AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE

AURA
Antimicrobial Use and Resistance in Australia

Preliminary Report on

Antimicrobial Use and Resistance in Australia

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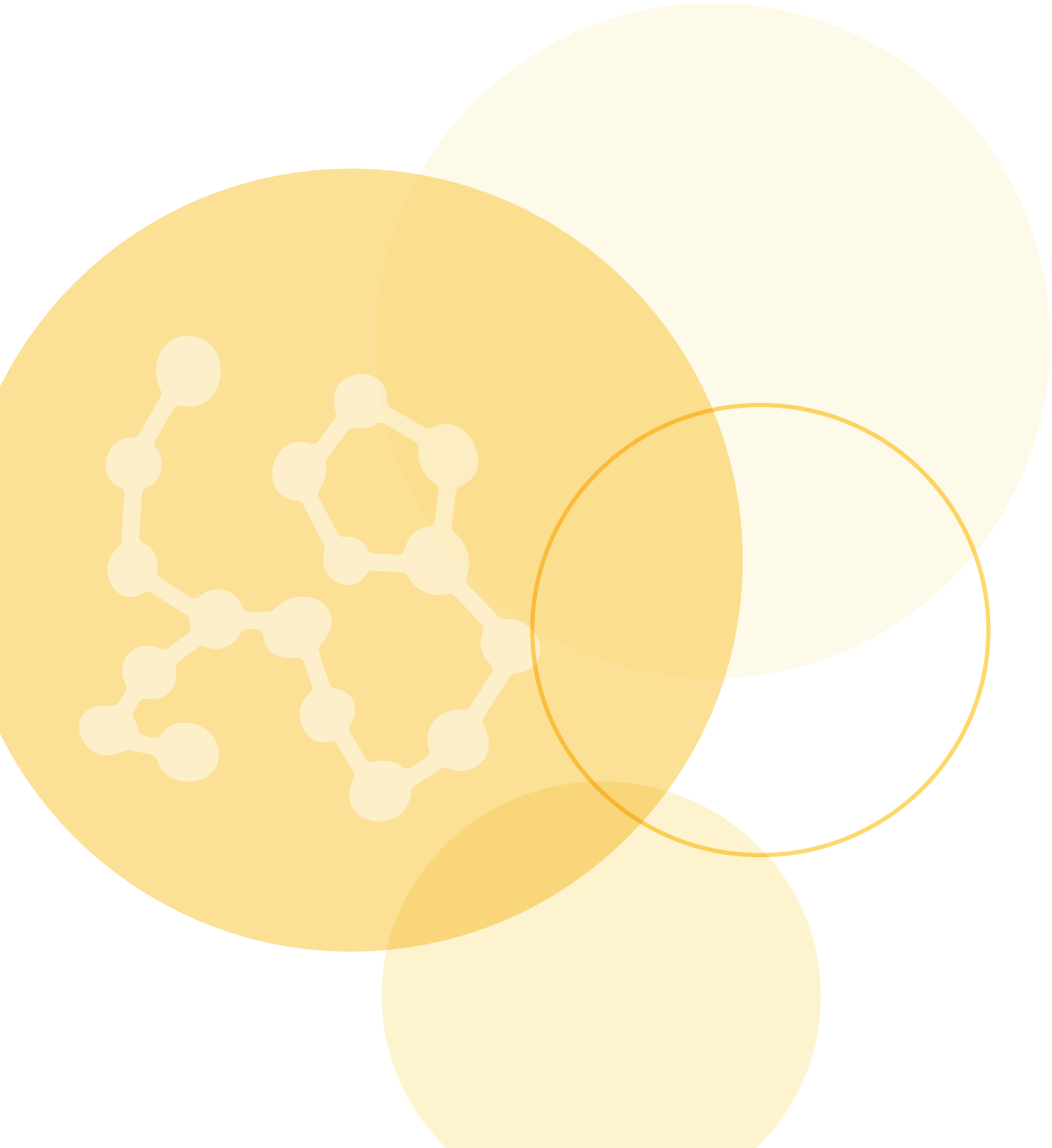
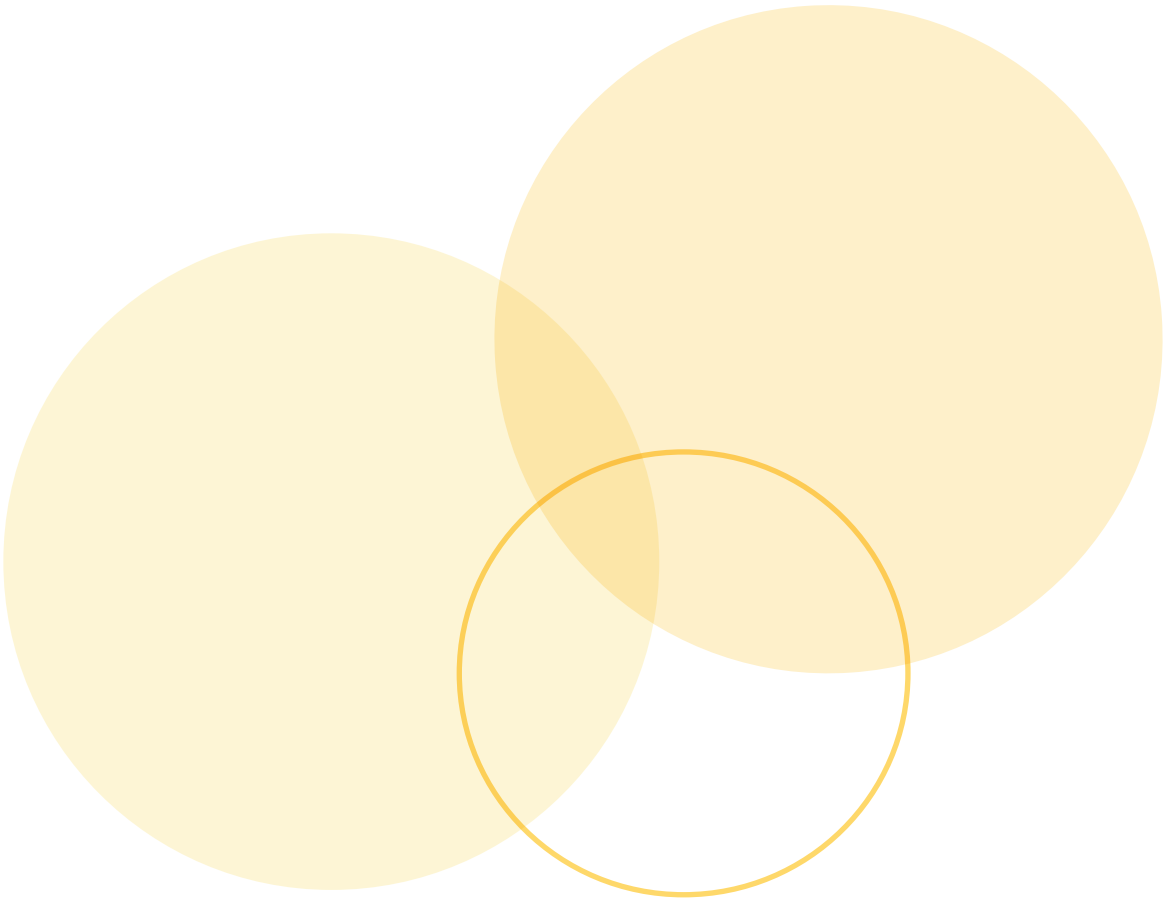


Contents



Executive summary

This document was developed following a comprehensive review of antimicrobial resistance (AMR) and antimicrobial use (AU) programs in Australia, and supports the response to the global problem of AMR.

The report has been developed following extensive consultation with the states and territories, clinicians, technical experts, health service providers and epidemiologists, to provide a picture of the range of AMR and AU activities across Australia in 2014. The document presents a baseline position with regard to AMR and AU as a Preliminary Report of the Antimicrobial Use and Resistance in Australia (AURA) Project.

Antimicrobial resistance

The data

Australian AMR data were still incomplete in their coverage of the bacteria and populations of interest. Valuable data were available from ongoing targeted surveillance programs for a range of bacteria. However, for other bacteria, data were only available from historical sources.

Much of the data available from a number of programs was from public sector hospital isolates (principally from the Australian Group on Antimicrobial Resistance – AGAR), with limited representation of isolates from the community or residential aged-care facility sectors. Exceptions existed for a small number of pathogens that cause notifiable diseases, for which data were gathered from all sectors.

Enterobacteriaceae, mainly *Escherichia coli* and *Klebsiella* species

Resistance to third-generation cephalosporins, due to extended-spectrum and plasmid-borne β-lactamases, was found in 7.5% (*E.coli*) and 6.3% (*K.pneumoniae*) of blood culture isolates nationally in 2013. Rates were higher (approximately double) in strains causing hospital-onset infections than in strains causing community-onset infections. Multidrug resistance, defined as acquired resistance to more than three antimicrobial classes, rose between 2008 and 2012 from 4.5% to 7.6% in *E. coli*, and from 4.4% to 5.1% in *Klebsiella* species. Although still uncommon, resistance to carbapenems attributable to carbapenemases appears to be rising, reaching 0.28% of all blood culture isolates of *Enterobacteriaceae* in 2013.[1]

Enterococcus species

Vancomycin-resistant strains of *E. faecium* were prevalent in many Australian hospitals, having first appeared in 1995. At the national level, vancomycin-resistant strains accounted for 39% of strains of this species in 2011. Ampicillin resistance was evident in more than 85% of strains of the species. The bulk of this resistance was encoded by the *vanB* gene complex. Vancomycin resistance in the more common *E. faecalis* was rare.

Haemophilus influenzae

In the most recent national survey, in 2006, 21.9% of strains of this species were ampicillin resistant. Resistance rates to tetracycline and trimethoprim–sulfamethoxazole were 12% and 20%, respectively.

Mycobacterium tuberculosis

Between 1995 and 2010, multidrug-resistant strains (defined as resistance to two or more antimycobacterial agents) increased from 0.7% to 3.5%.

Neisseria gonorrhoeae

Between 2006 and 2012, resistance to penicillin and ciprofloxacin remained stable (at around 30–40% of isolates). Reduced susceptibility to ceftriaxone emerged, reaching 3–5% of isolates in 2010–12.

Neisseria meningitidis

Resistance to penicillin remained rare (less than 1% of isolates), while resistance was not observed to ceftriaxone or ciprofloxacin over the 2006–12 period. Reduced susceptibility to rifampicin was observed more recently; in 2012, less than 2% of isolates showed reduced susceptibility to rifampicin.

Salmonella species

Data from the two reference laboratories undertaking susceptibility testing of *Salmonella* routinely showed similar results: 7–10% of isolates were nonsusceptible to ampicillin, 4–5% were nonsusceptible to ciprofloxacin, and approximately

0.5% were nonsusceptible to cefotaxime. Rates appeared to be stable between 2008 and 2012.

Staphylococcus aureus

Methicillin-resistant strains of *S. aureus* (MRSA) were prevalent nationally as a cause of both hospital-onset and community-onset infections (30.3% and 17.9%, respectively, in 2011–12). There were significant differences between jurisdictions in MRSA rates. In the past decade, there has been a noticeable reduction in the proportion of healthcare-associated multidrug-resistant MRSA clones, but a significant rise in community-associated non-multidrug-resistant clones.

Streptococcus pneumoniae

In the previous national survey, in 2007, rates of nonsusceptibility of isolates to penicillin were 2%, when applying interpretive criteria for infections outside the central nervous system, and 19.8%, when applying interpretive criteria for central nervous system infections. Rates of resistance to other classes ranged from 18% for tetracyclines to 29% for trimethoprim–sulfamethoxazole.

Acinetobacter species

Data, including trends, were only available for the Queensland public hospital system, through Queensland Health's OrgTRx. Between 2006 and 2014, rates of resistance to gentamicin, ciprofloxacin and meropenem fell from approximately 17–20% to approximately 2–4%. This fall was attributed to the control of multidrug-resistant clones at a number of tertiary care centres.

Antimicrobial use

The data

Comprehensive volume-of-use data for community prescribing were available from the Pharmaceutical Benefits Scheme (PBS). For hospital volume of use, the National Antimicrobial Utilisation Surveillance Program (NAUSP), coordinated by the South Australian Department of Health, had a sample from predominantly public hospitals across Australia.

The Queensland Health MedTRx system provides a statewide passive surveillance system that gives detailed reports on AU in the public hospital sector.

National targeted AU surveillance, focusing on appropriateness of use in the acute care setting, is conducted through the National Antimicrobial Prescribing Survey (NAPS), at the National Centre for Antimicrobial Stewardship at the Doherty Institute (a joint venture between the Royal Melbourne Hospital and the University of Melbourne). Data on appropriateness of use in the community are very limited and confined to intermittent surveys, such as those conducted through the Bettering the Evaluation and Care of Health (BEACH) study.

Volumes of use in community

Using the internationally accepted measure of defined daily dose (DDD) per 1000 inhabitants per day, overall consumption of systemic antimicrobials on the PBS in 2011 was 25.0 DDD/1000 inhabitants/day. This was higher than in most European countries in that year and similar to the United States. The top five antimicrobials (expressed as DDD/1000 inhabitants/day) were amoxycillin (6.2), amoxycillin with clavulanate (4.4), cephalexin (2.9), doxycycline (2.6) and roxithromycin (1.4). Total volume of use appears to have stabilised since 2008.

Volumes of use in hospital

Data from NAUSP for 2012–13 showed that the total volume of use in the hospitals' samples was 945 DDD/1000 occupied bed days. Penicillins, especially those combined with blactamase inhibitors, and cephalosporins are the most widely prescribed agents in Australian hospitals. Carbapenem usage rates were low, at only 2.3% of total use, while fluoroquinolones accounted for 4.5% of total use. Volumes of use in intensive care units were approximately 50% higher than overall hospital use.

Significant trends since 2008 included increases in the use of first-generation cephalosporins and decreases in the use of amoxycillin, ciprofloxacin and gentamicin. Overall, hospital use in Australia was higher than that of Sweden, the Netherlands and Denmark. These are the only countries with

publicly available national data on AU, and are also benchmark countries in terms of lower AU than almost all other countries worldwide.

Appropriateness of use in hospital

The NAPS of 2013 found a range of prescribing issues across Australia: more than 40% of surgical prophylaxis exceeded 24 hours duration, 40% of prescriptions for acute exacerbations of chronic obstructive pulmonary disease were inappropriate, and only 60% of prescriptions were compliant with the national prescribing guidelines (*Therapeutic guidelines: antibiotic*).

Links between antimicrobial use and antimicrobial resistance

Australian AU data are not currently linked with AMR surveillance data at a national level, but some limited evidence exists on the local relationships between AMR and AU. Data from some datasets were examined for indications where such relationships might exist.

The Queensland Health system collects data on both AMR and AU, and has been able to show where there was a definite link between use and resistance (such as use of piperacillin–tazobactam and resistance in *Pseudomonas aeruginosa*) and where there was no obvious link (such as use of ciprofloxacin and resistance in *P. aeruginosa*).

Conclusion

Australia has a number of firmly established AMR issues that directly affect medical care in hospitals and the community. These include third-generation cephalosporin-resistant *E. coli and Klebsiella* species, MRSA and vancomycin-resistant *E. faecium*. Recent concerning trends include the emergence of reduced susceptibility to ceftriaxone in *N. gonorrhoeae* and multidrug resistance in *M. tuberculosis*.

Much of the resistance in Australia is being driven by high AU in the community and in hospitals – the level of use is higher than in most developed countries. A recent national survey of Australian hospitals has shown considerable opportunities to improve the quality of prescribing; it is likely that similar opportunities for improvement exist in primary health care.

1 Introduction

Purpose and objectives

This document was developed following a comprehensive review of current antimicrobial resistance (AMR) and antimicrobial use (AU) programs in Australia, and supports the response to the global problem of AMR.

This Preliminary Report highlights the baseline activities being undertaken across Australia in regard to AMR and AU before the implementation of the Antimicrobial Use and Resistance in Australia (AURA) Project. This work included broad consultation, and a review of existing programs and systems, and will contribute to development of the requirements of the national surveillance system. The consultation was based on the analysis of datasets, peer-reviewed published literature, reports and other publicly available information, as well as additional reports published since 2000.

This document provides broad observations on trends and findings from available data and consultations. Information in this report is intended to inform the Australian Commission on Safety and Quality in Health Care (the Commission) and a range of stakeholders, support policy and program development, and provide a baseline for future evaluations and comparative assessments.

The document is also a resource for a range of healthcare and related services across Australia. It provides a basis for planning initiatives that will help to identify trends, evaluate interventions, compare and analyse data sources and systems, and support risk assessment. It presents key findings, provides a better understanding of the relationship between AMR and AU, identifies gaps in the availability of data, and describes the benefits and limitations of a range of datasets and systems.

In producing this report, the Commission developed a list of bacteria with high priority for surveillance, together with key antimicrobials. Information about these priority organisms and antimicrobials will continue to be gathered and reported through the AURA Project to improve Australia's capacity to detect and respond to emerging AMR of high importance for public health.

Reference is made to passive surveillance, which is the collation of data that has been generated for purposes other than surveillance, and targeted surveillance, which is gathering of data primarily for surveillance.

Scope

This report provides an overview of AMR and AU in the public and private health sectors for human health in Australia. It presents data from acute health care, community health care and residential aged care, where available. However, it is recognised that the currently available empirical data will give an incomplete and preliminary picture of AMR and AU in Australia.

The AURA Project will continue to build the comprehensiveness of surveillance programs to improve the understanding of AMR in Australia, as well as trends and action required.

What is antimicrobial resistance?

Antimicrobial resistance (AMR) can be defined in many ways. As described in this report, AMR occurs when an organism acquires a genetic trait that makes it resistant to the activity of a previously effective antimicrobial agent. This leads to a high likelihood of failure when that agent is used for treatment.

The genes that encode resistance traits can be acquired by organism-to-organism (horizontal) spread, or by mutation in the genes of an organism.

Most often, AMR is detected phenotypically using so-called susceptibility testing; some forms of AMR are best detected, or confirmed, genetically.

Background

In February 2013, the Australian Antimicrobial Resistance Prevention and Containment Steering Group was established to achieve an integrated 'One Health' approach to AMR in Australia. The steering group involves experts from human health, animal health and agriculture, working together to better understand and address the problem. It is jointly chaired by the Secretaries of the Australian Government Department of Health and the Australian Government Department of Agriculture and Water Resources; Australia's Chief Medical Officer and Chief Veterinary Officer are members. The steering group provides high-level national governance and leadership on AMR, and is charged with overseeing the development of a comprehensive national AMR prevention and containment strategy for Australia.

The states and territories have also undertaken a range of strategies to prevent and contain AMR.

The Department of Health has provided funding to the Commission to coordinate the human health surveillance activities for AMR and AU. The work of the Commission, in conjunction with that of the states and territories, and the private sector, will contribute to the objectives of the broader strategy of One Health. The outcome of the Commission's work through the AURA Project will be an integrated national AMR and AU surveillance system.

Priority organisms and associated antimicrobials

Monitoring and analysis of AMR are critical to detecting emerging threats, developing and measuring the impact of interventions, and understanding the epidemiology and spread of resistant clones of microorganisms.

A combination of passive and targeted surveillance is required for comprehensive and effective surveillance and response.

The Commission, with the support of its AURA Project Reference Group, developed a list of bacteria that are high priorities for surveillance, together with key antimicrobials (Table 1). Information about these priority organisms and antimicrobials will be gathered and reported by the Commission to improve Australia's capacity to detect and respond to emerging AMR of high importance for public health. The list formed the basis for the data to be explored and analysed in the Preliminary Report of the AURA Project.

The following rationale underpinned the four groups of organisms and antimicrobials:

- Set 1 – organisms with high public health importance and/or common pathogens, where the impact of resistance is substantial in both the hospital and community settings.
- Set 2 – organisms where the impact of resistance is substantial in hospital settings.
- Set 3 – organisms where resistance is a marker of epidemiological resistance and/or usage.
- Set 4 – organisms where resistance will be monitored through passive surveillance, and that will be prioritised for targeted surveillance if a signal emerges.

Table 1 AURA Project – priority organisms and antimicrobials for national reporting

Species	Core reportable antimicrobial agents
Set 1: Organisms with high public health importance and/or common pathogens, where the impact of resistance is substantial in both the hospital and community settings	
Enterobacteriaceae, mainly *Escherichia coli* and *Klebsiella* species	Ampicillin Cefazolin (spelt cephazolin in some programs) Ceftriaxone/cefotaxime Ciprofloxacin Gentamicin Meropenem Piperacillin–tazobactam
Enterococcus species	Ampicillin Vancomycin
Haemophilus influenzae type b (invasive)	Ampicillin Ceftriaxone/cefotaxime Ciprofloxacin Rifampicin
Mycobacterium tuberculosis	Ethambutol Isoniazid Pyrazinamide Rifampicin
Neisseria gonorrhoeae	Benzylpenicillin Ceftriaxone/cefotaxime Ciprofloxacin
Neisseria meningitidis	Benzylpenicillin Ceftriaxone/cefotaxime Ciprofloxacin Rifampicin
Salmonella species	Ampicillin Azithromycin Ceftriaxone/cefotaxime Ciprofloxacin
Shigella species	Ampicillin Azithromycin Ciprofloxacin Co-trimoxazole
Staphylococcus aureus	Cefoxitin (MRSA) Ciprofloxacin Clindamycin (including inducible resistance) Co-trimoxazole Erythromycin Gentamicin Oxacillin (MRSA) Tetracycline Vancomycin
Streptococcus pneumoniae (invasive)	Benzylpenicillin Ceftriaxone/cefotaxime Meropenem
Set 2: Organisms where the impact of resistance is substantial in hospital settings	
Acinetobacter baumannii complex	Meropenem
Enterobacteriaceae: *Enterobacter cloacae* and *E. aerogenes*	Ceftriaxone/cefotaxime Ciprofloxacin Gentamicin Meropenem
Pseudomonas aeruginosa	Ceftazidime Ciprofloxacin Gentamicin/tobramycin Piperacillin–tazobactam
Set 3: Organisms where resistance is a marker of epidemiological resistance and/or usage	
Campylobacter jejuni and *C. coli*	Moxifloxacin
Set 4: Organisms where resistance will be monitored through passive surveillance, and that will be prioritised for targeted surveillance if a signal emerges	
Clostridium difficile	Moxifloxacin
Streptococcus agalactiae	Benzylpenicillin Clindamycin Erythromycin
Streptococcus pyogenes	Benzylpenicillin Clindamycin Erythromycin

MRSA = methicillin-resistant *Staphylococcus aureus*

2 Antimicrobial resistance in Australia

Key findings

The data

A range of programs currently operating at a national level in Australia provide high-quality longitudinal data on trends in antimicrobial resistance (AMR) over time, as well as highlighting differences in AMR between jurisdictions. However, the data for AMR are not comprehensive because not all priority organisms are captured at a national level.

Much of the currently available data from a number of programs is heavily weighted towards public sector hospital isolates, with limited representation of isolates from the community or residential aged-care facility sectors. This is because, historically, resistance and multidrug resistance have been thought to be largely an issue for acute care. In recent decades, it has become clear that there are also significant resistance problems in the community. Exceptions to the incompleteness of data exist for a small number of pathogens that cause notifiable diseases, for which data are gathered from all sectors.

Comprehensive data are available from passive surveillance of isolates in Queensland hospitals from 2006 to 2014.

Trends in antimicrobial resistance

Targeted surveillance programs show the following trends:

- *Enterobacteriaceae*, including *Escherichia coli*, *Klebsiella* species and *Enterobacter* species
  - There has been an overall increase in the past decade in strains resistant to gentamicin, ciprofloxacin and β-lactam agents, especially third-generation cephalosporins.
  - Resistance to carbapenems is uncommon but increasing.
- *Enterococcus faecalis* and *E. faecium*
  - Ampicillin- and vancomycin-resistant strains increased substantially between 1995 and 2010, with vancomycin resistance in *E. faecium* now exceeding 30%.
- *Mycobacterium tuberculosis*
  - Multidrug resistance is uncommon but steadily increasing, accounting for 3.5% of isolates in 2010.
- *Neisseria gonorrhoeae*
  - Resistance to ciprofloxacin is high and stable at around 40%.
  - A small number of ceftriaxone nonsusceptible isolates have emerged in recent years.
- *Neisseria meningitidis*
  - Resistance to penicillin and other relevant agents remains rare.
- *Salmonella* species
  - Resistance to ciprofloxacin and cefotaxime appears to be stable at a low level – less than 5% and 1%, respectively.
- *Staphylococcus aureus*
  - There was a significant decline in hospital-onset methicillin-resistant *S. aureus* (MRSA) between 2000 and 2012, to just below 5% of clinical isolates.
  - Over the same period, there was a significant increase in community-associated MRSA, to levels exceeding 10% of clinical isolates.

Historical surveillance (targeted surveillance programs are not currently active or actively reporting for these organisms) shows the following:

- *Haemophilus influenzae* (all types, including non-encapsulated)
  - As at 2006, 22% of isolates were resistant to ampicillin.
- *Streptococcus pneumoniae*
  - As at 2007, penicillin resistance (minimum inhibitory concentration >2 mg/L) was 2%.

Introduction

This section presents data and trends for antimicrobial resistance (AMR) for many of the set 1 and set 2 priority organisms and antimicrobials (as shown in Table 1). The data were collated from passive and targeted surveillance and reporting of AMR in Australia. Data on set 3 and set 4 organisms were unavailable at the time of the Preliminary Report.

Current data on AMR rates in Australia are only readily available from a limited range of sources, including:

- Queensland Health's OrgTRx system[2] – mainly hospital-associated infections
- the Australian Group on Antimicrobial Resistance (AGAR[3]) – hospital-onset and community-onset isolates
- specialised pathogen programs, such as
  - the National Neisseria Network, for *Neisseria gonorrhoeae* and *N. meningitidis*
  - the National Enteric Pathogens Surveillance Network – two *Salmonella* reference laboratories
  - the Australian Mycobacterium Reference Laboratory Network, for *Mycobacterium tuberculosis* – 100% community-onset isolates.

The AGAR surveys and the specialised pathogen programs are voluntary, involving 24–32 public and private pathology laboratories across Australia. The Queensland Health system holds susceptibility data for all patient samples submitted to public laboratories across Queensland (>95% from public hospital inpatients and outpatients, and <5% from the private sector [community]).

Systems capable of generating antibiograms (summaries of the cumulative proportions of pathogens tested routinely that are susceptible to antimicrobials of interest) exist in some states and at least one private pathology laboratory, but are not readily accessible.

A combination of passive and targeted surveillance is important for comprehensive and effective surveillance and response. Passive surveillance is the collation of data that has been generated for purposes other than surveillance. Targeted surveillance is gathering of data primarily for surveillance.

Passive AMR surveillance is characterised by the routine collection of all, or most, available data on antimicrobial susceptibility of bacterial isolates from all clinical specimens routinely submitted for culture. It does not include specimens from environmental or infection control screening programs. Once the surveillance system has been established, little or no additional effort is required on the part of laboratory staff for the data to contribute to surveillance efforts.

Targeted AMR surveillance is typified by the collection of a set of isolates of a specific bacterial species or group of species, often from one specimen type or a limited range of specimen types, as specified in a surveillance protocol. Targeted surveillance requires additional effort and resources from each participating laboratory, usually including some or all of the following activities:

- identifying organisms and testing their susceptibility, according to defined protocols that may be different from, or in addition to, the work done for clinical reporting purposes
- isolating organisms in pure culture in a form suitable for transport
- packing and shipping isolates to a reference centre
- entering data into an online system or into files that can be sent to the reference centre
- obtaining clinical and/or patient outcome data that are not held in the laboratory
- responding to queries from the reference centre for clarification or providing missing data.

Enterobacteriaceae – mainly *Escherichia coli* and *Klebsiella* and *Enterobacter* species

Clinical importance: Species from three genera of *Enterobacteriaceae* – *Escherichia coli*, *Klebsiella* species and *Enterobacter* species – are common pathogens that are involved in a variety of infections, especially urinary tract infection and septicaemia. These bacteria are well known for harbouring and transferring resistance genes through mobile genetic elements, and multidrug resistance is a significant and growing problem. Resistance to the 'last line' carbapenem antimicrobials is of major worldwide concern, including in Australia.[4]

The data

In 2008, 2010 and 2012, AGAR conducted surveillance of community-onset infections by *E. coli*, *Klebsiella* species and *Enterobacter* species. Some of the infections identified might have originated in hospital, but they were classified as 'community onset' because they were identified when a patient with an infection returned to the emergency department or an outpatient clinic.

In 2013, AGAR's new surveillance method for community-onset infections improved and expanded the surveillance of these important organisms. These changes will provide higher-quality data in the future.

AMR trends for community-onset infections

Between 2008 and 2012, resistance in *E. coli* steadily increased for a number of important reserve agents, such as ceftriaxone, ciprofloxacin and gentamicin (Figure 1). Resistance in *Klebsiella* and *Enterobacter* species tended to be more stable during this period.

Resistance to ceftriaxone in *E. coli* and *Klebsiella* species is due to extended-spectrum blactamases (ESBLs). This resistance now appears to be well established in the Australian community. The AGAR surveillance showed that the resistance was predominantly of the *CTX-M* gene type, which is seen in communities worldwide. ESBLs are often linked to resistance to ciprofloxacin and/or gentamicin. In keeping with this, rates of multidrug resistance (acquired resistance to more than three drug classes) rose between 2008 and 2012, from 4.5% to 7.6% in *E. coli*, and from 4.4 to 5.1% in *Klebsiella* species.

Carbapenem resistance is currently at very low levels but is slowly increasing, largely because of the local dissemination of one particular resistance gene (*bla*[1]). In 2011–12, AGAR surveillance detected 9 strains of *E. coli*, *Klebsiella* and *Enterobacter* species out of a total of 5435 (0.17%) producing carbapenemases; all were of the *bla* type.[1]

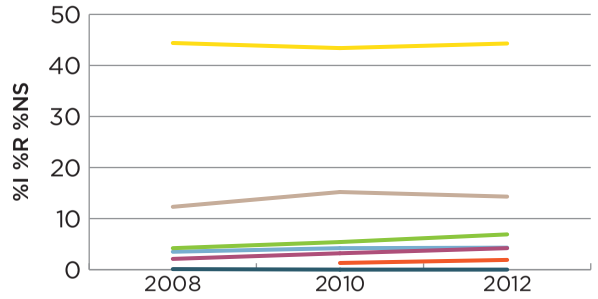
In 2013, AGAR switched surveillance methods to continuous collection of data from blood culture isolates, and included other species of *Enterobacteriaceae* besides *E. coli*, *Klebsiella* species and *Enterobacter* species (the Australian Enterobacteriaceae Sepsis Outcomes Programme). Episodes of sepsis that commenced less than 48 hours after admission were classified as community onset. This provided higher-quality data on more serious infections where resistance has its greatest impact, while at the same time aligning more closely with the type of surveillance conducted across Europe (European Antimicrobial Resistance Surveillance Network).

Of the 12 most common isolates in the 2013 survey (Table 2), three-quarters of all isolates were from community-onset sepsis. Of these 12 species, the overall rates of AMR for the three most common species (*E. coli*, *K. pneumoniae* and *E. cloacae*) (Table 3) is based on interpretative criteria from the Clinical and Laboratory Standards Institute M100 guideline.[8]

As expected, *E. coli* was the dominant pathogen, with the great majority of infections having their onset in the community. *Enterobacter* and *Serratia marcescens* infections were more likely than *E. coli* infections to arise in hospital. Resistances of concern were 10.3% and 7.5% nonsusceptibility to ciprofloxacin in *E. coli* and *K. pneumoniae*, respectively, and 7.5% and 6.3% nonsusceptibility to ceftriaxone (as a representative of third-generation cephalosporins) in the same two species. Fourteen of 4958 strains of *Enterobacteriaceae* harboured a carbapenemase (0.28%),[1] comprising nine IMP-4, three KPC-2 and two NDM-1.

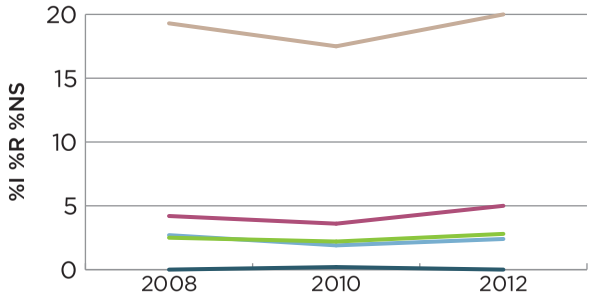
Figure 1 Resistance patterns in community-onset bacterial isolates for some key species/genera from the family *Enterobacteriaceae*, 2008, 2010 and 2012

Escherichia coli



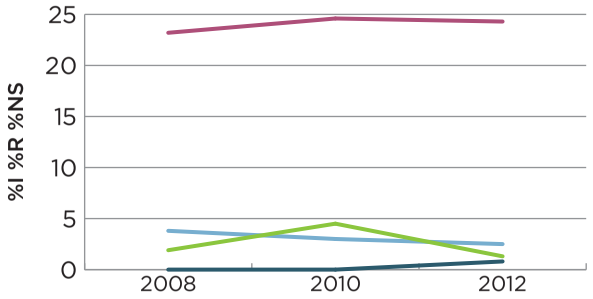
	2008	2010	2012
Ampicillin %I	–	1.3	1.9
Ampicillin %R	44.4	43.4	44.3
Cefazolin %R	12.3	15.2	14.3
Ceftriaxone %NS	2.1	3.2	4.2
Ciprofloxacin %NS	4.2	5.4	6.9
Gentamacin %R	3.5	4.2	4.3
Meropenem %NS	0.1	0.0	0.0

Klebsiella species



	2008	2010	2012
Cefazolin %R	19.3	17.5	20.0
Ceftriaxone %NS	4.2	3.6	5.0
Ciprofloxacin %NS	2.5	2.2	2.8
Gentamacin %R	2.7	1.9	2.4
Meropenem %NS	0.0	0.2	0.0

Enterobacter species



	2008	2010	2012
Ceftriaxone %NS	4.2	3.6	5.0
Ciprofloxacin %NS	2.5	2.2	2.8
Gentamacin %R	2.7	1.9	2.4
Meropenem %NS	0.0	0.2	0.0

Note: As described for each antimicrobial shown in the table below each graph, the y axis represents either %I (percentage of strains intermediate), %NS (percentage of strains nonsusceptible [intermediate + resistant]) or %R (percentage of strains resistant).

Sources: AGAR survey data from Turnidge et al.[5,6,7]

Table 2 **The 12 most common species of *Enterobacteriaceae* isolated from cases of sepsis, by category of onset**

Organism	Total	Community onset	Hospital onset	% hospital onset
Escherichia coli	2852	2398	454	15.9
Klebsiella pneumoniae	704	468	236	33.5
Enterobacter cloacae	302	157	145	48.0
Proteus mirabilis	178	135	43	24.2
Klebsiella oxytoca	158	99	59	37.3
Serratia marcescens	145	75	70	48.3
Enterobacter aerogenes	95	47	48	50.5
Salmonella species (non Typhi)	72	64	8	11.1
Morganella morganii	51	40	11	21.6
Citrobacter koseri	50	32	18	36.0
Citrobacter freundii	38	25	13	34.2
Salmonella Typhi/Paratyphi	23	23	0	0.0
Other species (*n* = 34)	116	74	42	36.2
All species	**4784**	**3637**	**1147**	**24.0**

Source: Turnidge et al.[9]

Table 3 **Percentage of the three most common isolates from both community- and hospital-onset infections that are nonsusceptible to antimicrobials**

Antimicrobial	Category	*E. coli*	*K. pneumoniae*	*E. cloacae*
Ampicillin	I+R	52.2	†	†
Amoxycillin with clavulanate	I+R	21.5	13.0	†
Piperacillin–tazobactam	R	3.1	4.2	17.3
Cefazolin	R	19.1	10.0	†
Ceftriaxone	I+R	7.5	6.3	26.8
Meropenem	I+R	0.1	0.7	4.2
Ciprofloxacin	I+R	10.3	7.5	3.6
Gentamicin	I+R	7.9	3.9	9.4
Trimethoprim	R	26.9	14.1	19.7

I = intermediate; R = resistant; † = considered intrinsically resistant
Source: Turnidge et al.[9]

Healthcare impact in the community

Resistance of *E. coli* to ampicillin and amoxycillin, which go hand in hand, emerged in the Australian community decades ago, and has remained stable at about 50% for at least 20 years. Resistance to trimethoprim and the combination of trimethoprim with sulfamethoxazole followed a similar path, and has remained at 25% for a similar period. Because *E. coli* is the commonest cause of urinary tract infection in the community, accounting for 90% of cases, the older agents have become significantly less effective, leading to treatment failures. These failures lead, in the most benign cases, to retreatment with a broader-spectrum antimicrobial agent (e.g. amoxycillin–clavulanate). In the worst cases, they lead to kidney and bloodstream infection, requiring hospitalisation, where there is dependence on reserve agents such as gentamicin, ceftriaxone and ciprofloxacin. It is a worrying trend to see resistance to these reserve agents arise in the community and create problems for the patients who need to go to hospital. Australia's experience with resistance to reserve antimicrobials in *E. coli* is part of a worldwide trend.

Klebsiella and *Enterobacter* infections occur in the community but are more common in hospitals. In the community, they mostly cause urinary tract infection. Both harbour intrinsic resistant to ampicillin and amoxycillin; *Enterobacter* species are also naturally resistant to first-generation cephalosporins and amoxycillin–clavulanate. Both have a propensity to harbour resistance to many other antimicrobials, especially the reserve agents. Treatment in the community of either of these pathogens often requires the prescription of an 'authority required' agent on the Pharmaceutical Benefits Scheme. Emerging resistance in these two organism groups to the fluoroquinolones, such as ciprofloxacin (an authority required agent), which can be given orally in the community, is of great concern, as there will often be no oral alternatives, and hospitalisation or hospital-in-the home treatment is required.

AMR trends for hospital-onset infections

AMR trends were generally worsening for hospitalised patients with infections of *E. coli*, *Klebsiella* species and *Enterobacter* species. Data from AGAR's biennial survey (2009 and 2011) of infections in patients hospitalised for more than 48 hours show that trends were adverse for resistance to reserve agents in *E. coli*, *Klebsiella* species and *Enterobacter* species (Figure 2).

Resistance rates in hospitals have traditionally been expected to be higher than those seen in the community. This is attributed to a combination of higher rates of antimicrobial exposure and in-hospital spread of more resistant clones. As an example, the rate of resistance (nonsusceptibility) to ceftriaxone in *E. coli* in hospital isolates in 2012 was approximately double that in community isolates in 2013.

Although small in number, cases of resistance to carbapenems attributable to carbapenemases also appear to be rising. This is partly due to an apparent low level of endemic resistance in three Australian states from a metallo-β-lactamase called IMP-4 in a range of bacterial species.[1]

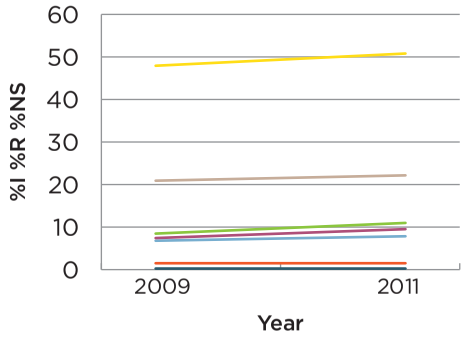
Longer-term trends for infections caused by *E. coli*, *Klebsiella* species and *Enterobacter* species in (largely) hospitalised patients can be observed in Queensland Health's OrgTRx surveillance system.[2] OrgTRx provides resistance trends by specimen type from 2006 to 2014 for large numbers of isolates from Queensland public pathology laboratories.

OrgTRx shows increasing resistance in *E. coli* and *K. pneumoniae* to all of the important antimicrobials except meropenem (Figure 3). Rates of resistance to ceftriaxone (mostly attributable to ESBL production) are lower than those observed in hospitalised patients nationally, in part because of the diluting effect of isolates from community patients presenting to emergency departments. Accounting for that, ceftriaxone resistance rates are not substantially different from those observed nationally. A worrying trend towards increasing resistance to meropenem in *Enterobacter* species is also evident.

Of course, these data represent only the public hospital sector of Queensland. It is unclear how representative this is of the private sector in Queensland, or of hospitals of any type outside Queensland.

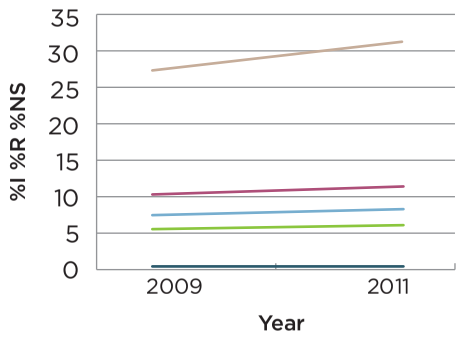
Figure 2 **Resistance patterns in hospital-onset bacterial isolates for some key species/genera from the family *Enterobacteriaceae*, 2009 and 2011**

Escherichia coli



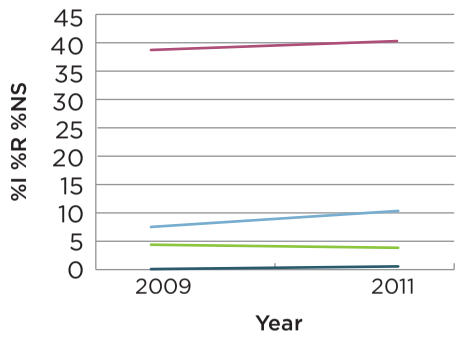
	2009	2011
Ampicillin %I	0.9	0.9
Ampicillin %R	47.8	50.5
Cefazolin %R	20.7	22.3
Ceftriaxone %NS	7.2	9.6
Ciprofloxacin %NS	8.1	10.6
Gentamacin %R	6.8	8.2
Meropenem %NS	0.0	0.1

Klebsiella species



	2009	2011
Cefazolin %R	27.2	31.0
Ceftriaxone %NS	10.2	11.4
Ciprofloxacin %NS	5.5	6.1
Gentamacin %R	7.3	8.4
Meropenem %NS	0.4	0.4

Enterobacter species



	2009	2011
Ceftriaxone %NS	38.4	40.1
Ciprofloxacin %NS	4.3	3.7
Gentamacin %R	7.5	10.4
Meropenem %NS	0.0	0.4

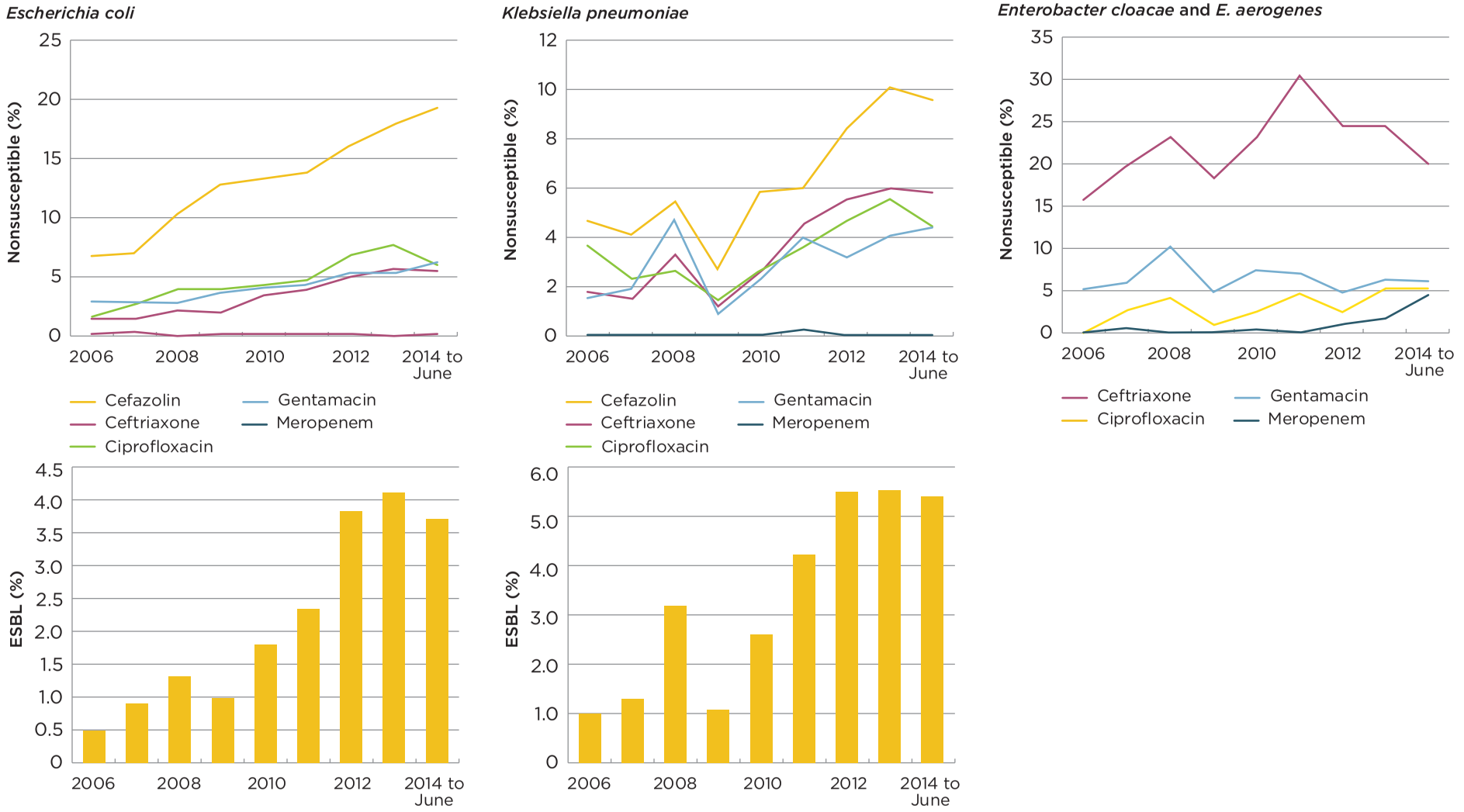
Note: As described for each antimicrobial shown in the table below each graph, the y axis represents either %I (percentage of strains intermediate), %NS (percentage of strains nonsusceptible) or %R (percentage of strains resistant).

Sources: Data from Turnidge et al,[10,11] Australian Group on Antimicrobial Resistance[1]

Healthcare impact in hospitals

E. coli, *Klebsiella* and *Enterobacter* are the three commonest causes of gram-negative infections in hospitals, causing catheter-associated urinary tract infection, post-operative wound and intra-abdominal infections, and bloodstream infection. The last of these is associated with significant rates of mortality. Until recently, multidrug-resistant strains of these organisms were more common in hospital, as a consequence of higher antimicrobial selection pressure. The Australian experience shows increasing resistance rates to antimicrobial classes such as the third-generation cephalosporins, aminoglycosides and fluoroquinolones, which have had an important role in treating the more serious infections in hospitalised patients. Resistance to these three classes is often linked in the same strain, leading to multidrug-resistant strains. These resistances have led to an increasing requirement for 'last line' antimicrobials, such as meropenem and other carbapenem agents. Australia is now witnessing the emergence of resistance to this antibiotic class as well, and strenuous efforts in infection control and antimicrobial stewardship will be required to contain it.

Figure 3 Resistance patterns in the Queensland public hospital sector for bacterial isolates from blood culture for species from the family *Enterobacteriaceae*, 2006 to June 2014



Note: Isolates were the first isolate per specimen per person per year. The upper panels show the percentage of nonsusceptible isolates for each antimicrobial. The lower panels show resistance to ceftriaxone, which is mostly attributable to production of extended-spectrum ß-lactamase (ESBL). ESBL was not determined for *Enterobacter* species.

Source: OrgTRx, Queensland Health[2]

Enterococcus species

Clinical importance: *Enterococcus* species have one of the highest propensities for cross-infection of all the hospital-acquired pathogens.[12] These are now endemic in some hospitals and cause occasional outbreaks in others.

Enterococcus species (from the family *Enterococcaceae*) are naturally resistant to many antimicrobial classes, including cephalosporins, and some species have acquired resistance to penicillins. Vancomycin-resistant strains (VRE) emerged in the mid-1990s in Australia.

The data

For community-onset infections, national data on resistance rates of *Enterococcus* species are not available.

For hospital-onset infections, AGAR conducted surveys from 1995 to 2010.[13,14] In 2011, AGAR changed to continuous surveillance of blood culture isolates of *Enterococcus* species, through the Australian Enterococcal Sepsis Outcomes Programme (AESOP).[15]

AMR trends for hospital-onset infections

Ampicillin resistance is now the norm in *E. faecium*, but is rare in *E. faecalis* (Figure 4). From 1995 to 2010, resistance to ampicillin and vancomycin increased significantly in *E. faecium.*[13,14] Vancomycin resistance in *Enterococcus* species has been seen in all states and territories. The dominant type of resistance is encoded by the *vanB* complex, in contrast with the situation in Europe and the United States, where the *vanA* complex dominates.[16]

In 2011, data from AGAR's AESOP showed that the great majority of isolates were from patients with hospital-onset infections. Vancomycin nonsusceptibility was not detected in any *E. faecalis* isolates, but was detected in 39% of *E. faecium*. AESOP surveillance was repeated in 2013, and the vancomycin nonsusceptibility rate for *E. faecium* was 40.9%, suggesting a levelling-off of VRE, at least at the national level.

Healthcare impact

Infections caused by enterococci include urinary tract infection, wound infections in conjunction with other organisms, and bloodstream infection, and are most often healthcare associated. The first two of these are relatively benign, but the last is often seen in the most vulnerable patients with multiple comorbidities; as a consequence, mortality can be substantial. Enterococci are naturally resistant to a broad range of antibiotic classes, including cephalosporins, macrolides, lincosamides and aminoglycosides. Treatment has relied heavily on ampicillin, amoxycillin and piperacillin–tazobactam. Vancomycin is the drug of choice for patients who are allergic to penicillins. The advent of vancomycin-resistant enterococci – notably vancomycin-resistant *E. faecium* harbouring the *vanB* gene complex (VREF) – in the mid-1990s, and their rapid rise in the mid-2000s, have created a major management problem for the treatment of healthcare-associated infections. VREF are almost always resistant to ampicillin also. Hence, great reliance is now placed on expensive reserve antimicrobials such as teicoplanin, linezolid and daptomycin for managing VREF infections. Cost-effective strategies for reducing VREF rates have yet to be identified.

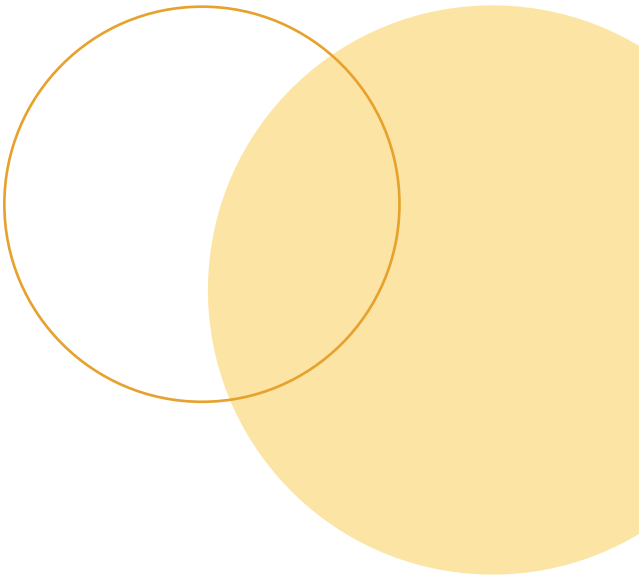
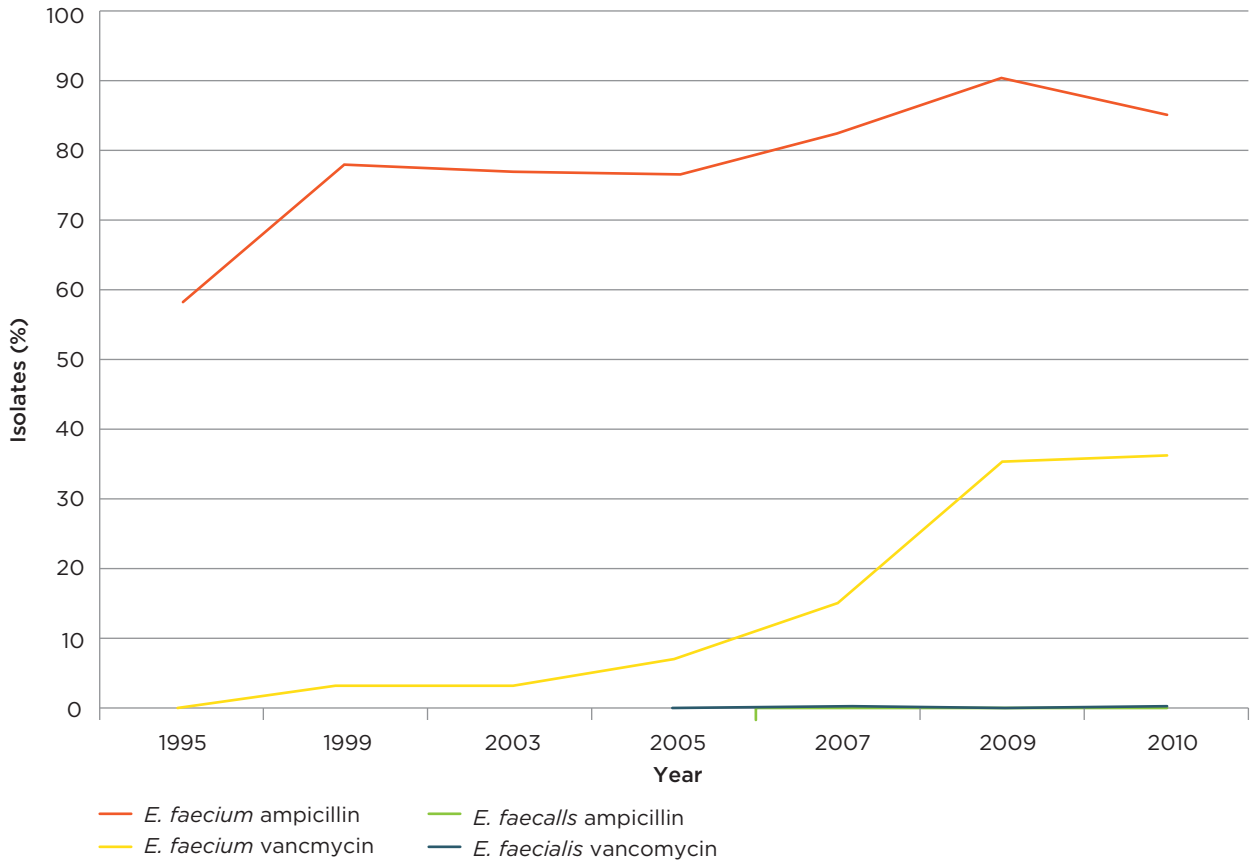


Figure 4 **Percentage of *Enterococcus faecium* and *E. faecalis* isolates that were nonsusceptible (resistant +/- intermediate) to ampicillin and vancomycin, 1995–2010**



Source: AGAR survey reports for *Enterococcus*, www.agargroup.org/surveys

Haemophilus influenzae type b

Clinical importance: *Haemophilus influenzae* type b is an important cause of life-threatening infections such as meningitis and epiglottitis. These conditions are now uncommon following the introduction of a vaccine against *H. influenzae* type b in the National Immunisation Program Schedule.

The data

Similar to *Streptococcus pneumoniae*, *H. influenzae* infections are almost always community onset. From the resistance surveillance perspective, it is the encapsulated type b invasive strains (*H. influenza* type b) that are of interest.

There is currently no resistance surveillance program that captures information about resistance rates in *H. influenzae* type b.

AMR trends for community-onset infections

The most recent data available on resistance in this species were generated by AGAR in 2006. AGAR collected data on all types of *H. influenzae* and did not report specifically on type b strains. Over all strains, β-lactamase production (leading to ampicillin resistance) was present in 21.9% of isolates. Nationally, 8.5% of strains were β-lactamase negative and ampicillin resistant; this type of resistance is due to altered penicillin-binding proteins and can also affect agents such as amoxycillin with clavulanate. Amoxycillin with clavulanate, chloramphenicol and cefaclor resistance remained low (1.9%, 2.5% and 7.5%, respectively), and had not increased significantly since the first AGAR survey in 1998–90. Resistance to tetracycline and trimethoprim–sulfamethoxazole was 11.8% and 20.1%, respectively – a significant increase from the 4.1% and 4.6% reported in the first AGAR survey in 1998–90.[17]

Healthcare impact

Invasive *H. influenzae* type b (Hib) infections, manifest as meningitis, epiglottitis and preseptal cellulitis, are largely confined to young children. There has been a great reduction in the incidence of invasive Hib infections in Australia since the introduction of the conjugate vaccine, with only about 15 cases per year seen across Australia (invasive Hib disease is notifiable in all states and territories). At the time of vaccine introduction, approximately 25% of Hib infections were resistant to ampicillin/amoxycillin. Third-generation cephalosporins became, and remain, the treatment of choice for invasive Hib disease. Resistance to this class has not yet emerged anywhere in the world, and thus the few cases that are seen in Australia each year are manageable. Resistance to agents – rifampicin and ciprofloxacin – used for prophylaxis in certain contacts of invasive Hib disease are also rare globally at present.

Mycobacterium tuberculosis

Clinical importance: *Mycobacterium tuberculosis* is the causative organism of most cases of tuberculosis (TB). Different strains of *M. tuberculosis* are associated with different geographical locations and have different susceptibilities to antimicrobial agents.

The data

TB is essentially a community-associated infection. Resistance data on *M. tuberculosis* are generated in state mycobacterial reference laboratories, and collated annually by the Australian Mycobacterium Reference Laboratory Network.

AMR trends for community-onset infections

The concern with *M. tuberculosis* is the emergence around the world of multidrug-resistant strains (MDR-TB). Even though Australia has low rates of TB compared with most other countries, the disease can spread to others and remain dormant for most of a patient's lifetime before reactivating. The consequences of failed treatment due to resistance are significant for the individual patient and the community as a result of ongoing contagion.

A small but significant trend towards an increase in MDR-TB was observed between 1995 and 2010 (Table 4).

Healthcare impact

Tuberculosis (TB) rates in Australia are low compared with most other countries, but have stabilised, despite longstanding control measures. This is probably a result of the reactivated disease occurring in new migrant populations from countries with high endemicity. Concordant with this is the potential for the introduction and establishment of multidrug-resistant strains (MDR-TB). At present, the rates of MDR-TB in Australia are very low, but there is some evidence of a slow increase. TB caused by MDR strains requires more extensive, more expensive and more prolonged therapy, so the management issues are significant. MDR-TB is also much slower to clear than susceptible TB, which increases the risk of transmission to contacts. A critical clinical implication of TB is its capacity to remain latent for many decades after acquisition, only to reactivate late in a person's life. Thus, not only does MDR-TB have a greater capacity to spread, but its spread will have implications for up to 100 years.

Table 4 Drug resistance patterns in multidrug-resistant strains (two or more drugs) of *Mycobacterium tuberculosis*, 1995–2010

	Number of isolates															
Agents	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Isoniazid + rifampicin	3	10	6	2	2	3	8	8	4	7	5	16	16	10	21	18
Isoniazid + rifampicin + ethambutol	1	1	1	1	1	1	1	1	2	2	3	1	2	3	1	1
Isoniazid + rifampicin + pyrazinamide	1	4	5	2	1	3	3	1	1	1	1	0	5	3	7	15
Isoniazid + rifampicin + ethambutol + pyrazinamide	0	0	2	1	0	1	0	1	0	1	3	5	1	5	2	3
XDR-TB	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
Total MDR strains (number)	5	15	14	6	4	8	12	12	7	12	12	22	24	21	30	37
Percentage of all laboratory isolates	0.7	2.0	1.9	0.9	0.5	1.0	1.6	1.7	0.9	1.5	1.5	2.4	2.8	2.4	2.9	3.5

MDR = multidrug resistant; TB = tuberculosis; XDR = extensively drug resistant
Source: Lumb et al.[18]

Neisseria gonorrhoeae

Clinical importance: *Neisseria gonorrhoeae* is one of the principal causes of sexually transmitted infection, most commonly manifesting clinically as urethritis in men and cervicitis in women.

Rates of gonococcal infections are increasing in Australia, and gonorrhoea remains a significant public health concern. In 2012, the World Health Organization called for enhanced surveillance as a basic component of its global action plan to control the spread and impact of AMR in *N. gonorrhoeae.*[19] Australia has been active in this area and now has the longest-running national surveillance program for gonococcal AMR in the world.

The data

Australia has a well-established network of reference laboratories through the National Neisseria Network (NNN). These laboratories collect and test all cultured strains of *N. gonorrhoeae* and *N. meningitidis* isolates in Australia. Information collected from the NNN shows that all infections due to these pathogens arise in the community.

AMR trends for community-onset infections

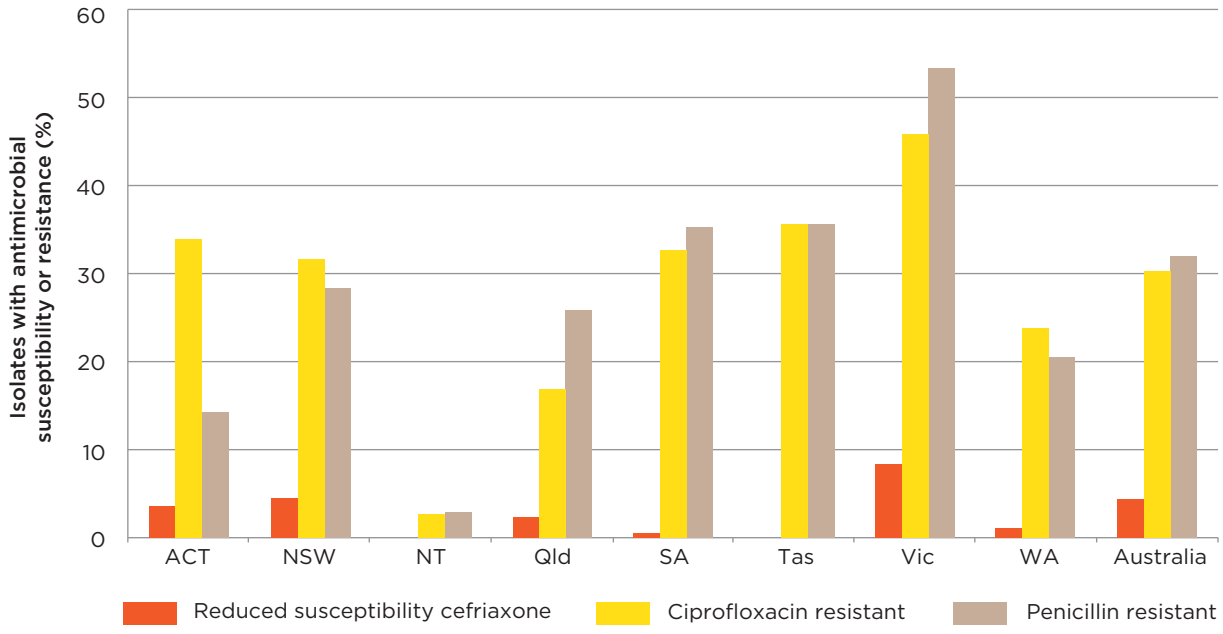
NNN data for Australia for 2006–12 (Table 5) show that penicillin resistance was sustained throughout this period, as was ciprofloxacin resistance. Low rates of resistance to ceftriaxone (the current antimicrobial of choice for treatment) are now being observed, as they are in other parts of the world.[20] Resistance to spectinomycin was not observed, although this agent is very rarely used for treatment.

A breakdown by jurisdiction reveals important differences, with rates of resistance in the Northern Territory being very low in 2012 (Figure 5).

Healthcare impact

Evolving resistance to antimicrobial agents in *Neisseria gonorrhoeae* has been an ongoing problem for decades, requiring regular review and updating of treatment guidelines. The use of penicillins and fluoroquinolones has come and gone, and great reliance is placed at present on ceftriaxone. Australia, like the rest of the world, is seeing the first cases of reduced susceptibility to ceftriaxone, which forebodes yet another change in first-line treatment. Although this has not happened yet in Australia, options for the treatment of strains with reduced ceftriaxone susceptibility are currently limited to older and unproven agents. The situation has been complicated by the switch to molecular methods for gonococcal detection, leading to greatly reduced culture rates, and thus to fewer data on susceptibility and emerging resistance. Efforts are under way to address this problem.

Figure 5 Antimicrobial resistance profiles for *Neisseria gonorrhoeae* by jurisdiction, 2012



Source: Lahra and Australian Gonococcal Surveillance Programme[22]

Table 5 Antimicrobial resistance trends for *Neisseria gonorrhoeae*, 2006–12

		2006	2007	2008	2009	2010	2011	2012
Number of isolates viable for antimicrobial susceptibility testing		3850	3042	3110	3157	3997	4133	4718
Penicillin								
MIC ≥1 mg/L (resistant)	Number of isolates	1306	1163	1367	1145	1161	1053	1513
	% isolates	34	38	44	36	29	25	32
Ceftriaxone								
MIC 0.06–0.25 mg/L (reduced susceptibility)	Number of isolates	23	23	34	64	191	134	207
	% isolates	1	1	1	2	5	3	4
Spectinomycin								
MIC ≥64 mg/L (resistant)	Number of isolates	0	0	0	0	0	0	0
	% isolates	0	0	0	0	0	0	0
Ciprofloxacin								
MIC ≥0.06 mg/L (reduced susceptibility)	Number of isolates	1455	1493	1685	1370	1385	1132	1428
	% isolates	38	49	54	43	35	27	30
MIC ≥1 mg/L (resistant)	Number of isolates	1413	1456	1651	1346	1342	1099	1407
	% isolates	37	48	53	43	34	27	30
Azithromycin[a]								
MIC ≥2 mg/L (any resistance)	Number of isolates	–	–	–	–	–	–	61
	% isolates	–	–	–	–	–	–	1
High-level tetracycline resistance[b]								
High-level resistance	Number of isolates	462	505	553	650	822	733	641
	% isolates	12	17	18	21	21	18	14

– = no data; MIC = minimum inhibitory concentration

a Before 2012, only some states and territories submitted data. The number of isolates for 2012 is an estimate based on the percentage reported.

b The number of isolates for 2006 is an estimate based on the percentage reported.

Source: Communicable disease surveillance systems annual reports[21]

Neisseria meningitidis

Clinical importance: *Neisseria meningitidis* is a commensal bacterium that can become invasive in a small number of individuals after acquisition. It causes septicaemia and meningitis, and has about a 10% overall mortality. Two serogroups have predominated in Australia: types B and C. A conjugate vaccine for type C was rolled out nationally in 2003.

The incidence of invasive meningococcal disease has significantly and sustainably decreased since 2004, following the introduction of a publicly funded serogroup C meningococcal conjugate vaccine. Despite this, invasive meningococcal disease remains a significant public health concern in Australia. Detailed analysis of locally circulating *N. meningitidis* strains continues to be a priority, particularly as serogroups other than serogroup C also cause invasive disease.

The data

Australia has a well-established network of reference laboratories through the NNN. These laboratories collect and test all cultured strains of *N. gonorrhoeae* and *N. meningitidis* isolates in Australia. Information collected from the NNN shows that all infections due to these pathogens arise in the community. This is high-quality national data.

AMR trends for community-onset infections

Of most interest are changes in susceptibility to (benzyl) penicillin and the alternative agent for treatment (ceftriaxone), as well as the two agents used in prophylaxis of close contacts of cases (ciprofloxacin and rifampicin). Strains truly resistant to penicillin appeared for the first time in 2011, albeit at a very low level, whereas resistance to the other agents is uncommon or absent (Table 6).

Healthcare impact

Neisseria meningitidis causes septicaemia and/or meningitis – so-called invasive meningococcal disease (IMD) – in otherwise healthy people. IMD rates have gradually decreased in Australia through progressive introduction of vaccines. Nevertheless, there are still a moderate number of cases and evidence of slowly decreasing rates of susceptibility to penicillins. Fortunately, there is no evidence of emerging resistance to third-generation cephalosporins, which are the mainstay of empirical therapy for invasive disease. As for *H. influenzae* type b, prophylaxis in certain contacts of IMD cases is used, relying on rifampicin and ciprofloxacin. Rates of resistance to these two agents remain very low and stable in Australia.

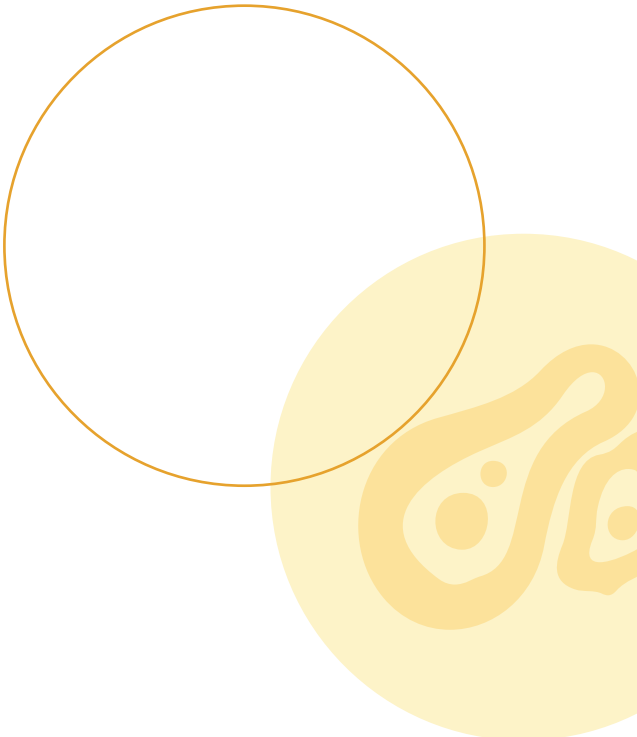


Table 6 Antimicrobial resistance trends for *Neisseria meningitidis*, 2006–12

		2006	2007	2008	2009	2010	2011	2012
Number of isolates confirmed by culture[a]		166	154	149	135	124	125	116
Penicillin								
MIC ≤0.03 mg/L (susceptible)	Number of isolates	55	33	41	44	25	16	19
	% isolates	33	21	28	33	20	13	16
MIC 0.06–0.5 mg/L (less susceptible)	Number of isolates	113	121	108	91	99	108	95
	% isolates	68	79	72	67	80	86	82
MIC ≥1 mg/L (resistant)	Number of isolates	0	0	0	0	0	1	1
	% isolates	0	0	0	0	0	1	1
Ceftriaxone								
MIC ≤0.06 mg/L (susceptible)	Number of isolates	166	154	149	135	124	125	116
	% isolates	100	100	100	100	100	100	100
Ciprofloxacin								
MIC ≤0.03 mg/L (susceptible)	Number of isolates	166	153	147	131	123	125	116
	% isolates	100	99	99	97	99	100	100
MIC 0.06–0.5 mg/L (less susceptible)	Number of isolates	0	1	2	4	1	0	0
	% isolates	0	1	1	3	1	0	0
Rifampicin								
MIC ≤0.25 mg/L (susceptible)	Number of isolates	165	153	148	135	124	124	114
	% isolates	99	99	99	10	100	99	98
MIC 0.5 mg/L (less susceptible)	Number of isolates	0	0	1	0	0	1	2
	% isolates	0	0	1	0	0	1	2
MIC 1.0 mg/L (slightly elevated)	Number of isolates	1	1	0	0	0	0	0
	% isolates	1	1	0	0	0	0	0

MIC = minimum inhibitory concentration
a Not all confirmed cases of invasive meningococcal disease are detected by culture.
Source: Communicable disease surveillance systems annual reports[21]

Salmonella species

Clinical importance: The principal form of infection from *Salmonella* species is gastroenteritis, which accounts for most of the isolates in Australia. With a rising trend in salmonellosis notifications in all states and territories, understanding AMR patterns is important. Transmission of these infections is usually via food, and the infections are not usually treated with antimicrobials.

The data

Two laboratories in Australia conduct susceptibility testing of enteric isolates and contribute to the National Enteric Pathogen Surveillance Scheme (NEPSS). Although these laboratories are not harmonised in their susceptibility testing, the outputs are of good quality and comparable, and provide insights into evolving resistances in this genus.

The vast majority of *Salmonella* infections arise in the community.

AMR trends for community-onset infections

The NEPSS annual report for 2010 also includes national data from 2004 to 2010. Data for three important antimicrobials are shown in Figure 6. A low percentage of strains have reduced susceptibility to ciprofloxacin and cefotaxime. It has been assumed that these strains were acquired overseas, given that quinolone antimicrobials are not permitted for use in Australian food animals, and third-generation cephalosporins have only low use in Australian food animals.[23] Surveillance of Australian animal isolates in the future should be able to test this assumption.

Figure 6 Percentage of *Salmonella* isolates tested by the National Enteric Pathogen Surveillance Scheme with reduced susceptibility, 2004–10

MIC = minimum inhibitory concentration; R = resistant
Source: National Enteric Pathogen Surveillance Scheme annual report data

Data from the Australian Salmonella Reference Centre in Adelaide are available for 2004–12 for the same three antimicrobials (Figure 7), and these show similar results to the NEPSS report (Figure 6).

Healthcare impact

Most cases of *Salmonella* infection, manifesting as gastroenteritis, are self-limiting and require no treatment. Occasionally, these organisms invade the bloodstream, and certain serotypes (*Salmonella* Typhi and *Salmonella* Paratyphi, which cause typhoid fever) always do so. Self-limiting gastroenteritis does not require antimicrobial treatment, so the impact of resistance is low. Resistance is only a problem for invasive disease. Australian strains of *Salmonella* have modest levels of resistance to ampicillin, fluoroquinolones and third-generation cephalosporins. Resistant strains of *Salmonella* Typhi and *Salmonella* Paratyphi are occasionally seen; almost all these infections are acquired overseas.

Figure 7 Percentage of *Salmonella* isolates tested by the Australian Salmonella Reference Centre with reduced susceptibility, 2004–12

Note: Concentrations in brackets represent breakpoints; the lines show the percentages of isolates above these breakpoints.
Source: Australian Salmonella Reference Centre data

Staphylococcus aureus

Clinical importance: *Staphylococcus aureus* is a very common pathogen, which causes a range of infections ranging from minor skin problems to life-threatening sepsis.

The principal resistance of concern in *S. aureus* is resistance to methicillin (methicillin-resistant *S. aureus* – MRSA). This type of resistance precludes the use of almost all ß-lactam antimicrobials for treatment. Multidrug-resistant healthcare-associated MRSA clones (HA-MRSA) emerged in public hospitals on the eastern seaboard of Australia in the late 1970s.[24] Since the early 1980s, there has been a slow but steady increase in the emergence and spread of non-multidrug-resistant clones of MRSA in the community (community-associated MRSA – CA-MRSA), starting in northern Western Australia.[24]

The data

AGAR has been tracking MRSA and other resistances in *S. aureus* in Australia since 1985, and undertaking multilocus sequence typing since 2000. As a result, it has been possible to follow trends of MRSA clones. To capture the differing trends between hospitals and the community, from 2000 to 2012, AGAR collected annual snapshot surveys of isolates from more than 30 laboratories across Australia, alternating each year between those with their onset in the community (presenting to outpatients and emergency departments) and isolates from patients hospitalised for more than 48 hours. Recently hospitalised patients returning to outpatients and emergency departments account for isolation of HA-MRSA in community-onset surveys ('recycled' HA-MRSA). Equally, patients colonised with CA-MRSA strains can develop an infection caused by CA-MRSA more than 48 hours after coming to hospital, and hence CA-MRSA will be found in hospital-onset surveys.

AMR trends for community-onset infections

AGAR surveys of community-onset infections show that rates of 'recycled' HA-MRSA clones and CA-MRSA were similar in 2000, but CA-MRSA dominated by 2012 (Figure 8). The 2012 survey found that rates of MRSA as a proportion of all *S. aureus* isolates vary widely between jurisdictions, ranging from 4% in the Australian Capital Territory to 26% in New South Wales.

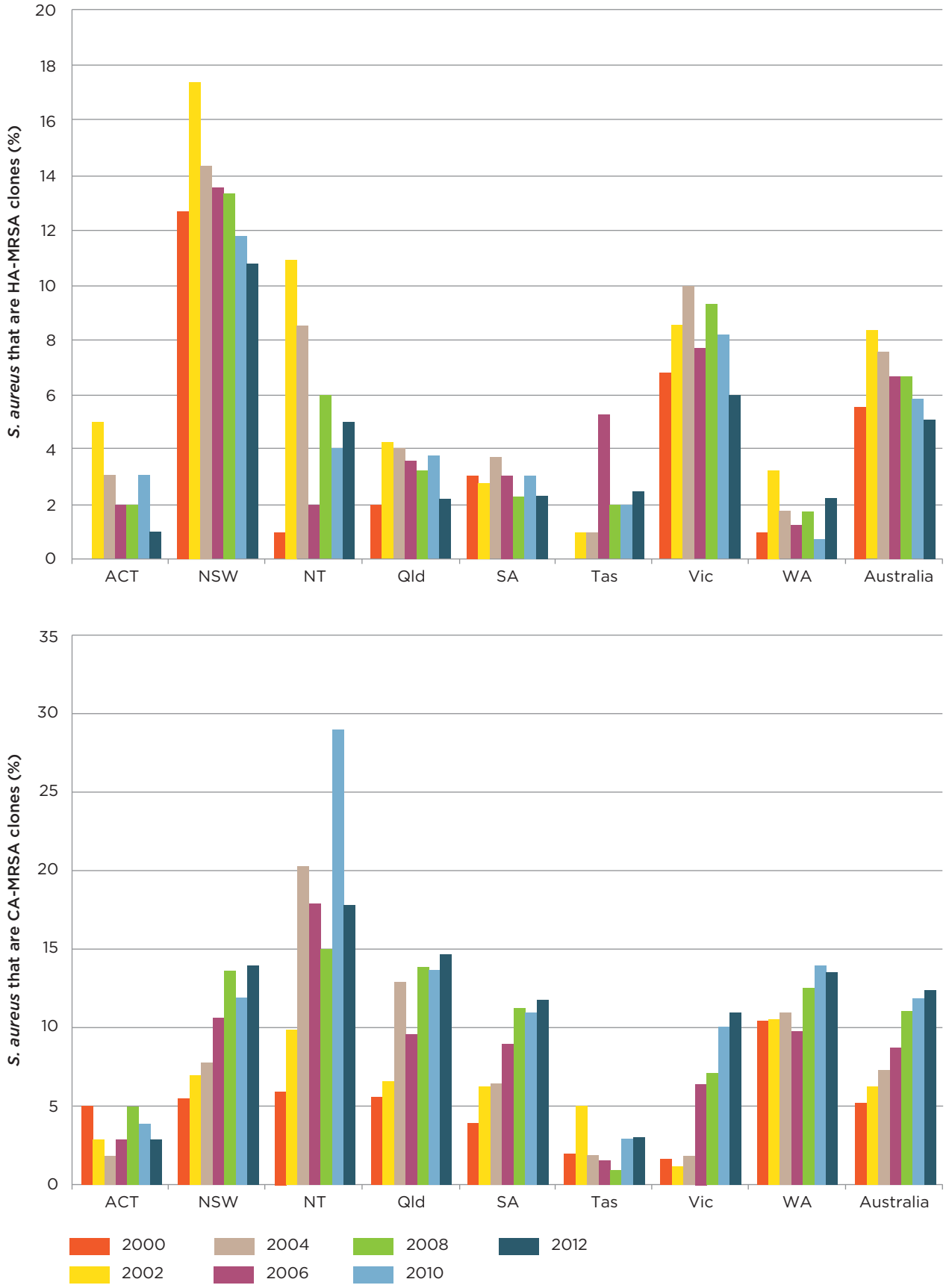
The typing data from the 2012 community-onset survey show the distribution of the HA-MRSA and CA-MRSA clones across Australia (Figure 9). In 2012, the introduced ST22 clone of HA-MRSA (also called EMRSA-15 from the United Kingdom) appears to have developed a reservoir in the community (particularly in residential aged-care facilities).[25]

There are clear regional differences in CA-MRSA clones. The most prominent CA-MRSA clone is ST93, which appeared in Australia (southern Queensland) for the first time in 1999–2000. This clone carries Panton–Valentine leukocidin, which is strongly associated with recurrent boils, deep abscess formation and necrotising pneumonia.

Healthcare impact in the community

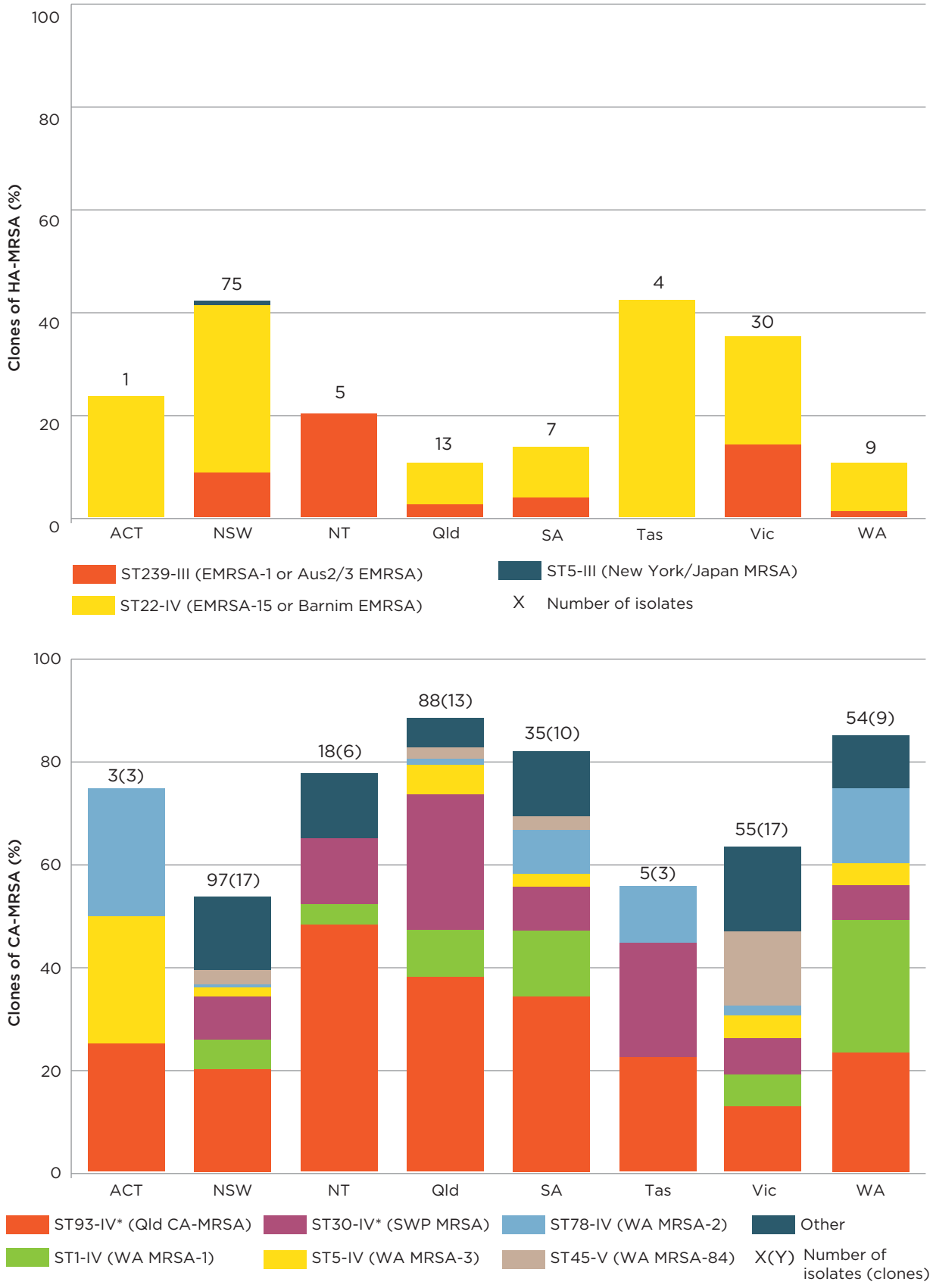
Staphylococcus aureus is a common cause of infection in the community, causing boils, carbuncles, cellulitis, wound infections and bullous impetigo. Many of these infections will respond to local treatment and/or drainage. Some require antimicrobial treatment. The drugs of choice for decades have been the so-called anti-staphylococcal penicillins, with the first-generation cephalosporins required in penicillin-allergic patients. Strains resistant to these agents, called methicillin-resistant *S. aureus* (MRSA), first emerged in Australia in the early 1990s. Since 2000, there has been a significant upsurge in community-associated MRSA. Three major clones are circulating, two of which harbour the toxin Panton–Valentine leukocidin, which is associated with higher rates of deep abscess formation (requiring surgical drainage) and recurrent boils, often requiring decolonisation to control. Community-associated MRSA must be treated with alternative agents, such as clindamycin or co-trimoxazole, both of which have notable uncommon adverse reactions. Community-associated MRSA is also found with increasing frequency in patients admitted to hospital with more serious or invasive staphylococcal infections.

Figure 8 Decline in HA-MRSA clones (top panel) and rise in CA-MRSA clones (bottom panel) in community-onset surveys, 2000 to 2012



ACT = Australian Capital Territory; CA-MRSA = community-associated methicillin-resistant *Staphylococcus aureus*; HA-MRSA = healthcare-associated methicillin-resistant *Staphylococcus aureus*; NSW = New South Wales; NT = Northern Territory; Qld = Queensland; SA = South Australia; Tas = Tasmania; Vic = Victoria; WA = Western Australia
Source: Coombs et al.[26]

Figure 9 Percentages and clones of HA-MRSA (top panel) and CA-MRSA (bottom panel) identified in the 2012 community-onset survey



CA-MRSA = community-associated methicillin-resistant *Staphylococcus aureus*; HA-MRSA = healthcare-associated methicillin-resistant *Staphylococcus aureus*

Note: Nationally, 28.9% of MRSA clones were indentified as HA-MRSA and 71.1% as CA-MRSA.

Source: Coombs et al.[26]

AMR trends for hospital-onset infections

AGAR surveys of hospital-onset infections also show a decline in the rates of HA-MRSA across Australia in the 2005–11 period, and a commensurate rise in CA-MRSA causing healthcare-associated infections (Figure 10). The rise in CA-MRSA is largely attributed to infections arising from the patient's endogenous flora. Documented outbreaks of CA-MRSA in hospitals are very uncommon. The 2013 survey found that 19.1% of *S. aureus* episodes were MRSA, which is significantly higher than reported in most European countries.[27]

A variety of explanations have been put forward for the decline in HA-MRSA. A number of infection control programs have been promulgated across Australia, including hand hygiene and central-line management, which may have contributed to the fall, although the decline appears to have commenced before these programs were rolled out nationally. Reporting of healthcare-associated *S. aureus* bacteraemia on the MyHospitals website has also focused the attention of hospitals on improvements in infection prevention.

The predominant clones of HA-MRSA in the hospital-onset surveys in 2011 were ST239 – the traditional eastern states' multidrug-resistant MRSA clone – and ST22 (Figure 11). The Western Australian policy to 'search-and-destroy' HA-MRSA from the eastern states has been very effective in keeping out the ST239 clone, but not the ST22 clone, which was introduced from the United Kingdom.[25] The ST22 clone may have been introduced into the country by foreign healthcare workers employed in the residential aged-care sector, which is not within the purview of the Western Australian policy.

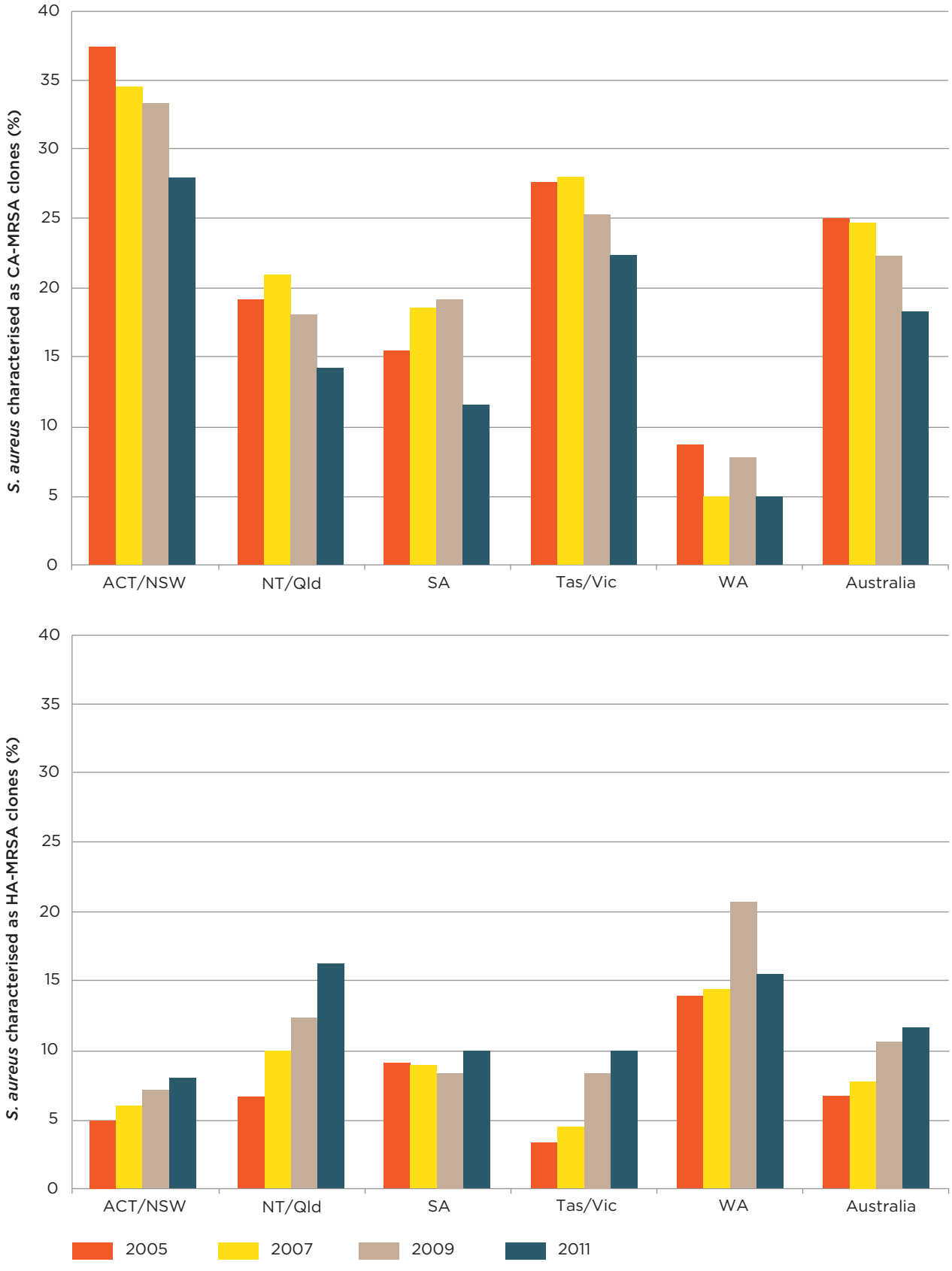
Healthcare impact in hospitals

Methicillin-resistant strains of *Staphylococcus aureus* became established in Australian hospitals on the eastern seaboard in the late 1970s, and subsequently become established in all state and territory hospitals except in Tasmania and Western Australia. Healthcare-associated MRSA in Australia were originally derived from a single clone (AUS) and are typically resistant to multiple classes of antimicrobials besides penicillins and cephalosporins: macrolides, lincosamides, tetracyclines, gentamicin and co-trimoxazole.

The turn of the century witnessed the introduction into Australia of another major healthcare-associated MRSA clone from the United Kingdom, called EMRSA-15. Although this has remained at lower levels than the AUS clone and is susceptible to a wider range of antimicrobial classes, it has shown a great capacity for spread in certain environments, including residential aged-care facilities. The past 10 years has seen a slow but steady decline in the rates of healthcare-associated MRSA. This preceded the advent of the National Hand Hygiene Initiative, but is likely to have been assisted by it.

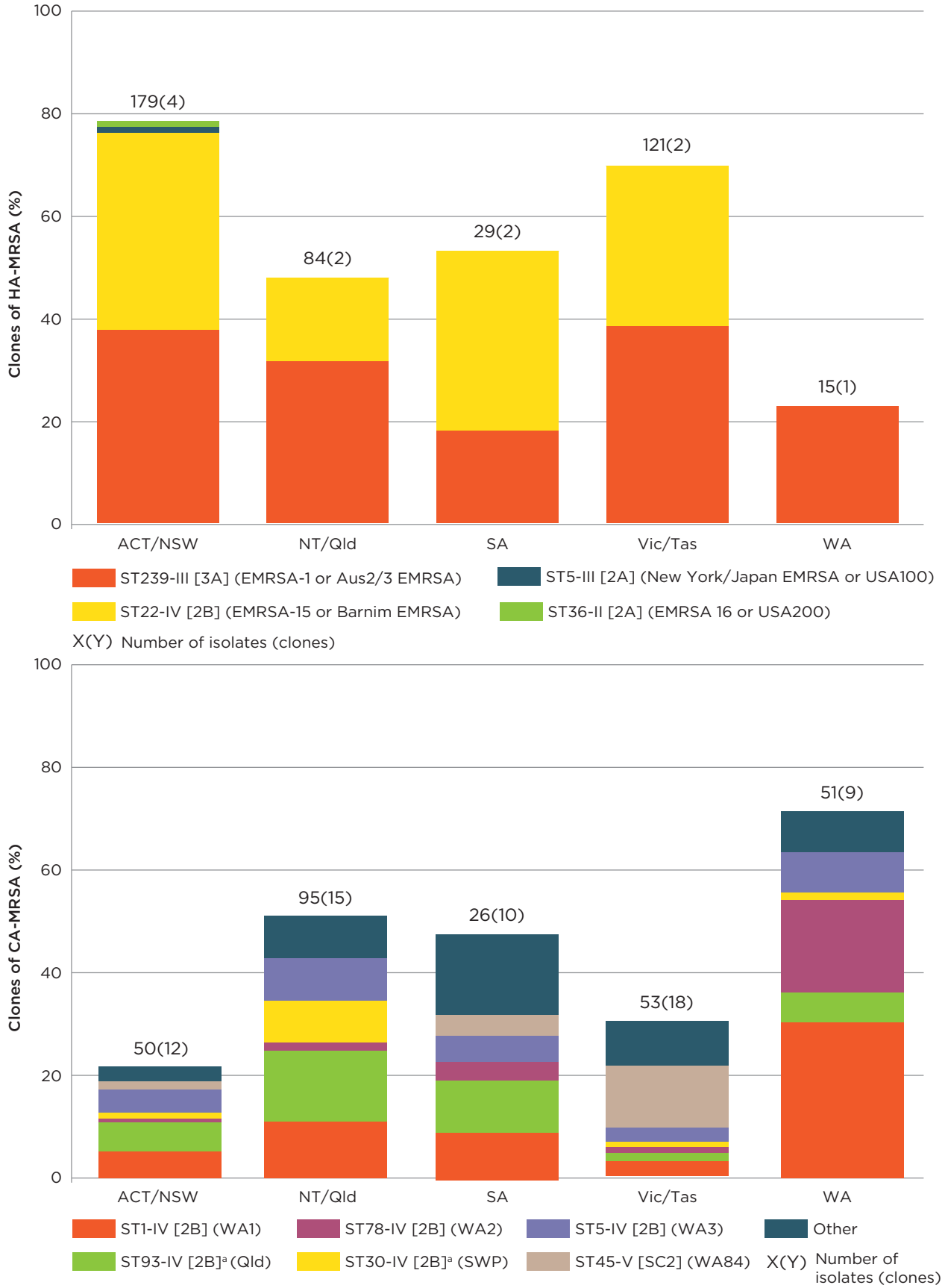
Treatment of the more serious infections cause by healthcare-associated MRSA requires the use of vancomycin, which is associated with inferior outcomes compared with treatment of susceptible strains with β-lactams. However, there are no known agents, even newer ones, with proven superior efficacy. Less serious infections require treatment with reserve antimicrobials such as rifampicin, fusidic acid and linezolid. The decrease in healthcare-associated clones of MRSA is welcome, but, at the same time, community-associated strains of MRSA are on the rise as a cause of staphylococcal infections requiring hospitalisation.

Figure 10 Decline in HA-MRSA clones and rise in CA-MRSA clones in hospital-onset surveys, 2005 to 2011



ACT = Australian Capital Territory; CA-MRSA = community-associated methicillin-resistant *Staphylococcus aureus*; HA-MRSA = healthcare-associated methicillin-resistant *Staphylococcus aureus*; NSW = New South Wales; NT = Northern Territory; Qld = Queensland; SA = South Australia; Tas = Tasmania; Vic = Victoria; WA = Western Australia
Source: Coombs et al.[28]

Figure 11 Percentages and clones of HA-MRSA (top panel) and CA-MRSA (bottom panel) identified in the 2011 hospital-onset survey



CA-MRSA = community-associated methicillin-resistant *Staphylococcus aureus*; HA-MRSA = healthcare-associated methicillin-resistant *Staphylococcus aureus*

a Panton–Valentine leukocidin positive clones

Note: Nationally, 60.9% of MRSA clones were identified as HA-MRSA and 39.1% as CA-MRSA.

Source: Coombs et al.[28]

Streptococcus pneumoniae

Clinical importance: *Streptococcus pneumoniae* is a major cause of respiratory tract infection and invasive disease, including meningitis. The incidence of invasive disease has fallen significantly since the introduction of the 7-valent (now 13-valent) conjugate vaccine into the National Immunisation Program Schedule. The vast majority of pneumococcal infections occur, or have their onset, in the community.

Note: In this pathogen, interpretation of resistance to β-lactam drugs using defined breakpoints differs, depending on whether the isolate being tested is associated with meningitis or is causing disease outside the central nervous system. This explains the presentation of the data on evolving resistance, below.

The data

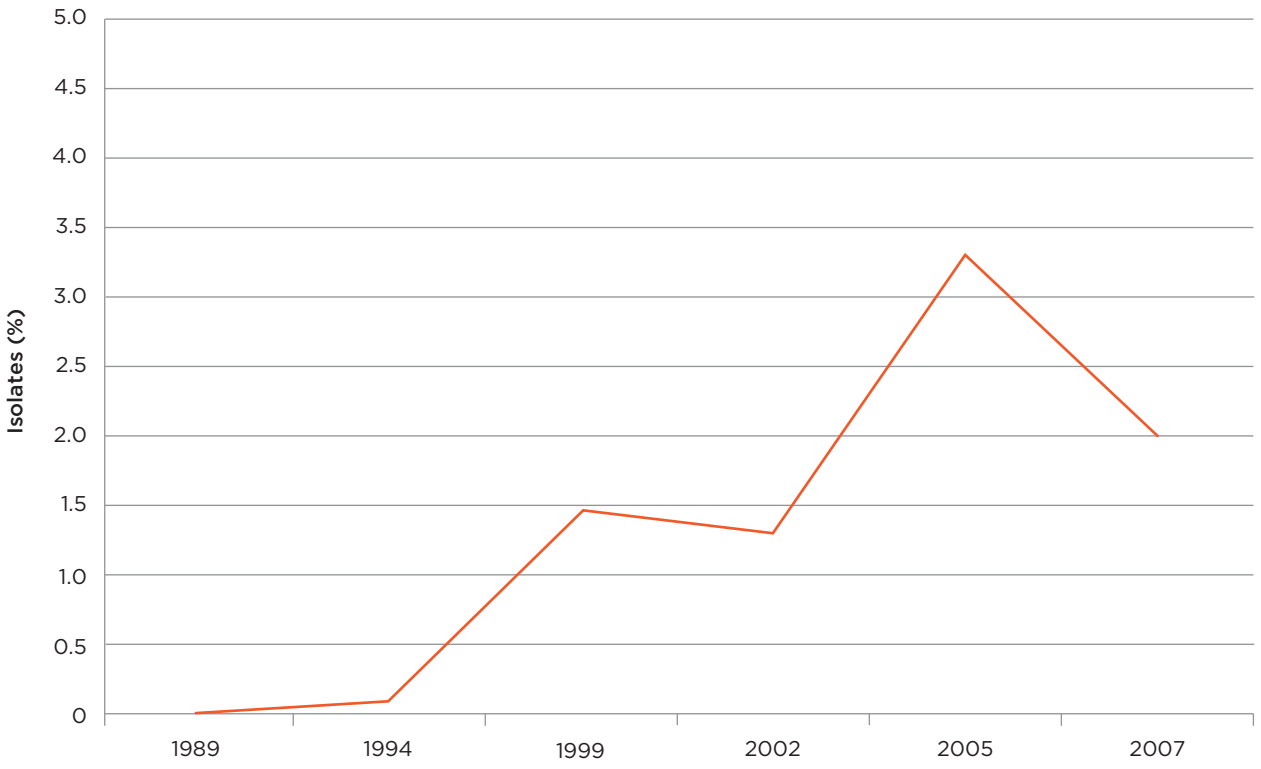
The most recent published data on *S. pneumoniae* come from an AGAR survey in 2007, which included comparisons, where relevant, with previous AGAR surveys.[29] No further surveys have been conducted by AGAR on this species.

AMR trends for community-onset infections

The percentages of *S. pneumoniae* strains that were nonsusceptible to penicillin over the six surveys from 1989 to 2007 are shown in Figure 12.[30] Penicillin resistance (minimum inhibitory concentration >2 mg/L) was seen in 2% of strains in 2007. In comparison, penicillin-resistant strains were largely absent from the 1989 and 1994 surveys (0.0% and 0.1%, respectively), reaching just over 1% in the 1999 and 2002 surveys, and reaching a high of 3.3% in the 2005 survey.

In noninvasive isolates, resistance to macrolides (21.7%), tetracyclines (18.4%) and trimethoprim–sulfamethoxazole (28.8%) was higher than for invasive isolates (rates of 13.9%, 14.2% and 23.5%, respectively). The number of isolates from cerebrospinal fluid (causing meningitis) in the study was low (12 isolates), but when applying the meningitis breakpoints to the complete set of isolates, the resistance rate was 19.8%. This has clear implications for the selection of empirical treatment of acute bacterial meningitis.

Figure 12 Percentage of *Streptococcus pneumoniae* isolates that were resistant to penicillin at a concentration of 2 mg/L, 1989–2007 (breakpoints for invasive infections outside the central nervous system)



Source: Gottlieb et al.[30]

Healthcare impact

Streptococcus pneumoniae causes a range of minor and serious infections: middle ear infection, sinusitis, acute exacerbations of chronic bronchitis, pneumonia and meningitis. The only current national data on resistance is 8 years old. The impact of resistance depends on whether the infection is minor or serious. Minor infections can usually be managed in the community with oral antimicrobials, although, with the emergence of resistance and reduced susceptibility to β-lactams, plus resistance to macrolides, tetracyclines and co-trimoxazole, multidrug-resistant strains are being observed with increasing frequency. Some of these now require hospitalisation for parenteral treatment, mostly with penicillins, although many clinicians mistakenly use third-generation cephalosporins. These agents are also standard treatment for pneumococcal pneumonia.

The impact of resistance is most acute in meningitis. Effective drugs classes for bacterial meningitis of any cause are limited because many drug classes do not reach the site of infection. High-dose penicillins and cephalosporins have been relied on since chloramphenicol was dropped from the armamentarium. Approximately 25% of pneumococci have reduced susceptibility to penicillins, making these agents ineffective in the treatment of meningitis, and placing greater reliance on third-generation cephalosporins and even vancomycin for treatment.

Introduction of the conjugate pneumococcal vaccines into Australia has reduced the incidence of pneumococcal disease, but has not eliminated it because the coverage of serotypes is only about 85%. As no resistance surveillance program was instituted at the time the conjugate vaccines were introduced, the impact of the vaccines on resistance rates is unknown at present.

Acinetobacter species

Clinical importance: *Acinetobacter* species, especially the *A. baumannii* complex, are uncommon pathogens in the community, but play a significant role in healthcare-associated infections, especially ventilator-associated pneumonia and septicaemia. The complex harbours a number of intrinsic resistances and has a high propensity to acquire additional resistance.

The data

National data on resistance rates of *Acinetobacter* species in the community are not available. Data are only available from the Queensland Health OrgTRx system.

AMR trends for hospital-onset infections

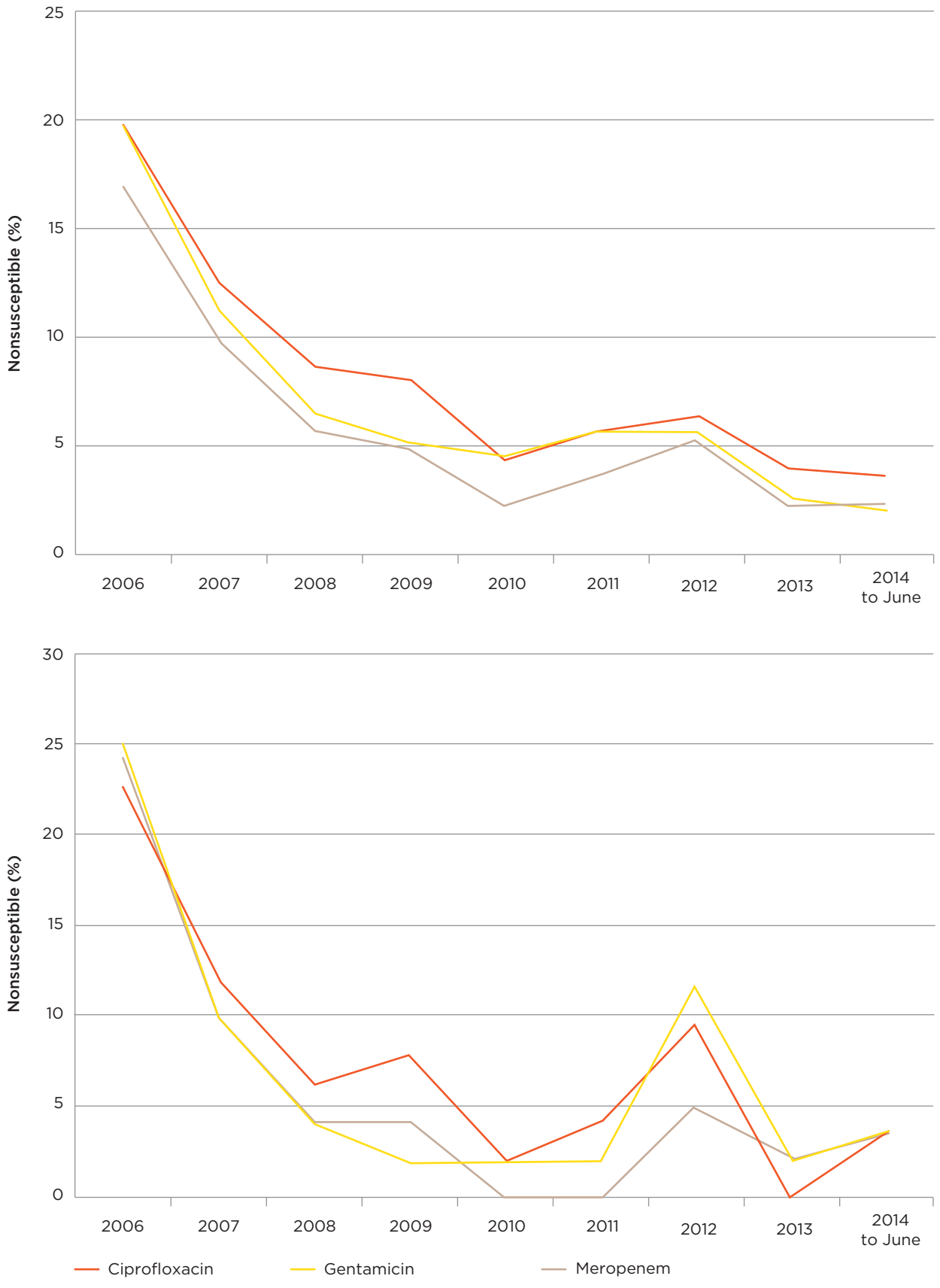
The Queensland OrgTRx data show a major improvement in resistance rates to three important agents between 2006 and 2014 (Figure 13), in both isolates from all clinical specimens and isolates from blood cultures. This has been attributed to strenuous efforts at infection control in hospitals where multidrug-resistant strains had become a problem.

Healthcare impact

Acinetobacter species are largely found as causes of hospital-associated infection, particularly ventilator-associated pneumonia. In some remote parts of Australia, they are also known to cause community-acquired pneumonia. They are also associated with wound infections after major traumatic injuries (e.g. for patients involved in the Bali bombing). The main species involved, the *A. baumannii* complex, is naturally resistant to ampicillin/amoxycillin, amoxycillin–clavulanate and first-generation cephalosporins, and it readily acquires additional resistances. Treatment with 'last line' carbapenems is required, and emerging resistance is being seen with increasing frequency, leading to treatment with colistin, a very old and rather toxic antimicrobial.

The most troublesome problems occur when a multidrug-resistant strain of *A. baumannii* becomes established in an intensive care unit or burns unit. Extensive efforts at infection control are required to control such outbreaks, which can extend for months or years. The Queensland experience presented above shows the outcome of such extensive infection control efforts.

Figure 13 Percentages of nonsusceptible isolates (top panel: all specimens; bottom panel: blood culture isolates) of *Acinetobacter baumannii* in Queensland public hospitals, 2006 to June 2014



Note: Isolates were the first isolate per person per year.

Source: OrgTRx, Queensland Health[2]

3 Antimicrobial use in Australia

Key findings

The data

Limited systems currently exist in Australia for the passive or targeted surveillance of antimicrobial use (AU). This report provides highlights from selected systems. Australian AU data are incomplete and, with one exception, are not linked with resistance surveillance data:

- National passive AU surveillance in the hospital/acute care setting is principally available through data collected by the National Antimicrobial Utilisation Surveillance Program (NAUSP).
- The Queensland Health MedTRx system is a statewide passive surveillance system that can be linked to resistance surveillance (Queensland Health OrgTRx system).
- National targeted AU surveillance in the hospital/acute care setting is largely covered by the National Antimicrobial Prescribing Survey (NAPS). At the time of this report, similar data for targeted AU surveillance in the community/primary care setting were not available.

Trends in antimicrobial use

Data on microbial use are taken from targeted surveillance programs and suggest the following trends:

- Based on Pharmaceutical Benefits Scheme data, AU in the Australian community is comparatively high by international standards (for Europe and North America). Dominant agents used in the community are amoxycillin, amoxycillin with clavulanate, cephalexin and doxycycline. Use of the restricted class of fluoroquinolones is low but slowly increasing.
- Based on data from NAUSP 2012–13, overall hospital antimicrobial use in Australia is similar to that in Denmark but significantly higher than in Sweden and the Netherlands. The data indicate that:
  - the dominant antimicrobials used in hospitals, on a defined daily dose per 1000 hospital bed-days basis, are β-lactamase inhibitor combinations, first-generation cephalosporins, extended-spectrum penicillins and β-lactamase-resistant penicillins
  - carbapenems account for only 2.3% and fluoroquinolones for 4.5% of hospital prescribing
  - prescribing rates in intensive care units are 62% higher than the overall hospital rates.
- The NAPS data demonstrate that:
  - the reason for prescribing was documented in the case record only 71% of the time
  - only 60% of prescriptions were compliant with national prescribing guidelines
  - more than 40% of surgical prophylaxis was administered for more than 24 hours.

Introduction

Overuse or inappropriate use of antimicrobial agents contributes to antimicrobial resistance (AMR) worldwide, including in Australia. This makes surveillance of antimicrobial use (AU) important for the development of a national strategy for prevention and containment of AMR.

AU data are routinely collected in Australia for many different purposes, including:

- the process of prescribing, dispensing, supplying and administering medicines in a range of healthcare settings
- the regulation of the availability of medicines
- clinical governance and antimicrobial stewardship programs
- quality improvement activities
- reimbursement and funding mechanisms
- AU surveillance, and the monitoring and managing of AMR.

AU rates are expressed differently in hospital and community settings. In the hospital setting, the rate is expressed as defined daily dose (DDD, as defined by a World Health Organization–supporting international centre in Norway[31]) per 1000 occupied bed days (DDD/1000 OBD). Note that, in Queensland, the hospital AU rate is expressed as DDDs per 1000 patient days, which is slightly different. In keeping with international practice, community AU rates are expressed as DDDs per 1000 inhabitants per day (DDD/1000 inhabitants/day).

AU surveillance in Australia is undertaken through a range of passive and targeted surveillance programs, at both the national and jurisdictional levels. Numerous local datasets also exist, held by individual health professionals and health service organisations, several of which use the same data source. National AU datasets include:

- Pharmaceutical Benefits Scheme (PBS) claims
- Pharmacy Guild of Australia Dispensing Survey
- Australian Statistics on Medicines
- Australian Institute of Health and Welfare
- Organisation for Economic Co-operation and Development
- National Antimicrobial Utilisation Surveillance Program (NAUSP)
- National Antimicrobial Prescribing Survey (NAPS)
- National Prescribing Service (NPS MedicineWise)
- Bettering the Evaluation and Care of Health (BEACH) survey.

The benefits and limitations of these programs are shown in Appendix A.

Antimicrobial use in the community

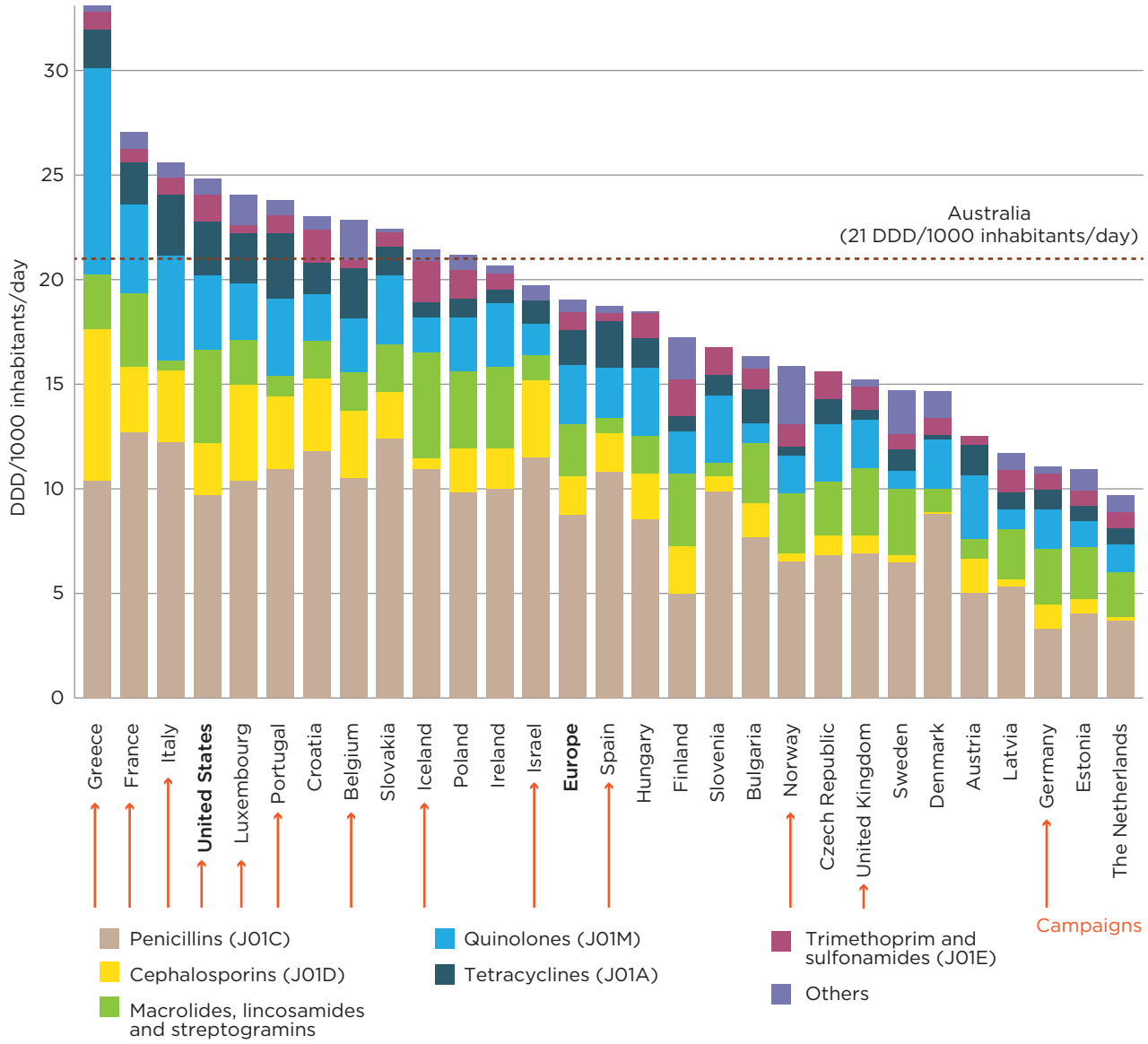
International comparisons

Using the international conventions for expressing AU rates in the community (DDD/1000 inhabitants/day) allows international comparisons, but does not account for significant local variations in dosing regimens from the DDD (higher routine dosing will increase the measured DDD without changing the number of individuals exposed). It also fails to identify the number of individuals in Australia who took one or more courses of antimicrobials.

Notwithstanding these reservations, the volume of AU in the Australian community is high compared with most European countries.[32] In terms of DDDs for the J01 class of systemic antimicrobials, Australia ranked between fifth and sixth highest of 29 countries.

Figure 14 shows the difference in per-capita consumption of antimicrobials in outpatient/community settings in the United States and 27 European countries. Australia is positioned in the middle of the range, with AU of 21 DDD/1000 inhabitants/day, which is more than twice that of the Netherlands.

Figure 14 Consumption of antimicrobials in outpatient/community settings in the United States and 27 European countries, 2004



DDD = defined daily dose
Source: Adapted from Goossens et al.[33]

Usage rates for antimicrobials – passive surveillance

Data are collected, for other purposes, on all antimicrobials dispensed under the PBS. This is prescription data collected from community pharmacies and outpatient hospital services. It should be noted that the database does not include any information on the condition for which a medicine has been prescribed. This makes it difficult to use the database to monitor medicine use for specific conditions, particularly for those medicines that can be used for multiple indications.

Data collected under the PBS include:

- subsidised (under co-payment) PBS/ Repatriation Pharmaceutical Benefits Scheme (RPBS) prescriptions
- nonsubsidised and PBS/RPBS prescriptions
- public hospital outpatient subsidised prescriptions (excluding the Australian Capital Territory and New South Wales). Since 2002, an increasing number of hospitals have provided medicines to outpatient and discharged patients that are subsidised by the Australian Government PBS.

The latest available data, published in *Australian statistics on medicines* (2011), list antibacterial agents for systemic use and their associated Anatomical Therapeutic Chemical (ATC) group. The data represent estimates of the aggregate use of prescription medicines in Australia.[34] In 2011, the DDD/1000 inhabitants/day for systemic antimicrobials was nearly 24.8. The top five antimicrobial agents prescribed in Australia (in DDD/1000 inhabitants/day) are amoxycillin (6.2), amoxycillin with clavulanate (4.4), cephalexin (2.9), doxycycline (2.6) and roxithromycin (1.4).

Overall trends (Table 7 and Figure 15) in prescribing show a steady upward trend in community use since 2002, largely accounted for by an increase in combinations of penicillins, including ß-lactamase inhibitors. Trends for individual agents are shown in Appendix B.

Healthcare impact

Australia has high community antimicrobial use (AU) compared with many other developed countries. On a defined daily dose/1000 inhabitants/day basis, AU increased from 2006 to 2011; this increase remains unexplained. Importantly, AU in Australia is more than twice that of the Netherlands, the international benchmark country. It is likely that antimicrobials have become 'part of the culture' in Australia, with high expectation for receiving an antimicrobial prescription after visiting the doctor for any infection, especially viral respiratory infections. Assuming that the mix and rate of common infections in the Netherlands community are similar to those of Australia, and that the Netherlands population is not suffering adverse outcome from 'untreated' infections, the community use of antimicrobials in Australia is at least double what it needs to be. Put another way, 50% of AU in Australia is unnecessary; it exposes 50% of 'consumers' to unwarranted side effects, and wastes taxpayer dollars.

The drivers of this high and unnecessary AU are not clear. More than half the consumption is made up of three agents: amoxycillin, amoxycillin–clavulanate and cephalexin. These β-lactam agents are likely to be contributing to the selection and amplification of common and emerging resistances to antimicrobials that are valuable for treating seriously ill patients, such as extended-spectrum blactamase-producing *E. coli* and community-associated methicillin-resistant *Staphylococcus aureus*.

Table 7 Antimicrobial use in 2011 (ATC group J01 – anti-infectives for systemic use)

Antimicrobial	Subsidised on PBS/RPBS (DDD/1000 inhabitants/day)	% of total subsidised	Nonsubsidised survey components (DDD/1000 inhabitants/day)	% of total nonsubsidised	Total (DDD/1000 inhabitants / day)
β-lactam antimicrobials, penicillins (J01C)	**5.307**	**44.1**	**6.680**	**52.5**	**11.987**
Amoxycillin	2.667		3.537		6.204
Amoxycillin with clavulanate	2.036		2.317		4.353
Phenoxymethylpenicillin	0.186		0.441		0.627
Flucloxacillin	0.227		0.216		0.443
Dicloxacillin	0.142		0.133		0.275
Benzathine phenoxymethylpenicillin	0.018		0.036		0.054
Procaine penicillin	0.014		0.000		0.014
Ticarcillin with clavulanate	0.009		0.000		0.009
Benzylpenicillin	0.004		0.000		0.004
Ampicillin	0.003		0.000		0.003
Benzathine penicillin	0.001		0.000		0.001
Macrolides, lincosamides and streptogramins (J01F)	**1.795**	**14.9**	**2.088**	**16.4**	**3.883**
Roxithromycin	0.736		0.695		1.431
Erythromycin	0.467		0.670		1.137
Clarithromycin	0.475		0.557		1.032
Azithromycin	0.023		0.127		0.150
Clindamycin	0.093		0.039		0.132
Lincomycin	0.001		0.000		0.001
Other β-lactam antimicrobials (J01D)	**1.874**	**15.6**	**1.649**	**12.9**	**3.523**
Cephalexin	1.599		1.350		2.949
Cefaclor	0.179		0.245		0.424
Cefuroxime	0.056		0.053		0.109
Ceftriaxone	0.018		0.001		0.019
Cefazolin	0.016		0.000		0.016
Cephalothin	0.005		0.000		0.005

(continued)

Table 7 (continued)

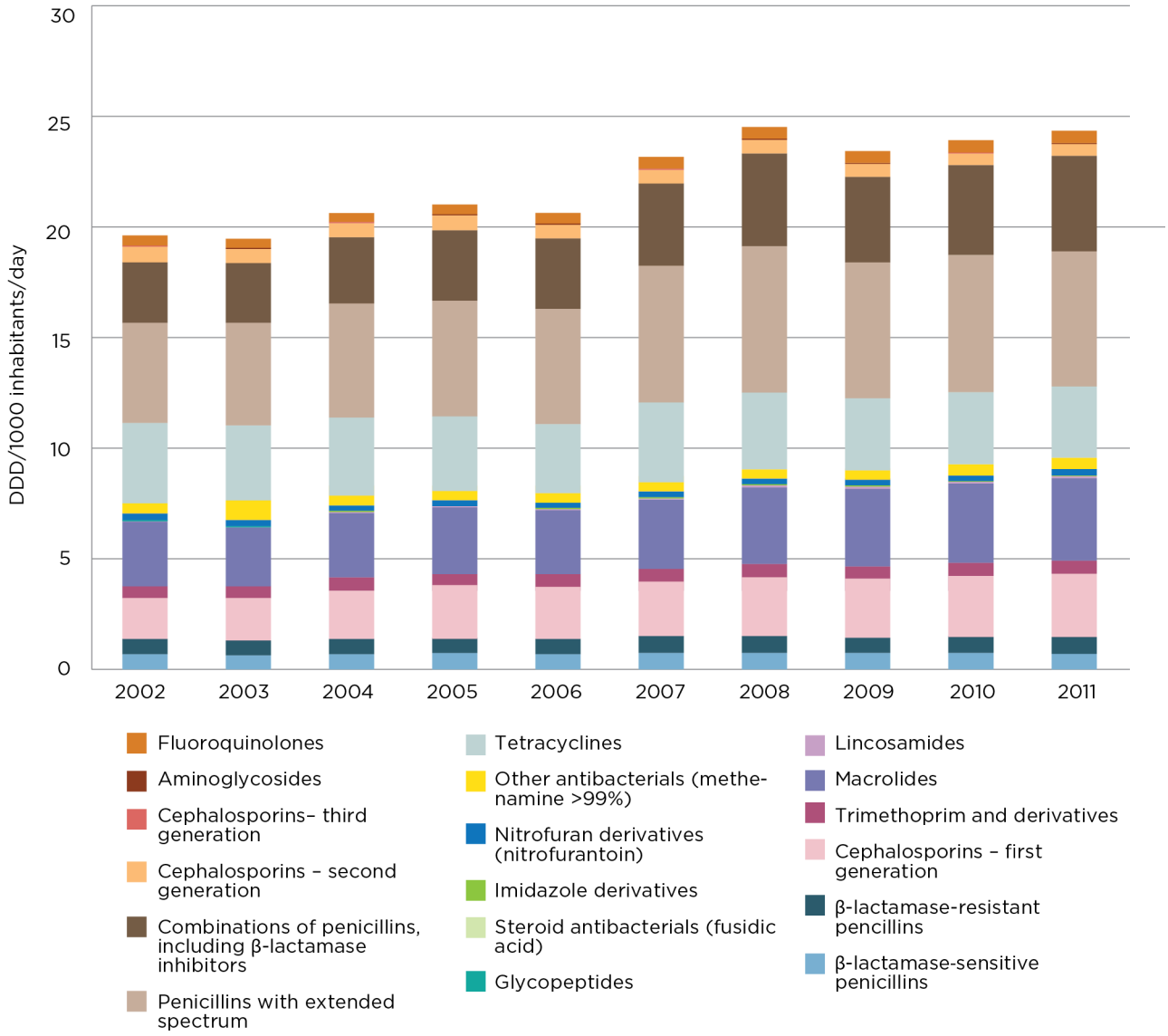
Antimicrobial	Subsidised on PBS/RPBS (DDD/1000 inhabitants/day)	% of total subsidised	Nonsubsidised survey components (DDD/1000 inhabitants/day)	% of total nonsubsidised	Total (DDD/1000 inhabitants / day)
Cefepime	0.001		0.000		0.001
Cefotaxime	0.000		0.000		0.000
Tetracyclines (J01A)	**1.406**	**11.7**	**1.884**	**14.8**	**3.290**
Doxycycline	1.177		1.419		2.596
Minocycline	0.229		0.465		0.694
Other J01 substances	**0.849**	**7.1**	**0.059**	**0.5**	**0.908**
Hexamine hippurate	0.601		0.002		0.603
Nitrofurantoin	0.190		0.055		0.245
Fusidic acid	0.035		0.000		0.035
Gentamicin sulfate	0.007		0.002		0.009
Vancomycin	0.007		0.000		0.007
Tobramycin	0.006		0.000		0.006
Metronidazole	0.003		0.000		0.003
Neomycin	–		0.000		0.000
Quinolone antimicrobials (J01M)	**0.427**	**3.6**	**0.171**	**1.3**	**0.598**
Ciprofloxacin	0.282		0.043		0.325
Norfloxacin	0.145		0.124		0.269
Moxifloxacin	–		0.004		0.004
Sulfonamides and trimethoprim (J01E)	**0.365**	**3.0**	**0.205**	**1.6**	**0.570**
Trimethoprim	0.365		0.205		0.570
Trimethoprim–sulfamethoxazole	–		–		0.263[a]
Total	**12.023**	**100**	**12.736**	**100**	**25.022**[a]

ATC = Anatomical Therapeutic Chemical; DDD = defined daily dose; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

a The PBS does not provide a breakdown by subsidy for this agent, but it has been included in the overall total.

Source: Australian Government Department of Health[34]

Figure 15 Overall trends by class for antimicrobial use (ATC group J01 – anti-infectives for systemic use), 2011



ATC = Anatomical Therapeutic Chemical; DDD = defined daily dose

Source: Australian Government Department of Health[34]

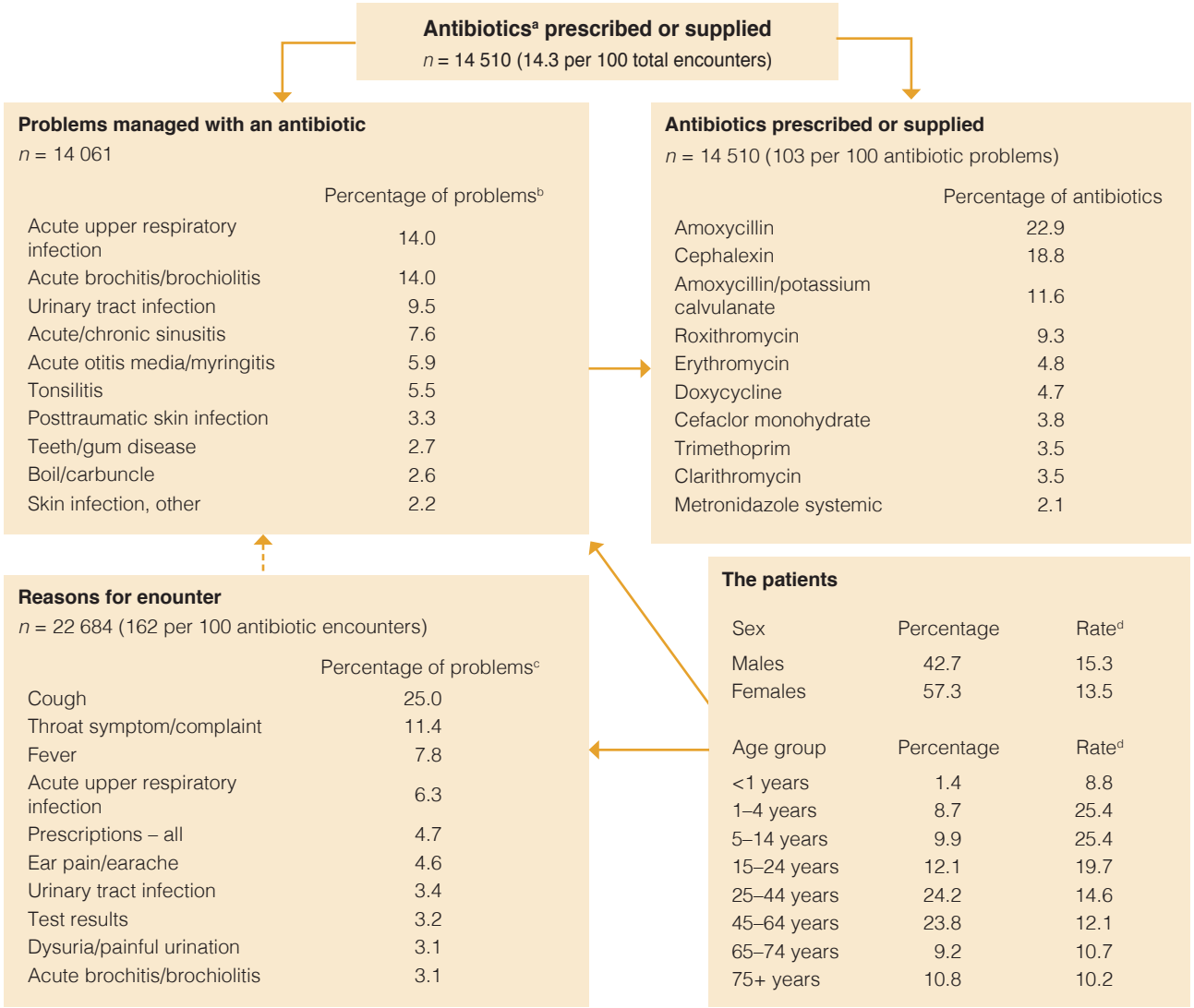
Appropriate use of antimicrobials in the community – targeted surveillance

Two organisations in Australia are involved in collecting data on the appropriate use (or overuse or misuse) of antimicrobials in the community setting: NPS MedicineWise and the Family Medicine Research Centre at the University of Sydney.

For more than a decade, NPS MedicineWise has run surveys on prescribing changes in general practice. These surveys were run to gauge the effectiveness of various activities of NPS MedicineWise in reducing inappropriate antimicrobial prescribing in Australia. NPS MedicineWise had collected data from 229 practices across Australia as of July 2014, although reports on AU have not yet been released.

The Family Medicine Research Centre at the University of Sydney operates the BEACH program. The BEACH program is a continuous national study of general practice clinical activity, in which data are collected from ever-changing samples of approximately 1000 general practitioners (GPs) per year. Each GP provides details of about 100 patient encounters, and this produces a national sample of about 100 000 encounter records per year. BEACH antimicrobial data include information on the problems managed with an antimicrobial, types of antimicrobials prescribed or supplied, patient reasons for the encounter, and patient demographics.[35]

Figure 16 Systemic antimicrobials prescribed or supplied in general practice, 2009–10



a Includes medications from the Antibacterials for Systemic Use ATC group (J01).
b Expressed as a percentage of problems managed with an antibiotic.
c Expressed as a rate per 100 encounters at which an antibiotic was prescribed or supplied.
d Age- and sex-specific rate per 100 encounters in each age and sex group.
Source: Britt et al.[35]

In the 2009–10 BEACH survey, the reasons for prescribing were examined, as well as the reasons for the GP to attend to the patient and the type of antimicrobial supplied (Figure 16).

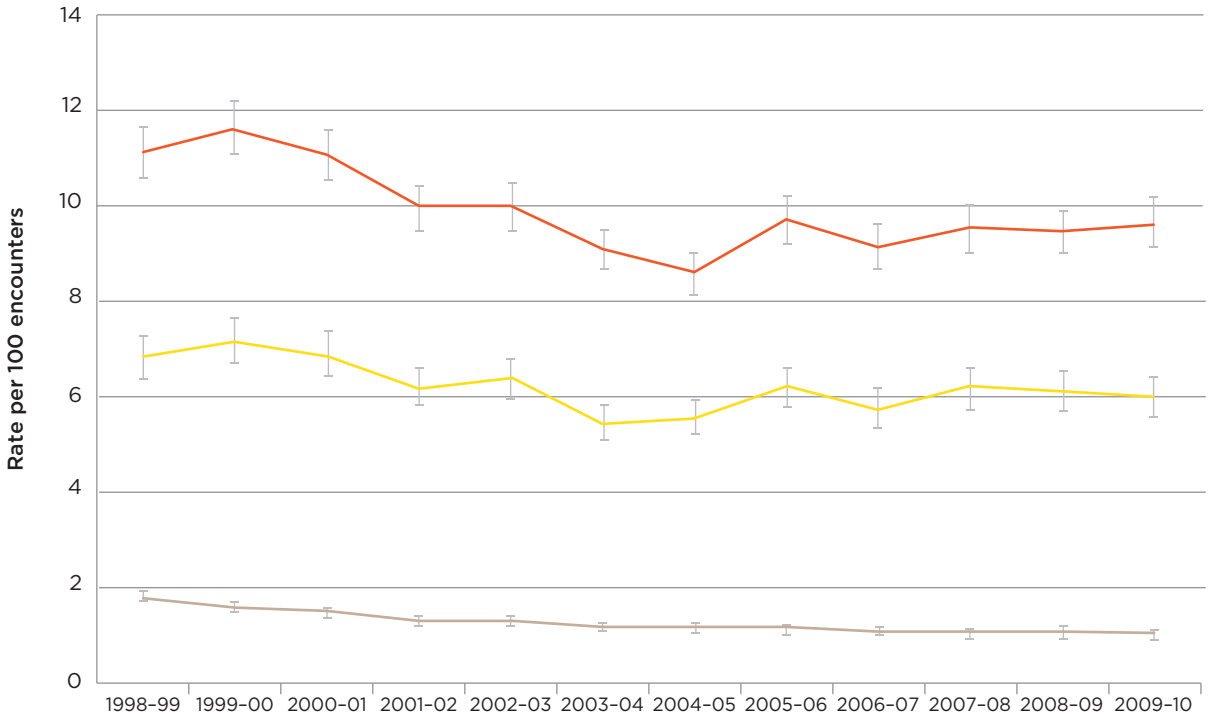
The data from the BEACH survey show that:

- the most frequently supplied antimicrobials in 2010 were amoxycillin (22.9% of all antimicrobial prescriptions), cephalexin (18.8%) and amoxycillin with clavulanate (11.6%)
- more than one-quarter of antimicrobial prescriptions were used to manage acute upper respiratory tract infection (URTI) and acute bronchitis/bronchiolitis (28%); this is despite recommendations in *Therapeutic guidelines: antibiotic*[36] that the use of antimicrobials for these conditions is not indicated
- other conditions for which antimicrobials were prescribed include acute/chronic sinusitis, tonsillitis and acute otitis media/myringitis; these are conditions where antimicrobials are indicated in only a proportion of patients.

The BEACH results provide ample evidence of inappropriate prescribing in the community setting.

Historical data collected from the BEACH surveys from 1998–99 to 2009–10 have not shown any significant reduction in unnecessary prescribing for acute URTI since 2003–04, although there has been an observable reduction in prescribing for acute otitis media (Figure 17).

Figure 17 Systemic antimicrobial prescribing in respiratory tract infections, 1998–99 to 2009–10



	1998–99	1999–00	2000–01	2001–02	2002–03	2003–04	2004–05	2005–06	2006–07	2007–08	2008–09	2009–10
Acute URTI	6.2	7.2	6.9	6.2	6.4	5.5	5.6	6.2	5.8	6.2	6.1	6.0
Other URTIs	11.1	11.6	11.1	10.0	10.0	9.1	8.6	9.7	9.2	9.5	9.5	9.6
Otitis media	1.8	1.6	1.5	1.3	1.3	1.2	1.2	1.2	1.1	1.1	1.1	1.0

URTI = upper respiratory tract infection
Source: BEACH surveys from 1998–99 to 2009–10

Healthcare impact

The high rate of antimicrobial prescribing for presumptive viral respiratory infections in the Australian community is disturbing. This type of prescribing probably accounts for the vast bulk of unnecessary prescribing in Australia, but so far has proven very difficult to reduce. NPS MedicineWise has conducted high-quality campaigns to reduce unnecessary antimicrobial prescribing for more than a decade. However, prescribing practice and the expectations of patients with regard to antibiotics do not appear to have been significantly affected.

Antimicrobial use in residential aged-care facilities

Currently, limited AU data are available from the residential aged-care sector. Some data have been reported for residential aged-care facilities (RACFs) in studies described in peer-reviewed journal articles,[37,38] but the number of residents in these studies are small, so the results cannot be considered to be representative of all RACFs in Australia. However, the data do highlight key issues associated with AU and surveillance in this healthcare sector:

- The clinical diagnosis of infection is often imprecise, and antimicrobials may be started 'in case' infection is present.

- The diagnostic accuracy of clinical features of infection in the residents is often poor, and a history is also often difficult to obtain because many residents are cognitively impaired.
- The limited use of laboratory services (because of difficulties in obtaining specimens and poor laboratory access) means that treatment is often empirical and, when started, de-escalation of antimicrobial therapy is not possible.
- On average, 40% of therapeutic antimicrobial prescriptions within RACFs did not meet clinical criteria for infection. This compares with international reports showing that 25–75% of systemic antimicrobials can be considered inappropriate in this setting.
- Without microbiological data to direct AU, resistance may be promoted.
- Multiple pathology providers make the task of surveillance for outbreaks of multidrug-resistant organisms almost impossible.
- Surveillance of AU is hindered by the use of privatised community-based pharmacies.

A targeted AU program in Victoria now includes all public RACFs and is structured as an annual point-prevalence tool (currently, with voluntary participation by private RACFs). NAPS will be offered to RACFs across Australia in 2015.

Healthcare impact

It is becoming increasingly clear that antimicrobial use in residential aged-care facilities is not optimal. As the life expectancy in Australia increases, it is likely that a greater percentage of the population will be in residential care. High standards of antimicrobial prescribing and infection control are as important in residential aged-care as they are in hospitals, because similar conditions apply, and the residential aged-care population has increased vulnerability to infection due to multiple comorbidities.

Antimicrobial use in hospitals

Passive AU surveillance relies on reporting volume-of-use data.

NAUSP has been operating in Australia since 2004, building on initial implementation in South Australia. The program collects volume-of-use data from participating hospital pharmacies, including a small number of private hospitals, and analyses the data for both total hospital use and intensive care unit (ICU) use, using the internationally accepted metric of DDDs per 1000 OBDs.

Data from the national NAUSP report for 2012–13 are presented here. There were 52 contributing hospitals (48 public, 4 private) in this period, during which the average aggregate annual rate for contributors was 945 DDD/1000 OBD, compared with 973 in the previous 12-month period – a 3% decrease.

Total hospital AU rates show that five antimicrobial classes accounted for 55% of total hospital AU in the year to June 2013 (Table 8). These were:

- penicillin/ß-lactamase inhibitor combinations (amoxycillin with clavulanate) (14%)
- first-generation cephalosporins (e.g. cephazolin) (13%)
- extended-spectrum penicillins (e.g. amoxycillin) (11%)
- ß-lactamase-resistant penicillins (e.g. flucloxacillin) (10%)
- macrolides (e.g. azithromycin) (8%).

The breakdown of the trends for some of the individual agents is shown in Appendixes B and C.

Penicillins, especially those combined with ß-lactamase inhibitors and cephalosporins, are the most widely prescribed agents in Australian hospitals. Carbapenem usage rates are low, at only 2.3% of total use, while fluoroquinolones account for 4.5% of total use. The most notable trends are declines in the use of amoxycillin, ciprofloxacin, vancomycin and gentamicin, and increases in the use of first-generation cephalosporins (cefazolin and cephalexin), lincomycin and doxycycline.

Table 8 Total hospital usage rates for systemic antimicrobials – from contributors to the NAUSP, 2012–13

WHO antimicrobial group	Total hospital usage rates (DDD/1000 OBD)	% of total usage rate
ß-lactamase inhibitor combinations (amoxycillin with clavulanate)	134.7	14.2
Cephalosporins – first generation	124.5	13.2
Extended-spectrum penicillins (ampicillin/amoxycillin)	102.4	10.8
ß-lactamase-resistant penicillins	90.0	9.5
Macrolides	71.5	7.6
ß-lactamase inhibitor combinations (antipseudomonal)	49.1	5.2
Cephalosporins – third generation	45.8	4.8
Tetracyclines	44.0	4.7
Nitroimidazoles	43.9	4.6
Fluoroquinolones	42.7	4.5
Aminoglycosides	42.1	4.5
Glycopeptides	31.7	3.4
ß-lactamase-sensitive penicillins	25.4	2.7
Carbapenems	21.5	2.3
Trimethoprim	18.8	2.0
Sulfonamide/trimethoprim combinations	17.9	1.9
Lincosamides	15.3	1.6
Cephalosporins – fourth generation	5.9	0.6
Rifamycins	5.6	0.6
Cephalosporins – second generation	5.0	0.5
Other antibacterials (linezolid, daptomycin)	2.7	0.3
Steroids (fusidic acid)	1.8	0.2
Polymyxins (colistin)	1.1	0.1
Nitrofurans	0.8	0.1
Streptogramins	0.7	0.1
Monobactams	0.5	0.1
Streptomycins	0.0	0.0
Total	**945.3**	**100.0**

DDD/1000 OBD = defined daily doses per 1000 occupied bed days; NAUSP = National Antimicrobial Utilisation Surveillance Program; WHO = World Health Organization
Source: SA Health[39]

Antimicrobial use in intensive care

Rates of AU were approximately 70% higher in ICUs than for total hospital use, as might be expected in caring for the sickest patients (Table 9). The overall usage rate calculated for ICUs was 1531 DDD/1000 OBD, compared with 1615 in the previous year (a 5.2% decrease).

In the ICU setting, antipseudomonal penicillin/ß-lactamase inhibitor combinations (now predominantly piperacillin–tazobactam) are the antimicrobials used to the greatest extent.

Use of highly reserved agents such as colistin, daptomycin, linezolid and tigecycline is low (rates less than 5 DDD/1000 OBD in the majority of hospitals). Daptomycin usage rates are increasing, although they are extremely low (less than 2 DDD/1000 OBD).

AU trends over time showed an apparent slight decline in overall use between 2008–09 and 2012–13 (Figure 18), although during this period the number of hospitals recruited to NAUSP rose from 30 to 56, and the mix of hospital types also changed.

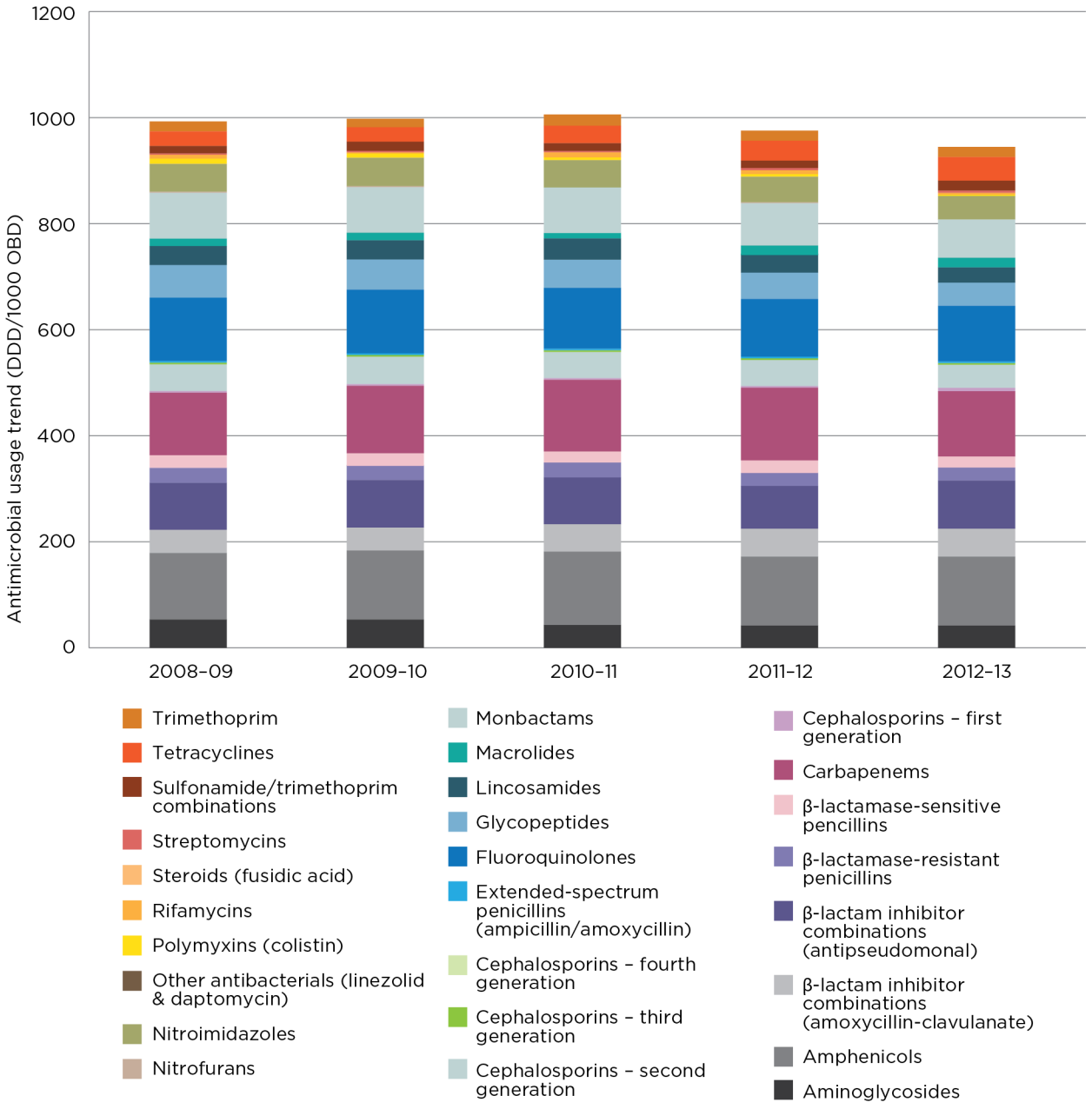
More interestingly, there are also substantial differences in rates of use between ICUs – more than might otherwise be expected. Figure 19 shows that the interhospital annual average AU rates ranged from 608 to 2407 DDD/1000 OBD for 2012–13.

Table 9 Antimicrobial use rates in intensive care units for NAUSP contributors, 2012–13

WHO antimicrobial group	ICU usage rates (DDD/1000 OBD)	%
ß-lactamase inhibitor combinations (antipseudomonal)	197.8	12.9
Glycopeptides	160.5	10.5
Macrolides	160.4	10.5
Carbapenems	141.7	9.3
Cephalosporins – first generation	122.1	8.0
ß-lactamase-resistant penicillins	110.0	7.2
Cephalosporins – third generation	101.3	6.6
Extended-spectrum penicillins (ampicillin/amoxycillin)	92.6	6.0
Fluoroquinolones	88.1	5.8
Nitroimidazoles	64.4	4.2
ß-lactamase inhibitor combinations (amoxycillin with clavulanate)	56.6	3.7
ß-lactamase-sensitive penicillins	45.5	3.0
Sulfonamide/trimethoprim combinations	44.2	2.9
Aminoglycosides	42.1	2.8
Tetracyclines	27.4	1.8
Lincosamides	22.1	1.4
Cephalosporins – fourth generation	20.1	1.3
Other antibacterials (linezolid and daptomycin)	13.3	0.9
Rifamycins	6.8	0.4
Trimethoprim	4.7	0.3
Polymyxins (colistin)	4.4	0.3
Steroids (fusidic acid)	1.7	0.1
Cephalosporins – second generation	1.3	0.1
Monobactams	1.1	0.1
Streptogramins	0.3	0.0
Nitrofurans	0.2	0.0
Streptomycins	0.1	0.0
Total	**1530.7**	**100.0**

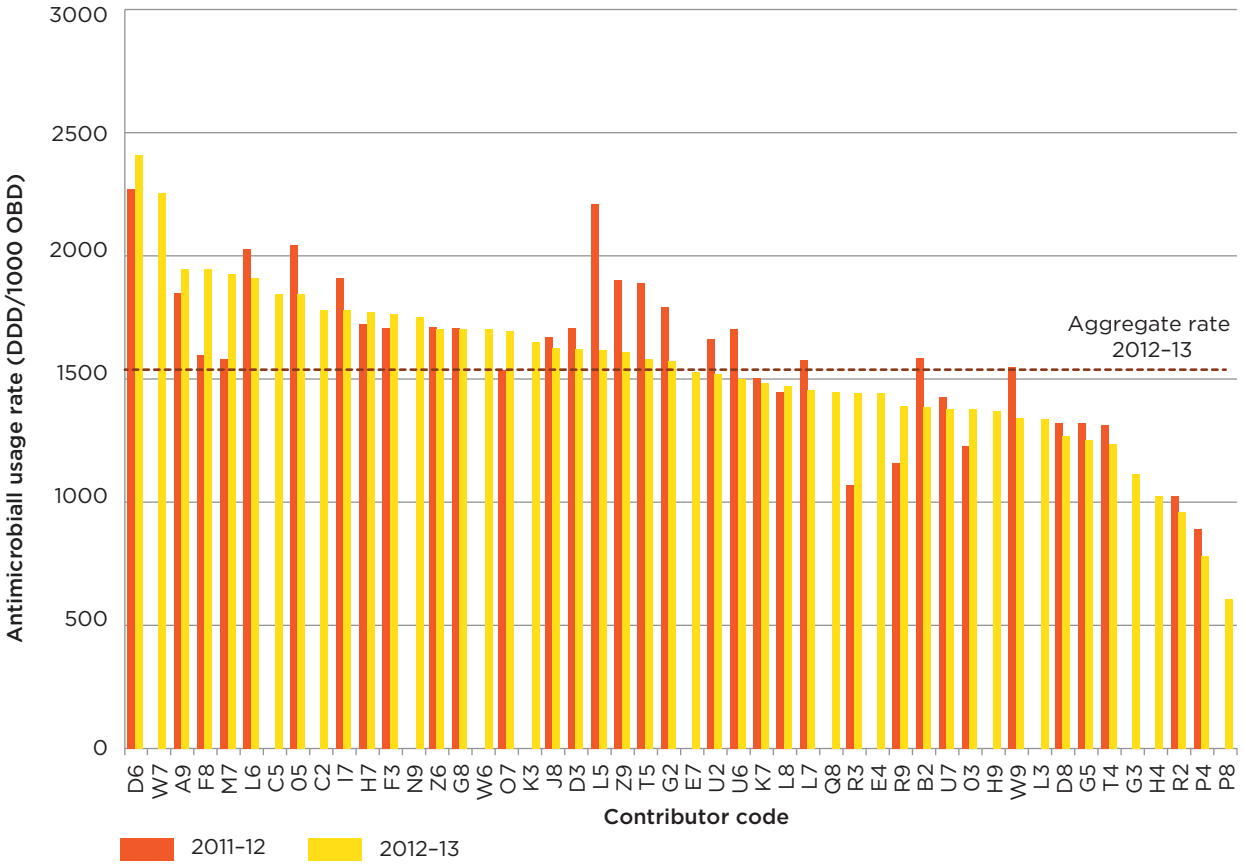
DDD/1000 OBD = defined daily doses per 1000 occupied bed days; ICU = intensive care unit; NAUSP = National Antimicrobial Utilisation Surveillance Program; WHO = World Health Organization
Source: SA Health[39]

Figure 18 Antimicrobial use trends in intensive care units, by WHO antimicrobial ATC group, for total hospital component of NAUSP, 2008–09 to 2012–13



ATC = Anatomical Therapeutic Chemical; DDD/1000 OBD = defined daily doses per 1000 occupied bed days; NAUSP = National Antimicrobial Utilisation Surveillance Program; WHO = World Health Organization
Source: SA Health[39]

Figure 19 Average yearly antimicrobial use rates in intensive care units for hospitals contributing to NAUSP, 2011–12 and 2012–13



DDD/1000 OBD = defined daily doses per 1000 occupied bed days; NAUSP = National Antimicrobial Utilisation Surveillance Program
Source: SA Health[39]

Healthcare impact of hospital and intensive care use

Australia, like most other nations, has high use of β-lactam agents in hospital care. Combination β-lactam/β-lactamase inhibitor combinations are heavily relied upon for empirical and directed treatment of a wide range of infections, with piperacillin–tazobactam widely used for parenteral therapy and amoxicillin–clavulanate used for oral therapy. The other dominant agents are ampicillin/amoxycillin, macrolides (especially azithromycin) and cephalosporins. First-generation cephalosporins, mainly cephazolin, are very widely used for surgical prophylaxis, alone or in combination, followed by third-generation cephalosporins, which are widely used for treatment of a range of infections. Third-generation cephalosporins are more likely to drive certain types of resistance than the other commonly used classes. Pleasingly, fluoroquinolone use is comparatively low, in line with the practice of keeping these agents in reserve for treating infections caused by bacteria that are resistant to other antimicrobial classes. Indeed, the evidence shows a continuing downward trend in its use since 2008. Notably, the use of aminoglycosides, principally gentamicin, is declining nationally as prescribers seek 'safer' alternative agents such as the third-generation cephalosporins. Whether this will have had an adverse ecological impact with rising resistance rates remains to be seen. Some of the reduction in aminoglycoside use could be attributed to the evolving practice of using aminoglycosides as empirical therapy for only 48–72 hours pending culture results before changing to 'safer' alternatives.

Use in intensive care units in Australia is quite variable, but overall is about 50% higher than in the general wards. As expected for the management of the sickest patients, the use of broader-spectrum and reserve agents is high in this setting, with glycopeptides, mainly vancomycin, and carbapenems, mainly meropenem, featuring near the top of the list.

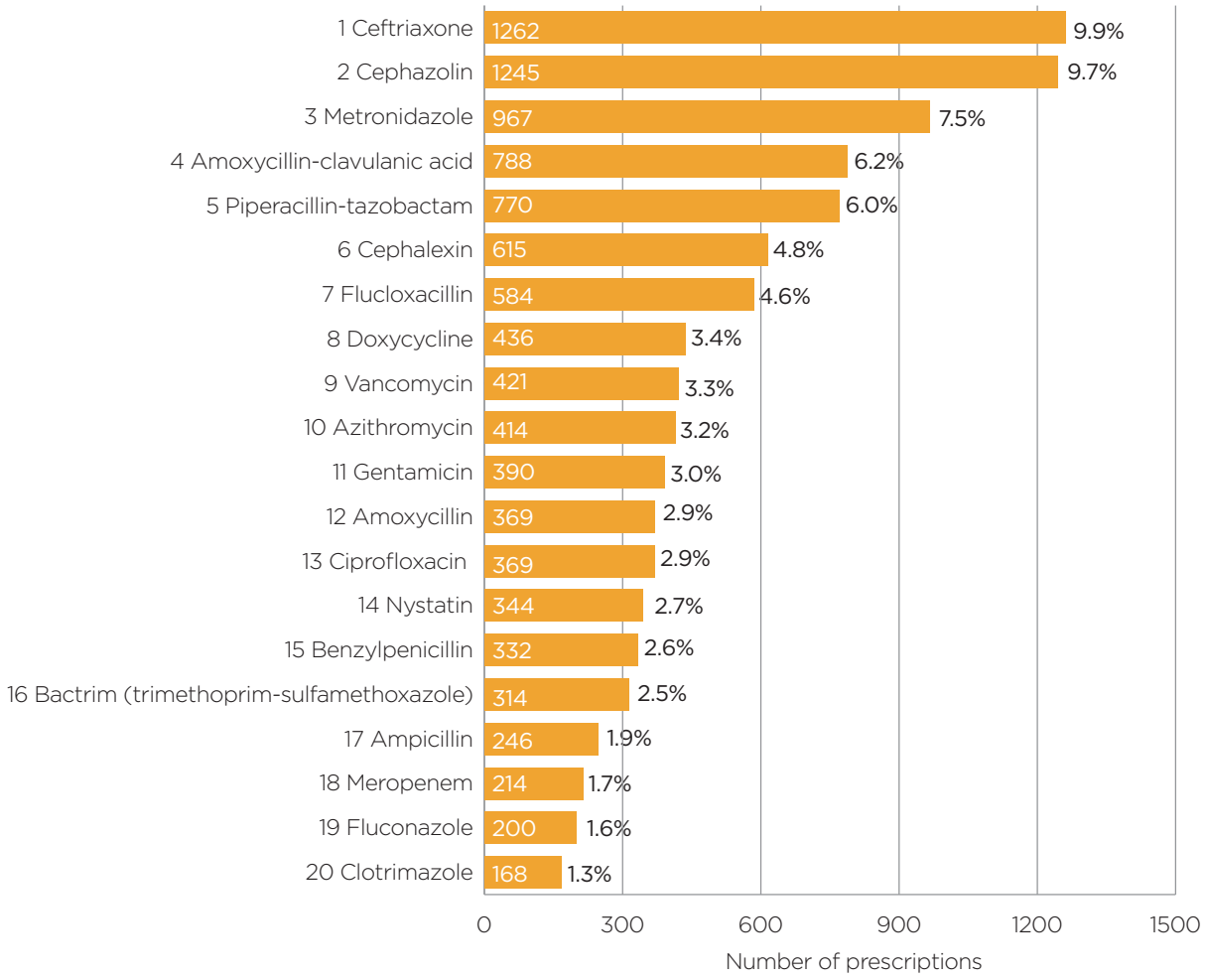
Appropriate use of antimicrobials in hospitals – targeted surveillance

Recently, Australia has seen the development of NAPS. This was an initiative of Melbourne Health/ Doherty Institute as holders of an NHRMC-funded Centre of Research Excellence on antimicrobial stewardship. In 2013, the NAPS team developed an online data entry tool that allowed participating hospitals (both public and private) to undertake a point-in-time survey of the appropriateness of AU in their hospital. The data from 151 hospitals (including 19 private hospitals) have been published in a joint report between the Commission and Melbourne Health/Doherty Institute.[40] Highlights are presented below.

Ceftriaxone was the most commonly prescribed antimicrobial (Figure 20), followed closely by cephazolin, the latter mostly used for surgical prophylaxis. The most common therapeutic indication was community-acquired pneumonia (Figure 21).

The reason for prescribing (indication) was documented in the case record only 71% of the time (Table 11). Only 60% of prescriptions were compliant with national prescribing guidelines,

Figure 20 National Antimicrobial Practice Survey 2013 – top 20 most commonly prescribed antimicrobials



Source: Australian Commission on Safety and Quality in Health Care[40]

and only 71% of prescriptions were considered appropriate (using agreed criteria, as published in the report).

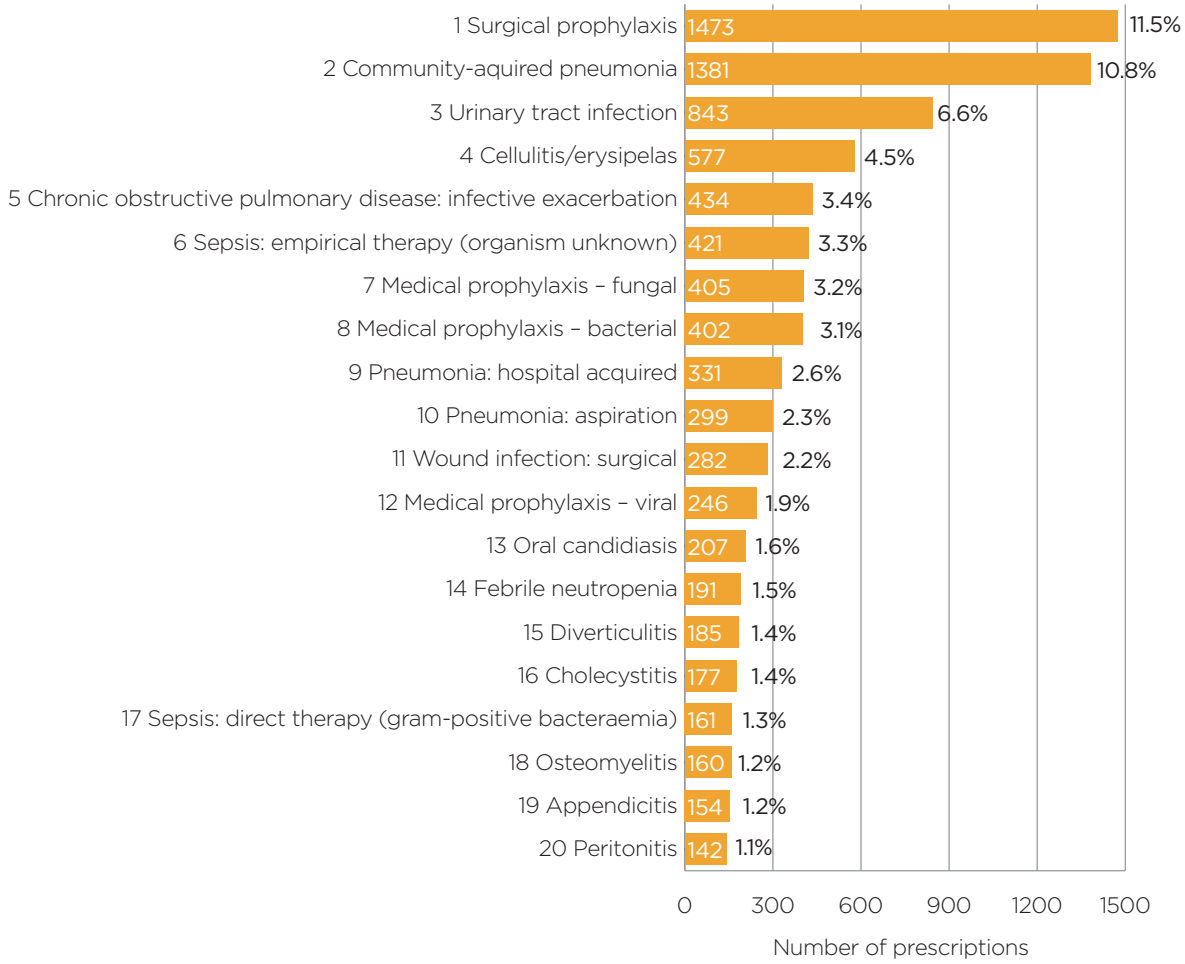
Other notable features were as follows:

- More than 40% of surgical prophylaxis was administered for more than 24 hours (the great majority should be single dose, as recommended in *Therapeutic guidelines: antibiotic*).
- Only 60% of prescriptions for acute exacerbations of chronic obstructive pulmonary disease were considered appropriate.
- Appropriateness was highest when narrow-spectrum antimicrobials were prescribed.

Healthcare impact

The 2013 NAPS has revealed a range of suboptimal prescribing practices, including lack of documentation of indication in the medical record, excessive durations for surgical prophylaxis, only moderate rates of compliance with guidelines, and inappropriateness of use. These practices present many opportunities for improvement that can be delivered by antimicrobial stewardship systems as they evolve and mature.

Figure 21 National Antimicrobial Practice Survey 2013 – top 20 most common indications

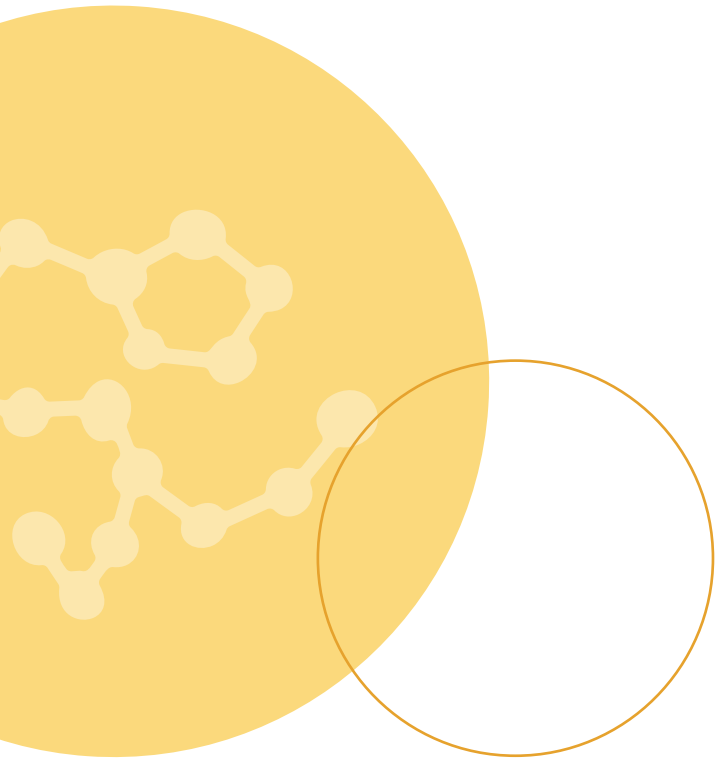


Source: Australian Commission on Safety and Quality in Health Care[40]

Table 11 Results of key indicators for all contributing hospitals – National Antimicrobial Practice Survey 2013

Key indicator		% of total prescriptions	% of total assessable prescriptions[a]
Indication documented in medical notes (best practice >95%)		70.9	
Surgical prophylaxis given for >24 hours (best practice <5%)		41.5[b]	
Compliance with guidelines	Compliant with *Therapeutic guidelines: antibiotic* or endorsed local guidelines	59.7	72.2
	Noncompliant	23.0	27.6
	No guideline available	11.0	
	Not assessable	6.3	
Appropriateness	Appropriate (optimal + adequate)	70.8	75.6
	Inappropriate (suboptimal + inadequate)	22.9	24.4
	Not assessable	6.3	

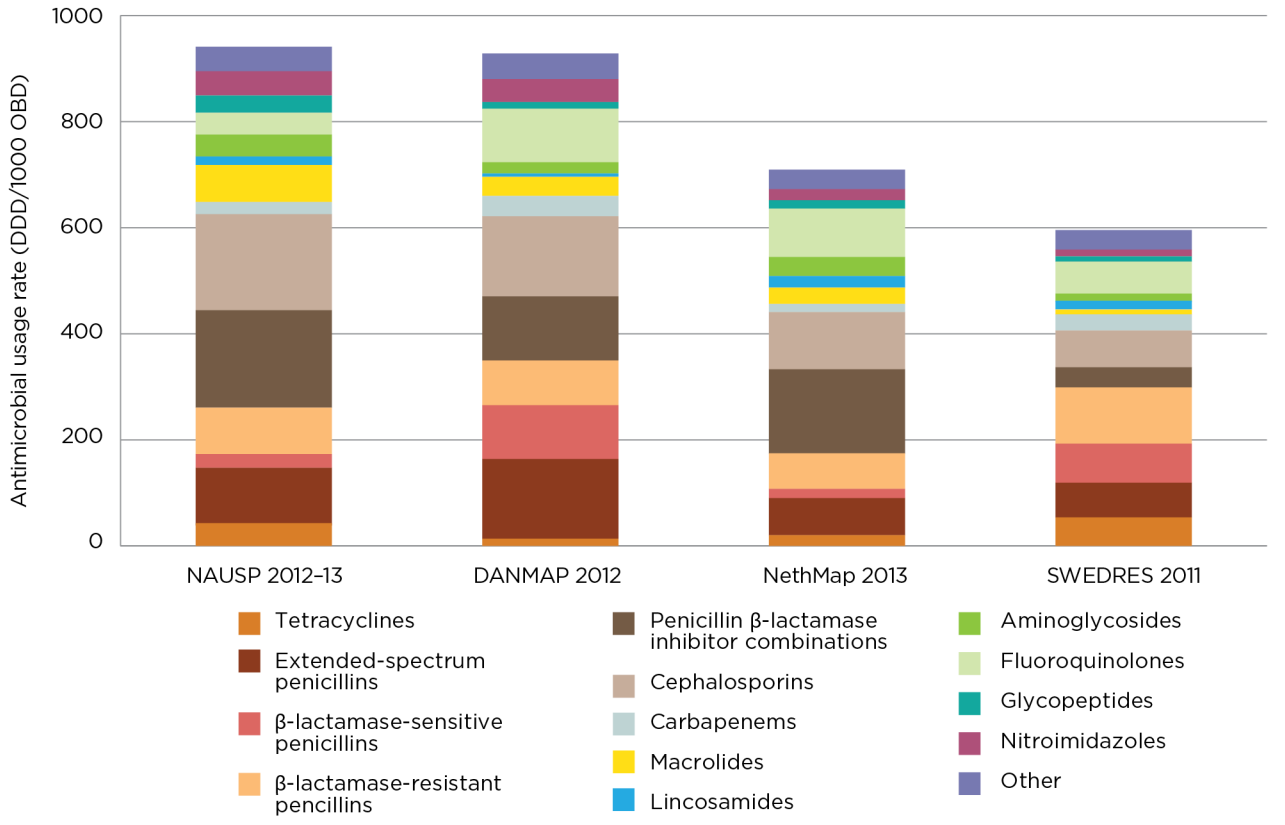
a Assessable means that the denominator excludes antimicrobial prescriptions marked 'Guideline not available' or 'Not assessable'.
b Where surgical prophylaxis was selected as the indication (1473 prescriptions)
Source: Australian Commission on Safety and Quality in Health Care[40]



International comparison with Australian antimicrobial use rates

Australian aggregated hospital AU rates can be compared with those from Sweden, Denmark and the Netherlands, which collect similar data from surveillance programs. Figure 22 shows that the Australian NAUSP hospitals record higher AU rates than those of the other countries, especially for macrolides, glycopeptides and nitroimidazoles. Of note is the relatively high use of fluoroquinolones in Denmark and the Netherlands compared with Australia. These differences may reflect differences in drug availability, prescribing patterns, microbial resistance patterns, policies and regulation.[39]

Figure 22 Antimicrobial use in hospitals in Australia compared with Denmark, Sweden and the Netherlands



DANMAP = data from Denmark; DDD/1000 OBDs = defined daily doses per 1000 occupied bed days; NETHMAP = data from the Netherlands; SWEDRES = data from Sweden

Notes:

1. NAUSP 2012–13 includes Australian data from July 2012 to June 2013.
2. DANMAP 2012 rates represent 2012 use.
3. NethMap 2013 rates represent 2011 use.
4. SWEDRES 2011 rates use denominator data from 2010.
5. 'Other' includes lipopeptides, monobactams, methenamine, nitrofurans, oxazolidinones, polymyxins, rifamycins, short-acting sulfonamides, streptogramins, steroids, sulfonamide/trimethoprim combinations, trimethoprim.

Source: SA Health[39]

4 Relationship between antimicrobial use and resistance

There have been no attempts to determine the relationship between antimicrobial use (AU) and antimicrobial resistance (AMR) in Australia at the national level. Analysing AU rates and AMR will support Australia's efforts to identify these relationships and design interventions. Such relationships are complex and greatly influenced by demographics, geographic location and infection control factors. The only attempt at modelling the relationship in Australia was in 2001, when Hay and Pettitt used sophisticated statistical techniques to show a strong relationship, in a single Australian hospital, between the amount of third-generation cephalosporins used across the hospital and extended-spectrum blactamase (ESBL)–producing *Klebsiella pneumoniae*.[41]

Of the more recent data sources available in Australia, the Queensland Health surveillance systems (OrgTRx and MedTRx) uniquely enable comparison of AU and AMR in the public hospital system in that state.

The data from Queensland clearly show that the relationship between AU and AMR is complex, and is different for every organism–antimicrobial combination. Over a 5.5-year period, two of the antimicrobial–organism combinations show stable usage patterns and stable resistance patterns (Figures 23 and 24), whereas other combinations show trends of increasing use and increasing resistance (Figures 25 and 26). These data provide some insights into whether there are strong relationships between AU and AMR. Where the relationship is strong (Figures 25 and 26), it suggests that resistance may be controlled or reduced by more judicious or controlled use of the agent. Where the relationship is poor (Figures 23 and 24), it suggests that other measures, such as infection control and prevention, may be better methods of managing resistance.

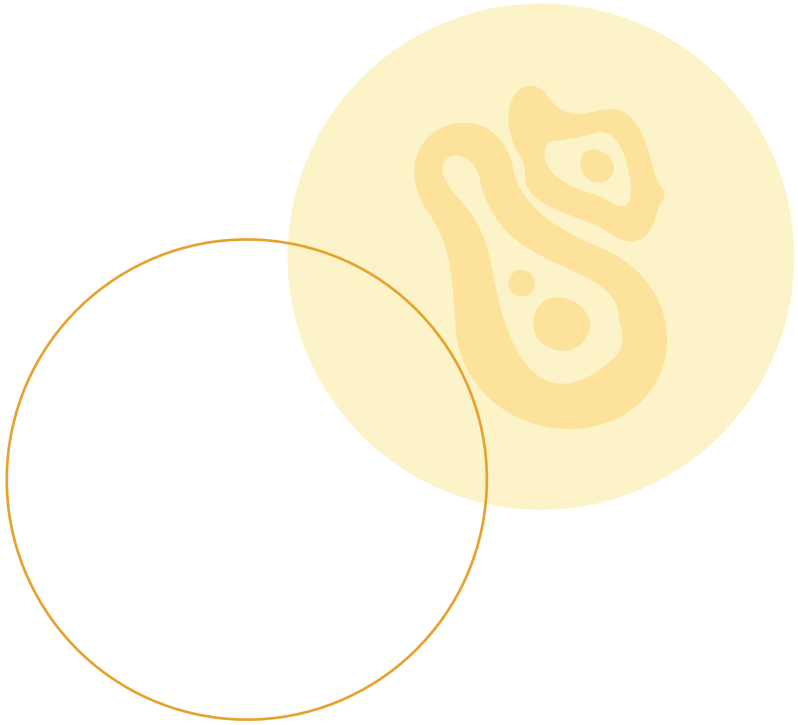
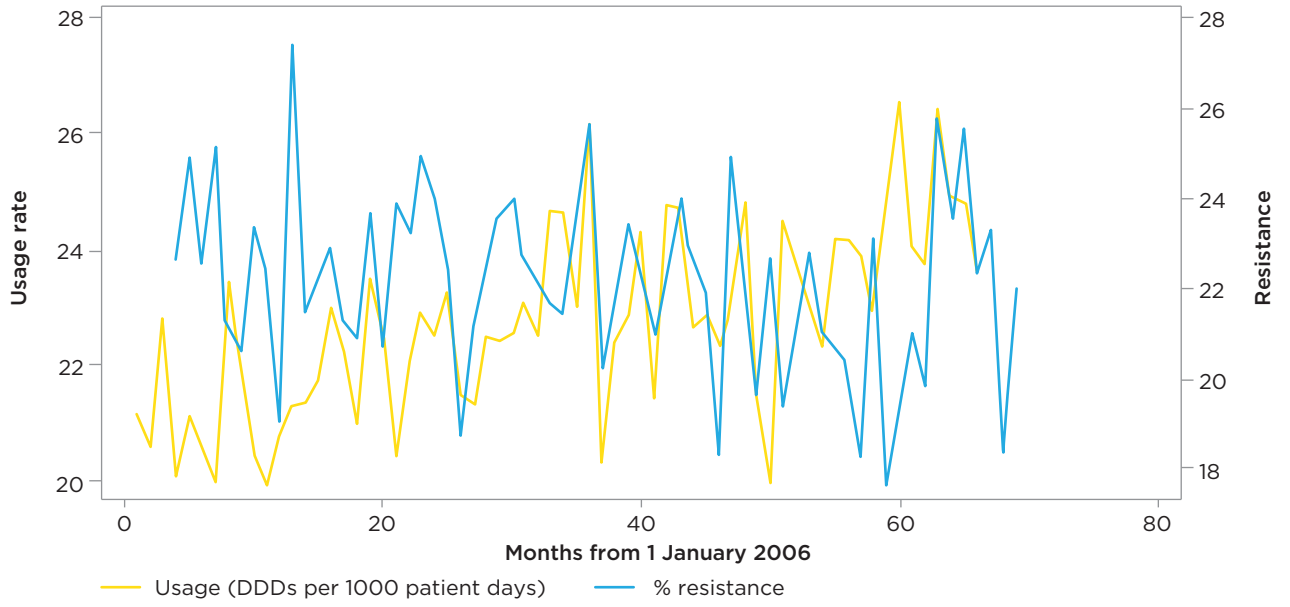


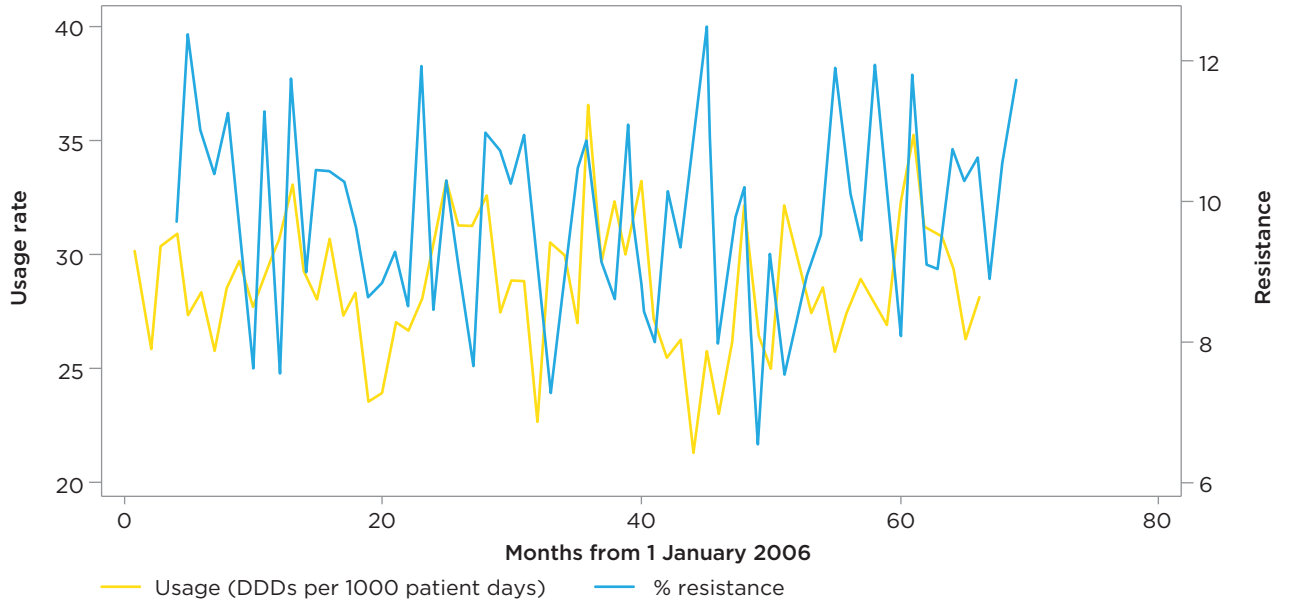
Figure 23 Ticarcillin–clavulanate use and *Pseudomonas aeruginosa* resistance in Queensland, showing a poor relationship between use and resistance



- 25% increase in use (19–24 DDDs per 1000 patient days)
- no change in % resistance (21%)
- no auto-correlation
- no cross-correlation
- 2 largest facilities also no correlation

DDD = defined daily dose
Source: Queensland Health's Communicable Diseases Unit, 2014

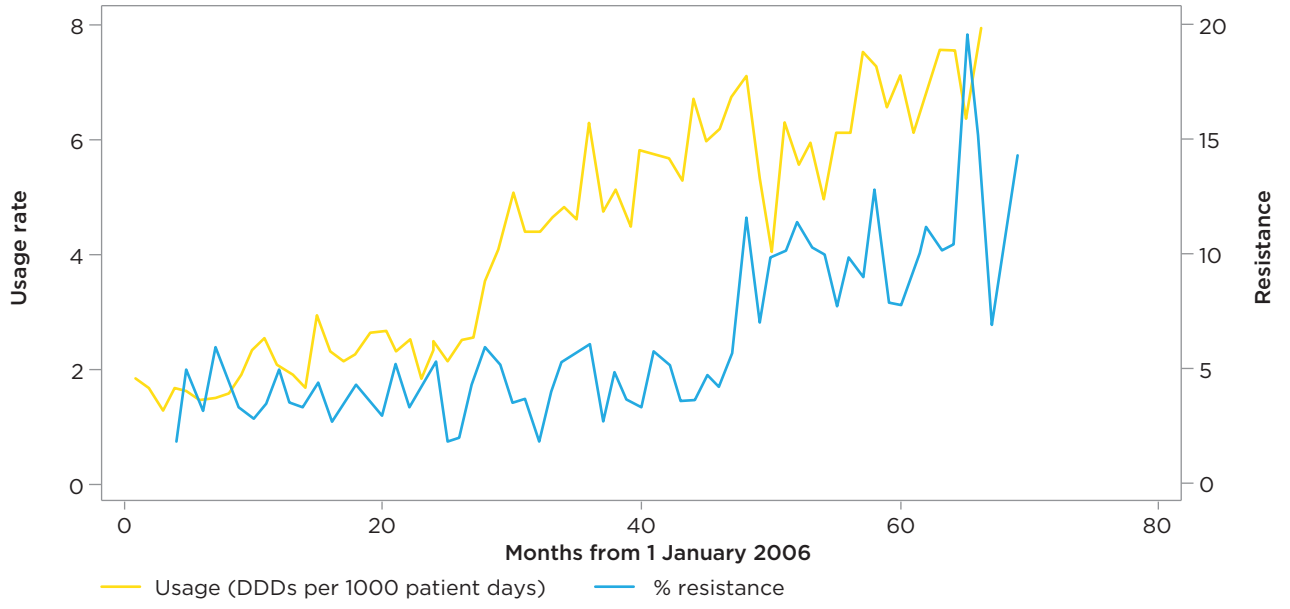
Figure 24 Ciprofloxacin use and *Pseudomonas aeruginosa* resistance in Queensland, showing a poor relationship between use and resistance



- no change in use (28 DDDs per 1000 patient days)
- no change in % resistance (10%)
- no auto-correlation
- no cross-correlation

DDD = defined daily dose
Source: Queensland Health's Communicable Diseases Unit, 2014

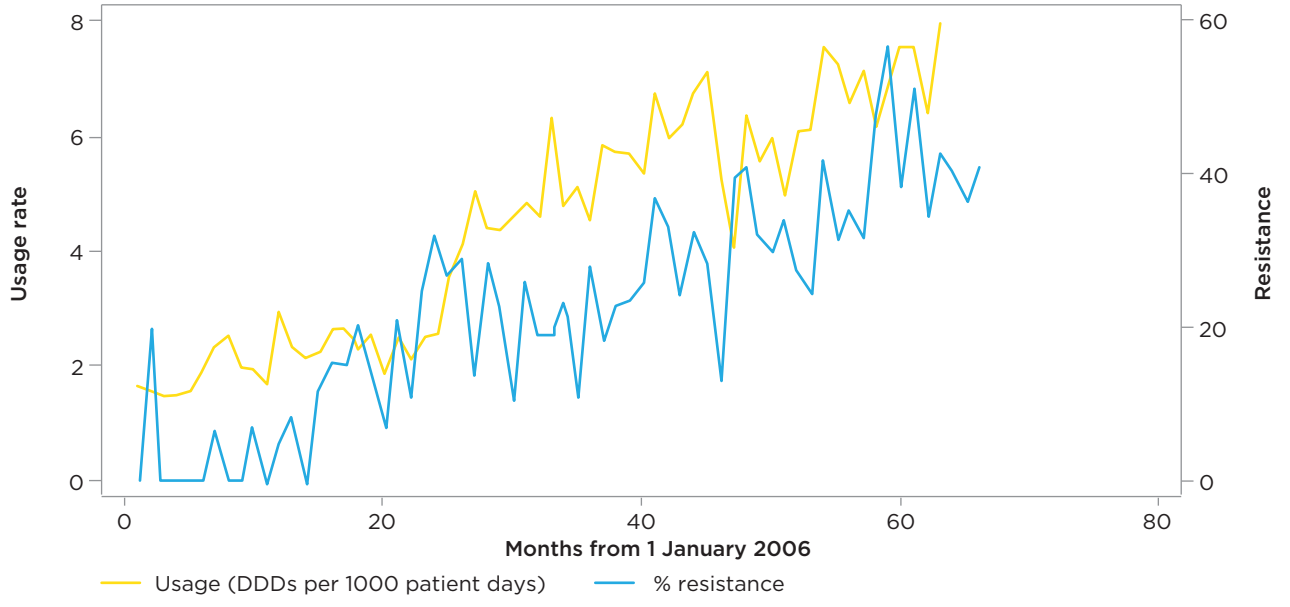
Figure 25 Piperacillin–tazobactam use and *Pseudomonas aeruginosa* resistance in Queensland, showing a strong relationship between use and evolving resistance



- use increase 2–7 DDDs per 1000 patient days (70% increase)
- % resistance increase 3.5–11%

DDD = defined daily dose
Source: Queensland Health's Communicable Diseases Unit, 2014

Figure 26 *Piperacillin–tazobactam* use and *Enterococcus faecium* resistance in Queensland, showing a strong relationship between use and evolving resistance



DDD = defined daily dose
Source: Queensland Health's Communicable Diseases Unit, 2014

5 Conclusion

Australia has a number of firmly established antimicrobial resistance (AMR) issues that impact directly on medical care in hospitals and the community. These include third-generation cephalosporin-resistant *E. coli* and *Klebsiella* species, methicillin-resistant *S. aureus*, and vancomycin-resistant *E. faecium*. Recent concerning trends include the emergence of reduced susceptibility to ceftriaxone in *Neisseria gonorrhoeae* and multidrug resistance in *Mycobacterium tuberculosis*.

Much of the resistance in Australia is being driven by high antimicrobial use (AU) in both the community and in hospitals, which is higher than in most developed countries. A recent national survey of Australian hospitals has shown considerable opportunities to improve the quality of prescribing. It is likely that similar opportunities for improvement exist in primary health care.

The Antimicrobial Use and Resistance in Australia (AURA) Project is using these findings, along with a significant body of new work, to build an effective and sustainable national surveillance system. AURA will establish new systems, as required, and integrate these with current programs that have been enhanced. In a number of areas, AURA will undertake new analyses and report on trends over time. It will examine the potential relationships between AMR and AU, and will also identify changes as interventions are introduced to contain AMR in Australia. The AURA Project will also provide reports and data to hospitals, jurisdictions and the community sector to inform policy and program development for AMR.

Appendix A Benefits and limitations of types of passive surveillance data for antimicrobial use

Data type	Data sources (number of software systems)	Benefits	Limitations
Amount prescribed	Electronic prescribing systems (>10)	Can link to clinical data (e.g. indication) Ability to use data to influence prescriber decision. More than 95% of GPs used these systems	No standardised data structures or reports Stand-alone systems not centrally linked Not uniformly used for prescribing in Australia
	Manual prescription chart audit (0)	Enables assessment of clinical appropriateness and context	Manual data collection is time intensive and not ongoing
	NPS MedicineInsight (1)	Will provide data from 300 representative community-based GP practices Link to reason for use and pathology test orders	Rollout is currently ongoing No AU reports yet
	BEACH data (1)	Data from 100 consecutive consultations with 1000 representative GPs	Not an ongoing data system Antimicrobial prescribing is not routinely surveyed

(continued)

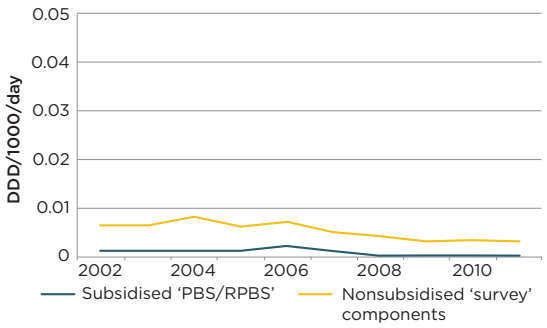
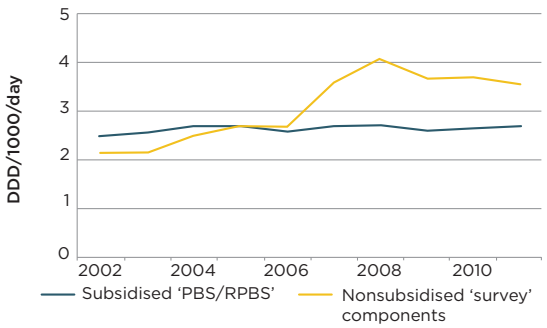
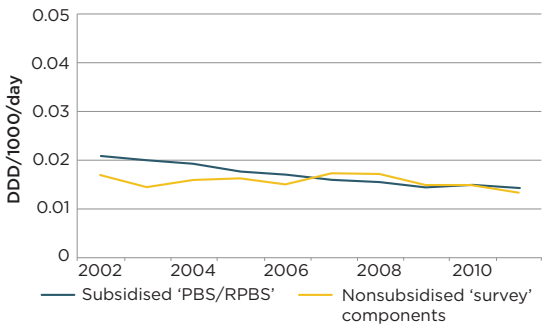
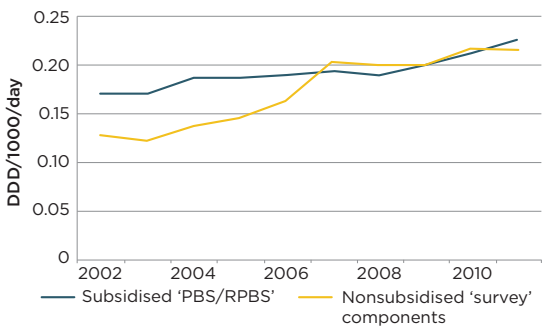
Data type	Data sources (number of software systems)	Benefits	Limitations
Amount dispensed	Statewide hospital pharmacy dispensing systems (ACT, NT, Qld, SA, Tas) (1)	Extensive tracking of all hospital dispensing procurement and supply Data fields standardised within each state (e.g. iPharmacy feeds all Qld use data to MedTRx)	Only in hospitals and only in some states Unable to report stock supplied on imprest (i.e. stored on ward for general use)
	Hospital pharmacy systems (NSW, Vic, WA) (>3)	Extensive tracking of all hospital dispensing procurement and supply	Stand-alone systems not centrally linked Hospital data not standardised
	Community pharmacy dispensing systems (>10)	Extensive tracking of all community dispensing procurement and supply – including RACFs and private hospitals serviced by the community pharmacy	Stand-alone systems not centrally linked
	Guild survey (0)	Representative survey of community pharmacy dispensing	Representative survey of only 500 community pharmacies Likely to underrepresent private usage Does not include non-PGA pharmacies (e.g. discount chains)
	RACF Webstercare unit dose systems (1)	Able to track RACF-specific dispensing Dose systems established	RACF only Community systems vary and may not be compatible with the Webstercare Unit
Amount procured or distributed	Hospital pharmacy procurement systems (>3)	Most comprehensive view of total amount procured (includes imprest stock)	Unable to account for actual used (e.g. includes loss, discarded stock, out-of-date stock, 'shrinkage' [stolen]) Not linked to patient or ward use (i.e. unable to convert to DDDs)
	Wholesalers and manufacturers	Provides gross national sales on AU Able to be compared internationally by manufacturers (i.e. allowing international comparison of drugs under patent)	Sales not directly linked to use (e.g. lag time from sale to use) Data not very granular (interpretation and use of data from analysis are limited) Data commercial in confidence and therefore not publicly available Limited manufacturer data with associated cost for reporting

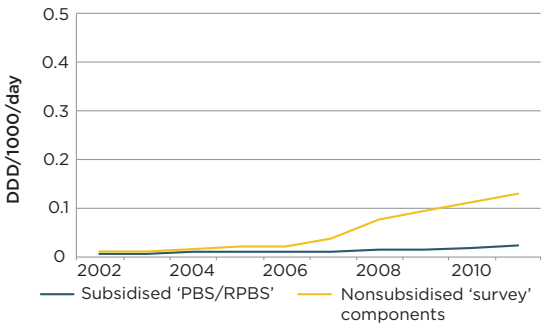
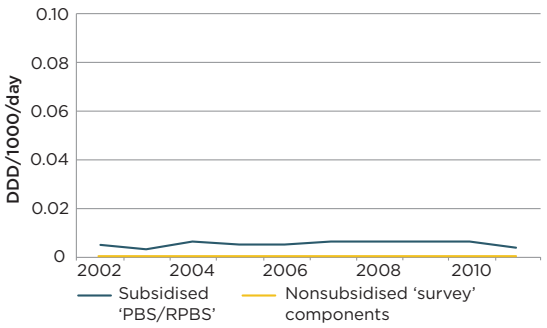
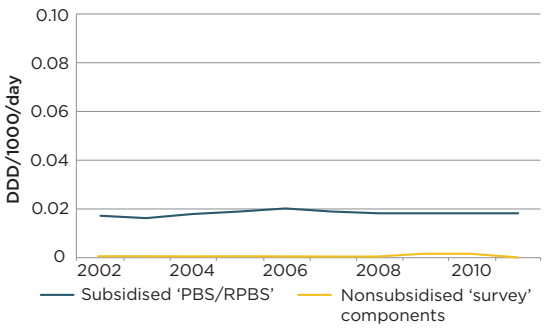
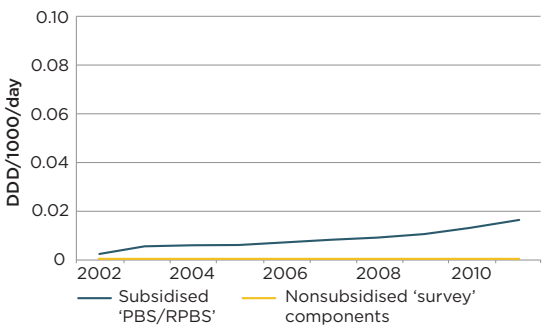
(continued)

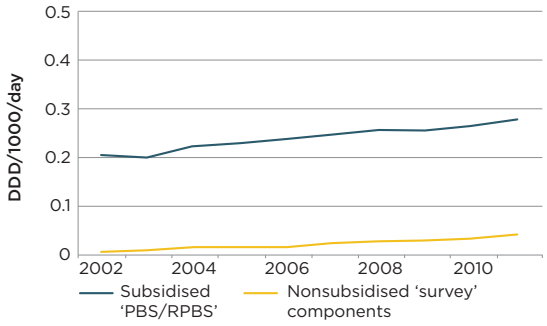
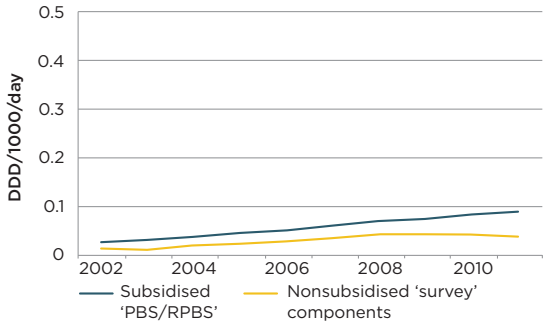
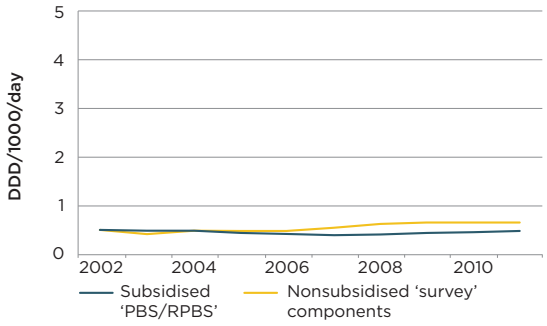
Data type	Data sources (number of software systems)	Benefits	Limitations
Amount administered to the patient	Electronic administration systems (e.g. ICU and EMR systems) (>5)	Contains extensive clinical data (for appropriateness of therapy and linking to AMR, etc.) Captures use in high-AMR clinical areas	Very limited clinical scenario Systems in limited use nationally (e.g. only used in individual wards)
	Manual medication administration chart audit (0)	Enables assessment of clinical appropriateness and context Used by NAPS	Manual data collection is time intensive and not always continuous (i.e. point prevalence)
	Antibiotics Reminder app (from NPS MedicineWise) (1)	Tracks patient record of administration	Very limited number of consumer users currently
Amount claimed for reimbursement	PBS claims system (including S100 authority) (3–5)	Includes dispensing data from all PBS claims (i.e. unrestricted, authority S100 antibiotics in community use, RACF, doctors bag, public hospital discharge PBS items, some public hospital outpatients, private hospital dispensed by pharmacy)	Data on items under co-payment only available from April 2012 Does not include private prescriptions, public hospital inpatients, 60% of discharges, some public outpatients or private hospital inpatient use (e.g. occupational therapy, ICU, non-PBS items), special access schemes, clinical trial or sample stock Unable to identify RACF prescriptions
	Private health fund claim data	Provides limited data on private prescriptions and non-PBS listed items	Does not include items under co-payment (usually $50) Restricted list (i.e. not comprehensive)

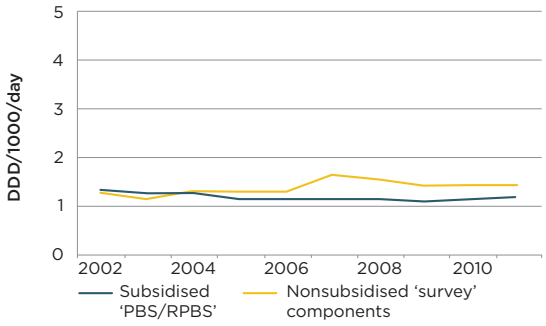
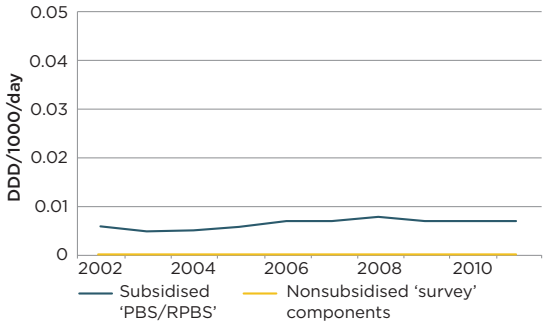
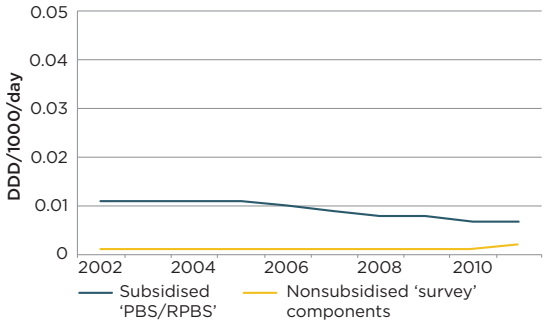
AMR = antimicrobial resistance; AU = antimicrobial use; BEACH = Bettering the Evaluation and Care of Health; DDD = daily defined dose; EMR = electronic medical record; GP = general practitioner; ICU = intensive care unit; imprest = a financial accounting system; NAPS = National Antimicrobial Prescribing Survey; NPS = National Prescribing Service; PBS = Pharmaceutical Benefits Scheme; PGA = Pharmacy Guild of Australia; RACF = residential aged-care facility

Appendix B Trends for antimicrobial use (ATC group J01) for individual agents, 2011

Agent	2002–11 usage trend
Ampicillin	
Amoxycillin	
Oxacillin – dicloxacillin	
Oxacillin – flucloxacillin	

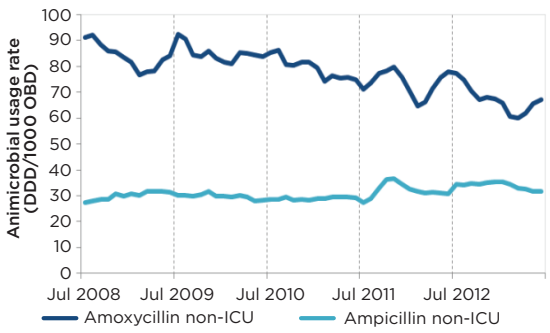
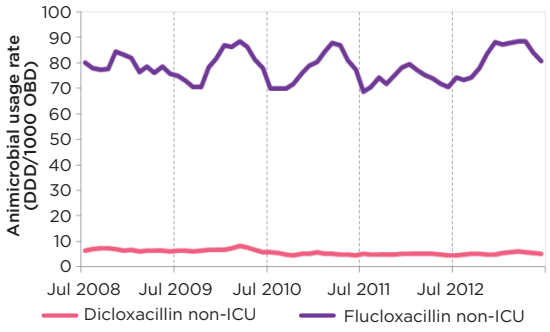
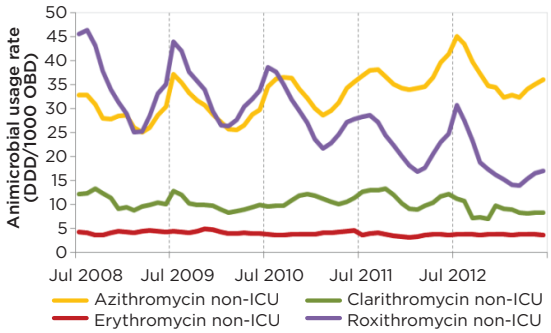
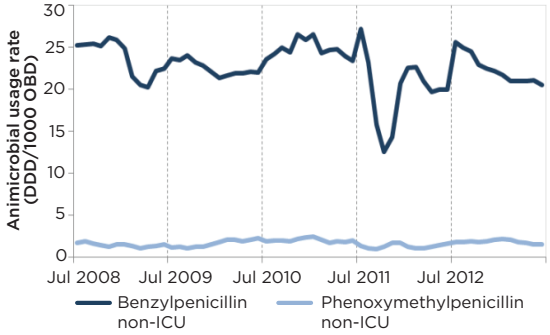
Agent	2002–11 usage trend
Azithromycin	
Benzyl-penicillin	
Ceftriaxone	
Cefazolin	

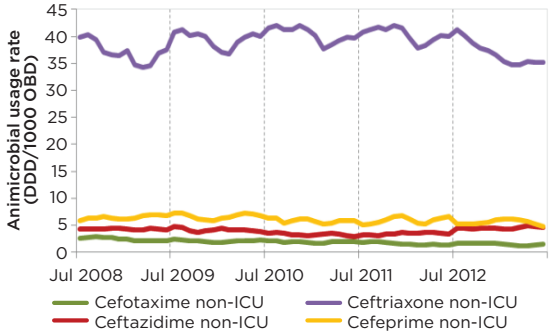
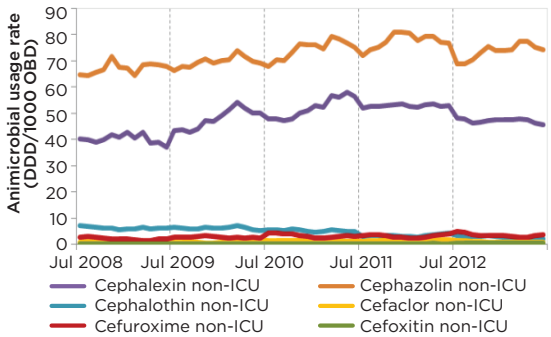
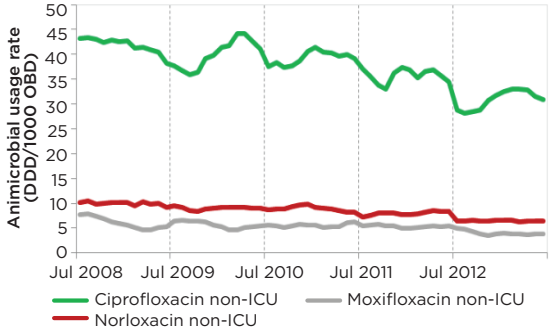
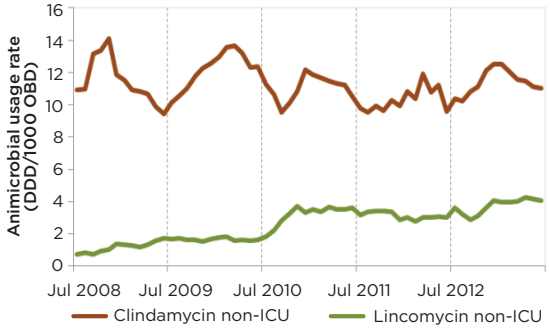
Agent	2002–11 usage trend
Ciprofloxacin	
Clindamycin	
Erythromycin	

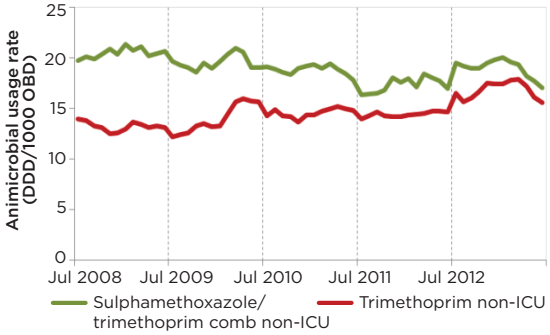
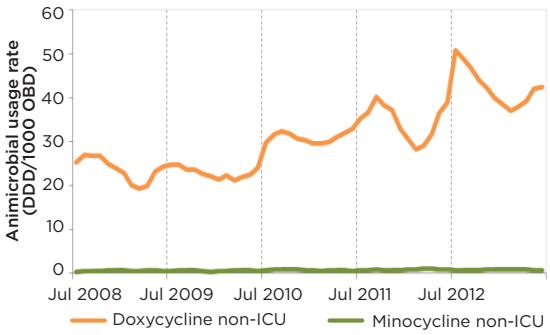
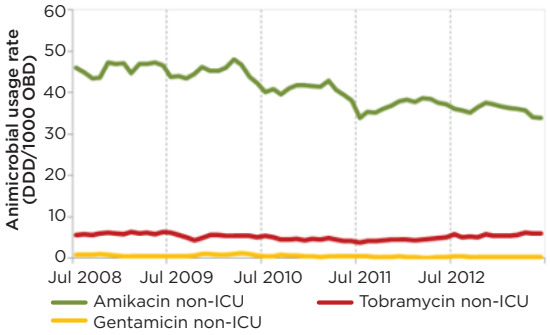
Agent	2002–11 usage trend
Doxycycline	
Vancomycin	
Gentamicin	

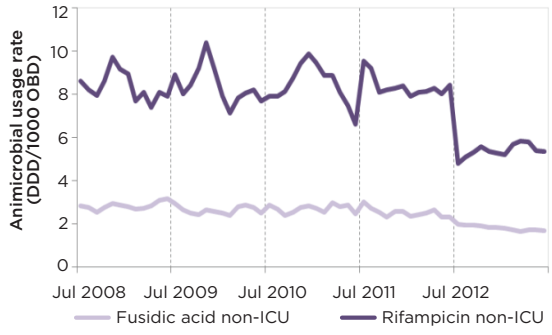
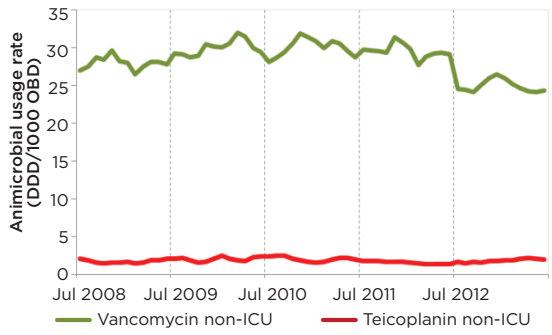
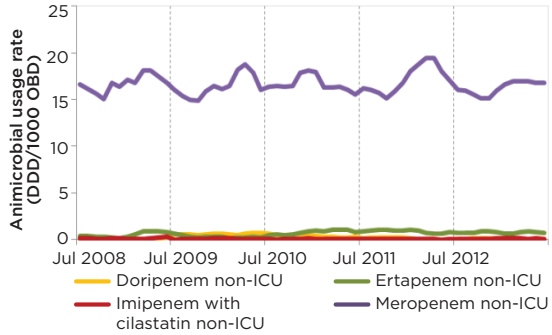
ATC = Anatomical Therapeutic Chemical; DDD/1000/day = defined daily doses per 1000 inhabitants per day; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
Source: Australian Government Department of Health[34]

Appendix C Trends in total hospital usage rates for relevant core agents for priority organisms, from contributors to NAUSP, 2008–13

Agent	July 2008 – July 2013 usage rates
Amoxycillin/ Ampicillin	
Isoxazoyl-penicillins	
Macrolides	
Benzyl-penicillin and phenoxy-methyl-penicillin	

Agent	July 2008 – July 2013 usage rates
Third- and fourth-generation cephalo-sporins	
First- and second-generation cephalo-sporins	
Fluoro-quilonones	
Lincos-amides	

Agent	July 2008 – July 2013 usage rates
Folate antagonists	
Tetracyclines	
Amino-glycosides	

Agent	July 2008 – July 2013 usage rates
Rifampicin and fusidic acid	
Glyco-peptides	
Carba-penems	

DDD/1000 OBD = defined daily doses per 1000 occupied bed days; ICU = intensive care unit; NAUSP = National Antimicrobial Utilisation Surveillance Program
Source: SA Health[39]

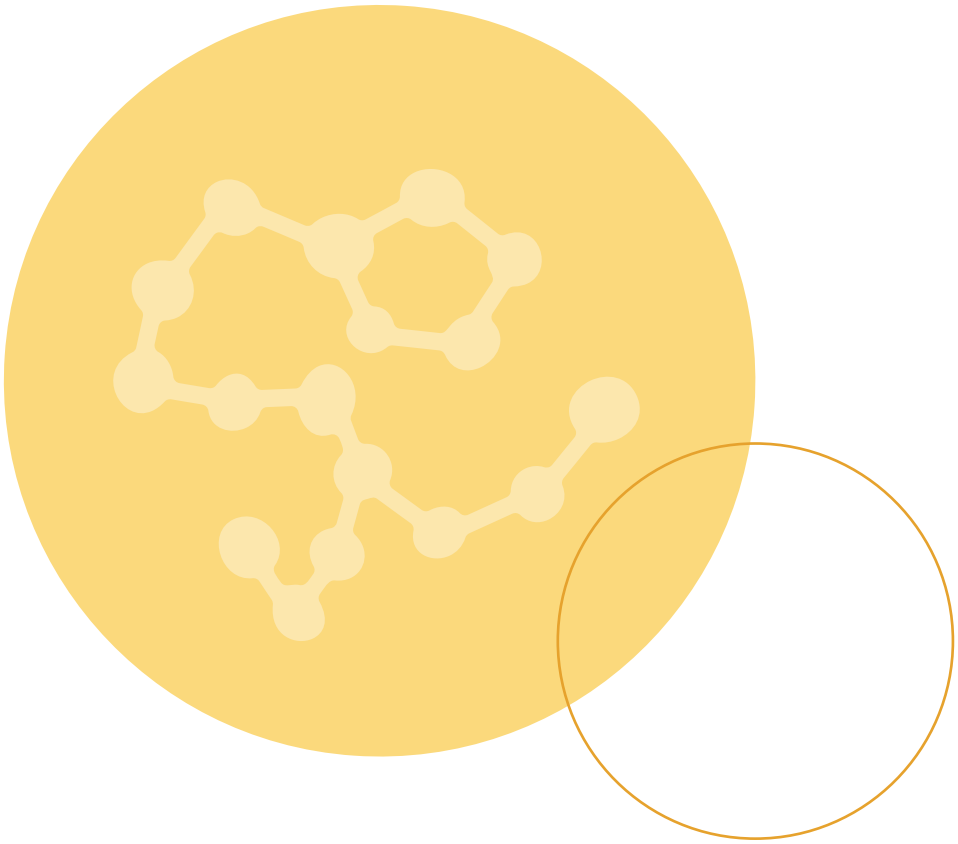
Acronyms and abbreviations

AGAR	Australian Group on Antimicrobial Resistance
AMR	antimicrobial resistance
AU	antimicrobial use
AURA Project	Antimicrobial Use and Resistance in Australia Project
BEACH	Bettering the Evaluation and Care of Health
CA-MRSA	community-associated methicillin-resistant *Staphylococcus aureus*
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Program
DDD	defined daily dose
ESBL	extended-spectrum β-lactamase
HA-MRSA	healthcare-associated methicillin-resistant *Staphylococcus aureus*
ICU	intensive care unit
IMP	integron–encoded metallo-β-lactamase
KPC	*Klebsiella pneumoniae* carbapenemase
MedTRx	Queensland Health's system for surveillance of antimicrobial use
MRSA	methicillin-resistant *Staphylococcus aureus*
NAPS	National Antimicrobial Prescribing Survey
NAUSP	National Antimicrobial Utilisation Surveillance Program
NDM	New Delhi metallo-β-lactamase
NEPSS	National Enteric Pathogen Surveillance Scheme
NethMap	Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands
NNN	National Neisseria Network
NPS	National Prescribing Service
OBD	occupied bed day
OrgTRx	Queensland Health's system for surveillance of antimicrobial resistance
PBS	Pharmaceutical Benefits Scheme
RACF	residential aged-care facility
RPBS	Repatriation Pharmaceutical Benefits Scheme
SWEDRES	Swedish Antibiotic Utilisation and Resistance in Human Medicine

Definitions

Term	Definition
Levels of bacterial resistance	
intermediate	Associated with uncertainty about the outcome of treatment with the nominated antimicrobial agent, based on the results of a susceptibility test in a defined test system.
resistant	Unlikely to respond to treatment with the nominated antimicrobial agent, based on the results of a susceptibility test in a defined test system.
susceptible	Likely to respond to treatment with the nominated antimicrobial agent, based on the results of a susceptibility test in a defined test system.
nonsusceptible	A combination of 'resistant' and 'intermediate' categories, or when there is no information about the likelihood of response as a result of absence or rarity of 'resistant' strains.
General terms	
antibiotic	Common term for an antimicrobial agent that can be used systemically in treatment, always implying that it is antibacterial in nature.
antimicrobial (agent)	Antimicrobial agents, in general terms, include substances with antibacterial, antifungal, antiviral, antiprotozoal or anthelminthic properties, which are used systemically for treatment of infection. They exclude antiseptics that are only used topically. In this report, it refers to antibacterial agents.
antimicrobial resistance	In this report, antimicrobial resistance occurs when an organism acquires a genetic trait that makes it resistant to the activity of a previously effective antimicrobial agent. This leads to a high likelihood of failure when that agent is used for treatment.
breakpoint	A laboratory value used to interpret the results of phenotypic laboratory tests for susceptibility and to categorise results into 'susceptible', 'intermediate' and 'resistant' for clinical reporting purposes.
community associated	Infection or bacterial clone that is characteristically spread in the community.
community onset	Infection or isolate of bacteria from specimens collected in the community, emergency departments or outpatient clinics.
gram-negative	Types of bacteria that do not retain Gram's stain (crystal violet), the conventional stain used in visualising bacteria in laboratory microbiology.
gram-positive	Types of bacteria that retain Gram's stain (crystal violet), the conventional stain used in visualising bacteria in laboratory microbiology.
healthcare associated	Infection or bacterial clone that is characteristically spread in the hospital or related environment.
hospital acquired	An infection acquired as a consequence of hospitalisation and its attendant interventions.
hospital onset	Infection or isolate of bacteria from specimens collected more than 48 hours after hospital admission.
invasive	Infection or isolate of bacteria from blood or sterile body sites (other than the urinary tract).

Term	Definition
minimum inhibitory concentration (MIC)	A laboratory-derived value arising from some forms of phenotypic susceptibility test. The MIC is the lowest concentration preventing the growth of the organism in vitro over a defined period, usually 18–24 hours.
multidrug resistance	Acquired resistance to more than one drug class.
noninvasive	Infection or isolate of bacteria from superficial sites or the urinary tract.
passive AMR surveillance	The routine collection of all, or most, available data regarding antimicrobial susceptibility of bacterial isolates from all clinical specimens routinely submitted for culture. It does not include specimens from environmental or infection control screening programs.
phenotypic testing	Testing based on the suppression of growth of an organism to detect antimicrobial resistance in that organism.
targeted AMR surveillance	The collection of a set of isolates of a specific bacterial species or group of species, often from one or a limited range of specimen types specified in a surveillance protocol.



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