials in primary care, percent change by group 2008 and 2009

Anatomical Therapeutic Classification Group	Anatomical Therapeutic Classification Group Code	% change between 2008 and 2009	
		Items/1000/day	DDDs/1000/day
Tetracyclines	J01A	7.4%	6.8%
Penicillins with extended spectrum	J01CA	-3.4%	-0.4%
Beta-lactamase sensitive penicillins	J01CE	-0.7%	2.9%
Beta-lactamase resistant penicillins	J01CF	4.6%	8.1%
Penicillin combinations	J01CR	-14.7%	-11.5%
Cephalosporins	J01DB	-21.2%	-19.2%
Sulphonamides and trimethoprim	J01DC	9.5%	7.0%
Macrolides	J01DD	-0.6%	2.7%
Fluoroquinolones	J01E	-7.1%	-2.7%
Nitrofurantoin	J01FA	47.1%	36.1%
Other	J01MA	3.2%	1.7%

encountered infections in primary care. In 2009 there was a small reduction in the use of amoxicillin compared to 2008.

Penicillin combinations

In 2009 co-amoxiclav accounted for almost all of the use of penicillin combinations. Co-amoxiclav is a combination of amoxicillin and a beta-lactamase inhibitor which extends the spectrum of activity. This broader spectrum is counterbalanced by the development of resistance and increased risk of CDI. The SAPG Management of Infection Guidance for Primary Care aims to restrict its use. The annual reduction in use of penicillin combinations shown in table 2 is the largest since 1999 and is as a result of reduced use of co-amoxiclav.

Fluoroquinolones

In 2009 ciprofloxacin accounted for 92% of fluoroquinolone use (items/1000/day). Fluoroquinolone antibacterials are not recommended in the SAPG Management of Infection Guidance for Primary Care as first line agents for empirical treatment of most commonly encountered infections in primary care. It is recognised that use of fluoroquinolones is associated with a significantly increased risk of CDI. In particular, outbreaks with the hypervirulent strain PCR ribotype 027 that cause CDI with high morbidity and mortality have been linked to use of fluoroquinolones. The small reduction in the use of fluoroquinolones presented in table 2 is the first annual reduction since 2002.

Cephalosporins

Cephalosporins are not recommended as first line agents for empirical treatment of commonly encountered infections in primary care. Their use is associated with an increased risk of CDI and the SAPG Management of Infection Guidance for Primary Care aims to restrict their use. Table 2 shows a considerable reduction in use of cephalosporins in 2009 compared with 2008.

Trimethoprim and Nitrofurantoin

Trimethoprim and nitrofurantoin are recommended as first line empirical treatments for urinary tract infection in the SAPG Management of Infection Guidance for Primary Care. Table 2 shows that in 2009 there was an increase in use of these antibacterials compared to 2008.

These changes in the use of antibacterial groups in 2009 compared to 2008 may provide an early indication that SAPG through working with NHS Board AMTs and others is having a positive impact in the quality of prescribing of antibacterials in primary care in Scotland.

In 2009 there was a 42% reduction in the rate of CDI in patients aged 65 years or over compared with 2008. There is a temporal association with this reduction of CDI and the reduction in use of antibacterials that are reported to have an increased risk of CDI.

Primary Care Prescribing Indicators

The European Surveillance of Antimicrobial Consumption (ESAC) is an international network of national surveillance systems collecting comparable and reliable data on antimicrobial use supported by the European Centre for Disease Prevention and Control (ECDC). In 2007 ESAC proposed a set of quality indicators for primary care antibacterial use. Following discussion at SAPG and after consultation with AMTs and other stakeholders, a set of national prescribing indicators relating to use of antibacterials in primary care based on ESAC proposals was developed. Prescribing indicators can be used to show comparative patterns of prescribing of antibacterials over time, against national averages or between geographical areas.

The national prescribing indicators are accessible as standard reports within the Prescribing Information System for Scotland (PRISMS). PRISMS is a web based system which is updated monthly and contains the last five years of use of all medicines dispensed in primary care. This means that registered users are able to view the most current information relating to antibacterial prescribing. PRISMS contains a total of 51 indicators representing use by antibacterial group and a number of individual agents. The purpose of these national prescribing indicators is to support AMTs by making data accessible that provides an overview of the use of all antibacterials in a primary care setting. They are intended to enable AMTs to identify areas for detailed local analysis and discussion with prescribers to support quality improvement in prescribing practice.

The data on use of antibacterials in primary care in Scotland presented above is accessible to PRISMS users in the form of national prescribing indicators. A report showing the key indicators focussing on the initial SAPG priority areas is available at http://www.isdscotland.org/isd/6125.html. The findings of the key national prescribing indicators are shown in Table 3

This shows that the use of antibacterials associated with a higher risk for CDI has fallen in 2009 compared with 2008. This annual reduction in use has been observed in almost all NHS Board areas in Scotland. This may indicate initial progress has been made to restrict and reduce the use of these high risk antibacterials.

Table 3: NHS Scotland percent change in key prescribing indicators 2008 and 2009

Prescribing Indicator	% change between 2008 and 2009	
	Items/1000/day	DDDs/1000/day
Antibacterials associated with a higher risk of CDI (co-amoxiclav, fluoroquinolones, cephalosporins and clindamycin)	-19.5	-14.7
SAPG recommended antibacterials (amoxicillin, doxycycline, clarithromycin, erythromycin, flucloxacillin, phenoxymethylpenicillin, nitrofurantoin and trimethoprim)	4.9	2.8

The use of antibacterials recommended by SAPG Management of Infection Guidance for Primary Care has increased. The increased use of these antibacterials may reflect the impact of prescribing policies implemented by AMTs.

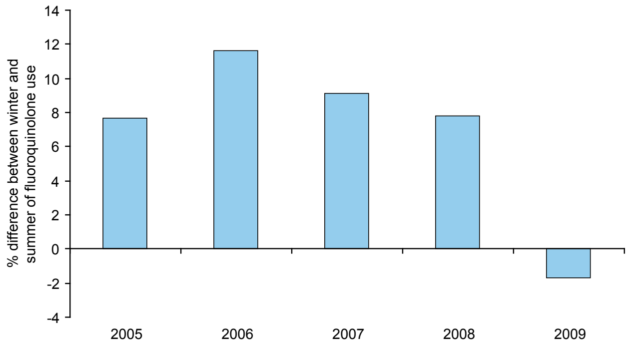
Reduction in CDI is a priority area for the Scottish Government and SAPG. CEL 11 (2009) issued by the Scottish Government in April 2009 defined a Health Efficiency and Access to Treatment (HEAT) target for NHS Boards in Scotland to reduce the rate of CDI among patients aged 65 and over by at least 30% by 31 March 2011. The primary care indicator developed to support achievement of this target is that seasonal variation in fluoroquinolone use should be less than 5%. This indicator is accessible as a standard report within PRISMS.

Seasonal variation is defined as the increase in use of antibacterials during the two winter quarters (October to March) relative to use in the preceding two summer quarters (April to September). In the winter quarters more respiratory tract infections are seen but many are caused by viruses, are self-limiting and do not require treatment with an antibacterial. Fluoroquinolones are not recommended for routine empirical treatment respiratory infections and a relative excess use in winter compared to summer may indicate inappropriate use in viral infections.

Figure 3 shows annual seasonal variation in use of fluoroquinolones expressed as DDD/1000/day in the winter compared to the preceding summer.

This shows that at national level good progress has been made toward the Scottish Government target of less than 5% seasonal variation in fluoroquinolone use. It also shows that for the first time in 2009 the Scottish Government target has been met at national level. This may reflect the impact of initiatives led by AMTs to support appropriate use of fluoroquinolones since the introduction of this indicator. The negative seasonal variation means there was a lower use of fluoroquinolones in the winter of 2009 than in the previous summer.

Figure 3: NHS Scotland use of fluoroquinolones in primary care, percent seasonal variation DDD/1000/day 2005-2009



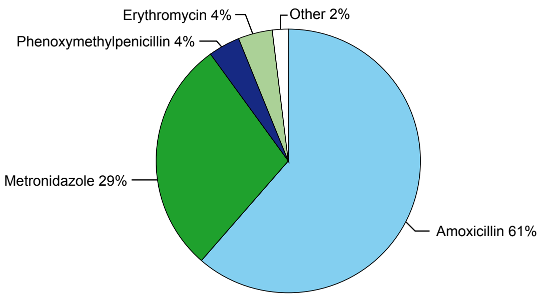
Use of antibacterials in dentistry

Dental practitioners in Scotland may only prescribe on NHS prescriptions from a limited list of medicines. This includes a range of 13 antibacterials; amoxicillin, ampicillin, azithromycin, cefalexin, cefradine, clindamycin, co-amoxiclav, doxycycline, erythromycin, metronidazole, oxytetracycline, phenoxymethylpenicillin and tetracycline.

In 2009, the overall use of antibacterials in dentistry was 0.2 items/1000/day. This is 2.5% higher than in 2008 and accounts for 8% of total use of antibacterials in primary care in Scotland.

Figure 4 presents the breakdown of antibacterial use in dentistry in Scotland in 2009. This illustrates that the amoxicillin and metronidazole account for 90% of all antibacterial use by dentists.

Figure 4: NHS Scotland: use of antibacterials in dentistry, items/1000/day percent of total items/1000/day in 2009



International comparison

Surveillance of antimicrobial use is undertaken in a number of other countries. The purpose of this section is to illustrate how the use of antibacterials in Scotland compares with other parts of the UK and Europe.

Table 4 presents the data on the use of antibacterials across the UK from prescriptions written by GPs and other non-medical prescribers. It shows that when expressed as items/1000/day use of antibacterials in Scotland is 17% higher than in England but is lower than in Wales and Northern Ireland. When expressed as DDD/1000/day use of antibacterials in Scotland is 26% higher than in England, 15% higher than Wales but lower than Northern Ireland.

Figure 5 shows ESAC data on the use of antibacterials expressed as DDD/1000/day in 2008 (2009 data not available) for Scotland compared to a number of European countries for which data is available.

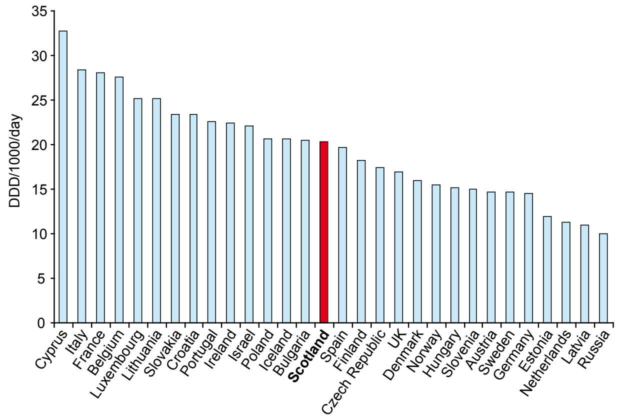
Table 4: Antibacterial use in primary care in 2009

Country	Items/1000/day	DDD/1000/day
Scotland	2.1	19.8
England	1.8	15.7
Wales	2.2	17.2
Northern Ireland	2.7	23.6

Wales – Welsh Antimicrobial Resistance Programme: Surveillance Unit

Northern Ireland – Health and Social Care Business Services Organisation

Figure 5: Use of antibacterials in primary care (DDD/1000/day), 2008



Source: European Surveillance of Antimicrobial Consumption (ESAC)

Secondary Care

In 2008 SAPG developed and issued guidance to AMTs on prescribing for surgical prophylaxis advising that cephalosporins, clindamycin, fluoroquinolones and where possible co-amoxiclav should be avoided and that narrower spectrum agents should be used to reduce the risk of CDI.

In 2009 the Scottish Government worked with SAPG to develop two hospital prescribing indicators to support the Scottish Government's HEAT target aimed at reducing the incidence of CDI among patients aged 65 and over by at least 30% by 31 March 2011. These were:

- hospital based empiric prescribing should have the reason for treatment recorded in the medical notes and the antimicrobial used should be in line with local prescribing policy in at least 95% of sampled cases,
- the duration of surgical antibiotic prophylaxis is less than 24 hours and compliant with local antimicrobial prescribing policy in at least 95% of sampled cases.

National point prevalence survey 2009

National standardised quantitative information on antibacterial use in hospitals was not available in 2009. To estimate the national prevalence and to identify areas for quality improvement Scotland took part in the 2009 ESAC point prevalence survey (PPS) of antimicrobial use in European hospitals. ESAC generally has participation from one or two hospitals from each country. However through promotion to AMTs and securing the support of senior NHS managers and clinicians SAPG co-ordinated the participation of 31 Scottish hospitals that reviewed 8,732 patients during May and June 2009. SAPG also provided support for data entry where this was not possible by AMTs.

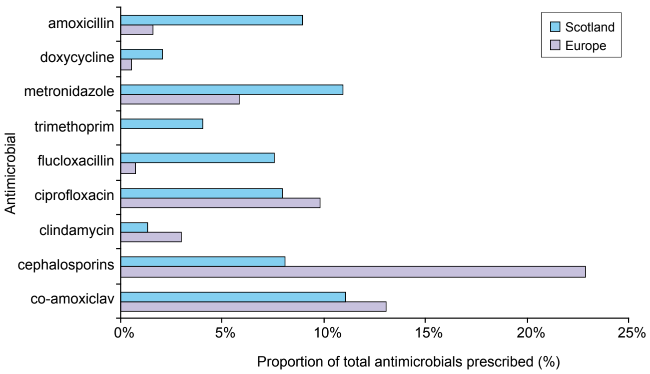
A comprehensive national report comparing the results in Scotland with European data was produced and disseminated to all NHS Boards to enable participating hospitals to benchmark local results against the national findings. The report is available at http://www.scottishmedicines.org.uk/smc/files/ESAC%20report%20final%20060510.pdf

Figure 6 presents the use of the most commonly prescribed antimicrobials in participating hospitals in Scotland compared with Europe. It illustrates that the use of antimicrobials associated with a higher risk of CDI (ciprofloxacin, cephalosporins, clindamycin and co-amoxiclav) was lower in Scotland compared to Europe and that there was a greater use of narrower spectrum

Table 5: Scotland and Europe comparison of key measures of prescribing, ESAC PPS 2009

Measure	Scotland (%)	Europe (%)
Reason for use recorded in notes	76.1	71.5
Compliance with local guidelines	57.9	54.5
Surgical prophylaxis for 24 hours or less	69.7	35.0

Figure 6: Scotland and Europe comparison of proportion of total antimicrobials prescribed, ESAC PPS 2009



antimicrobials such as amoxicillin, doxycycline, metronidazole, trimethoprim and flucloxacillin.

The national prevalence of antimicrobial use was 27.8% compared to 29.0% in Europe. The key areas for improvement are presented in table 5

The results in table 5 illustrate that the level of recording of the reason for use in the notes and the compliance with local guidance, though comparable to Europe require to improve in order to meet the target for the prescribing indicator for hospital based empiric prescribing by March 2011.

Table 5 also illustrates that 69.7% of antimicrobial use for surgical prophylaxis had a duration of 24 hours or less. This is higher than in participating hospitals in Europe but remains an area for improvement in order to meet the prescribing indicator for surgical prophylaxis by March 2011.

The results of the PPS showed that almost 40% of antimicrobials used for surgical prophylaxis in Scotland were cephalosporins. This is not in line with SAPG guidance on prescribing in surgical prophylaxis. This area for improvement will be monitored by SAPG using the prescribing indicator for surgical prophylaxis on an ongoing basis.

The results of this survey provide SAPG and AMTs with useful information on the quality of prescribing within participating hospitals in Scotland.

Future Developments

In 2010/11 we will continue to develop information resources to support SAPG and NHS Board AMTs to enable an enhanced understanding of the use of antibacterials across all healthcare sectors in Scotland.

A key priority for 2010/11 is the development of a tool to support local clinicians in primary care to collect more detailed qualitative information on use of antibacterials to assist in identifying areas for improvement.

In 2010/11 the national database of use of medicines in hospital will become available for the first time in Scotland. HMUD (Hospital Medicines Utilisation Database) will collect information from individual hospital pharmacy systems and present standardised information of the use of medicines at NHS board and national level via a web based system. HMUD is an important national development and the first main clinical area to benefit from this new national information will be the surveillance of use of antibacterials in a hospital setting. To support SAPG and NHS Board AMTs a series of standard and ad-hoc reports on hospital antimicrobial use will be developed and made accessible to users to complement the primary care information available via PRISMS.

A major development resulting from the Scottish Government's e-Pharmacy programme roll out enables capture of an individual's Community Health Index (CHI) on all NHS prescriptions issued in primary care in Scotland. This enriched information will enable analysis of the use of antibacterials by age, gender and deprivation category for the first time. This will provide a platform for SAPG and the wider NHS in Scotland to develop a deeper understanding of antimicrobial use and refine targets for quality improvement.

The impact of these developments will be monitored through the publication of an annual information report.

Chapter 2 - Antimicrobial resistance

Background

Resistance to antimicrobials is considered one of the greatest threats to human health in current times (World Health Organisation, 2001). Infections with resistant pathogens are associated with increased morbidity and mortality, increased healthcare costs and extended stays in hospitals due to failure of initial empirical antimicrobial therapy. Treatment of infections caused by multidrug-resistant Gram-negative organisms is of particular concern as few agents with activity against these pathogens are currently available, and to date development of new effective agents has not been successful (ECDC/EMEA report: The bacterial challenge: time to react, Sep 2010).

Collection and feedback of surveillance data on antimicrobial use and resistance is intended to support NHS Boards, AMTs and ICTs in their strategic planning, and in implementation and evaluation of antimicrobial stewardship and infection control measures aimed at minimising the evolution and spread of resistant pathogens, which will limit the harmful effect of these on the public.

In this second annual report we present antimicrobial susceptibility (AST) data on blood cultures from the most common pathogens causing bacteraemia in Scotland. Blood cultures are the single most reliably collected and reported type of patient specimen. Susceptibility data on blood cultures can be seen as markers of evolution of antimicrobial resistance and can alert the health service to potential clinical problems associated with a specific pathogen. The analysis of the Scottish data is modelled on the EARS-Net (European Antimicrobial Resistance Surveillance Network) Reporting Protocol, 2010 published by ECDC (which has replaced the previous EARSS protocol).

Please be aware that the national antimicrobial resistance surveillance system, described in this report only provides retrospective national trends, and does not alert the NHS Boards to individual cases of infections with resistant pathogens. An electronic AMR-alert system, that prompts NHS diagnostic laboratories to single isolates with unusual resistance profiles, was recently set up by HPS.

In this report we have included analysis of *Acinetobacter baumannii* data, as this organism has been reported to cause problems in acute and non-acute settings. Finally, we present a short summary of epidemiological and AST-data on *C. difficile*, which is contained by both prudent antimicrobial prescribing and infection prevention and control methods.

Methods

Susceptibility data (SIR-data)

Antimicrobial susceptibility data were extracted from ECOSS (Electronic Communication of Surveillance in Scotland, which is an electronic data link for microbiology laboratories to HPS). Data were obtained from all diagnostic laboratories in Scotland and participating reference laboratories (see ‘Data’ section below). The susceptibility data (originating from VITEK 2 systems and other manual susceptibility testing methods) were interpreted locally before they were submitted to ECOSS. It is assumed that the laboratories used Clinical and Laboratory Standards Institute (CLSI) breakpoints for categorising the data into Sensitive (S), Intermediate (I) and Resistant (R) (also referred to as the SIR data) in line with the nationally agreed approach to standard susceptibility testing.

The data from ECOSS were imported into a Microsoft Access® database and numerical analyses were undertaken on the interpreted susceptibility SIR-data on key organisms from blood cultures.

> ***Case definition (adapted from EARS-Net):***
>
> A case of bacteraemia is a patient from whom an organism has been isolated from the patient’s blood, and who has not previously had the same organism isolated within the same quarter.

Deduplication was done in Microsoft Access®. Only the first blood isolate (of one specific organism per patient per quarter) is reported as a case of bacteraemia. This is equivalent to one episode.

Resistance proportions in this report refer to the percentages of isolates reported as resistant (“R”) to the antimicrobial.

Proportions of combined cephalosporin and fluoroquinolone resistance, and combined cephalosporin and aminoglycosides resistance for *E. coli*, *K. pneumoniae and P. aeruginosa* were also calculated. These were calculated as the number of isolates resistant to ceftriaxone/ceftazidime and ciprofloxacin, or to ceftriaxone/ceftazidime and gentamicin, divided by the number of reports containing susceptibility data on both of these antimicrobials.

Extended spectrum beta-lactamase (ESBL)-producing organisms for *E. coli* and *K. pneumoniae* were reported to HPS based on local laboratory tests. The frequency of cases infected with ESBL producing organisms was calculated using the total number of cases as denominator.

Proportions of resistance were compared to previously published data from Sweden (STRAMA) and Norway (NORM/NORM-VET) where available. No comparative reprorts covering 2009 data were available from the rest of the UK when producing this report.

Confidence intervals (95%) for proportions were calculated to indicate robustness of the proportions presented. Where large or unusual differences in proportions were observed between 2008 and 2009 these were statistically tested using a Normal approximation with $p<0.05$ considered as a statistically significant difference.

Multidrug resistance

A recent ECDC expert proposal recommends a standardized international terminology and methodology for reporting on the emergence of multidrug-resistant (MDR) bacteria in healthcare settings, which will allow worldwide comparison of data. We used this proposal as a framework to calculate the number of Scottish isolates of *E. coli* and *K. pneumoniae* which fall into each "antimicrobial category" (Magiorakos et al, Draft, 2010) (see Appendix 1 for antimicrobial categories).

MDR was defined as "non-susceptibility" to at least 1 agent in at least 3 antimicrobial categories. In this report we have ***defined non-susceptibility as resistance*** to a particular agent in each category, as the term "intermediate susceptibility" results was used inconsistently in NHS Boards in 2009. Since not all isolates were tested against all antibiotics (and all antimicrobial categories) the estimated percentages of MDR given in this report may be under-estimates.

Data quality

All susceptibility data (except for those on *C. difficile*) in this report were derived from cases of bacteraemia. Susceptibility testing of the Gram-negative organisms and *Enterococcus* spp. was not standardised across Scotland during this data collection period (2009). In addition to the VITEK 2 systems a number of different laboratory methods were used to determine the susceptibilities, including disc diffusion, agar dilution and Etest®. Selective reporting may also have occurred, where laboratories have chosen only to test and/or report susceptibility results against certain agents for clinical reasons (the number of reported isolates for each antibiotic are indicated in Table 7).

The use of different methodologies and selective reporting potentially weakens comparison of data between different laboratories and could also underestimate the occurrence of multidrug resistance.

Work is ongoing to standardise antimicrobial susceptibility testing across Scotland through implementation of VITEK 2 automated susceptibility testing systems and the associated software Observa 3 in all Scottish diagnostic microbiology laboratories as per the agreed national strategy, ScotMARAP.

At the time of writing this report ten diagnostic laboratories were routinely submitting standardised susceptibility data on Gram-negative bacteraemia, including minimum inhibitory concentration (MIC)-data, derived from the VITEK 2 systems. Data derived from the VITEK 2 systems will allow NHS Boards and HPS to detect emergence of new resistances and changes in MIC-distributions (to less susceptible states) before resistance has emerged. Consequently, it is of great importance that all diagnostic laboratories submit standardised susceptibility data to HPS.

Data on *S. aureus* and S. *pneumoniae*, provided by the Scottish Meticillin Resistant *S. aureus* Reference Laboratory (SMRSARL) and the Scottish Haemophilus, Legionella, Meningococcus and Pneumococcus Reference Laboratory (SHLMPRL) respectively, are already standardised as a consistent laboratory method has been applied to all Scottish isolates. Likewise, standardised susceptibility data on *C. difficile* was obtained from the Scottish Salmonella, Shigella and Clostridium difficile Reference Laboratory (SSSCDRL).

Clostridium difficile Infection (CDI)

Calculated rates of CDI per 1000 total occupied bed days (for those aged 65 years and above) for 2009, previously published by HPS, are presented in this report. A short summary of susceptibility to metronidazole and vancomycin and other antimicrobials tested by SSSCDRL are also presented.

Results

Gram-negative bacteraemia

Reporting of Gram-negative bacteraemia to HPS increased considerably in the period 2008-2009 as electronic reporting of AST-data via ECOSS was completed for all laboratories (See Table 6). This is reflected in the increased number of cases in 2009.

Based on the respective numbers of cases reported from each laboratory that began reporting via ECOSS during 2008-2009, we have estimated that 80% of the total increase in cases of *E. coli* bacteraemia and 75% of the increase in *K. pneumoniae* bacteraemia may have been caused by increased reporting. The true increase in number of cases of Gram-negative bacteraemia from 2008 to 2009 cannot be determined.

The frequencies of ESBL-producers among *E. coli* and *K. pneumoniae* did not change significantly between 2008 and 2009 (see Table 6). One isolate of *P. aeruginosa* reported in 2009 produced ESBL.

Table 6: Gram-negative bacteraemias in 2008 and 2009; number of cases according to EARS-net definition and percentage of ESBL producers

	Number of cases of bacteraemia reported (% ESBL)					
	E. coli		*K. pneumoniae*		*P. aeruginosa*	
	All	ESBL	All	ESBL	All	ESBL
2008	2499	179 (7.2%)	512	43 (8.4%)	196	0
2009*	3486	262 (7.5%)	672	59 (8.8%)	269	1 (0.4%)

*Please note: there has been increased reporting frequency throughout 2008-2009 for a number of laboratories.

Table 7: Resistance in Gram-negative bacteraemias in 2008 and 2009

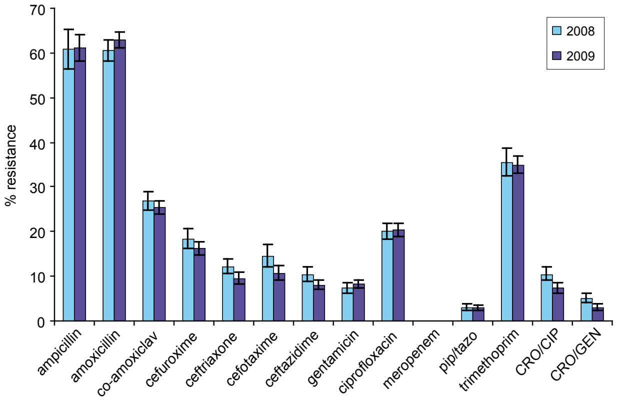
	% Resistance (number of isolates susceptibility tested)							
	E. coli		*K. pneumoniae*		*P. aeruginosa*		*A. baumannii*	
	2008 n=2499	2009 n=3486	2008 n=512	2009 n=672	2008 n=196	2009 n=269	2008 n=53	2009 n=64
ampicillin	61.0 (464)	61.2 (975)	i.r.	i.r.	i.r.	i.r.	-	-
amoxicillin	60.6 (1841)	62.8 (2725)	i.r.	i.r.	i.r.	i.r.	-	-
cefoxitin	3.2 (813)	5.7 (1977)	5.5 (163)	4.5 (380)	i.r.	i.r.	-	-
aztreonam	11.5 (730)	8.3 (2014)	16.6 (157)	10.6 (387)	30.6 (49)	21.7 (161)	-	-
co-amoxiclav	26.8 (1935)	25.4 (3053)	13.7 (437)	10.1 (603)	i.r.	i.r.	-	-
cefuroxime	18.4 (1128)	16.3 (2317)	22.3 (229)	16.3 (443)	i.r.	i.r.	-	-
ceftriaxone	12.1 (1658)	9.6 (2086)	15.6 (327)	13.3 (420)	i.r.	i.r.	-	-
cefotaxime	14.3 (753)	10.7 (1554)	12.4 (170)	10.8 (305)	i.r.	i.r.	-	-
ceftazidime	10.3 (1489)	8.1 (2685)	12.5 (304)	9.2 (512)	8.3 (133)	8.9 (214)	20.0 (30)	22.2 (45)
gentamicin	7.3 (2305)	8.2 (3312)	9.7 (465)	10.1 (636)	2.3 (171)	2.4 (254)	6.8 (44)	1.7 (60)
ciprofloxacin	20.0 (2191)	20.4 (3046)	10.9 (440)	10.0 (598)	11.8 (161)	6.6 (244)	22.0 (41)	1.8 (55)
meropenem	0.0 (1459)	0.0 (2523)	0.0 (316)	0.0 (506)	5.3 (114)	4.7 (192)	0.0 (33)	0.0 (45)
piperacillin-tazobactam	3.0 (1687)	2.9 (2169)	7.3 (328)	3.8 (426)	8.3 (133)	9.8 (183)	12.1 (33)	17.8 (45)
trimethoprim	35.6 (891)	34.9 (2338)	18.1 (171)	18.3 (447)	95.1 (41)	98.1 (108)	-	-
3G CEPH/FQ	10.5 (1550)	7.4 (1980)	9.3 (301)	9.7 (401)	2.4 (127)	2.8 (211)	10.3 (29)	2.3 (44)
3G CEPH /AMG	5.0 (1649)	3.0 (2083)	10.2 (323)	11.0 (420)	0.8 (133)	0.9 (214)	3.4 (29)	2.2 (45)

i.r.: intrinsic resistance in organism

Escherichia coli

E. coli was, as in 2008, the most frequent cause of bacteraemia reported in Scotland in 2009. Resistance to a wide range of important antibiotics classes occurred frequently among the *E. coli* bacteraemia isolates. An overview of the susceptibility results can be found in Table 7 above and Figure 7.

Figure 7: Figure 7. Antimicrobial resistance in *E. coli* isolated from blood cultures in 2008 (n=2499) and 2009 (n=3486). One isolate was resistant to meropenem in 2009 (0.3%). Not all isolates were tested against all agents (See Table 7).



No major increases in proportions of resistance were observed for any of the antibiotic classes reported here. This is an interesting finding, as it would be expected that resistance would increase with time as selective pressure is continuously applied.

Resistance to the majority of broad-spectrum penicillins, with or without beta-lactamase inhibitors, remained high in the Scottish *E. coli* isolates (61-63% for ampicillin/amoxicillin, 25% for co-amoxiclav and 3% for tazocin).

Resistance to second and third generation cephalosporins decreased 2-3% from 2008 but confidence intervals were overlapping. The decrease was statistically significant for the third generation cephalosporins ($p<0.05$ for both ceftriaxone, cefotaxime and ceftazidime).

Approximately 50% of isolates resistant to second and 70% of isolates resistant third generation cephalosporins were carrying ESBL.

All tested *E. coli* bacteraemia isolates were susceptible to meropenem, and 99% of reported MIC-values were ≤ 0.25 mg/L).

Resistance to aminoglycosides increased from 7.3% to 8.2% but again confidence intervals were overlapping. Nonetheless this needs to be carefully monitored as aminoglycoside usage replaces third generation cephalosporins as part of the interventions to reduce CDI.

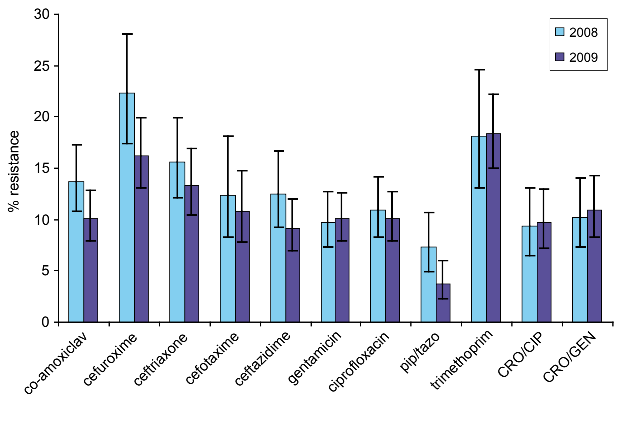
Combined resistance to third generation cephalosporins and fluoroquinolones decreased from 10.5% to 7.4%, and combined resistance to third generation cephalosporins and aminoglycosides has decreased from 5.0% to 3.0% ($p<0.01$ for both combinations).

In comparison, considerably lower proportions of resistance were reported among Swedish *E. coli* bacteraemia isolates for 2009. Only 32.8% were resistant to aminopenicillins, 3% to third generation cephalosporins, 3.7% to aminoglycosides and 15.5% to fluoroquinolone (SWEDRES, 2009).

Klebsiella pneumoniae

K. pneumoniae is with 672 cases reported in 2009 the second most common cause of Gram-negative bacteraemia. Resistance to a wide range of antibiotics classes is also reported for *K. pneumoniae* during this period. An overview of the susceptibility results can be found in Table 7 and Figure 8.

Figure 8: Antimicrobial resistance in *K. pneumoniae* isolated from blood cultures in 2008 (n=512) and 2009 (n=672). Not all isolates were tested against all agents (See Table 7).



K. pneumoniae is intrinsically resistant to aminopenicillins (e.g. ampicillin) as it carries chromosomal encoded beta-lactamases, but is susceptible to most combination agents (i.e. penicillins + beta-lactamase inhibitors).

Resistance to co-amoxiclav and piperacillin-tazobactam have both decreased over 3% since 2008. For piperacillin-tazobactam the decrease was significant ($p<0.05$).

Resistance to both second and third generation cephalosporins (6% decrease for cefuroxime, and 1-3% decrease for ceftriaxone, cefotaxime and ceftazidime) among *K. pneumoniae* also decreased from 2008 to 2009, although these changes were not statistically significant.

Approximately 45% of isolates resistant to second generation cephalosporins and 65% of isolates resistant third generation cephalosporins were carrying ESBL.

None of the *K. pneumoniae* bacteraemia isolates were resistant to carbapenems but one isolate had reduced susceptibility to meropenem.

Resistance to aminoglycosides and fluoroquinolones did not change between 2008 and 2009, remaining at approximately 10% for both agents.

Combined resistance in *K. pneumoniae* to third generation cephalosporins + fluoroquinolones and to third generation cephalosporins + aminoglycosides increased slightly between 2008 and 2009, but the changes were not significant.

For the same period Sweden reported much lower resistance proportions for third generation cephalosporins (1.8%) and aminoglycosides (1%), while ciprofloxacin resistance was higher (12.2%).

Pseudomonas aeruginosa

A total of 269 cases of *P. aeruginosa* bacteraemia were reported in 2009. *P. aeruginosa* is intrinsically resistant to a broad range of antimicrobials.

Resistance to all anti-pseudomonal agents, including piperacillin-tazobactam, ceftazidime, carbapenems, fluoroquinolones and aminoglycosides, was observed among the Scottish isolates in 2008 and 2009 (for an overview of susceptibility results, see Table 7 and Figure 9)

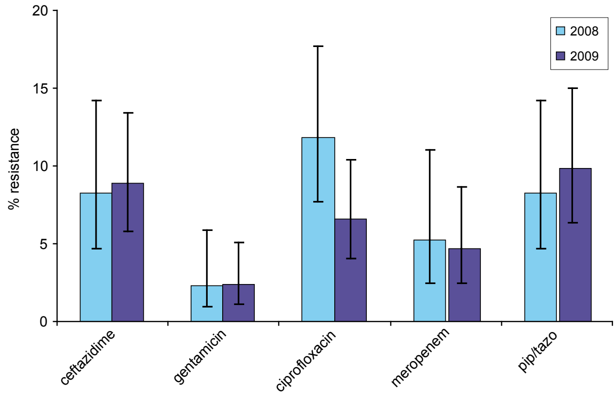
Resistance to piperacillin-tazobactam increased from 8.3 to 9.8% from 2008 to 2009, while resistance to fluoroquinolones decreased from 11.8 to 6.6% in the same period. None of these changes were significant.

Resistance to cephalosporins (ceftazidime) (~8%), carbapenems (meropenem) (~5%) and aminoglycosides (gentamicin) (~2%) remained largely unchanged from 2008 to 2009.

Multidrug resistance (defined as resistance to at least 3 categories of anti-pseudomonal antimicrobials) was detected in seven *P. aeruginosa* isolates (corresponding to 2.6% of the isolates). None of the isolates were resistant to all 5 tested antimicrobial categories.

While fluoroquinolone resistance decreased in Scottish isolates of *P. aeruginosa* in 2009 it increased (from 8% to 10%) among the Swedish isolates. Resistance to ceftazidime (3%) was lower in the Swedish isolates and resistance to aminoglycosides was not observed. The proportion of isolates resistant to carbapenems (7.5%) was slightly higher among the Swedish isolates.

Figure 9: Antimicrobial resistance in *P. aeruginosa* isolated from blood cultures in 2008 (n=196) and 2009 (n=269). Not all isolates were tested against all agents (See Table 7).



Acinetobacter baumannii

A total of 53 isolates of *A. baumannii* were reported in 2008, and 64 isolates were reported in 2009 (see Table 7 for susceptibility results). High proportions of resistance to ceftazidime (20-22%) and tazocin (12-18%) were observed among the Scottish isolates in this 2-year period. Resistance to aminoglycosides and fluoroquinolones varied between 2008 and 2009. No isolates were found resistant to carbapenems.

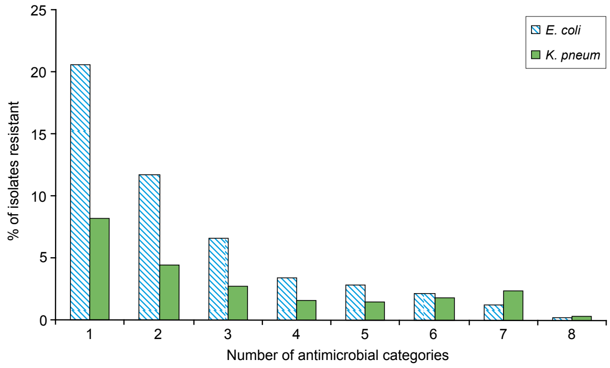
Multidrug resistance

Using the ECDC proposal for a standardized international terminology of multidrug resistance (Magiorakos, et al, draft, 2010), the number of antimicrobial categories in which resistance was detected to at least one agent was determined for the Scottish isolates (see appendix 1). The Scottish *E. coli* isolates were tested against agents representing up to 12 of the recommended antimicrobial categories, while the *K. pneumoniae* isolates were tested against agents representing up to 10 of the recommended antimicrobial categories (note that not all isolates were tested against all agents, see Table 7 for number of isolates tested). The results of this analysis are presented in Figure 10.

For *E. coli* resistance was detected in up to 8 antimicrobial categories. In total 16.6% of all the Scottish *E. coli* bacteraemia isolates could be categorised as MDR (multidrug resistant). For *K. pneumoniae* resistance was also detected in up to 8 antimicrobial categories, while 10.3% of all isolates could be categorised as MDR.

No isolates could be categorised as extensively drug

Figure 10: Percentage of *E. coli* and *K. pneumoniae* isolates resistant to number of antimicrobial categories.



resistant, XDR, classified as resistance to all but 2 categories, or pandrug resistant, PDR, classified as resistance to all categories.

It is important to note that this analysis could be an underestimate of the occurrence of multidrug resistance among the Scottish bacteraemia isolates as there were large variations in the number of agents each isolate was tested against (ranging from 28-95% of the total number of reported isolates).

Carbapenemase-producing Enterobacteriaceae - a significant risk to public health worldwide

Enterobacteriaceae (a large family of bacteria which include *E. coli*, *K. pneumoniae* and *Enterobacter* spp.) are among the most common naturally occurring bacteria in humans and constitute a considerable part of the normal gut flora. Under some circumstances, they also cause community-acquired and healthcare associated infections such as urinary tract infections, bloodstream infections and intra-abdominal infections. *Enterobacteriaceae* readily develop antimicrobial multi-drug resistance through a range of mutations and by acquiring mobile genetic elements encoding resistance mechanisms (including enzymes that can destroy antimicrobials such as penicillins, cephalopsorins and carbapenems). Humans are frequently exposed to new bacterial strains, some of which are resistant to multiple antimicrobials, through food, water, the environment, hospitals and during travels abroad.

Since the 1950s a wide range of resistance mechanisms have evolved in *Enterobacteriaceae* enabling these microorganisms to evade or survive effects of increasingly potent antibiotics. The first of these were beta-lactamases, which is a group of bacterial enzymes that make the bacteria resistant to penicillins and narrow-spectrum cephalosporins by degrading these. In the 1980s a new group of antibiotic degrading enzymes were detected, the 'extended spectrum beta-lactamases' (ESBLs), which conferred resistance to the newer extended spectrum cephalosporins but not to the very potent and broad-spectrum carbapenems. At this stage the carbapenems became the treatment of choice for infections caused by ESBL-producing bacteria which are often also resistant to other antibiotics. It was recently estimated that 70-90% of *Enterobacteriaceae* in India are ESBL-producers (Kumarasamy *et al.*, 2010). Countries with high rates of ESBL-producers will be forced to use carbapenems on a routine basis to control infections with *Enterobacteriaceae.*

The new carbapenem-degrading enzymes, the 'carbapenemases', were detected a decade later, but remained relatively rare until outbreaks of carbapenemase-producing *K. pneumoniae* (carrying VIM or KPC beta-lactamases) were reported from Greece, Israel and the United States. In 2008, the enzyme 'New Delhi metallo beta-lactamase' (NDM-1) was first reported in an isolate from a patient in Sweden who returned home after being treated in a hospital in New Delhi in India. Most carbapenemases are extensively resistant to antimicrobials and only remain susceptible to colistin and tigecycline (both of which have a range of side effects).

A recent publication reported frequent identifications of NDM-1 isolates in India, Bangladesh, Pakistan and the United Kingdom (UK) (Kumarasamy *et al.*, 2010). Although the strains isolated from the UK and India were not genetically related, most of the British cases had been travelling in India or Pakistan, and at least some of those had received medical treatment while in these countries. Furthermore, many patients with NDM-1 infection (or colonisation) had co-morbidities, including diabetes, cancer, chronic renal failure, organ transplant and had undergone invasive procedures.

The ECDC have recognised carbapenemase-producing *Enterobacteriaceae* as a 'significant potential risk for public health in Europe and worldwide' as treatment options are currently very limited (ECDC Threat Assessment, August 2010)

In Scotland monitoring resistance to carbapenemase-producing *Enterobacteriaceae* is part of the national surveillance programme and any such organisms should be reported to HPS. Isolates with an unusual resistance profile reported through ECOSS that potentially could be carbapenem-resistant are "flagged" up by a real-time resistance alert system – and the relevant diagnostic laboratory is contacted to prompt further investigations.

In 2009, 10 isolates of carbapenemase-producers were identified and characterised at the Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL), Colindale. Four of these were VIM-producing *P. aeruginosa*, two were KPC-producing *K. pneumoniae*, three were VIM/KPC producing Enterobacter species, and one was NDM-1 producing *Citrobacter freundii*.

Further surveillance systems are under development to monitor carbapenemase-producers among urinary tract infections.

Gram-positive bacteraemia

Reporting of *S. aureus* and *S. pneumoniae* bacteraemia data to HPS comes directly from the SMRSARL and SHLMPRL respectively. There remains good compliance with these surveillance systems and the datasets are validated and robust. It is important to note that the *S. aureus* dataset is de-duplicated according to the EARS-Net definition and as such differs from the HPS Scottish *S. aureus* bacteraemia surveillance programme where a two week episode definition is applied. Data pertaining to *Enterococcus* spp. is submitted to HPS from the Scottish NHS diagnostic laboratories via ECOSS. Reporting via this mechanism has improved over the recent years; however the true number of cases of *Enterococcus* spp. bacteremias remains unknown.

Table 8: Gram-positive bacteraemias in 2008 and 2009; number of cases according to EARS-Net definition

	Number of cases of bacteraemia reported						
	Enterococcus sp.			***S. aureus***			***S. pneumoniae***
	All	***E. faecalis***	***E. faecium***	**All**	**MRSA**	**MSSA**	
2008	648	379	269	1846	605	1241	607
2009	702	447	255	1826	478	1348	579

Table 9: Resistance in Gram-positive bacteraemias in 2008 and 2009. All isolates were susceptibility tested

	% Resistance									
	E. faecalis		***E. faecium***		**MRSA**		**MSSA**		***S. pneumoniae***	
	2008 n=379	**2009 n=447**	**2008 n=269**	**2009 n=255**	**2008 n=605**	**2009 n=478**	**2008 n=1241**	**2009 n=1348**	**2008 n=607**	**2009 n=579**
chloramphenicol	-	-	-	-	0.5	0.4	0.2	0.1	-	-
ciprofloxacin	-	-	-	-	96.0	91.0	7.1	7.4	1.0	1.2
clindamycin	-	-	-	-	32.1	33.3	0.9	2.8	-	-
erythromycin	-	-	-	-	76.8	72.0	10.5	9.3	3.1	2.4
fusidic acid	-	-	-	-	6.9	2.7	10.6	2.5	-	-
gentamicin	-	-	-	-	7.3	9.6	1.2	0.7	-	-
kanamycin	-	-	-	-	15.9	14.0	2.3	0.7	-	-
linezolid	-	-	-	-	0	0	0	0	-	-
mupirocin	-	-	-	-	5.3	6.3	0.3	0.1	-	-
penicillin	-	-	-	-	-	-	-	-	0.2	0.2
rifampicin	-	-	-	-	2.5	2.3	0.1	0.1	-	-
teicoplanin	-	-	-	-	0	0	0	0	-	-
tetracycline	-	-	-	-	9.8	10.5	5.3	4.7	-	-
tobramycin	-	-	-	-	20.7	13.2	2.1	0.7	-	-
trimethoprim	-	-	-	-	27.8	19.7	15.6	3.0	-	-
vancomycin	0.3	0.9	16.7	27.8	0	0	0	0	-	-

Staphylococcus aureus

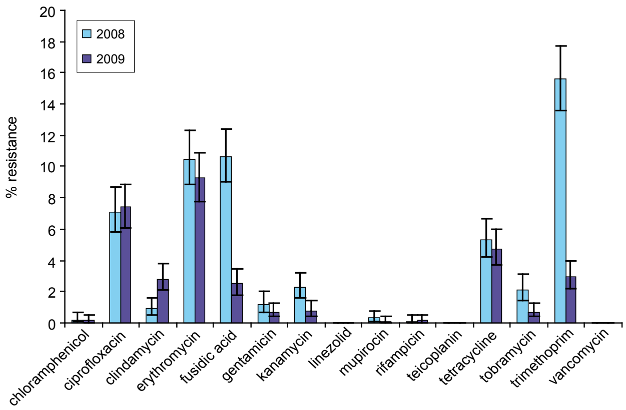
The total number of recorded cases of *S. aureus* bacteraemia in 2009 was 1826. The net change in *S. aureus* is caused by a relative decrease in MRSA and relative increase in MSSA. This is marginally lower than the total number of cases reported in 2008 (1846). In 2009, 26.2% of cases were attributable to MRSA, compared to 32.8% in 2008.

Meticillin sensitive *S. aureus* (MSSA)

The number of reported MSSA bacteraemias in 2009 was 1348. This is an increase on the number of cases reported in 2008 (1241). Antimicrobial susceptibility of MSSA remains similar to that observed in 2008 (with the majority of confidence intervals overlapping). There are two notable exceptions to this, and it would appear that there has been a statistically significant increase in susceptibility to fusidic acid and trimethoprim. However, further investigations demonstrated that the increase in susceptibility to these drugs could be explained by improved antimicrobial susceptibility testing methods (namely SMRSARL transition from VITEK 1 to VITEK 2). The highest resistance proportions were reported for erythromycin (9.3%), ciprofloxacin (7.4%), tetracycline (4.7%) and trimethoprim (3.0%). There are no available international comparisons.

An overview of the susceptibility results can be found in Table 9 and Figure 11.

Figure 11: Antimicrobial resistance in MSSA isolated from blood cultures in 2008 (n=1241) and 2009 (n=1348).



Meticillin resistant *S. aureus* (MRSA)

The numbers of MRSA bacteraemias being reported to HPS has fallen from 605 in 2008 to 478 in 2009. The highest resistance proportions were reported for ciprofloxacin (91.0%), erythromycin (72.0%), clindamycin (33.3%) and trimethoprim (19.7%). There was no significant change from 2008 to 2009. There are no available international comparisons.

Figure 12: Antimicrobial resistance in MRSA isolated from blood cultures in 2008 (n=605) and 2009 (n=478).

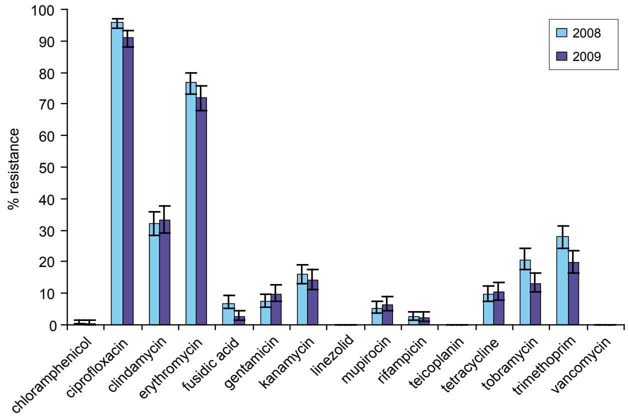
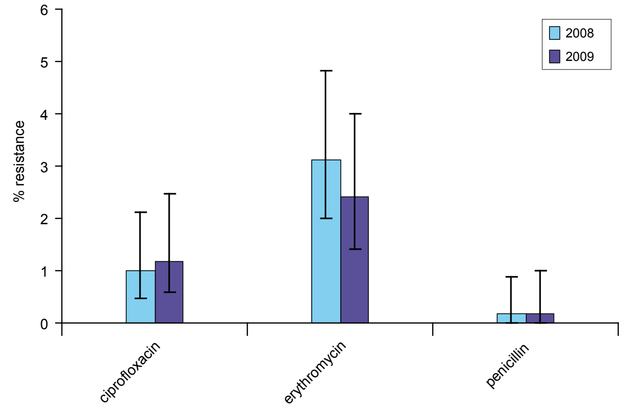


Figure 13: Antimicrobial resistance in *S. pneumoniae* isolated from blood cultures in 2008 (n=607) and 2009 (n=579).



An overview of the susceptibility results can be found in Table 9 and Figure 12.

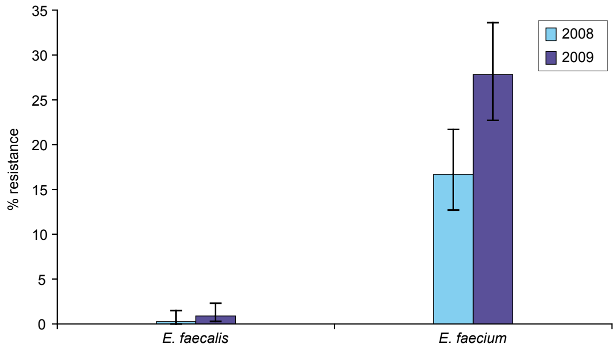
Streptococcus pneumoniae

The number of reported cases of *S. pneumoniae* bacteraemias in 2009 was 579. Resistance proportions to ciprofloxacin, erythromycin and penicillin were 1.2%, 2.4% and 0.2% respectively. There are no significant changes to resistance proportions from 2008 to 2009. Norway (NORM/NORM-VET 2009) reports resistance proportions to penicillin and erythromycin as 0% and 4.6%.

Enterococcus spp.

The total number of *E. faecalis* and *E. faecium* reported were 447 and 255 respectively. The proportion of *E. faecalis* isolates resistant to vancomycin remained below 1%. Vancomycin resistance in *E. faecium* has increased from 16.7% in 2008 to 27.8% in 2009. In comparison, Sweden reported no vancomycin resistance for *E. faecalis* and 0.8% for *E. faecium* (SWEDRES, 2009). Norway

Figure 14: Antimicrobial resistance in *E. faecalis* in 2008 (n=379), 2009 (n=447) and *E. faecium* in 2008 (n=269), 2009 (n=255) isolated from blood cultures.



reported 1.8% vancomycin resistance for *Enterococcus* spp. but 0% for *E. faecalis* and *E. faecium.*

Due to the infancy of this surveillance programme it is not possible to be certain that this has been a true decrease in vancomycin susceptibility in *E. faecium*, or whether it can be attributed to improvements in identification of species, antimicrobial susceptibility testing etc. None the less, it is important to remain vigilant in the monitoring of this resistance.

Emerging resistance- Mupirocin resistant MRSA

Mupirocin (pseudomonic acid A) is a topical antimicrobial agent that inhibits bacterial protein and RNA synthesis, which has been used to treat skin and soft tissue infections and to eradicate staphylococcal nasal carriage in patients pre-operatively. It has also been used to control the transmission of MRSA within healthcare facilities. A consequence of the extensive use of this agent is an increase in mupirocin resistance in MRSA in certain healthcare settings (Cookson, 1990, Rossney and O'Connell, 2008, Hogue *et al*., 2010).

Mupirocin resistance is separated into two categories: low level resistance with a minimum inhibitory concentration (MIC) from 8 to 256 mg/L and high level resistance with MICs ≥512 mg/L. The majority of isolates that demonstrate high level resistance have acquired the plasmid-mediated *mupA* gene *(ileS2*)*,* which encodes an isoleucyl-tRNA synthetase. Isolates with low level resistance usually have point mutations in the chromosomally encoded *ileS* gene. (It should also be noted that MRSA isolates that are *mupA* positive by PCR but mupirocin susceptible have also been reported (i.e.) the gene is not expressed)

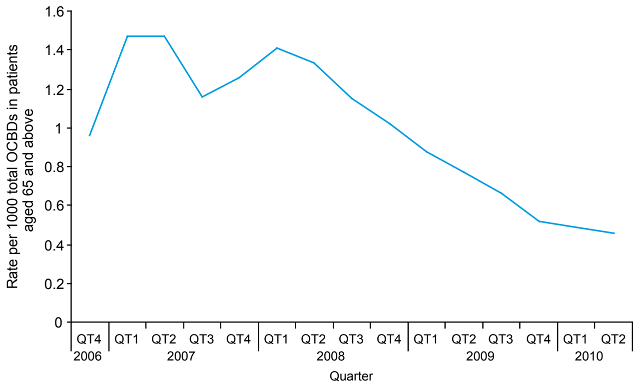
Treatment with mupirocin is unlikely to be effective in the presence of high level mupirocin resistance, and there is some evidence to suggest that low-level resistance may also predict treatment failure. With the roll-out of the National MRSA Screening Programme across Scotland, it is expected that the amount of mupirocin prescribed will increase. HPS, in conjunction with the SMRSARL, will monitor both high and low-level resistance. This will include monitoring both non-susceptible isolates and carriers of the *mupA* gene.

Clostridium difficile Infection (CDI)

Mandatory surveillance of CDI in patients aged 65 years and over showed a continuing decline in rates (per 1000 occupied bed days) during 2009. Over the four quarters of 2009 the overall CDI rate dropped consecutively: 0.88 in Q1, 0.77 in Q2, 0.66 in Q3 and 0.52 in Q4, for an overall decrease of 41% during 2009. This trend has continued into 2010 although the rate of decline appears to slowing (see Figure 15). Compared to 2008, the number of cases dropped 43% (6322 to 3625) and the overall rate for Scotland decreased by 42% (1.23 to 0.71).

There is a temporal association between the introduction of restrictive antimicrobial policies in line with SAPG guidance and the declining rates of CDI in Scotland. However it is difficult to quantify the true impact of this type of intervention separately from the others that have been implemented concurrently to control and prevent CDI.

Figure 15: Overall quarterly CDI rates for Scotland in patients aged 65 and over (per 1000 total occupied bed days) for fourteen quarters of mandatory surveillance covering the period October 2006-March 2010.



Typing of *C. difficile* isolates from severe cases and outbreaks showed that the five most common strains in Scotland were 106, 001, 027, 002 and 005, respectively. Out of a total of 793 isolates (including other types in addition to those above), almost all were found to be resistant to clindamycin. The majority of ribotypes 106, 001, 027 were found to be multi-resistant to the antibiotics levofloxacin, moxifloxacin, cefotaxime, clindamycin and erythromycin. All of the 793 ribotypes tested were sensitive to metronidazole and vancomycin.

The multiple resistances observed in the epidemic strains (001, 106 and 027) of *C. difficile* may reflect the importance that the use of these classes of antimicrobials may play in the spread and persistence of these types in Scotland.

Future developments

Standardised susceptibility testing has been introduced in diagnostic microbiology laboratories across Scotland by installation of VITEK 2 automated susceptibility testing systems. The procurement of the VITEK 2 systems forms part of an ambitious national strategy that aims at improving the quality of antimicrobial prescribing and containing resistance in order to preserve the effectiveness of antimicrobials in Scotland in the future.

Most laboratories use the VITEK 2 system for testing blood cultures as a minimum, and a number of laboratories also use it for testing urines, sputum and other types of specimens. The use of manufactured antimicrobial testing panels (with a set panel of testing antibiotics) and automated susceptibility testing in all laboratories are key to providing standardised high quality surveillance data. It eliminates the variation caused by variation in testing method and testing panels, and by selective testing and reporting.

The analysis of multidrug resistance in blood cultures of *E. coli* and *K. pneumoniae* presented in this report demonstrated that strains with multiple resistances are emerging in relatively high frequencies, which suggest that extensively drug resistant (XDR) or pandrug resistant (PDR) strains may emerge in Scotland in the future.

Selective testing and reporting, primarily set up to support clinical management of patients, may be insufficient to capture these new untreatable strains. The estimates of frequencies of multidrug resistance are most likely conservative estimates since the testing frequencies varied greatly for each antibiotic.

A key priority for 2011 is to further develop and consolidate the standardisation of susceptibility testing in all NHS Boards through testing and reporting via the VITEK 2 systems. At the time of writing this report, ten Scottish diagnostic laboratories transfer VITEK 2 data directly to ECOSS, which gives HPS access to the full datasets including phenotypic data on antimicrobial-pathogen combinations without omitting the suppressed susceptibility data (that normally are withheld for clinical reasons).

The recent emergence of carbapenem resistant *Enterobacteriaceae* in the UK and in other countries has highlighted the need for enhanced surveillance and awareness of these organisms. Currently carbapenemase-producers are monitored retrospectively within the national surveillance programme (presented in this report) and in real-time by the 'electronic resistance alert system' within ECOSS. In 2011 we aim to further develop the surveillance of carbapenem resistant *Enterobacteriaceae* through collaboration with ARMRL (Colindale) and the diagnostic laboratories in Scotland.

The changes in antimicrobial prescribing patterns, caused by the introduction of the national antimicrobial stewardship programme, are creating new selective pressures on the microbial flora found in humans and the environment of both hospitals and the community, and potentially cause new clinical problems, referred to as 'unintended consequences'. These include the emergence of new multidrug resistant strains, side effects of the 'new' recommended antibiotics, reduced clinical effectiveness and re-emergence of infections that previously were uncommon. Some of these, such as gentamicin induced nephro- and ototoxicity, may occur quickly whilst others such as resistance may take years to manifest but which could severely obstruct infection management and infection control if not detected in time. Ongoing surveillance of antimicrobial resistance is therefore essential to monitor the changes in resistance patterns alongside the development of systems to identify and quantify unintended consequences. Development of systems that monitor unintended consequences in all NHS Boards is another key action for 2011.

Conclusion

This is the second SAPG joint annual report on antimicrobial use and resistance in Scotland. It consolidates the surveillance systems and provides data from the first year following the implementation of a national antimicrobial stewardship programme. The report highlights specific trends in antimicrobial use and patterns of antimicrobial resistance. The report aims to support NHS Boards, hospitals and primary care in their long-term planning of antimicrobial prescribing. In particular this report should be of use to antimicrobial management teams (AMTs), infection control teams (ICTs) and microbiologists.

Appendix 1

Antimicrobial categories and corresponding antibiotics used to define multidrug resistance (MDR) in *E. coli* and *K. pneumoniae*

Antibiotic	Antimicrobial category	Exceptions
ampicillin	penicillins	N/A for *K. pneumoniae*
aztreonam	monobactams	
cefoxitin	cephamycins	
ceftriaxone	extended-spectrum cephalosporins (3rd generation)	
cefuroxime	cephalosporins (2nd generation)	
chloramphenicol	phenicols	
ciprofloxacin	fluoroquinolones	
co-amoxyclav	penicillins + inhibitors	
gentamicin	aminoglycosides	
meropenem	carbapenems	
piperacillin-tazobactam	anti-pseudomonal penicillins + inhibitors	N/A for *K. pneumoniae*
trimethoprim	folate pathway inhibitors	

Multidrug resistance (MDR) was defined as resistance to (at least) 1 antibiotic in at least 3 antimicrobial categories.

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