NHS National Services Scotland

Scottish antimicrobial use and resistance in humans in 2015.

Health Protection Scotland

ISD SCOTLAND

Scottish Antimicrobial Prescribing Group

Scottish Medicines Consortium

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Executive Summary

The threat to health and healthcare from antimicrobial resistance (AMR) is very important. AMR occurs when microorganisms, such as bacteria, adapt the ability to survive exposure to a treatment that would normally kill them. The overuse and inappropriate use of antibiotics speeds up the development of AMR.

Primary Care Antibiotic Use

Total use was **2.4% lower** than 2014 and is the third successive annual reduction.

9.5% lower than the highest rate of use in 2012

Only once in the last **20** years (2004) has prescribing rate been **lower**.

Acute hospital antibiotic use

In 2015, **84%** of antibiotic use in hospitals was in acute hospitals and **16%** in non-acute/community hospitals.

In 2015 antibiotic use was **3.5% higher** than in 2014 and **9.9%**[R] **higher** than in 2012.

A new quality indicator with associated targets to optimise antibiotic use through timely clinical review of all patients on antibiotics will be introduced in 2017.

Very broad spectrum antibiotic use

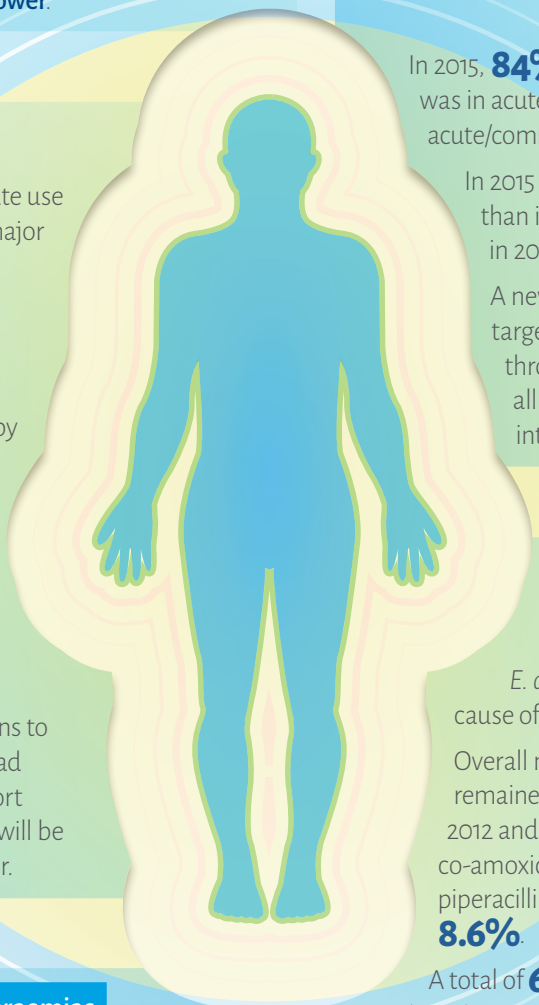
Increased use and especially inappropriate use of very broad spectrum antibiotics is a major factor in the development of resistance.

Carbapenems use **increased** by **6.5%** in 2015 compared to 2014 and is **9.3% higher** than 2012.

Piperacillin-tazobactam use **decreased** by **7.9%** in 2015, the first reduction since 2009 (when data became available)

Use of very broad spectrum sparing antibiotics remained **low** overall but use of aztreonam has more than **doubled** in 2015.

The Scottish Antimicrobial Prescribing Group will continue to work with clinicians to protect and preserve the use of very broad spectrum antibiotics. Measures to support reduction in the use of these antibiotics will be included within the new quality indicator.



Resistance in Gram-negative bacteraemias

E. coli continued to be the most frequent cause of Gram-negative bacteraemia in Scotland.

Overall non-susceptibility to most antimicrobials remained **stable** for *E. coli* bacteraemia between 2012 and 2015, except for non-susceptibility to co-amoxiclav which **increased** by **6.1%** and piperacillin- tazobactam which **increased** by **8.6%**.

A total of **63** carbapenemase-producing organisms (CPOs) were reported from the Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit Public Health England (PHE) in 2015, in comparison with **47** reported isolates in 2014.

Resistance in Gram-positive bacteraemias

6.8% of *S. aureus* bacteraemias were MRSA in 2015.

Susceptibility of MRSA and MSSA to the majority of antibiotics tested has remained **stable** since 2012.

The proportion of *E. faecium* blood stream infection isolates that were non-susceptible to vancomycin in 2015 was **34.7%** (n=92). There has been a statistically significant **increasing** trend observed in vancomycin resistance since 2012 (p=0.006) and an overall **increase** of **16.6%**.

Health Protection Scotland will take forward work to investigate the causes and potential interventions for this emerging vancomycin resistance issue.

Figures denoted [R] were subject to minor errors in the publication of 30 August 2016 and have been revised in this publication. Please see the introduction note for more details.

List of abbreviations and acronyms

ADM	Admissions
AMR	Antimicrobial resistance
AMRHAI	Antimicrobial Resistance and Healthcare Associated Infections
AMTs	Antimicrobial management teams
ARU	Anaerobic Reference Unit
AST	Antimicrobial susceptibility testing
CARS	Controlling Antimicrobial Resistance in Scotland
CC	Clonal Complex
CDI	*Clostridium difficile* infection
CHI	Community Health Index
CPE	Carbapenemase producing Enterobacteriaceae
CPO	Carbapenemase-producing organism
DDD	Defined daily dose
EARS-Net	European Antimicrobial Resistance Surveillance Network (formerly EARSS)
ECDC	European Centre for Disease Prevention and Control
ECOSS	Electronic Communication of Surveillance in Scotland
EEA	European Economic Area
ESBL	Extended spectrum beta-lactamase
ESMI	Enhanced surveillance of Mycobacterial infection
ESPAUR	English Surveillance Programme for Antimicrobial Utilisation and Resistance
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
HAI	Healthcare associated infection
HL-AziR	High-level azithromycin resistant
HPS	Health Protection Scotland
IIP	Infection Intelligence Platform
IMI	Imipenem-hydrolyzing β-lactamase
ISD	Information Services Division
KPC	*Klebsiella pneumoniae* carbapenemase
MCR-1	Plasmid-mediated colistin resistance
MDR	Multi-drug resistance

MIC	Minimum inhibitory concentration
MRSA	Meticillin resistant *Staphylococcus aureus*
MSSA	Meticillin sensitive *Staphylococcus aureus*
NDM	New Delhi metallo beta-lactamase
NES	NHS Education for Scotland
OBD	Occupied bed days
OPAT	Outpatient parenteral antibiotic therapy
PHE	Public Health England
PID	Pelvic inflamatory disease
POP	Population
SAPG	Scottish Antimicrobial Prescribing Group
SARHAI	Scottish Antimicrobial Resistance and Healthcare Associated Infection
SBSTIRL	Scottish Bacterial Sexually Transmitted Infection Reference Laboratory
ScotMARAP	Scottish Management of Antimicrobial Resistance Action Plan
SHLMPRL	Scottish *Haemophilus*, *Legionella*, Meningococcus and Pneumococcus Reference Laboratory
SIMD	Scottish Index of Multiple Deprivation
SMRSARL	Scottish Meticillin Resistant *Staphylococcus aureus* Reference Laboratory
SMVN	Scottish Microbiology and Virology Network
ST	Sequence type
TB	Tuberculosis
UK	United Kingdom
UTI	Urinary Tract Infection
VMD	Veterinary Medicines Directorate
VIM	Verona integron-encoded metallo-beta-lactamase
VRE	Vancomycin resistant enterococci
VREF	Vancomycin resistant *Enterococcus faecium*
WHO	World Health Organisation

1. Introduction

The scale and threat of antimicrobial resistance (AMR) is such that a global post antibiotic era is a real possibility. Antimicrobial resistance occurs when a microorganism (including bacteria, viruses, parasites and fungi) becomes resistant to antimicrobials. Minor infections that, in the past, were easily treated will have the potential to be life threatening. In addition, simple surgical procedures and minor injuries will pose a serious threat to health.

This, the eighth Scottish annual report on antimicrobial use and resistance in humans, reports on antimicrobial prescribing and rates of AMR in Scotland during 2015, drawing comparisons with the situation in England and across Europe. The report also describes measures to improve antibiotic use and control the development of resistance. The information presented in this report provides the evidence required to develop local and national policy for clinical and public health action.

Substantial work has been undertaken to support the aims of the Controlling Antimicrobial Resistance in Scotland (CARS) group and the Scottish Management of Antimicrobial Resistance Action Plan (SCOTMARAP) 2014–18.[1] The CARS group, established to implement the UK wide AMR strategy in Scotland, is working with partners to control the development of resistance across all human, animal, food and environmental settings. The action plan was refreshed following the publication of the UK Five Year Antimicrobial Resistance Strategy.[2] It informs the operational delivery plans of the Scottish Antimicrobial Prescribing Group (SAPG) and also underpins the work plan of local and national stakeholders.

Antibiotics are vital for the treatment of bacterial infections but the bacteria that cause infection are becoming increasingly resistant to antibiotics. Inappropriate and unnecessary use of antibiotics is the key driver in the development of infections caused by antibiotic resistant bacteria. Optimising prescribing is everyone's responsibility. Clinicians, managers, researchers and the public must work together to preserve the effectiveness of the currently available antibiotics.

In 2014, the UK Prime Minister commissioned Lord O'Neil to undertake an independent review of AMR, producing a series of reports (amr-review.org/Publications). The final report was published in May 2016 with recommendations on to how to combat AMR on a global scale.[3] Underlining the tragic human and global economic costs of AMR, ten key action areas were identified, comprising:

- a global awareness campaign;
- improving hygiene to prevent spread of infection;
- reducing inappropriate antimicrobial use in agriculture;
- improving antimicrobial use and resistance surveillance systems on a global scale in both humans and animals;
- the development of rapid diagnostics;
- the development of alternatives to antimicrobials such as vaccines;
- increased recognition of those working in the area of infectious disease;
- creation of a global fund to support the production of new therapeutic options;
- provision of incentives to develop new drugs (or improve existing ones); and
- building a global coalition.

An immediate global concerted effort to tackle these areas is required if Lord O'Neil's prediction that there will be 10 million deaths every year by 2050 is to be averted.

Please note that two minor errors were found in the antimicrobial use analysis for the Report on Antimicrobial Use and Resistance in Humans report published on 30 August 2016. These are in the calculation of two age band denominators for 2015 data and a minor inflation of the Defined Daily Doses in acute hospital antimicrobial use in 2012 and subsequent comparison to 2015 figures. These errors and subsequent revisions will not affect the overall interpretation or conclusions drawn from the previously published data. A revised publication to correct these was released on 22 November 2016 and should be referred to instead.

2. Antibiotic use

2.1 Primary care antibiotic use

Antibiotics are critical not only for treating bacterial infections but are a cornerstone of routine healthcare as they prevent infections following surgery and cancer chemotherapy. Over 80% of antibiotic use is within primary care. Overuse and inappropriate use of antibiotics can unnecessarily increase the development of AMR. As limited new antibiotics are under development it is vital that health professionals and the public work together to optimise the way antibiotics are used to preserve their effectiveness for future generations.

2.1.1 Is unnecessary antibiotic use reducing?

In 2015, SAPG has continued with its key priority in primary care to co-ordinate the implementation of interventions to support clinicians to reduce unnecessary antibiotic prescribing. This is primarily targeted at reducing antibiotic use for self-limiting respiratory infections such as coughs and colds. There has been continued progress in reducing total antibiotic use. In 2015, the use of systemic antibiotics (excluding dental) was 2.0 items/1000/day (items per 1,000 population per day); 2.4% lower and 88 490 fewer items than in 2014. This is the third successive annual reduction and was 374 500 fewer items and 9.5% lower than the highest rate of prescribing observed in 2012. Only once in the last 20 years (2004) has the prescribing rate been lower than in 2015. The proportion of the Scottish population who received at least one antibiotic item was 29.6% in 2015 and is the lowest proportion on record since 2010, when data was first available. In the third year, following introduction of a national quality indicator, there was continued improvement with 11 of 14 NHS boards and 67.2% of Scottish GP practices meeting the target. SAPG will agree how the quality indicator can be refreshed to act as a stimulus to further reduce unnecessary antibiotic use in primary care.

Reducing antibiotic use is not straightforward, so this continued reduction is welcome. It may reflect the impact of interventions which aim to encourage clinicians to change their prescribing behaviour to reduce unnecessary prescribing. Despite this progress there is still considerable variation between GP practices in antibiotic prescribing rates, and opportunities remain to reduce unnecessary prescribing in the majority of practices—especially in those practices with higher rates of antibiotic use.

During winter 2015/16, SAPG tested the feasibility of using C-reactive protein near patient testing as a diagnostic aid to support clinicians to reduce antibiotic prescribing in lower respiratory tract infections. This demonstrated the benefits of using this test in supporting appropriate prescribing, confirmed it could be integrated within current GP consultation processes, and also showed that patients were reassured by use of the test.

In April 2016, the phased introduction of a programme to provide GP practices with personalised feedback on their own antibiotic prescribing data commenced. Practices will receive quarterly reports containing their rates of antibiotic prescribing compared to local and national benchmarks. The reports also contain suggested actions that practices can implement and details of the available support resources.

To drive further improvements in 2016, SAPG will collaborate with stakeholders to disseminate visually and clinically meaningful information on antibiotic use to NHS staff and the public.

SAPG will continue the focus on reducing unnecessary antibiotic use in primary care to reduce the pressure for development of AMR.

2.1.2 Who is prescribing?

General medical prescribers accounted for 86.6% of antibiotic use in primary care in 2015. There was a continued increase in nurse antibiotic prescribing in 2015; 17.7% more items than in 2014. Nurse prescribing accounted for 5.4% of total antibiotic use. Nurses prescribe a relatively limited range of antibiotics with the ten most frequently prescribed antibiotics accounting for 96.4% of nurses' antibiotic prescriptions. This reflects good compliance by nurses with recommendations in local antibiotic policies. Antibiotic use by dentists in 2015 was 9.2% lower than in 2014 and dentists accounted for 7.9% of total antibiotic use in primary care. Four antibiotics (amoxicillin, erythromycin, metronidazole and phenoxymethlypenicillin) which are recommended in national dental guidance accounted for 98.8% of dental antibiotic use in 2015.

2.1.3 Which antibiotics are being used?

The second key strategic objective of primary care antimicrobial stewardship led by SAPG is to reduce the inappropriate use of broad spectrum antibiotics. The initial focus on reducing broad spectrum antibiotic use was intended to support the reduction of *Clostridium difficile* infection (CDI), as the use of particular broad spectrum antibiotics (including cephalosporins, co-amoxiclav and fluoroquinolones) is associated with a higher risk of CDI.

In 2015, there were reductions in the use of co-amoxiclav (4.9%), fluoroquinolones (5.8%) and cephalosporins (6.0%) and these broad spectrum antibiotics together accounted for 8.0% of total antibiotic use in primary care, the lowest proportion on record. Following its establishment, SAPG supported standardisation of antibiotic prescribing policies in primary care which has had a considerable impact on the choice of antibiotic used with a 62.8% reduction in the use of broad spectrum antibiotics since 2008. It is increasingly recognised that it is equally important to reduce inappropriate use of broad spectrum antibiotics to preserve their effectiveness and slow the development of AMR.

Antibiotics recommended for empirical treatment of commonly encountered infections in primary care accounted for 81.4% of total antibiotic use in 2015 (unchanged from 2014).

The reduction of CDI remains an important clinical priority across NHSScotland and improving antibiotic use remains an important part of the strategy. Information on the burden of disease caused by CDI across NHSScotland is included within the acute hospital antibiotic use section.

2.1.4 How does deprivation affect antibiotic prescribing?

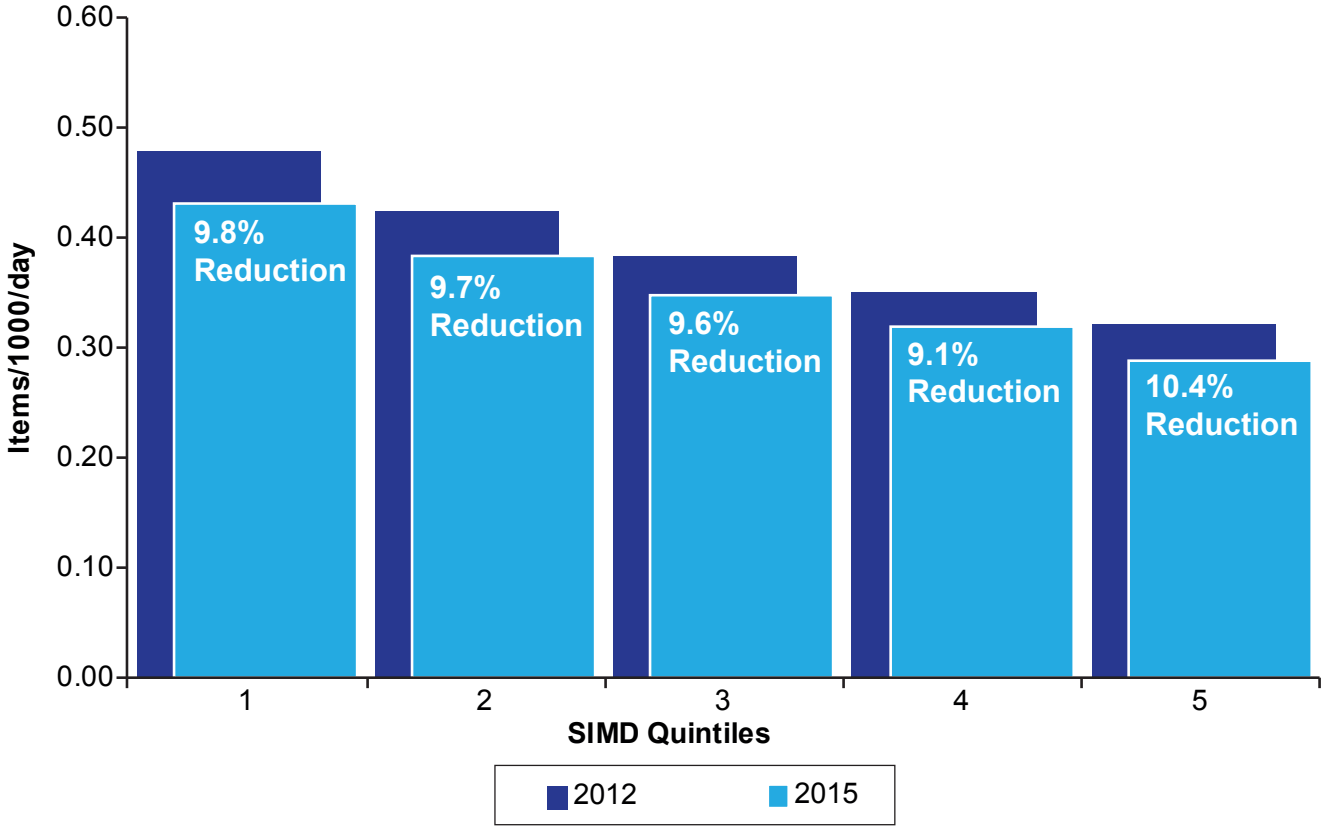
Reducing health inequalities and making Scotland a better, healthier place for everyone is an aim of the Scottish Government. As the majority of prescriptions for antibiotics capture the individuals' Community Health Index (CHI) number it is possible to undertake anonymised analysis of patterns of antibiotic use between the least and most disadvantaged areas and to examine to what extent the improvements in antibiotic use observed in the recent past are equally seen across these groups.

In 2015, the total antibiotic rate in Scottish Index of Multiple Deprivation (SIMD) quintile 1 (most deprived) was 0.43 items/1000/day, 49.9% higher than in SIMD quintile 5 (least deprived) which had a rate of 0.29 items/1000/day. Since 2012, there has been a reduction in total antibiotic use in each of the SIMD quintiles, the 9.8% reduction in SIMD quintile 1 being similar to that observed in other quintiles (9.1% to 10.4%) (Figure 1).

In SIMD quintile 1, broad spectrum agents made up 7.3% of total antibiotic use. This is lower than in other SIMD quintiles where broad spectrum antibiotic use made up 8.1%–8.3% of total use. There has been a decrease in the rate of broad spectrum antibiotic prescribing in all SIMD quintiles since 2012. The decrease was most pronounced in the most deprived quintile which observed a 24.6% decrease compared to 21.3% in the least deprived quintile.

Deprivation has an association with increased rates of antibiotic prescribing. This is important and when planning locality based interventions to optimise antibiotic prescribing in primary care the impact of deprivation should be considered.

Figure 1 NHSScotland rate of antibiotic prescribing by SIMD Quintiles (1=most deprived, 5=least deprived), per 1,000 national population, 2012 to 2015.



2.1.5 Antibiotic use among care home residents

Care home residents are a vulnerable patient population who may be more susceptible to infection as a result of increasing age and co-morbidities. As they live in close proximity with other older people there is an increased risk of transmission of infection. Care home settings play an important role in the epidemiology of AMR and may become a reservoir for resistant strains of bacteria.

When an individual becomes a care home resident their CHI number is linked with a marker which designates them as living within a care home. As CHI numbers are captured on NHS prescriptions, anonymised analysis of antibiotic use among care home residents becomes possible.

In 2015, there were 90 530 antibiotic items dispensed to people known to be care home residents, accounting for 2.3% of total antibiotic use in primary care in Scotland.

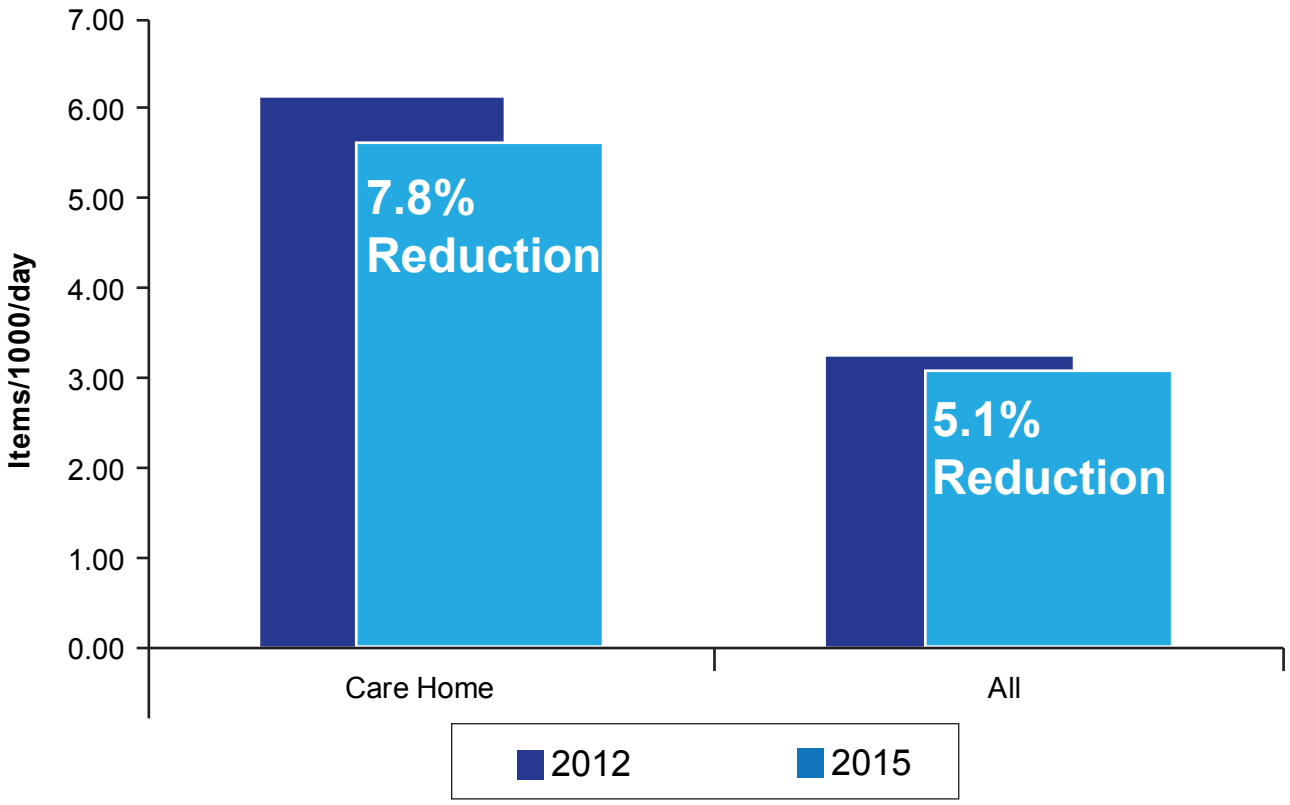
The rate of antibiotic prescribing in care home residents ≥65 years was 5.6 items/1000/day which is 83.1% higher than observed in all individuals aged ≥65 years (3.1 items/1000/day). Since 2012, there has been a more pronounced reduction in the antibiotic prescribing rate in care home residents aged ≥65 years (7.8%) compared to all individuals aged ≥65 years (5.1%) (Figure 2).

In 2015, care home residents broad spectrum antibiotic use accounted for 10.2% of total antibiotic use. This is the same proportion as for all individuals aged ≥65 years.

Antibiotics which are predominantly prescribed for urinary tract infection (UTI), such as cefalexin, nitrofurantoin or trimethoprim, made up 51.5% of all antibiotics prescribed in care homes in 2015 (Figure 2). In 2015, 1308 (3.1%) of care home residents were prescribed one of these antibiotics commonly used for UTI ≥6 times, which may suggest long term use for prophylaxis of recurrent UTI.

When planning local interventions to support improved antimicrobial stewardship in primary care the specific needs of care home residents should be considered.

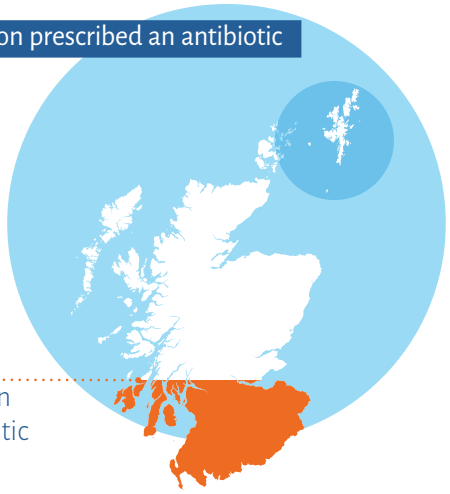
Figure 2 NHSScotland antibiotic use for those aged >65 years in care homes and non–care homes, 2012 and 2015.



Primary Care Antibiotic Use

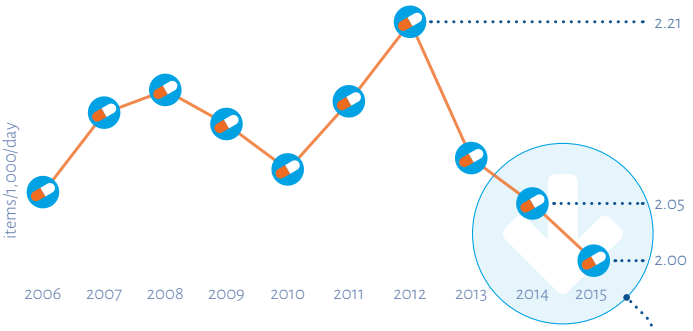
Antimicrobial resistance is a growing threat to modern medicine. Resistance is a natural consequence of using antibiotics but overuse and inappropriate use of antibiotics can unnecessarily increase development of resistance. Over 80% of antibiotic use occurs in primary care. Few new antibiotics are under development so it is vital for health professionals and patients to work together to optimise the way antibiotics are used to preserve their effectiveness for the future.

Proportion of population prescribed an antibiotic



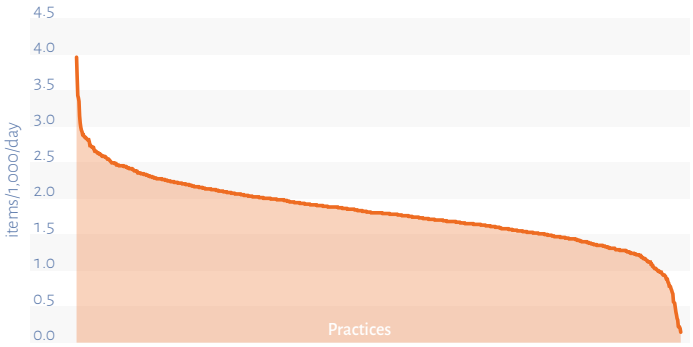
29.6%
of Scottish population
prescribed an antibiotic

Total antibiotic use

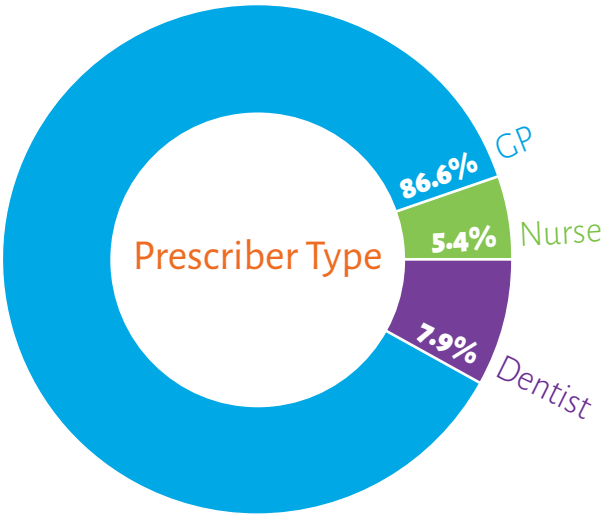


2.4% reduction in items per 1,000 population per day since **2014**
88,490 items fewer since **2014**
3rd year of successive **reductions**

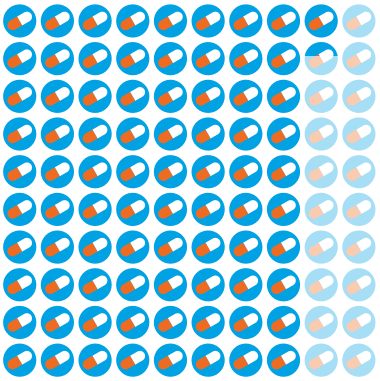
Total antibiotic use — variability across practices



Total antibiotic use by prescriber type

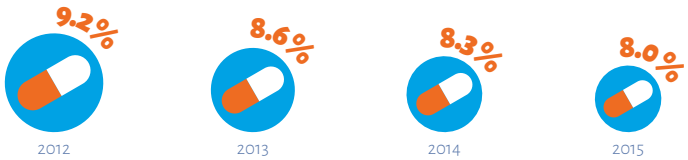


Recommended antibacterials



recommended antibacterials
make up **81.4%**
of all antibacterial prescribing

Broad spectrum antibiotics as a proportion of all antibiotics



2.2 Acute hospital antibiotic use

Antibiotics save, extend and improve quality of life. In patients with sepsis or serious infection the prompt initiation of antibiotic treatment reduces morbidity and saves lives, and the use of antibiotics prevents infections in patients receiving cancer chemotherapy and those having surgical procedures. The antimicrobial stewardship programme coordinated by SAPG is a balance between using antibiotics optimally to ensure the best clinical outcomes for patients while minimising harm to patients receiving antibiotics and to the wider population. Ensuring rational, safe and effective use of antibiotics in acute hospitals is a key issue for SAPG.

2.2.1 Total antibiotic use

In 2015, 84% of hospital antibiotic use was within acute hospitals in Scotland. There was an increase of 194 663 defined daily doses (DDD) (2.9%) in total use of systemic antibiotics from 2014 to 2015. As hospitals do not serve a specific population, when reviewing local antibiotic use understanding hospital activity becomes important. Using population (POP) as the denominator, total use of antibiotics was 129 DDD/100POP (2.5% higher than 2014). Using admissions (ADM) the rate was 588/100ADM (3.5% higher than in 2014) and using occupied bed days (OBD) as the denominator, the rate in 2015 was 152/100OBD (4.3% higher than 2014).

Table 1 NHSScotland total antibiotic use, using defined daily doses (DDD) and denominators of admissions, bed-days and population, 2012 to 2015.

Year	Raw DDD	DDD/100 population	DDD/100 admissions	DDD/100 bed-days
2012	6 167 014	116	535	137
2013	6 425 135	121	554	141
2014	6 735 166	126	568	146
2015	6 929 829	129	588	152
Difference 2012–2015	**12.4%**	**11.1%**	**9.9%**	**10.7%**
Difference 2014–2015	**2.9%**	**2.5%**	**3.5%**	**4.3%**

Between 2012 and 2015 the use of antibiotics has steadily increased in acute hospitals (Table 1). When use is expressed as DDD/100ADM there has been an increase of 9.9%. Using DDD/100OBD, use in 2015 was 10.7% higher than in 2012 and was higher still (11.1%) using DDD/100POP. Using admissions data as a denominator gives a better estimate of hospital activity where length of stay is short and outpatient activity frequent, and bed-days is more useful in units where longer lengths of stay are frequent. In acute hospitals in Scotland the average length of stay has been steadily reducing for several years, from 5.0 days in 2010/11 to 4.3 days in 2014/15. Hereafter in this report the key metric used will be DDD/100ADM as this enables direct comparison with information published by Public Health England (PHE). Information on antibiotic use presented as DDD/100OBD and DDD/100POP are included in the data appendix.

There are a number of drivers for this increase in antibiotic use in acute hospitals. The implementation of 'sepsis 6' and other initiatives to improve the recognition and management of sepsis have had beneficial outcomes for patients but may have resulted in increased antibiotic use. Similarly the implementation of and compliance with antibiotic prescribing policies has led to an increase in use of combinations of narrow-spectrum antibiotics rather than a single broad spectrum agent. This leads to an apparent increase in antibiotic use when the number of DDD is the numerator used. Information from one NHS board, which conducts regular point prevalence surveys of antibiotic use, has shown between 2010 and 2015 an increasing proportion of patients in hospital have been prescribed antibiotics.

Reducing the pressure for selection of AMR through reducing antibiotic use in acute hospitals will be a key focus of the antimicrobial stewardship programme in Scotland in 2016/17 and beyond. In 2016, SAPG will work with stakeholders to develop and test a national quality indicator for acute hospital antibiotic use for introduction in 2017/18. The goal of the quality indicator and its associated targets will be to promote antimicrobial stewardship through reduction in systemic antibiotic use by encouraging clinical teams to undertake timely review of patients receiving intravenous antibiotics and to document the outcome of this review. Moreover the quality indicator will support documentation of duration of treatment for oral antibiotics. It is anticipated this approach will act as the catalyst to reduce unnecessary antibiotic use by ensuring prompt de-escalation, switch from intravenous to oral therapy and stopping antibiotics when infection has been excluded. This ensures patients are not unnecessarily exposed to antibiotics and placed at risk of adverse effects when there is no clinical benefit. More importantly it will also reduce the pressure for selection of AMR.

2.2.2 Very broad spectrum antibiotics

In Scotland the levels of multi-drug resistance (MDR) among Gram-negative bacteria are stable, but extended spectrum beta-lactamase (ESBL) producing bacteria are widespread and carbapenemase-producing organisms (CPOs) have now been reported in almost every NHS board.

Increased use and, especially, inappropriate use of broad, and especially very broad spectrum, antibiotics such as carbapenems and piperacillin-tazobactam can select organisms with resistance and, by increasing their numbers, also increases their chance of spread.

With limited new antibiotics for treatment of MDR infections, optimisation of use of antibiotics with a very broad spectrum is an important component of stewardship programmes. The protection and preservation of the effectiveness of these critically important agents is vital for the successful management of patients with serious infections in the future.

In 2015, the use of carbapenems in acute hospitals was 8.2 DDD/100ADM (6.5% higher than in 2014) building on the increases seen in previous years. Since 2012, there has been a 9.3% increase in the use of carbapenems in acute hospitals.

Between 2012 and 2014 there was an increase (15.5%) in use of piperacillin-tazobactam but in 2015 there was a 7.9% reduction compared to 2014. This is the first year where a reduction in use of piperacillin-tazobactam has been observed since 2009 (when data on hospital use of medicines became available).

In 2016, SAPG updated its recommendations for Antimicrobial Management Teams (AMTs) and infection specialists with practical advice on managing MDR Gram-negative infections to support development of local guidance that will protect and preserve the use of carbapenems. The guidance highlights the importance of clinical assessment, including performing baseline microbiological investigation before starting antibiotics. Moreover the importance of avoiding premature empirical escalation during the initial 24–48 hours of treatment is highlighted as a potential contributor to the inappropriate use of very broad spectrum antibiotics. The SAPG advice also provides recommendations on the use of antibiotics which can be considered as very broad spectrum antibiotic sparing agents.

These are antibiotics that can be used as alternatives to carbapenems in suspected or confirmed MDR infections. In 2015, the use of these alternative antibiotics remained low. Aztreonam use more than doubled from 1.2 DDD/100 ADM in 2014 to 2.6 DDD/100 ADM in 2015. Across NHS boards there is variation in the extent to which of these very broad spectrum antibiotic sparing agents have been used but supply problems may have contributed to this. Gentamicin in combination with other antibiotics is also used as an alternative to very broad spectrum antibiotics. In 2015, gentamicin use was 16.9% higher than in 2012 and 5.9% higher than in 2014.

In collaboration with the University of Strathclyde, SAPG has evaluated the implementation of prescribing guidance for very broad spectrum antibiotics in NHSScotland. A survey of NHS boards to examine their guidance for carbapenems and piperacillin-tazobactam and a prevalence survey of their use in Scottish hospitals was completed in 2015. This indicated that for both antibiotics the documentation of review date was low, prescribing controls were common for carbapenems but uncommon for piperacillin-tazobactam, and the very broad spectrum sparing agents were not widely used. The work is ongoing through in-depth case studies being conducted with clinicians to understand how to more effectively protect the use of these important antibiotics.

2.2.3 Broad spectrum antibiotics

Since its establishment, SAPG has supported the implementation of prescribing policies to optimise the empirical use of antibiotics in acute hospitals. This is now a central feature of the Scottish framework for antimicrobial stewardship and aims to slow the development of AMR through minimising inappropriate use of broad spectrum antibiotics. As the use of particular broad spectrum antibiotics (including cephalosporins, clindamycin, co-amoxiclav and fluoroquinolones) is associated with a higher risk of CDI, SAPG has since 2008 recommended restriction of these antibiotics to reduce the burden of illness caused by CDI in Scotland.

CDI remains an important healthcare associated infection (HAI). In Scotland, the trend in annual incidence rates over the last five years has been one of almost continuous decline between 2011 and 2014 in patients aged ≥65 years and those aged 15–64 years. However in 2015, CDI increased in those aged 15–64 years, whereas it continued to decline in those aged ≥65 years. Detailed information on the significant burden of disease caused by CDI across NHSScotland is included within the HAI Annual Report 2015 available: www.hps.scot.nhs.uk/haiic/publicationsdetail.aspx?id=68107

Co-amoxiclav use accounted for 14.1% of total acute hospital antibiotic use in 2015. After an increasing trend in use of co-amoxiclav from 2012 to 2014 there was a 2.3% reduction in 2015.

As a group, fluoroquinolone use accounted for 6.4% of total antibiotic use in acute hospitals in 2015. Use of fluoroquinolones was 6.2% higher than in 2014. For ciprofloxacin (the most commonly used fluoroquinolone), use was 3.1% lower in 2015. In contrast there was increased use of levofloxacin (50.3%) which is indicated for pneumonia in patients allergic to penicillin and ofloxacin (27.5%), which is recommended in prescribing guidelines for prostatitis. The increased use of levofloxacin and ofloxacin has resulted in the overall increase in use of fluoroquinolones.

Cephalosporin antibiotics accounted for 2.2% of acute hospital antibiotic use in 2015. Cephalosporin use was 6.7% higher than in 2014 as a result of increased use of ceftriaxone (used in out-patient parenteral antibiotic (OPAT) services) and cefuroxime (for surgical prophylaxis).

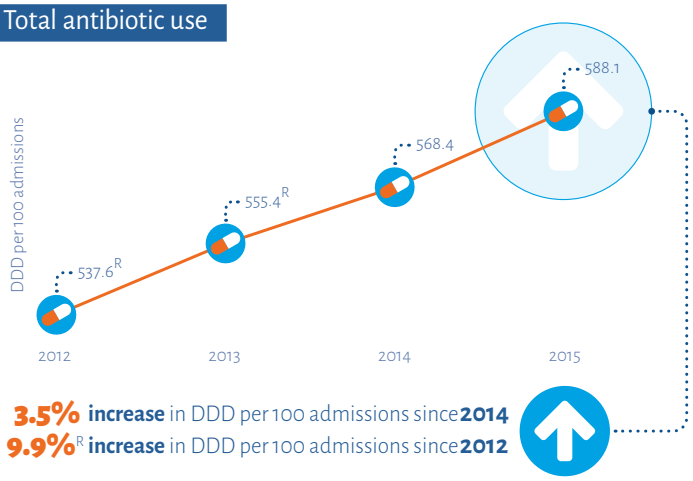
Although use of clindamycin accounted for only 1.4% of total antibiotic use, it did increase by 14.1% in 2015 continuing a steady increase (20.9%) in use since 2012.

In 2008, when the reduction in CDI was the key priority, it was appropriate to consider these broad spectrum antibiotics as a group around which to focus improvement activity by restricting their use. These antibiotics are not, however, a homogenous group with respect to their risk of CDI or in their therapeutic use. The infection landscape in Scotland has evolved with lower levels of CDI than when the national stewardship programme co-ordinated by SAPG was established. This is against a backdrop of an increasing threat of MDR Gram-negative infections. Although reducing inappropriate use of broad spectrum antibiotics remains an important element of the antimicrobial stewardship programme in Scotland, there is a need to consider individual broad spectrum antibiotics separately and to balance the benefits of their use in achieving diversity of antibiotic use against their CDI risk in particular clinical situations.

Acute Hospital Antibiotic Use

Antibiotics revolutionised medical practice after their introduction. In patients with infection use of antibiotics save lives and they are a cornerstone of routine hospital care such as preventing infections following surgery and cancer chemotherapy. However the bacteria that cause infections are becoming more resistant to antibiotics. Clinicians and other hospital staff must work together to optimise antibiotic use in hospitals. Antimicrobial stewardship in hospitals is everyone's business.

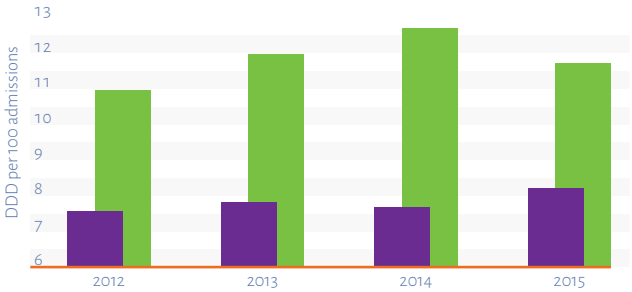
Total antibiotic use



3.5% **increase** in DDD per 100 admissions since **2014**

9.9%[R] **increase** in DDD per 100 admissions since **2012**

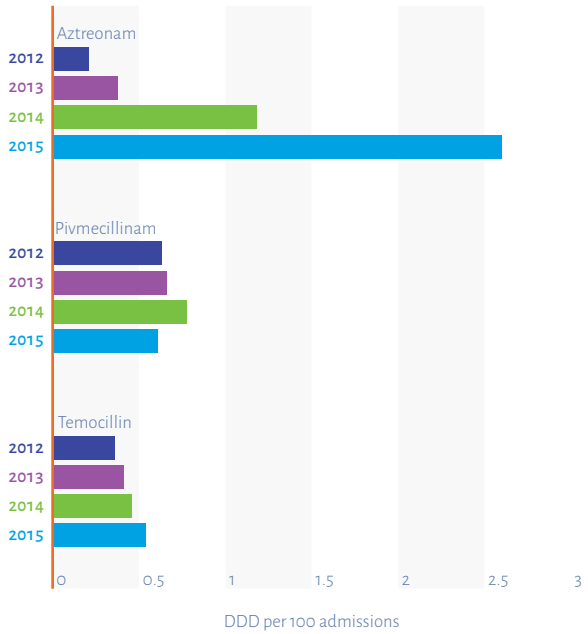
Very broad spectrum antibiotics



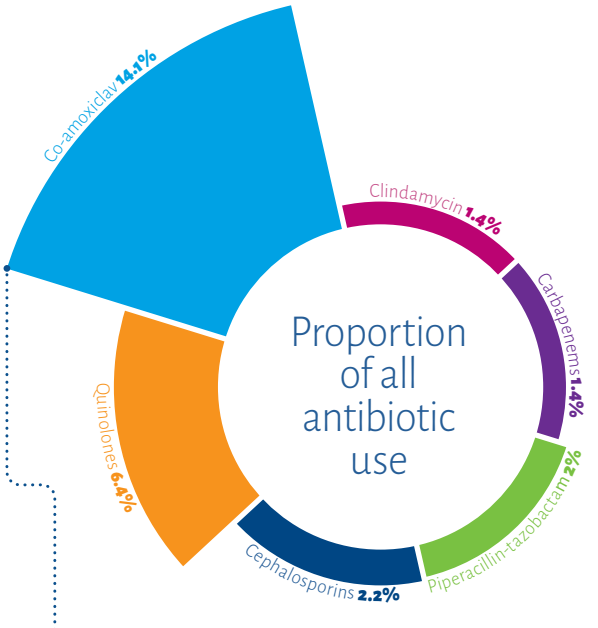
Carbapenems **6.5%** **increase** in **2015**

Piperacillin-tazobactam **7.9%** **decrease** in **2015**

Very-broad spectrum sparing antibiotics



Broad spectrum antibiotics



2.3% **decrease** in DDD per 100 admissions since **2014**

11.1% **increase** in DDD per 100 admissions since **2012**

Figures denoted [R] were subject to minor errors in the publication of 30 August 2016 and have been revised in this publication. Please see the introduction note for more details.

3. Antimicrobial Resistance in Scotland

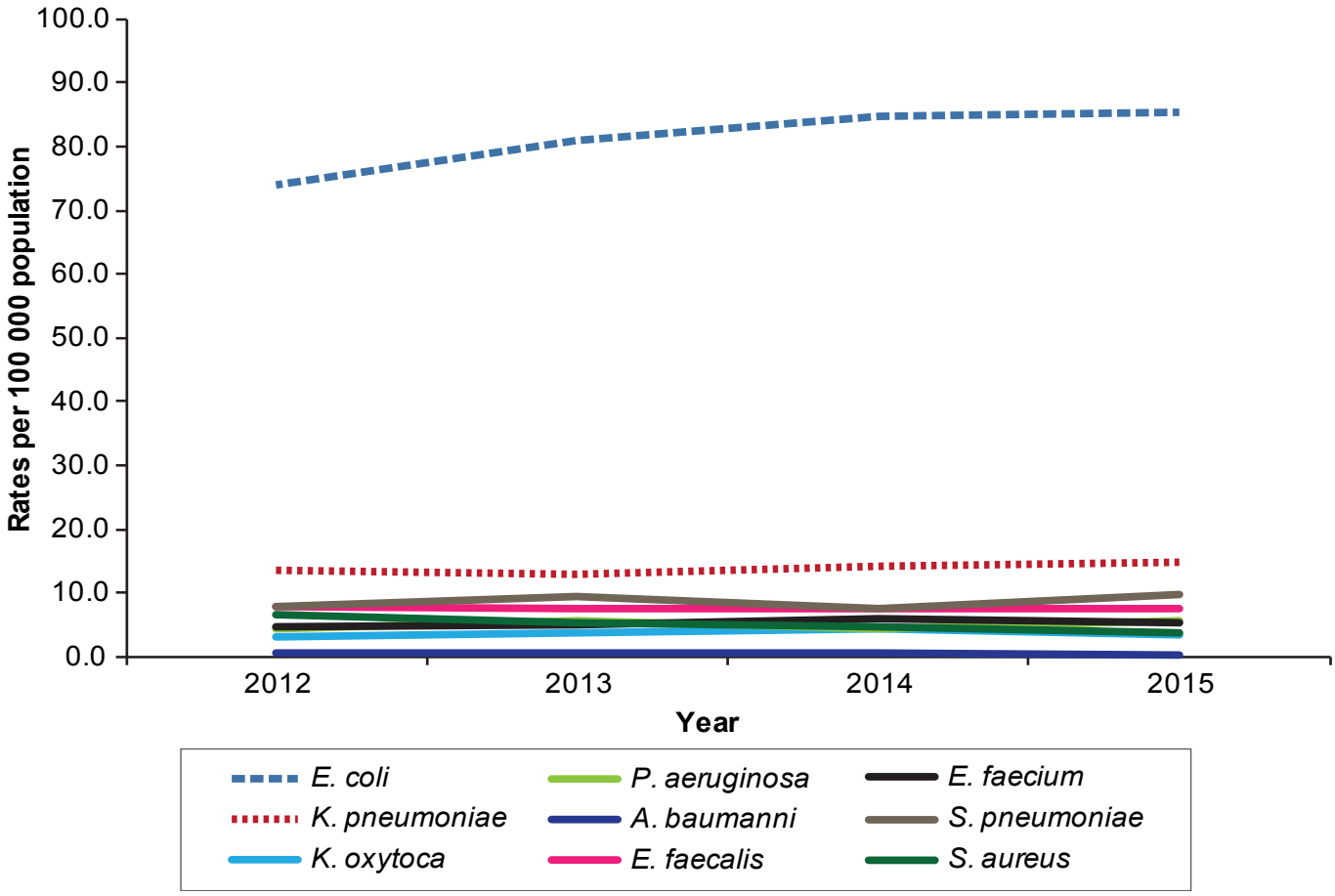
Antimicrobial resistance is one of the biggest threats to health and the global economy. Resistance develops when a microorganism no longer responds to an antibiotic to which it was originally sensitive. Consequently, infections become more difficult to treat and the risk of the spread of infection is increased. As a result, illness and hospital stays are prolonged, with added economic and social costs, and the risk of death is increased. The loss of effective antibiotics undermines our ability to fight infectious diseases and manage the infectious complications common in immunocompromised patients.

AMR surveillance is essential to inform and improve antibiotic treatment, track the spread of significant resistant organisms, and guide policy and decision making. This chapter contains information on trends of resistance to key antibiotics among bacteria of public health concern.

The 'drug/bug' combinations analysed in this report are aligned with both the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2015[4] and the European Centre for Disease Prevention and Control (ECDC) European Antimicrobial Resistance Surveillance Network (EARS-Net) Report, 2014.[5] All 'drug/bug' combinations and statistical trends over a four year period are contained within this report and an appendix. As was introduced last year, non-susceptibility data are presented which is defined as the number of resistant isolates plus those that have an intermediate resistance. Resistance data of note are presented here in the text and where there is no statistical change given in the appendix only.

The incidence rate of the most common bloodstream infections in Scotland are shown in Figure 3.

Figure 3 Incidence of bloodstream infections due to the most commonly reported pathogens, 2012 to 2015.



Of the organisms under review, *Escherichia coli* was the commonest cause of bloodstream infection with an incidence rate of 85.5 per 100 000 population in 2015. The incidence of *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterococcus* spp., and *Streptococcus pneumoniae* bacteraemias have remained relatively constant since 2012.

3.1 Antimicrobial susceptibility in Gram-negative bacteria

3.1.1 Carbapenemase-producing organisms

Gram-negative bacteria are among the most important causes of serious hospital-acquired and community-onset bacterial infections in humans and resistance to antibiotics in these bacteria has become an increasing problem. Of special concern is the development of resistance to the carbapenems, since these agents are often the last line of effective therapy available for the treatment of infections caused by multi-resistant bacteria. Most important is the recognition of isolates that produce carbapenemases, which cause resistance to the carbapenems.

In Scotland, a total of 63 CPOs were reported from the Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit, PHE in 2015 and 37 were reported in the first six months of 2016, in comparison with 47 reported isolates in 2014. Of the 63 CPOs identified in 2015, 56 were carbapenemase-producing Enterobacteriaciae (CPE) and 7 were other CPOs.

Figure 4 Total number of carbapenemase enzymes, 2003 to 2016 (2016 data until end of June).

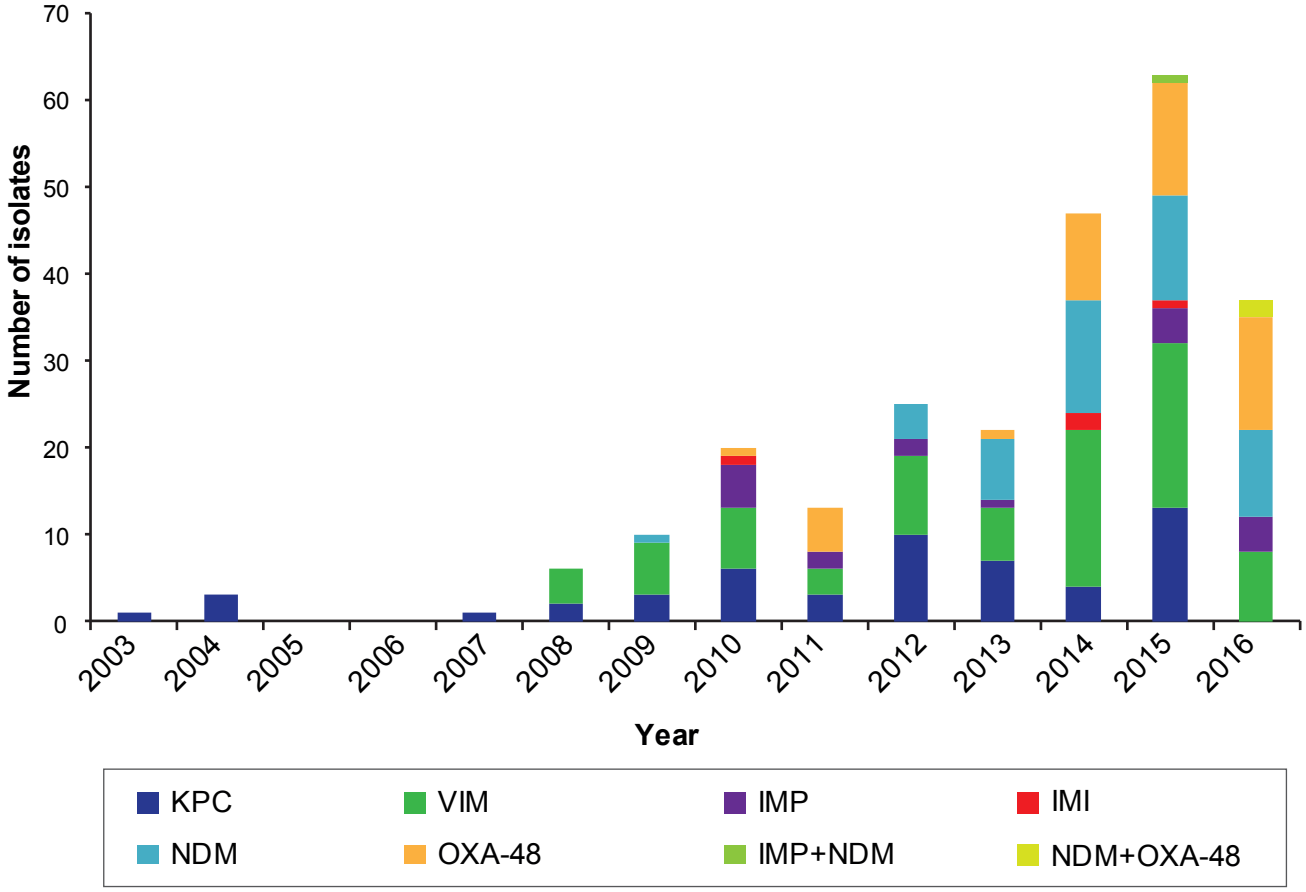


Figure 4 shows the number of CPOs by type of carbapenemase. (A de-duplication criterion of one patient, per quarter, per organism or enzyme has been applied to these data. It should be noted that there is currently no agreed episode definition for CPOs. Work is underway to define an appropriate definition at a UK level.)

In 2015, there was an increase in the number of each carbapenemase enzyme type compared to 2014 apart from those CPOs producing New Delhi metallo-beta-lactamase (NDM) and imipenem-hydrolyzing β-lactamase (IMI). (Please note, as the result of a validation exercise, the numbers reported in Figure 4 differ to those in last years report).[6]

Although total numbers remain low there has been a growing trend in Scottish CPO reports since surveillance began, which may be partly the result of improved awareness of CPOs and the introduction of CPE screening in Scotland.

3.1.1.1 Quality Improvement and Interventions to Reduce CPOs

Measures to prevent and control outbreaks and spread of CPOs have focussed particularly on CPE. In hospitals and other healthcare settings activities include active surveillance (including identification of high-risk patients and admission screening), isolation of suspected and confirmed cases, standard and transmission based infection control precautions, education of staff and the prudent use of antibiotics.[7;8]

In 2013, a joint Chief Medical Officer/Chief Nursing Officer/Chief Pharmacy Officer letter described the emerging threat from CPE and the requirements for an acute hospital admission screening programme for CPE.[9] The two step clinical risk assessment based screening policy (risk assessment, followed by screening sample) identifies a subset of patients at high risk of CPE colonisation who are then tested for CPE.[10]

Identification of patients who are colonised with CPE or have a high risk of colonisation on admission to hospital, and their appropriate management, is essential to prevent the spread of CPE in Scottish hospitals. Health Protection Scotland (HPS) continues to support boards in the implementation CPE screening.

Standardised national staff and patient information leaflets on CPE screening were published in May 2015, and an educational resource is under development. The purpose of these materials is to support frontline staff and ensure patients can make informed decisions about consenting to screening. The Scottish Infection Research Network (SIRN) research study to identify the barriers and drivers to the implementation of acute hospital admission screening also includes a CPE screening staff and patient acceptability study. The findings from this study will ensure that existing and future HAI screening programmes are evidence based and as acceptable as possible to patients.

HPS developed the 'Toolkit for the early detection, management and control of carbapenemase-producing Enterobacteriaceae in Scottish acute settings' and this was published in May, 2016 (www.hps.scot.nhs.uk/haiic/amr/guidelines.aspx). These resources are linked to the Scottish National Infection Prevention and Control Manual.[11]

HPS have supported various pieces of research in relation to the epidemiology of carbapenemases over the last year. This included working with colleagues across the UK evaluating the epidemiology of *Klebsiella pneumoniae* carbapenamase (KPC) enzymes in the UK (outwith the North-West of England) which demonstrated that plasmid spread plays a major role in KPC dissemination between *K. pneumoniae* and also other enterobacterial species.[12] In the coming year the introduction of a CPO enhanced surveillance system will build on some of this work.

3.1.1.2 Novel Plasmid-Mediated Polymixin Resistance Mechanism (MCR-1)

Treatment options for serious infections caused by CPOs are limited. Polymixins (colistin and polymixin B) are one of the last remaining agents that can be used to treat infections caused by CPOs, and they are classified by the World Health Organisation as critically important for human medicine.[13]

Until recently, resistance to polymixins was caused by chromosomal mutations that were generally not transmissible between bacteria and therefore not widely spread; however, a novel plasmid-mediated

colistin resistance mechanism (MCR-1) has been identified in *E. coli* from food animals in China.[14] The investigators found that a plasmid bearing the gene encoding MCR-1 was readily passed between *E. coli* strains and into other bacteria such as *K. pneumoniae* and *P. aeruginosa*. Subsequently the *mcr*-1 gene has been found to have spread into South Asia, Europe, Africa and South America.[15–18] Of concern is the potential spread of the *mcr*-1 gene into carbapenem resistant Gram-negative bacteria resulting in few, if any, treatment options for such organisms.

ECDC recently published a rapid risk assessment of plasmid-mediated colistin resistance (available at: ecdc.europa.eu/en/publications/Publications/enterobacteriaceae-risk-assessment-diseases-caused-by-antimicrobial-resistant-microorganisms-europe-june-2016.pdf) which pointed out that accurate detection of colistin resistance in diagnostic laboratories is technically very difficult. HPS are in discussion with AMRHAI and the Scottish Microbiology and Virology Network (SMVN) to consider the best alternative methodologies to those currently in place in Scotland.

These findings underline the importance of continued reassessment of microbiological surveillance to allow the early detection of new resistance mechanisms. It emphasises the need for a coordinated global effort to control emergence and spread of multi-drug resistant bacteria. HPS will continue to coordinate Scotland's part in this global agenda.

Carbapenemase-producing organisms (CPOs)

Multidrug resistance among Gram-negative bacteria has been increasingly reported in the last ten years. The emergence of carbapenemase-producing organisms (CPOs) is of particular concern as it leaves very few therapeutic options for treatment.

CPOs by type reported in Scotland by AMRHAI (PHE)

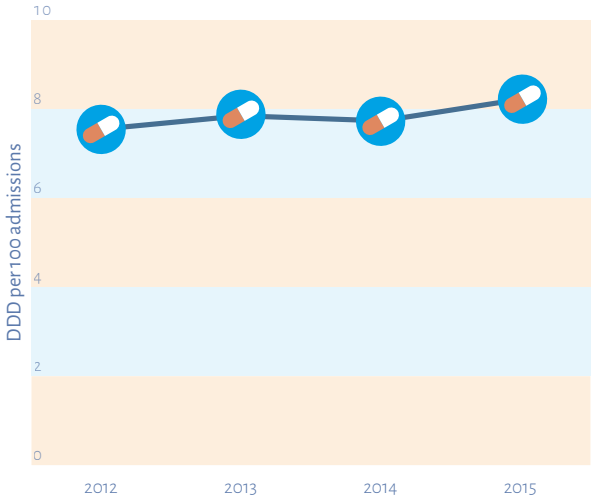
Enzyme	Number of isolates												
IMP+ NDM-1													1
VIM						4	5	7	3	9	6	18	19
OXA-48								1	5		1	10	13
NDM							1			4	7	13	12
KPC	1	2			1	2	4	6	3	10	7	4	13
IMP								5	2	2	1	2	4
IMI								1					1
Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Total	1	2	0	0	1	6	10	20	13	25	22	47	63

It is critical to **preserve** use of the antibiotics due to the **lack of new** antimicrobials under development.

The overall occurrence of carbapenem resistance in bacteraemias and UTIs is **low** in Scotland, but is increasing.

Increase in CPOs could be due to **improved awareness** resulting in **more frequent testing**.

Trend in carbapenem use in Scotland



Since 2012 there has been an **8.7%** increase in the use of carbapenems in acute hospitals—this continues the **upward trend** observed in previous years.

3.1.2 *Escherichia coli*

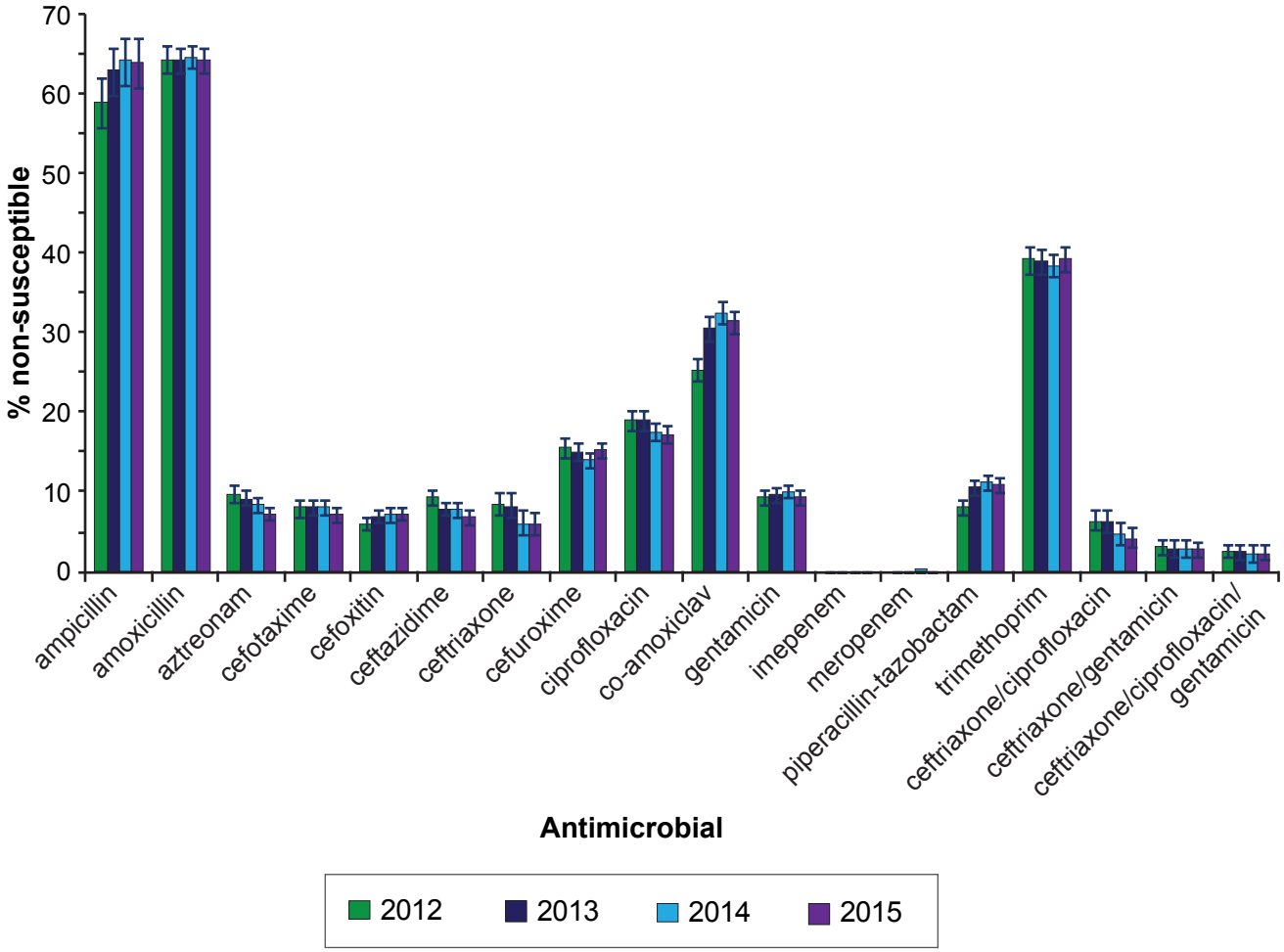
E. coli is a frequent cause of infection worldwide. *E. coli* can cause a wide range of infections such as community/hospital-acquired UTIs, diarrhoea, pneumonia and bacteraemia.[5]

3.1.2.1 Antimicrobial non-susceptibility in bloodstream infections

In 2015, *E. coli* continued to be the most frequent cause of Gram-negative bacteraemia in Scotland with an incidence rate of 85.5 per 100 000 population in 2015. This incidence rate has increased from 73.8 per 100 000 population in 2012 with an increasing year on year trend of 4.9% in the incidence rate for the period 2012 to 2015 (p<0.001).

Figure 5 demonstrates that overall non-susceptibility has remained stable for *E. coli* bacteraemia between 2012 and 2015 and echoes the findings of a recent UK wide study.[19]

Figure 5 Percentage of non-susceptible *E. coli* bacteraemias, 2012 to 2015.



However, non-susceptibility to co-amoxiclav increased 6.1% between 2012 and 2015 (p<0.001). During this time period there was increased usage of this antibiotic in secondary care. In 2015, co-amoxiclav accounted for 14.1% of total acute hospital antibiotic use.

Non-susceptibility to piperacillin-tazobactam increased 8.6% between 2012 and 2015 (p=0.002), which is a cause for concern given that this very broad spectrum antibiotic is important for the management of patients with serious infections. (Please note that the increase in non-susceptibility to both co-amoxiclav and piperacillin-tazobactam should be interpreted with caution as these could be attributable to a change towards the European Committee on Antimicrobial Susceptibility Testing (EUCAST) testing methodology).

Despite an increase in the use of aztreonam in 2015, a 9.1% decrease in non-susceptibility (p=0.001) from 2012 to 2015 was noted. Monitoring of alternatives to carbapenems and piperacillin-tazobactam such as aztreonam will be an important part of future reports.

Some *E. coli* have the ability to produce ESBL enzymes which make beta-lactam antibiotics, including penicillins and some cephalosporins, ineffective. In 2015, 5.5% of *E. coli* bacteraemia isolates were ESBL producers although the frequency has decreased since 2012 (5.6% change, p=0.03). This decrease should be interpreted with caution as reporting of ESBLs in Scotland is not consistent across NHS boards. As part of a larger planned project to improve the quality of AMR data, consistent reporting practices for ESBL will be evaluated in 2016–17.

In comparison with Europe, EARS-Net reported[5] that *E. coli* remains the most frequently isolated Gram-negative organism from blood cultures with more than half of the isolates reported being resistant to at least one observed antibiotic group. The European Union/European Economic Area (EU/EEA) population-weighted mean for fluoroquinolone resistance is higher (22.4% in 2014) than that of Scotland's (17.2% for ciprofloxacin in 2015). For aminoglycosides the EU/EEA population-weighted mean resistance (9.8% in 2014) was comparable to Scotland with non-susceptibly to gentamicin in Scotland being 9.3% in 2015. The range of non-susceptibilty to the third-generation cephalosporins (ceftriaxone, ceftazidime and cefotaxime) in Scotland was 5.9% to 7.2% with a mean of 6.9%. This compared favourably to the EU/EEA population-weighted mean resistance for third-generation cephalosporins which was 12% in 2014.

3.1.2.2 Antimicrobial non-susceptibility in urinary isolates

Non-susceptibility in UTIs is monitored in a subset of samples from each NHS board (reporting on 400 consecutive non-repeat samples each quarter). Data for NHS Greater Glasgow & Clyde, NHS Grampian, NHS Highland and NHS Western Isles has been excluded from analysis in this report due to a temporary issue with the transfer of data.

Resistance in UTIs is seen as an early warning of resistance in more serious infections. In addition to reporting on single drug non-susceptibility among the urinary isolates, combined resistance to antibiotics recommended for treatment of UTI (co-amoxiclav, ciprofloxacin, nitrofurantoin and trimethoprim) is also reported as a measure of the overall sensitivity of the bacterial populations as co-selection for resistance by first-line agents is a common problem among pathogens causing UTI due to genetically linked resistances.

A decrease in non-susceptibility trends between 2012 and 2015 was observed for nitrofurantoin (23.2% change, p<0.001).

Combined resistance to trimethoprim and nitrofurantoin (2.4%) and to other multi-drug resistance combinations remains low (Table 2).

Table 2 Percentage of multi-drug resistance in *E. coli* urinary isolates.* **

Antimicrobial	% Resistance (number of isolates tested)		
	2014	2015	Statistical significance of % change
trimethoprim / nitrofurantoin	2.4 (10 234)	2.4 (9838)	↔
trimethoprim / nitrofurantoin/ciprofloxacin	1.4 (10 323)	1.2 (9837)	↔
trimethoprim / nitrofurantoin / co-amoxiclav	1.5 (10 324)	1.3 (9838)	↔
trimethoprim / nitrofurantoin / ciprofloxacin / co-amoxiclav	1.0 (10 323)	0.8 (9837)	↔

* Data for NHS Greater Glasgow & Clyde, NHS Grampian, NHS Highland and NHS Western Isles has been excluded from analysis due to a temporary issue with transfer of data.

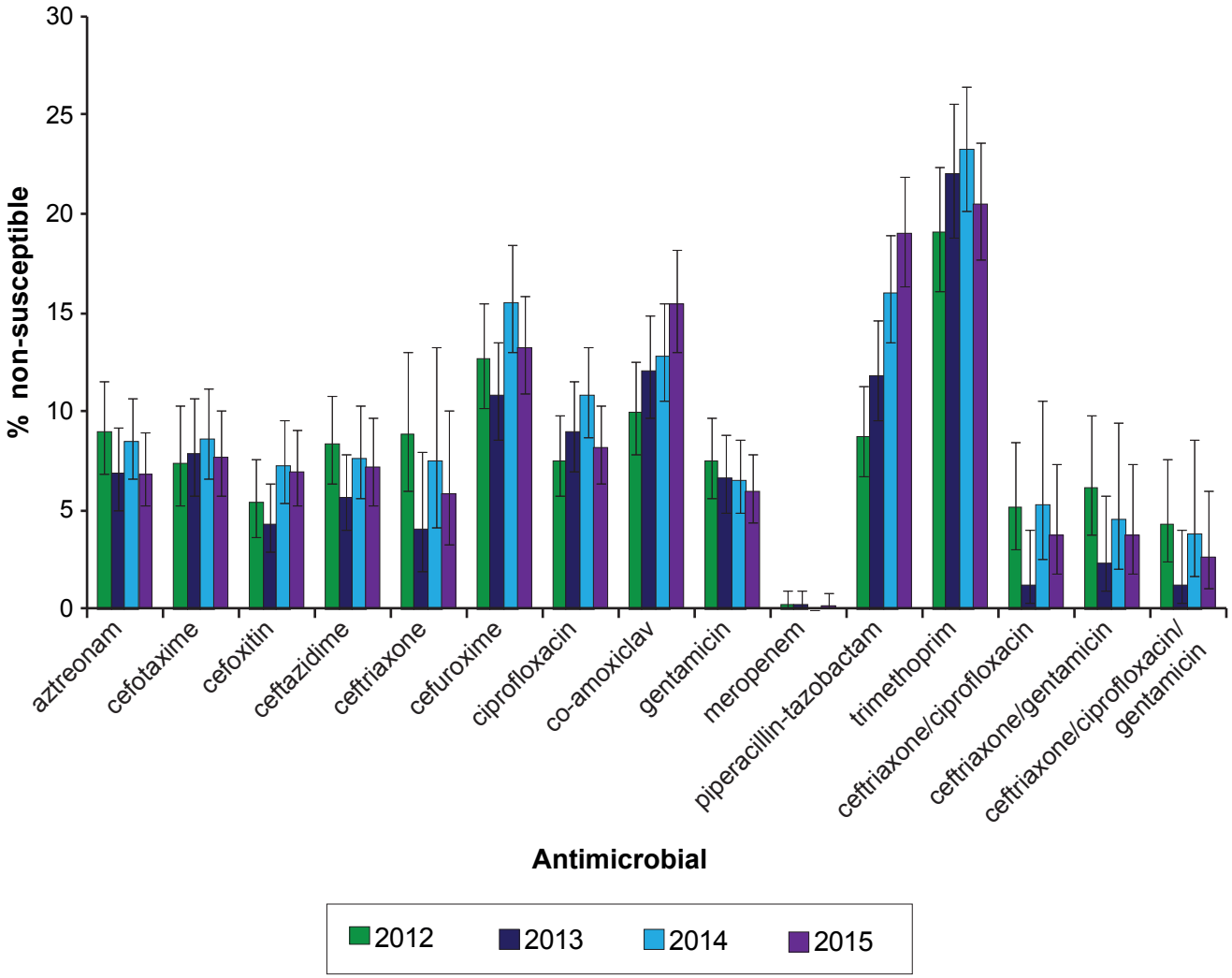
** This data is only resistant isolates and not non-susceptible isolates (i.e. intermediate+resistant).

3.1.3 *Klebsiella pneumoniae*

The majority of infections caused by *K. pneumoniae* are healthcare-associated and can spread quickly between colonised or infected patients.[5] It can cause a wide variety of healthcare-associated infections such as pneumonia, bloodstream infections, wound or surgical site infections and meningitis.

Overall susceptibility trends between 2012 and 2015 were unchanged with the exception of co-amoxiclav and piperacillin-tazobactam demonstrating a 14.8% (p=0.01) and 28.7% (p<0.001) increase respectively for this time period (Figure 6) This is concerning as the safeguarding of these important agents is imperative for the management of serious infection, though caution on the interpretation of co-amoxiclav and piperacillin-tazobactam results is noted on page 20. The proportion of *K. pneumoniae* bacteraemia ESBL producers has remained stable since 2012, with 4.6% of cases being ESBL producers in 2015.

Figure 6 Percentage of non-susceptible *K. pneumoniae* bacteraemias, 2012 to 2015.



The latest ESPAUR report[4] demonstrates similar trends to Scotland for *K. pneumoniae*. The EU/EEA population-weighted mean for resistance in all antibiotic groups analysed are higher than the Scottish non-susceptibility results for 2015[5]. Additionally there is a wide range of resistance to the analysed antibiotic groups across Europe; however, the reported UK results are towards the lower end for all antibiotic groups. ECDC reported that fluoroquinolone resistance ranged from 3.6% to 70.8% with the UK reporting 7.7%. Significantly increasing trends (2011 to 2014) in resistance to third generation cephalosporins was noted for the UK and other EU/EAA countries in the EARS-Net report; however, this is not apparent in the Scottish 2012 to 2015 trends analyses.

3.1.4 Resistance in *Neisseria gonorrhoeae*

N. gonorrhoeae is exclusively a human pathogen. Infections may present as a broad range of symptoms and can affect urogenital, anorectal, pharyngeal and conjunctival areas. Severe cases can lead to disseminated gonococcal infections, endocarditis and meningitis; and in women, to pelvic inflammatory disease (PID).

Resistance to seven antibiotics was determined for 1100 episodes of *N. gonorrhoeae* infection where isolates were available to the Scottish Bacterial Sexually Transmitted Infections Reference Laboratory (SBSTIRL) in 2015. Non-susceptability to the current first line treatment regimen, consisting of azithromycin plus ceftriaxone dual therapy, remained low and no treatment failures have been reported. No episodes of ceftriaxone non-susceptability (minimum inhibitory concentration (MIC) >0.12 mg/l) were detected. Twenty-five isolates resistant to azithromycin were detected (2.3 %), with three being high-level azithromycin resistant (HL-AziR) isolates (MIC >256 mg/l). Since November 2014 more than 30 episodes of HL-AziR gonorrhoea have been recorded by PHE.[20] Comparison of the Scottish and PHE isolates by Sanger sequencing has shown that the Scottish isolates are unrelated to each other or to this outbreak. In 2015, non-susceptability to previous first line therapies was reduced for cefixime (n=2, 0.2%) and penicillin (n=207, 18.8 %) but increased for ciprofloxacin (n=375, 34.1 %) compared to 2014.[21]

Gram-negative bacteraemia

Surveillance of AMR in organisms causing **blood-stream infections** (bacteraemias) is **critical to ensure** availability of **successful treatments**, as these can be serious, life-threatening conditions.

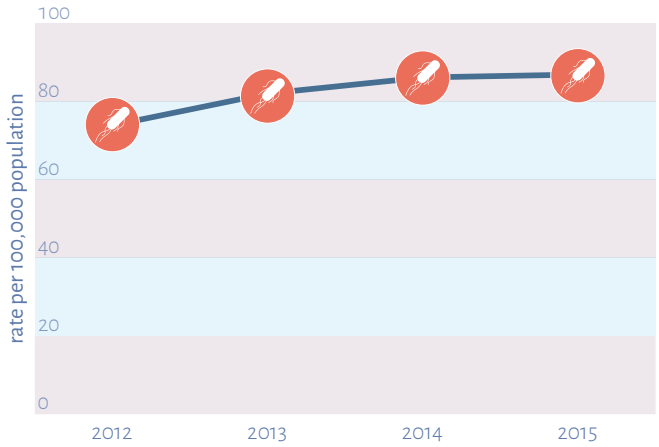
The **key pathogen and antibiotics** under surveillance are **those which are** the **most frequent cause of infections** in the **community and hospital**, and those which are particularly **common in vulnerable patients**.

Incidence rates of common organisms causing bacteraemias in Scotland

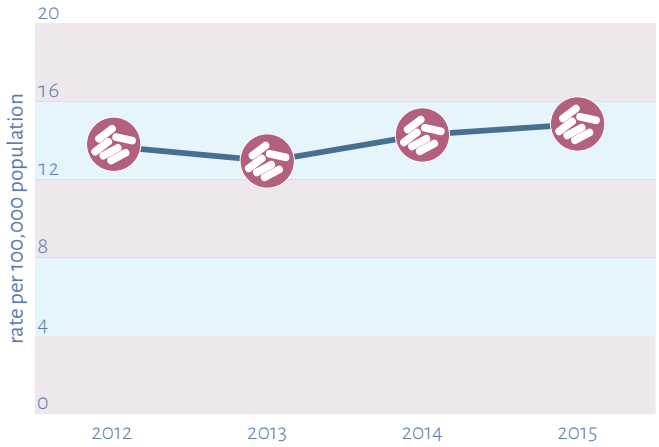
E. coli is the most common cause of community and healthcare-associated UTIs and the most common cause of bacteraemias in Scotland.

K. pneumoniae is a common cause of infection among vulnerable patients in hospital, and is the second most common cause of bacteraemias in Scotland.

E. coli annual rate trend



K. pneumoniae annual rate trend



Non-susceptibility (NS) among *E. coli* and *K. pneumoniae* to key antibiotics (2012 compared to 2015)

	E. coli		*K. pneumoniae*	
	% NS in 2015	% change 2012 vs 2015	% NS in 2015	% change 2012 vs 2015
Aztreonam	7.3%	-9.1%	6.9%	-5.7%
Co-amoxiclav	31.4%	6.1%	15.4%	14.8%
Gentamicin	9.3%	0.5%	5.9%	-6.8%
Piperacillin-tazobactam	10.9%	8.6%	19.0%	28.7%

Statistically significant increase | Statistically significant decrease | Non-significant change

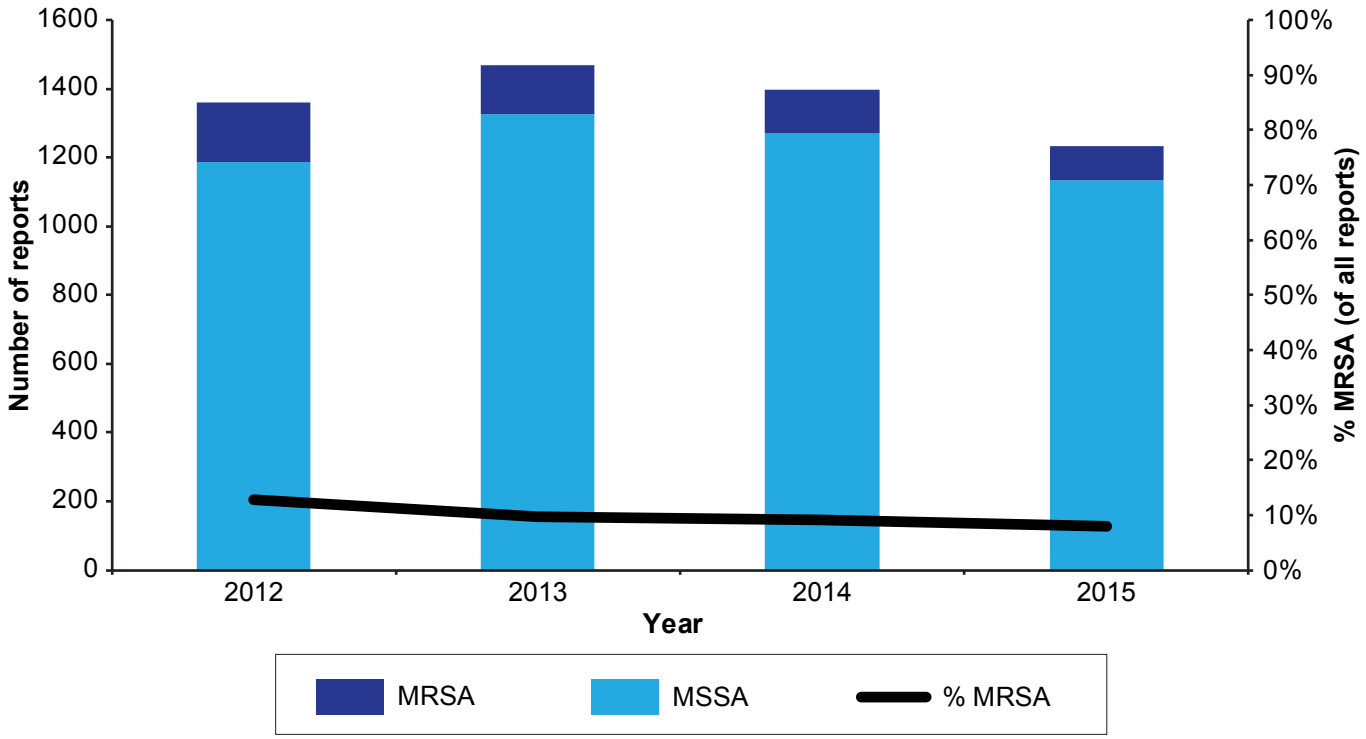
3.2 Susceptibility in Gram-positive bacteria

3.2.1 Susceptibility in *Staphylococcus aureus*

S. aureus bacteria are present in the nasal cavity of approximately 30% of the population and may also be found on the skin. It causes infection most commonly at sites of lowered host resistance, e.g. damaged skin and mucous membranes. When the skin is breached, *S. aureus* can enter the bloodstream resulting in a bacteraemia.

The proportion of meticillin resistant *S. aureus* (MRSA) among all *S. aureus* bacteraemias decreased 16.8% year on year ($p<0.001$) between 2012 and 2015. In 2015, the proportion of MRSA was 6.8% which compares favourably to the rest of Europe with EARS-Net reporting an EU/EEA population-weighted mean of 17.4% and a range of 0% to 56.0%. The number of reports of MRSA has decreased in the last four years (Figure 7).

Figure 7 Counts of MRSA and MSSA and proportion of total *S. aureus* isolates that are meticillin resistant, 2012 to 2015.



In 2015, non-susceptibility to key agents including ciprofloxacin, trimethoprim and tetracycline in MRSA remained high (83.5%, 41.2% and 18.6% respectively).

Susceptibility of meticillin sensitive *S. aureus* (MSSA) to the majority of antibacterials tested has remained stable since 2012.

3.2.2 Antimicrobial susceptibility in *Enterococcus* spp. bacteraemias

Enterococci are distributed widely in nature and are found in humans, animals, soil, food and plants. They are considered low grade pathogens and are a commensal of the gastrointestinal tract of most species, including humans. They are a common cause of UTIs but have also been associated with more serious types of infections such as intra-abdominal infections, endocarditis, bloodstream infections, neonatal infections and meningitis.

The proportion of *E. faecium* bacteraemia isolates that were non-susceptible to vancomycin in 2015 was 34.7%. There has been a statistically significant increasing trend observed in vancomycin resistance

as a proportion of *E. faecium* bacteraemias since 2012 (p=0.006) and an overall increase of 16.6% (see appendix). The ESPAUR 2010 to 2014 report published by PHE in 2015 reported an increasing resistance proportion of 17% in 2010 to 25% in 2014.[4] ECDC reported a statistically significant increase in the EU/EEA population weighted mean percentage of 6.2% in 2011 to 7.9% in 2014. Cyprus and Ireland are the only two countries in the EU/EEA that are reporting higher resistance proportions of 40.0% and 45.1% respectively.[5]

There were no isolates of *E. faecalis* that were non-susceptible to vancomycin in Scotland in 2015. Vancomycin resistance in *E. faecalis* remains low throughout the whole of Europe.

Despite the total number of vancomycin resistant enterococci (VRE) bacteraemias remaining relatively low in Scotland and subsequently the burden of disease, this is still of concern. It is worth noting that EARS-Net is reporting a change in the epidemiology of VREs across the EU/EEA member states. Previously the incidence of vancomycin resistance was stable, however there are now an increasing number of countries demonstrating a significantly increasing trend.

ECDC reported on the emergence of an important healthcare-associated polyclonal complex, *E. faecium* clonal complex (CC)17, and also CC2 and CC9 in *E. faecalis*.[5] Additionally seven high-risk clones of vancomycin-resistant *E. faecium* (VREF) belonging to CC17 have been reported. Among these isolates, a new hospital-associated sequence type (ST795), VanB2-type teicoplanin-resistant strain was detected. The characteristics of adaptation and persistence in the hospital environment of ST795 were emphasised by the presence of genes and clusters recognised to be specific for hospital-associated VREF.[22]

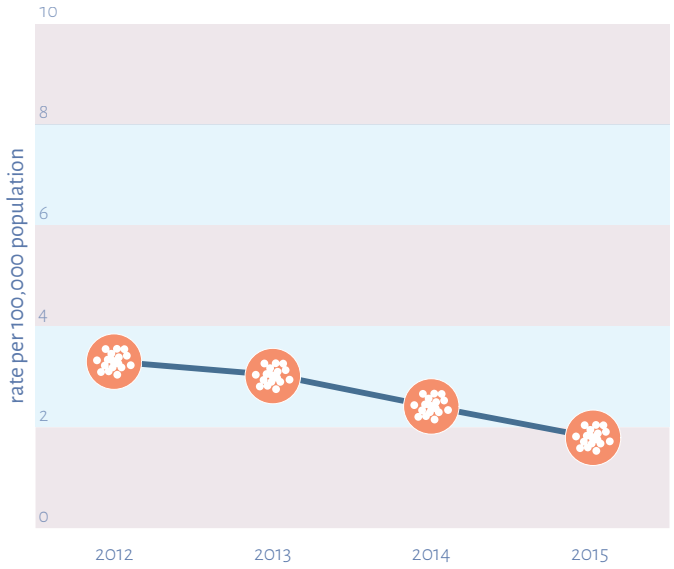
In 2015, one *E. faecium* isolate and one *E. faecalis* isolate were reported as being non-susceptible to linezolid (a member of the oxazolidinone group of antibiotics). The isolate of *E. faecium* was non-susceptible to both vancomycin and linezolid. Strains of VRE non-susceptible to both tigecycline (a glycylcycline derived from the tetracycline family of antibiotics) and linezolid have been previously reported in Scotland, although there were none in 2015. These antibiotics are used to treat vancomycin resistant strains of enterococci and the emergence of this resistance is of concern as it limits the available therapeutic options.

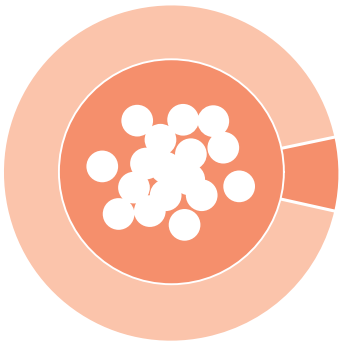
The *cfr* gene confers resistance to linezolid. This gene can be transferred to MRSA.[23] Additionally, in June 2016, a UK wide public health alert was issued describing *optrA* gene mediated transferable oxazolidinone resistance.[24] This resistance mechanism had been previously reported in several countries including the Republic of Ireland however it is not widely tested for. During retrospective screening undertaken by PHE's AMRHAI Reference Unit, the *optrA* gene was detected in five *E. faecalis* isolates over a three year period. This is the first time this type of resistance had been found in the UK.

Further work is required to fully understand the drivers for this change in epidemiology and plans are being developed as part of the CARS programme to understand the causes for these changes to help identify potential interventions.

Gram-positive bacteraemia

MRSA bacteraemia annual rate trend

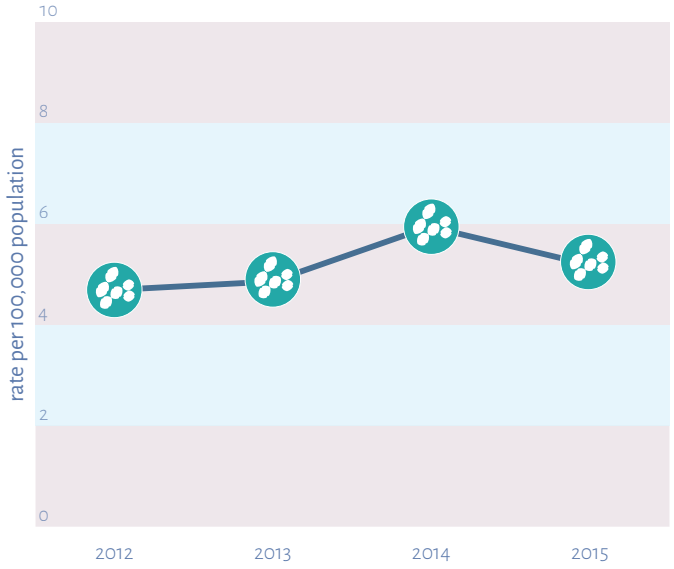




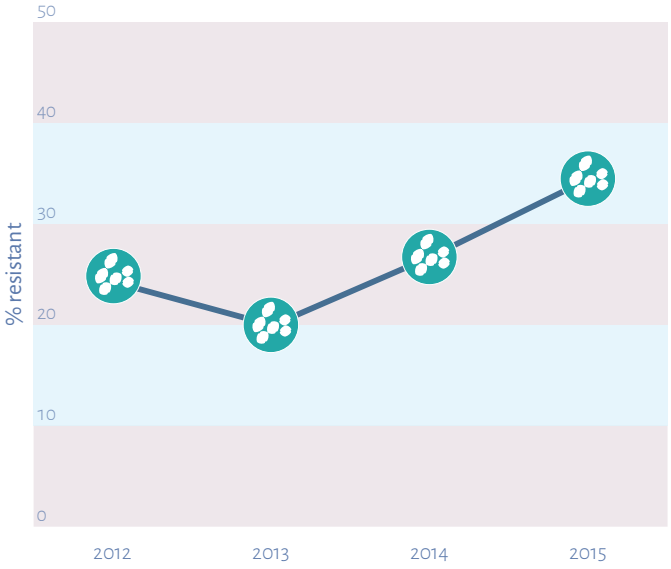
6.8%
of ***S. aureus*** bacteraemias were **MRSA** in 2015

Susceptibility of **MRSA** and **MSSA** to the majority of antibiotics tested has remained **stable** since 2012.

E. faecium bacteraemia annual rate trend



Trend in *E. faecium* bacteraemia non-susceptibility to vancomycin



34.7%
of ***E. faecium*** were non-susceptible to **vancomycin**

There has been a statistically significant **increasing** trend observed in *E. faecium* vancomycin non-susceptibility since 2012 and an overall **increase** of **16.6%**. There were no reports of vancomycin non-susceptible *E. faecalis*.

3.3 Anaerobes

For the first time this report includes information on resistance in strictly anaerobic organisms. The data presented are from January 2015 to June 2016.

During this period the Anaerobic Reference Unit (ARU), Public Health Wales, received approximately 150 isolates from Scotland; however, antibiotic susceptibility testing is only performed at the request of the referring laboratory. Approximately one third of isolates were tested against metronidazole, clindamycin, meropenem, piperacillin-tazobactam, co-amoxiclav, vancomycin, penicillin and ceftriaxone.

A range of non-susceptibility in a variety of isolates was reported (see Table 3).

Table 3 Non-susceptibility in anaerobic isolates.

Organism (total number)	Antimicrobial (non-susceptible)
Bacteroides thetaiotaomicron (n=1)	metronidazole; co-amoxiclav; clindamycin
Actinomyces radingae (n=1)	clindamycin
Clostridium perfringens (n=1)	clindamycin; penicillin
Bacteroides xylanisolvens (n=1)	clindamycin; piperacillin-tazobactam
Fingeoldia magna (n=1)	metronidazole
Bacteroides xylanisolvens (n=1)	clindamycin
Parabacteroides distasonis (n=1)	metronidazole; co-amoxiclav; clindamycin

Non-susceptibility to agents such as metronidazole, clindamycin and co-amoxiclav may be an emerging issue and requires to be closely monitored by Scottish diagnostic laboratories and HPS. Isolates should be submitted to the ARU if non-susceptibility to key antibiotics is suspected.

3.4 Mycobacterial Infections

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis*, *M. bovis*, *M. africanum*, *M. canetti* or *M. microti*, which together form the *Mycobacterium tuberculosis* complex. TB can affect the lungs and can also cause infection elsewhere in the body.

Transmission of TB is by inhalation of infected droplets and requires prolonged close contact with an infected individual. A key feature of TB is that, after infection, the bacteria can remain latent in the body for a long time causing no symptoms of disease. People with latent TB infection are not infectious; however, under favourable conditions the bacteria can start multiplying and cause clinical disease.

In December 2015, HPS published the 'Enhanced Surveillance of Mycobacterial Infections (ESMI) in Scotland: 2015 tuberculosis annual report for Scotland'. (Note: The report contains data from 2014.)[25] This national surveillance system provides information on drug resistance as well as total numbers, demographics, characteristics and treatment outcomes. Isoniazid, rifampicin, ethambutol and pyrazinamide are considered first-line drugs for the treatment of tuberculosis.

There were 237 culture confirmed cases of tuberculosis reported in 2014 of which 231 (97.5%) had drug susceptibility tests for both isoniazid and rifampicin. Resistance to at least one first-line drug at the start of treatment was reported for 22 cases (9.5%), 18 (7.8%) isolates being resistant to isoniazid, two (0.9%) being resistant to rifampicin and eight (3.4%) being resistant to pyrazinamide.

In 2014, there was an increase in the number and proportion of cases resistant to any first-line drug (22 cases, 9.5%). These are the highest levels of drug resistance reported since 2000 but remain within the recommended range of less than 10%. There were two cases of multi-drug resistant TB reported in 2014 (0.9%).

4. Improvements

4.1 Surveillance and linkage

Following on from the UK Five Year AMR Strategy[2] and ScotMARAP2[1] recommendations regarding improved access and use of surveillance data, HPS undertook a review of their current AMR surveillance systems. Part of this review involved consulting with experts in the health protection sector and also directed research using online resources of public health organisations to identify relevant policies, guidance or grey literature.

All Scottish diagnostic laboratories submit data to HPS using 'The Electronic Communication of Surveillance in Scotland' (ECOSS). Throughout 2015, HPS have undertaken a substantial validation exercise of the data being submitted and work has commenced addressing the governance and processes underpinning the ECOSS system.

This work will support various AMR initiatives in 2016 including the NHSScotland Infection Intelligence Platform (IIP) programme. The NHS is becoming increasingly driven by information and IIP has started to develop capacity and capability in infection informatics across Scotland. IIP is starting to enable clinicians to begin to draw conclusions from 'big data' on infection to meet the IIP vision of improving patient outcomes and reducing harm from infection in NHSScotland.

The first phase of IIP (August 2013 to March 2016) has included extensive technical development to build the new informatics platform and test its capability to provide information to support clinicians to improve patient care. The central element of the IIP phase 1 work programme was a number of clinical studies that aimed to generate new evidence for improved clinical practice and to shape national and local antibiotic prescribing policy. The key findings and implications of some of these studies are shown in the infographic below and on the IIP website study outputs page, available here.

How has the Infection Intelligence Platform helped evidence for improved clinical practice?

The NHS Scotland Infection Intelligence Platform (IIP) is an ambitious informatics programme which supports clinicians to improve outcomes and reduce harm for patients with or at risk from infection. Please see below for examples of work undertaken in the platform and key messages from these studies.

To what extent is community use of antibiotics associated with resistance in urinary isolates?

This study showed the following individuals were more likely to have a specimen with antimicrobial resistance: Charlson co-morbidity score ≥5 (**1.2 times**), care home residence (**3.8 times**) and prior use in previous six months of ≥29 DDD trimethoprim (**12.0 times**), ≥29 DDD nitrofurantoin (**9.0 times**).

These findings will support development of clinical decision support tools to optimise initial antibiotic treatment for patients with UTI.

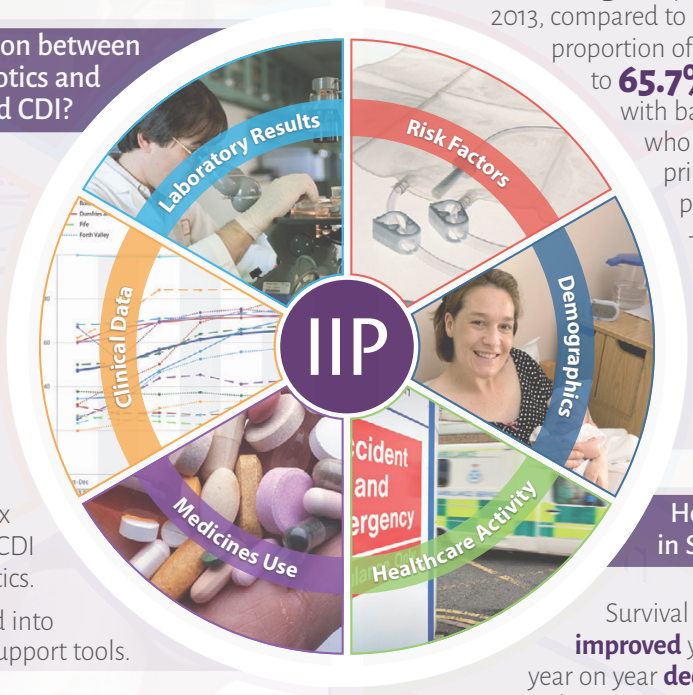
What is the association between community use of antibiotics and community associated CDI?

Those who had any antibiotics in the previous six months were **2.6 times** more likely to have CDI than those who had no antibiotics.

Use of high risk antibiotics **increased** this risk further (**5.7 times**).

Increased cumulative exposure **increased** this risk further; ≥29 DDD of high risk antibiotics in a six month period **increasing** odds of CDI **18 times** greater than no antibiotics.

These findings will be incorporated into development of clinical decision support tools.



Are interventions to reduce unnecessary antibiotic use having unintended consequences?

It is important to consider unintended consequences of reducing antibiotic prescribing in primary care.

Between 2010 and 2014, the proportion of the Scottish population receiving antibiotic prescriptions in primary care **reduced** from **32.2%** in 2011 to **31.4%** in 2013, compared to a **small increase** in the proportion of patients (from **64.5%** to **65.7%**) admitted to hospital with bacterial respiratory infections who had received antibiotics in primary care in the 30 days prior to admission.

These findings indicate that reductions in antibiotic prescribing can be achieved without adversely impacting on patients who do require antibiotics for respiratory infections.

How have outcomes after CDI in Scotland changed over time?

Survival among CDI patients **improved** year on year with a **5.6%** year on year **decrease** in mortality between 2009 and 2013.

Older patients, those with a greater number of illnesses and certain specific conditions, were associated with increased mortality.

Further work to identify which factors are associated with the increased survival will improve CDI patient care and outcomes for the individual patient.

Surgical antibiotic prophylaxis and post-operative acute kidney injury

Data from one NHS board analysed in IIP provides further evidence to support the SAPG recommendation in June 2012 to review the use of flucloxacillin and gentamicin for orthopaedic prophylaxis.

This study also demonstrates the value of linking biochemistry data to evaluate the impact of antimicrobial stewardship interventions. This methodology could be repeated at national level when a national laboratory datamart is established.

More information on these studies is available is available on IIP website: www.isdscotland.org/iip.

4.2 Controlling Antimicrobial Resistance in Scotland

In September 2013, the Department of Health published the UK Five Year (2013 to 2018) AMR Strategy with three strategic aims:

- improve the knowledge and understanding of AMR;
- conserve and steward the effectiveness of existing treatments; and
- stimulate the development of new antibiotics, diagnostics and novel therapies.

These are being delivered via seven key action areas:

1. Improving infection prevention and control practice;
2. Improved education, training and public engagement;
3. Better access to and use of surveillance;
4. Better identification and prioritisation of AMR research needs;
5. Optimising prescribing practice;
6. Developing new drugs treatments and diagnostics; and
7. Strengthened international collaboration.

Aligned to the UK strategy, and adopting a 'One Health' i.e. ecological ethos, the Scottish Government established the CARS programme to deliver on objectives 2, (with NHS Education for Scotland (NES) and SAPG), 3, 4 and 5 for human and animal health, and 5 for animal health (SAPG undertakes this for human health). Objective 6 is incorporated in 4, and 7 is undertaken at the UK level. Objective 1 is the remit of the HAI and Infection Prevention and Control section within HPS.

The CARS programme reports to Scottish Antimicrobial Resistance and Healthcare Acquired Infection (SARHAI) strategy group and the Chief Medical Officer CARS policy group. The Scottish government and CARS programme are represented on the UK AMR strategy High Level Steering Group, the PHE AMR programme board and the Veterinary Medicines Directorate (VMD).

The CARS programme adds an over-arching strategic component to a wider AMR landscape in Scotland (with links to sister organisations in England and Europe, e.g. ECDC, as appropriate) in relation to infection control, antimicrobial stewardship, clinical microbiology, public health/health protection, animal and environmental health (including food).

The CARS programme comprises four overlapping work streams:

- AMR intelligence;
- AMR research prioritisation and coordination;
- Engagement and education in AMR; and
- Controlling AMR in animal health.
- The programme aims to build the structures, processes and capacity to allow Scotland to control AMR now and in the future.

Early achievements include contributing to the 'UK One Health' report, inaugural meetings of the Scottish Animal Health and AMR group and the Scottish AMR Research Consortium, reviews on veterinary prescribing guidance, infection prevention guidance and infrastructure, antimicrobial susceptibility data and surveillance systems, biosecurity/disease avoidance, AMR research literature, and a stocktake on AMR human and animal data submitted to ECOSS.

Work planned in 2016/17 will include report on behaviours driving clinical antimicrobial prescription and patient treatment expectations/intervention evaluations and recommendations, initial investigation

into the potential relationship between human and animal AMR, recommendations on capturing non-bacterial AMR data, recommendations on the delivery of AMR research priorities in Scotland, and modelling the health and economic impact of AMR in Scotland.

4.3 Future Developments

In 2016, HPS will continue to develop antimicrobial susceptibility testing (AST) standardisation in conjunction with the SMVN. This standardisation will assist in the development of reliable early warning systems and more robust AMR surveillance.

This will include the capture of all AST data within the ECOSS database through existing ECOSS data transfer routes, in turn, resulting in a single source of comprehensively validated and consistent specimen/AST data from each laboratory.

In the coming year, the links between HPS and the reference laboratories that generate antimicrobial resistance data will be reviewed. Where necessary these links will be strengthened, with a focus on detailed interrogation of the AMR results provided.

A CPO enhanced surveillance system will be further developed in order to describe and monitor the changes in the epidemiology of carbapenemase-producing Gram-negative bacteria in Scotland. The main objectives of this enhanced surveillance system are to describe the epidemiology of CPOs in Scotland, monitor occurrence of CPOs in Scotland, and communicate the findings to NHS boards and other key stakeholders to inform the control of carbapenemase-producing Gram-negative bacteria in the healthcare setting. The expected benefits of this enhanced surveillance system are: identification of risk factors for future prevention efforts; improved treatment pathways for CPO cases; and increased awareness of CPO epidemiology in Scotland among the wider health/scientific audience.

IIP is now in its second phase. Clinical engagement with infection specialists and other clinicians has ensured continued alignment of IIP with the clinical priorities for antimicrobial stewardship and infection prevention and management across Scotland. The aim of the second phase will be to continue to focus on increasing the platform's capability to influence day to day clinical practice through developing real-time patient care applications. IIP will begin work to use data to model patient-specific risk factors and develop decision rules to populate clinical decision support tools to inform management of individual patient episodes to support patient centred care. The initial priority will be decision support tools for initial treatment of UTI in primary care. The other key delivery area for IIP phase 2 will be to maximise the use of currently available data through provision of timely information to support quality improvement. IIP reports will provide visually and clinically meaningful information to frontline clinicians and will enable continuous monitoring of the impact of infection prevention and treatment interventions on patient outcomes.

Finally, as per the recommendations of the UK Five Year Antimicrobial Resistance Strategy, a Scottish 'One Health' Report will be published in 2017. The report will contain antimicrobial use and resistance data in humans, animals and the environment. This is in line with the aims of the global 'One-Health' approach which spans people, animals, agriculture and the wider environment.

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