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AURA
Antimicrobial Use and Resistance in Australia

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Antimicrobial Use in Australia

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Introduction

This paper supports the publication *AURA 2016: First Australian report on antimicrobial use and resistance in human health* (AURA 2016),[1] and provides more detailed information on antimicrobial[1] use in hospitals and in the community. Further details on all citations and data sources included in this paper are available in AURA 2016.

Australia has high antimicrobial use compared with many other countries of similar socioeconomic status, both in hospitals and in community settings.[2] There is evidence that some of this prescribing and use is unnecessary and inappropriate.[1]

This paper focuses on the antibacterials most often prescribed and used in Australia – in particular the first-generation cephalosporins (for example cefazolin and cephalexin), extended-spectrum penicillins (for example ampicillin and amoxicillin) and β-lactamase inhibitor combinations (for example piperacillin with tazobactam; and amoxicillin with clavulanate).

Which antibacterials are used most often in hospitals?

Data from the National Antimicrobial Prescribing Survey (NAPS) showed that during the 2014 survey period, 38.4% of people in Australian hospitals were prescribed an antibacterial, antifungal or antiviral medicine.[1] Data from the National Antimicrobial Utilisation Surveillance Program (NAUSP) showed that antibacterial use in hospitals has gradually declined since its peak in 2010 (for example, Table 1 shows how use of first-generation cephalosporins, extended spectrum penicillins and β-lactamase inhibitor combinations has declined since 2010), and that use varies widely between the states and territories, for reasons that are unclear.[1]

Table 1: Total hospital antibacterial usage rates, by defined daily dose per 1000 occupied bed days, for selected antibacterial classes, 2010–14[3]

Antibacterial class	2010 (*n* = 53)	2011 (*n* = 61)	2012 (*n* = 79)	2013 (*n* = 114)	2014 (*n* = 129)
First-generation cephalosporins (e.g. cefazolin, cephalexin)	139.04	142.48	132.39	133.66	130.90
Extended-spectrum penicillins (e.g. ampicillin, amoxicillin)	117.04	112.10	107.52	104.83	103.39
β-lactamase inhibitor combinations (e.g. piperacillin with tazobactam, amoxicillin with clavulanate)	185.15	186.99	187.57	186.82	180.70

n = number of participating hospitals
Source: National Antimicrobial Utilisation Surveillance Program 2014

[1] The term 'antimicrobial' is an umbrella term encompassing antibacterial, antifungal, antiviral, antimycobacterial and antiparasitic medicines. This report focuses mainly on antibacterials.

The NAUSP data also showed that 20 antibacterials represented 92% of all antibacterial use in Australian hospitals using the World Health Organization (WHO) standardised measure of use: DDD/1000 OBD (defined daily doses per 1000 occupied bed days). Six antibacterials – amoxicillin with clavulanate, flucloxacillin, cefazolin, amoxicillin, doxycycline and cephalexin – represented more than 50% of all use.[1] By way of comparison, the NAPS data showed that six antibacterials – cefazolin, ceftriaxone, metronidazole, piperacillin with tazobactam, amoxicillin with clavulanate, and cephalexin – represented 43.8% of all prescribed antibacterials (see Table 2).[1] The differences may be explained by the different types of data collected and analysed: the NAUSP data represent the volume-of-use aggregated monthly at the hospital level while the NAPS data are from a single-day audit of prescribing and appropriateness of prescribing within the hospital (see Table 8, page 9).

Table 2: Most frequently prescribed and supplied antimicrobials in hospitals, as a percentage of all antimicrobials prescribed and supplied in hospitals, 2014[1]

Rank	Most frequently prescribed (NAPS)	Most frequently supplied (NAUSP)
1	Cefazolin (11.1%)	Amoxicillin–clavulanate (14.3%)
2	Ceftriaxone (9.1%)	Amoxicillin/ampicillin (11.1%)
3	Metronidazole (6.5%)	Flucloxacillin (9.1%)
4	Piperacillin–tazobactam (6.1%)	Cefazolin (8.5%)
5	Amoxicillin–clavulanate (6.0%)	Doxycycline (5.7%)
6	Cephalexin (5.0%)	Cephalexin (5.3%)
7	Flucloxacillin (4.5%)	Piperacillin–tazobactam (4.7%)
8	Doxycycline (3.9%)	Ceftriaxone (4.5%)
9	Benzylpenicillin (3.2%)	Metronidazole (4.3%)
10	Amoxicillin/ampicillin (2.8%)	Azithromycin (4.1%)

Sources: National Antimicrobial Prescribing Survey (NAPS) report, 2014; National Antimicrobial Utilisation Surveillance Program (NAUSP) report, 2014

Which antibacterials are used most often in the community?

Almost half (46%) of Australians were dispensed at least one antibacterial prescription under the Pharmaceutical Benefits Scheme (PBS) during 2014 – an overall rate of 23.8 DDD/1000 inhabitants/day.[1] Our prescribing rate ranks eighth highest among member countries of the Organisation for Economic Co-operation and Development (OECD), and is more than double that of countries that have low prescribing rates, such as the Netherlands and Scandinavian countries.[1] Antibacterial use in the community is now 6.7% lower than its peak of 25.5 DDD/1000 inhabitants/day in 2008, although there has been little change in overall rates from year to year.[1]

Antibacterial prescribing in the community varies between different age groups; it is highest in children (0–9 years) and older people (65 years or over).[1] Prescribing also varies between states and territories and local areas.[2] For example, the average number of antibacterial

[2] The Australian Bureau of Statistics (ABS) refers to local areas as 'Statistical Areas Level 3 (SA3)'. SA3s are geographic areas defined in the *ABS Australian Statistical Geography Standard* (ASGS). The aim of SA3s is to create a standard framework for the analysis of ABS data at the regional level through clustering groups that

prescriptions dispensed varied from 1021 per 1000 inhabitants in Western Australia to 1329 per 1000 inhabitants in Queensland;[1] and the amount of antibacterial prescribing varies by 1.9–2.7 times between local areas.[2]
In the community, the three antibacterial classes most often dispensed, representing 61% of all antibacterials dispensed nationally, were the same three classes as in hospitals (see Table 1, page 2 and Table 3 below).[1]

Table 3: Most frequently dispensed antibacterials in the community (number of PBS prescriptions) by antibacterial class, 2014[1]

Antibacterial class	% of dispensed antibacterials
Extended-spectrum penicillins (e.g. amoxicillin)	22%
First-generation cephalosporins (e.g. cephalexin)	21%
β-lactamase inhibitor combinations (e.g. amoxicillin with clavulanate)	18%

Source: Australian Government Department of Human Services pharmacy claim database, October 2015

Antibacterials and antifungals are widely used in residential aged-care facilities. The aged care National Antimicrobial Survey (acNAPS) data showed that, during the survey period, 11.3% of residents were prescribed an antibacterial or an antifungal.[1] In contrast to the rest of the community, topical antibacterials and antifungals represented 37.0% of all prescribing (see Table 4).[1]

have similar regional characteristics. There are 333 spatial SA3s covering the whole of Australia without gaps or overlaps. SA3s usually have a population of between 30 000 and 130 000 people. At 30 June 2011, about 50 had fewer than 30 000 people and 35 had more than 130 000 people. In the major cities, SA3s represent areas serviced by major transport and commercial hubs. They often closely align with large urban local government areas (for example Parramatta and Geelong). In regional areas, they represent areas serviced by regional cities with populations of more than 20 000 people. In outer regional and remote areas, they represent areas that are widely recognised as having a distinct identity and similar social and economic characteristics (for example the Macedon Ranges in Victoria and the Southern Highlands in NSW). There are a few 'zero SA3s', which have a very small or zero population and these are mainly very large national parks close to the outskirts of major cities.

Table 4: Top five antibacterials and antifungals prescribed in residential aged-care facilities (RACFs), 2015[4]

Antibacterial or antifungal prescribed in RACFs	% of antibacterials and antifungals prescribed
Cephalexin	16.7%
Clotrimazole (topical)	16.5%
Amoxicillin with clavulanate	6.5%
Trimethorpim	6.5%
Chloramphenicol (topical)	6.4%

Source: Aged care National Antimicrobial Prescribing Survey 2015

How appropriate is antibacterial use in hospitals?

Unnecessary or inappropriate use of antibacterials leads to a higher risk of adverse effects, unnecessary spending and increased risk of population- and individual-level antimicrobial resistance.[2]

The NAPS data showed that about one in four prescriptions were inappropriate (23.0%) or did not comply with guidelines (24.3%).[1] The top two reasons for inappropriate prescribing were that the prescribing was unnecessary or the spectrum was too broad (see Table 5).[1]

Table 5: Reasons for inappropriate prescribing in hospitals, 2014[3]

Reason prescribing inappropriate	Reason found (%)	Reason not found (%)	Not specified (%)
Antimicrobial not indicated	26.4	47.7	25.8
Spectrum too broad	20.6	54.3	25.1
Incorrect duration	18.8	57.3	23.9
Incorrect dose or frequency	18.3	59.0	22.7
Microbiology mismatch	6.4	93.6	0.0
Spectrum too narrow	5.9	66.9	27.2
Incorrect route	4.9	70.3	24.9
Allergy mismatch	2.2	97.8	0.0

Source: National Antimicrobial Prescribing Survey report, 2014

Inappropriate prescribing was highest for respiratory tract infections and surgical prophylaxis (see Table 6).[1] Of these surgical prophylaxis prescriptions, 35.9% continued beyond 24 hours, which is similar to that reported in the 2013 survey (less than 5% is considered best practice).[1] Prescribing that did not comply with guidelines occurred most often for surgical prophylaxis and infective exacerbation of chronic obstructive pulmonary disease.[1]

Table 6: Appropriateness of antimicrobial prescribing in hospitals for the 20 most common indications, 2014[3]

Rank of inapprop. prescribing	Rank of indication[a]	Indication	Number of prescriptions	Appropriate (%)	Inappropriate (%)	Not assessable (%)
1	1	Surgical prophylaxis	2246	56.9	40.2	2.9
2	7	COPD: infective exacerbation	552	62.3	36.8	0.9
3	16	Cholecystitis	209	72.2	27.8	0.0
4	2	Community-acquired pneumonia	1936	73.9	25.0	1.1
5	4	Urinary tract infection	1156	73.1	25.0	1.9
6	5	Cellulitis/ Erysipelas	759	74.7	24.8	0.5
7	20	Appendicitis	159	76.7	22.6	0.6
8	9	Wound infection: surgical	369	74.5	21.4	4.1
9	10	Pneumonia: aspiration	362	77.1	21.3	1.7
10	8	Hospital-acquired pneumonia	401	77.8	21.2	1.0
11	17	Abscess	190	77.9	19.5	2.6
12	6	Sepsis: empiric therapy	563	80.8	17.1	2.1
13	15	Diverticulitis	219	85.8	14.2	0.0
14	14	Osteomyelitis	249	81.9	13.3	4.8
15	18	Sepsis: Gram-negative bacteraemia	188	87.2	12.8	0.0
16	19	Diabetic infection (including foot)	169	88.2	11.2	0.6
17	12	Sepsis: Gram-positive bacteraemia	261	89.7	10.0	0.4
18	13	Febrile neutropenia	258	92.6	6.6	0.8
19	3	Medical prophylaxis (bacterial, viral and fungal)	1320	89.9	6.4	3.6
20	11	Oral candidiasis	332	89.8	5.7	4.5

COPD = chronic obstructive pulmonary disease
a Rank in the 20 most common indications, where 1 is the most common indication
Source: National Antimicrobial Prescribing Survey, 2014

How appropriate is antibacterial use in the community?

The NPS MedicineWise MedicineInsight program data showed that around 30% of people prescribed an antibacterial had an indication recorded for it in their medical record. Of these people, more than half of those who had colds and other upper respiratory tract infections were prescribed an antibacterial where none was indicated.[1]

Many people with acute tonsillitis, acute or chronic sinusitis, acute otitis media or acute bronchitis were prescribed an antibacterial even when such prescribing is either not recommended by or is not in line with *Therapeutic Guidelines: Antibiotic* recommendations (see Table 7).[1] For example, 91% of people were prescribed an antibacterial for acute tonsillitis, which is above the acceptable range[3] of 0–20%. Of these, 48% (95% CI 42–54%) were prescribed phenoxymethyl penicillin in line with *Therapeutic Guidelines: Antibiotic* recommendations, which is below the acceptable range of 80–100%. In contrast, 68% of people with pneumonia were prescribed an antibacterial, which is below the acceptable range of 90–100%. Of these, 24% (95% CI 19–29%) were prescribed either amoxicillin or doxycycline in line with *Therapeutic Guidelines: Antibiotic* recommendations, which is below the acceptable range of 80–100% (see Table 7).

Table 7: Patients prescribed systemic antibacterials for select conditions, 2014[1]

Condition	Patient category	Number	%	95% CI	Acceptable range[b] (%)
Acute URTI	Older than 1 year prescribed antibacterials[a]	45 743	47	44–56	0–20
Acute bronchitis or bronchiolitis	Aged 18–75 years prescribed antibacterials[a]	23 619	90	89–91	0–30
Acute tonsillitis	Older than 1 year prescribed antibacterials	13 135	91	90–92	0–20
	And prescribed the TG-recommended phenoxymethyl penicillin	6 243	48	42–54	80–100
Sinusitis (chronic or acute)	Older than 18 years prescribed antibacterials	17 300	86	84–87	0–20
	And prescribed the TG-recommended amoxicillin	5 607	32	29–36	80–100
Acute otitis media/myringitis	Older than 2 years prescribed antibacterials	11 387	91	90–92	0–20
	And prescribed the TG-recommended amoxicillin	7 154	63	59–67	80–100
Pneumonia	Aged 18–65 years prescribed antibacterials	607	68	64–71	90–100
	And prescribed the TG-recommended antibacterial (for mild CAP – amoxicillin or doxycycline)	146	24	19–29	80–100

[3] Values for an acceptable range of prescribing vary between conditions: for some conditions low values of 0–20% represent better quality of care whereas for other conditions high values of 90–100% represent better quality of care.[5]

Condition	Patient category	Number	%	95% CI	Acceptable range[b] (%)
Cystitis or other UTI	Females older than 18 years prescribed antibacterials	18 898	94	93–95	80–100
	And prescribed the TG-recommended trimethoprim	8 858	47	44–49	80–100

CAP = community-acquired pneumonia; CI = confidence interval; TG = *Therapeutic Guidelines: antibiotic*; URTI = upper respiratory tract infection; UTI = urinary tract infection

a No recommendations made by *Therapeutic Guidelines: antibiotic.*

b Values for an acceptable range of prescribing vary between conditions: for some conditions low values of 0–20% represent better quality of care whereas for other conditions high values of 90–100% represent better quality of care.[5]

Source: NPS MedicineWise MedicineInsight

These upper respiratory tract infection data are similar to that reported in the annual *Report on government services* (ROGS).[6] The ROGS publishes data about acute upper respiratory tract infection management as an Australian Government indicator of appropriate antibacterial use in the community.[6] This indicator has two measures:

1. filled general practitioner (GP) prescriptions for selected antibacterials per 1000 people[4]
2. proportion of visits to GPs for acute upper respiratory tract infections where antibacterials were prescribed.

Low or decreasing rates of these measures can show that GPs are managing upper respiratory tract infections more closely in accordance to guidelines. The latest data show that the:

- filled GP prescription rate for selected antibacterials was 295 per 1000 people in 2013-14[5]
- proportion of visits to GPs for acute upper respiratory tract infections where antibacterials were prescribed increased from 29.6% in 2009–10 to 32.8% in 2011–12 and decreased to 29.0% in 2013–14.

In residential aged-care facilities, the acNAPS data showed that about one in five prescriptions (21.7%; 119 of 548) were for residents with no signs or symptoms of infection during the week before the antibacterial or antifungal was prescribed.[4] It is likely that these were prescribed inappropriately.[4] For residents showing signs or symptoms of infection during the week before an antibacterial or antifungal was prescribed, about one in three prescriptions (33.6%; 158 of 470) were for indications that met the McGeer infection criteria.[6,4,7] It is possible that about two in three of these were prescribed inappropriately (using McGeer infection criteria as a surrogate measure of appropriateness).[4] Only 11.9% of residents with urinary tract infections, 30.5% with respiratory tract infections, and 48.3% with skin, soft tissue, eye or oral infections prescribed an antibacterial or an antifungal had infections that met the McGeer criteria. Finally, about one in three prescriptions (31.4%) were for more than six months before the audit date and only 2% of these had a review or stop-date documented.[1]

[4] PBS and RPBS data on antibacterials most often used to treat acute upper respiratory tract infection: phenoxymethylpenicillin, amoxicillin, amoxicillin–clavulanate, clarithromycin, erythromycin, roxithromycin, cefaclor, cefuroxime and doxycycline

[5] Because of changes to how this data is collected, it is impossible to draw comparisons with previous years.

[6] These are a set of clinical and other criteria used for surveillance of infection rates (not appropriateness of antimicrobial prescribing) in long-term care facilities that enable inter-facility comparison.

Data sources

Data about prescribing, use and appropriateness comes from several sources (see Table 8). Together these data provide information from hospitals, the community and residential aged-care facilities. For more information about these data – including limitations and considerations for interpretation – refer to Chapter 2 and Appendix 1 of AURA 2016.[1]

Table 8: AURA data sources

Data source	Data details	Program details
In hospitals		
National Antimicrobial Utilisation Surveillance Program (NAUSP)	Collects, analyses and reports data on the volume of antimicrobial use at the hospital level (and for some hospitals, at the intensive care level). The data collected are provided by pharmacy departments of participating hospitals. Quantities dispensed to patients and wards are aggregated monthly as grams and converted to defined daily doses (DDD) Data in this report refer to antibacterials.	The NAUSP has collected data from Australian hospitals since 2004. From 2010–14, the number of public and private hospitals contributing data to the NAUSP grew from 53 to 129. The number of large public hospitals grew from 18 to 51 and the number of medium sized public hospitals increased from 9 to 26. Data are reported for the calendar year 2014 and represents >90% of principal referral hospitals and 82% of total beds in public hospitals with >50 beds.
National Antimicrobial Prescribing Survey (NAPS)	Collects, analyses and reports on the volume and appropriateness of prescribing within the hospital. Audit data are collected by trained staff who assesses and report on prescribing practices and appropriateness of prescribing against guidelines within the hospital. Data in this report refers to antibacterials.	The NAPS was piloted in 32 hospitals in 2011 and by 2014 had increased to 248 hospitals. Data for this report were collected from October 2014 to February 2015.
In the community		
Australian Government Department of Human Services (DHS) Medicare pharmacy claims database	Analysis of data collected on volume of antibacterials dispensed as Pharmaceutical Benefits Scheme/Repatriation Pharmaceutical Benefits Scheme (PBS/RPBS) prescriptions including those under the co-payment (but not including an estimate of private prescriptions).	Data are reported from the 30 million prescriptions dispensed under the PBS/RPBS for the 2014 calendar year. This data was compared with long-term historical trend data held by the Drug Utilisation Sub-Committee.
NPS MedicineWise MedicineInsight program	Collects, analyses and reports data on antibacterial prescribing practices and appropriateness of prescribing from general practitioners participating in the program.	Participating general practitioners provide this data to the MedicineInsight program via their electronic records. Data for this report were collected from 182 general practices between 1 January and 31 December 2014 and represent 352 318 patient visits.

Data source	Data details	Program details
Aged care National Antimicrobial Prescribing Survey (acNAPS)	Collects, analyses and reports on the volume and appropriateness of antibacterial and antifungal prescribing in residential aged-care facilities. Audit data is collected by trained staff and include prevalence of signs and symptoms of infection and antibacterial and antifungal use within the residential aged-care facility. McGeer infection criteria are used as a surrogate measure of appropriateness of prescribing.	The acNAPS includes data from 975 prescriptions for 824 residents in 186 Australian residential aged care facilities. Data for this report are from the acNAPS pilot conducted in 2015.

First-generation cephalosporins: cefazolin and cephalexin

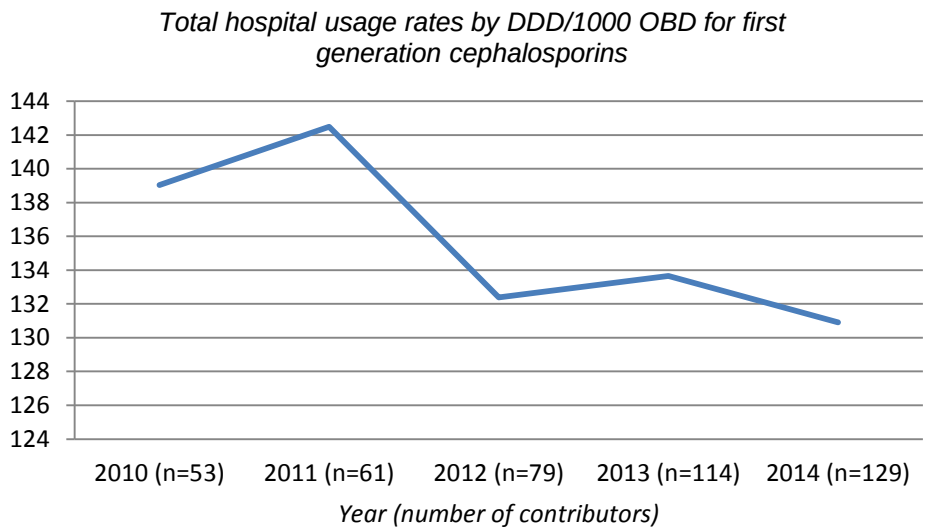
What organisms are they used to treat?

Cefazolin and cephalexin are first-generation moderate spectrum cephalosporins active against streptococci and staphylococci, including β-lactamase–producing staphylococci, but inactive against enterococci and *Listeria monocytogenes*. They are active against some gram-negative bacteria (including *Escherichia coli* and some *Klebsiella* species).[8] Cefazolin is given parenterally and cefalexlin is available in several oral formulations. Together with cefalothin, these comprise the three first-generation cephalosporins available in Australia.

How much is used in hospitals?

First-generation cephalosporins are amongst the most widely used antibacterial classes in Australian hospitals and in the community, including residential aged-care facilities.[9]
The NAUSP data showed that total use of first-generation cephalosporins has declined slightly since 2010 even as the number of contributors increased (Figure 1). In 2014, cefazolin and cephalexin were the third and sixth most used antibacterials, respectively accounting for 8.5% and 5.5% of all use.[10] In the same year, the NAPS data showed that cefazolin was prescribed to more people than any other antibacterial (11.1%).[11]

Figure 1: Hospital usage rates by defined daily doses per occupied bed day (DDD/1000 OBD) for first-generation cephalosporins: NAUSP contributors, 2010–14[10]

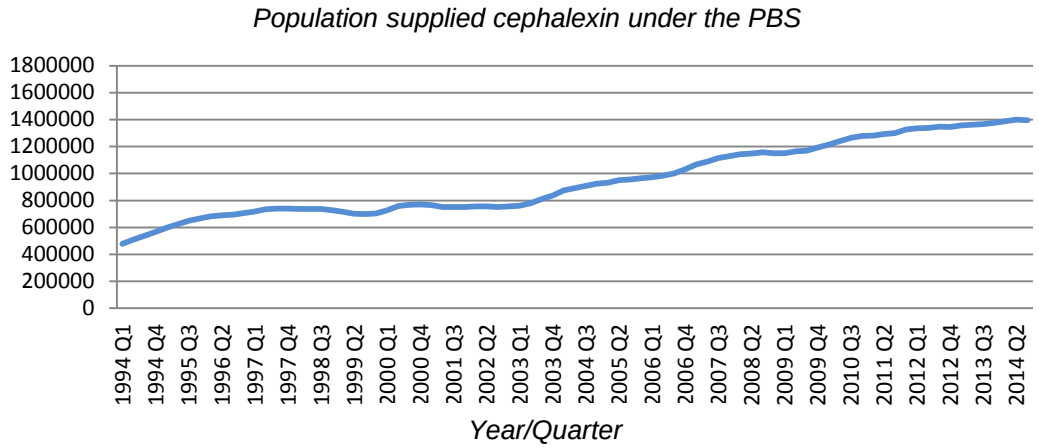


*DDD/1000 OBD = defined daily doses per 1000 occupied bed days
Source: National Antimicrobial Utilisation Surveillance Program 2014

How much is used in the community?

PBS/RPBS data show that cephalexin is the second most often dispensed antibacterial in the community and use has been increasing year by year (Figure 2).[1] It increased by about 2.5% from 5 413 046 prescriptions (234 prescriptions/1000 people) in 2013 to 5 549 606 prescriptions (236 prescriptions/1000 people) in 2014.[1] The acNAPS data from residential aged-care facilities showed that cephalexin was the antibacterial prescribed most often (16.7%).[4]

Figure 2: Cephalexin supplied to the population under the PBS, 1994–2004 (four-point moving average)[1]



Source: University of South Australia Division of Health Sciences unpublished analysis of PBS data

How appropriate is the use of first-generation cephalosporins in hospitals?

Hospital prescribing of first-generation cephalosporins is often inappropriate. In 2014, about four in ten cephalexin prescriptions and about one in three cefazolin prescriptions were inappropriate (Table 9).[11] About three in four cefazolin prescriptions were for surgical prophylaxis (73.7%). Of these, about one in three were inappropriate (30.7%) or did not comply with guidelines (32.2%).[11] Figure 3 shows that cefazolin and cephalexin are the two most commonly prescribed antibacterials for surgical prophylaxis and are the two antibacterials most often prescribed inappropriately.[1] Although most of the inappropriate prescribing was because cefazolin and cephalexin were prescribed for too long, some of it was because the antibacterial chosen was inappropriate.[1]

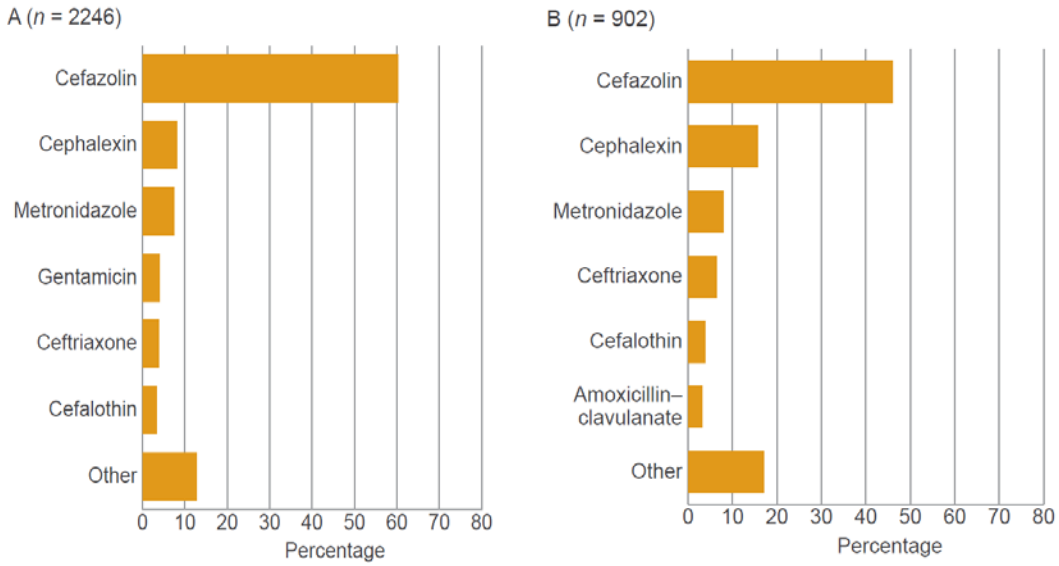
The Commission is working with key stakeholders to explore options to address inappropriate prescribing for surgical prophylaxis. This includes identifying strategies and policies that can be implemented at local, state and territory and national levels to improve appropriate use in surgical settings, particularly around choice and duration of therapy.

Table 9: Appropriateness of prescribing for cefazolin and cephalexin in hospitals, 2014[11]

Antibacterial	Number of prescriptions	Appropriate (%)	Inappropriate (%)	Not assessable (%)
Cefazolin	1908	66.0	31.6	2.4
Cephalexin	853	50.1	39.9	10.1

Source: National Antimicrobial Prescribing Survey 2014

Figure 3: Antibacterials used for (A) surgical prophylaxis overall and (B) when prescribed inappropriately for surgical prophylaxis, 2014[11]



Source: National Antimicrobial Prescribing Survey 2014

How appropriate is the use of first-generation cephalosporins in the community?

Similarly, cephalexin prescribing and use in the community is often inappropriate. The acNAPS data show that in residential aged-care facilities, cephalexin was widely used for urinary tract infections and skin or soft tissue infections, although guidelines do not recommend cephalexin as a first-line treatment for these indications.[4, 8] Similarly, PBS/RPBS data show that older people (65 years and over) were dispensed more cephalexin than other age groups, some of which was inappropriate (see Table 10).[1]

Table 10: Patterns of use, indications for prescribing, repeat prescribing, and differences between PBS/RPBS and private prescriptions for cephalexin, 2014[1]

Antibacterial (PBS/RPBS benefit)	Patients issued a prescription (%)[a]	Most common indications (%)	Patient cohort	Repeats prescribed	Differences between PBS/RPBS and private prescriptions
Cephalexin (general benefit)	9.8	Skin and wound infections (35%) UTIs[b] (20%) Respiratory infections (minority of cases)	Higher use in chronic disease and elderly people Variation in use across states	Minority receive repeat prescriptions Repeats more common for COPD, pneumonia, serious infections, acne, bronchitis or sinusitis	Negligible private use

[a] Percentage of patients who visited a GP at least once, or had one or more prescriptions in 2014 that were for the specified antimicrobial.
[b] Urinary tract infection
Source: NPS MedicineWise MedicineInsight

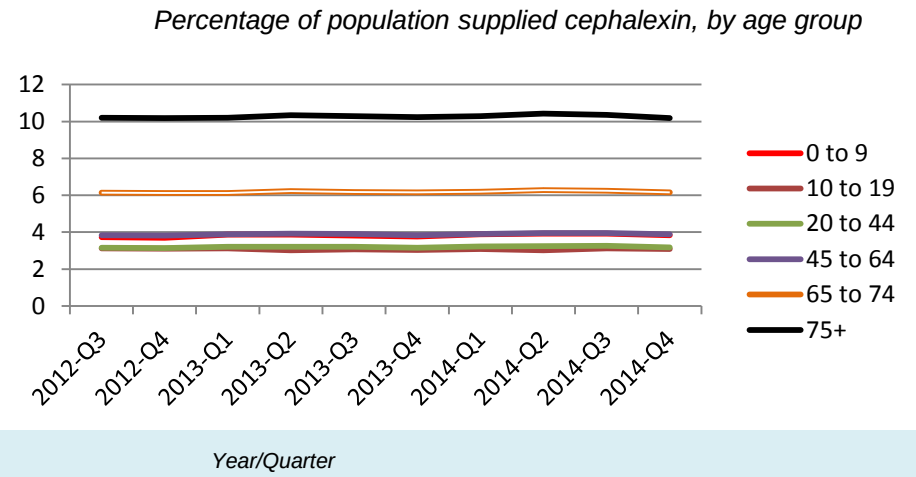
Case Study 1: Use a narrow spectrum antibacterial wherever possible (instead of cephalexin)

Cephalexin has a moderate spectrum that includes common enteric gram-negative bacilli as well as staphylococci and streptococci. In 2014, most cephalexin was prescribed for people over the age of 65 (Figure B1). For many older people, cephalexin is prescribed when a narrower-spectrum antibacterial is recommended – for example, skin and wound infections that are often caused by staphylococci (for which flucloxacillin or dicloxacillin are recommended[8]); and UTIs (for which trimethoprim is recommended as first choice).[8] The NPS MedicineWise MedicineInsight data show that 35% of cephalexin prescribing was for skin and wound infections and 20% was for urinary tract infectionss (Table 10). For skin and wound infections, cephalexin may be prescribed because its side effect profile may be thought to be safer than that of flucloxacillin (or dicloxacillin).[1]

In this context, while cephalexin has no restrictions around its prescribing on the PBS, prescribing of oral formulations of flucloxacillin are restricted to serious staphylococcal infection. The PBS restriction includes a caution about the risk of serious cholestatic hepatitis, including risk factors such as age over 55 years and treatment for more than 14 days.[12] Flucloxacillin is one of two medicines that most commonly cause drug-induced liver injury, especially in older people.[13, 14] Perhaps as a result of publicity in 1996 by the former Adverse Drug Reactions Advisory Committee (ADRAC) and others, the use of flucloxacillin reduced in line with the number of reports of flucloxacillin-induced liver injury.[14] Early in 1997, dicloxacillin became available as an alternative to flucloxacillin to treat staphylococcal infections because of its lower risk of drug-induced liver injury.[15] After two years, with a similar level of reporting for both antibacteriaials, there were fewer reports of drug-induced liver injury with dicloxacillin compared with flucloxacillin.[15] Like flucloxacillin, dicloxacillin is restricted on the PBS to prescribing for serious staphylococcal infection, but unlike flucloxacillin, dicloxacillin does not have cautions about the risk of serious cholestatic hepatitis.

In 2014, cephalexin accounted for about one in five (19.6%) of all prescriptions for systemic antibacterials (J01 class) dispensed on the PBS/RPBS, compared to 2.5% for flucloxacillin and 0.85% for dicloxacillin. Because cephalexin has a broader spectrum of activity than flucloxacillin or dicloxacillin, it is more likely to contribute to gram-negative resistance. It is more appropriate to use the narrower-spectrum dicloxacillin for skin and wound infections, especially in residential aged-care, unless the patient is allergic to penicillins.

Figure B1 Community population supplied cephalexin by age group (3-point moving average), Quarter 3 2012 to Quarter 4 2014[3]



Sources: Drug Utilisation Sub-Committee; PBS

Key message: Reduce selection pressure for gram-negative resistance: use dicloxacillin instead of cephalexin for skin and soft tissue infections.

Extended-spectrum penicillins: ampicillin and amoxicillin

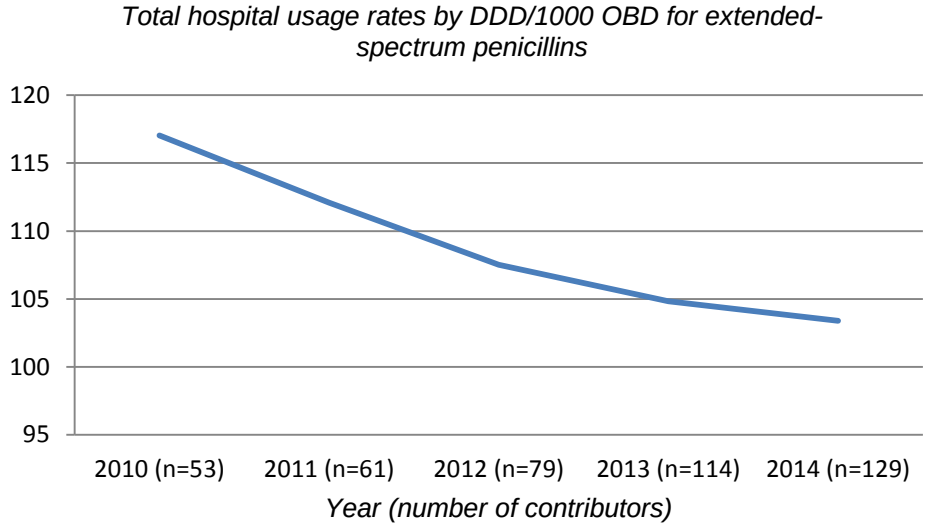
What organisms are they used to treat?

Extended-spectrum penicillins, ampicillin and amoxicillin, are moderate-spectrum penicillins active against some gram-negative bacteria (including *Escherichia coli* and *Haemophilus influenzae*) but are inactivated by strains that produce β-lactamase enzymes.[8] They are the antibacterial of choice for enterococcal infections.[8] Ampicillin and amoxicillin are equivalent for parenteral use. Amoxicillin is preferred for oral use because it is better absorbed, is not affected by food and requires fewer doses per day than oral ampicillin. Amoxicillin is available in several oral formulations.

How much is used in hospitals?

The NAUSP data showed that total hospital use of extended-spectrum penicillins has declined slightly since 2010 even as the number of contributors increased (Figure 4). In 2014 the extended-spectrum penicillins were the third most used antibacterial class in Australian hospitals, accounting for 11.5% of all use.[10] In the same year, the NAPS data showed that ampicillin/amoxicillin were the eighth most prescribed antibacterials, accounting for 2.8% of all prescriptions.[11]

Figure 4: Hospital usage rates by defined daily doses per 1000 occupied bed days (DDD/1000 OBD) for extended-spectrum penicillins: NAUSP contributors, 2010–14[10]



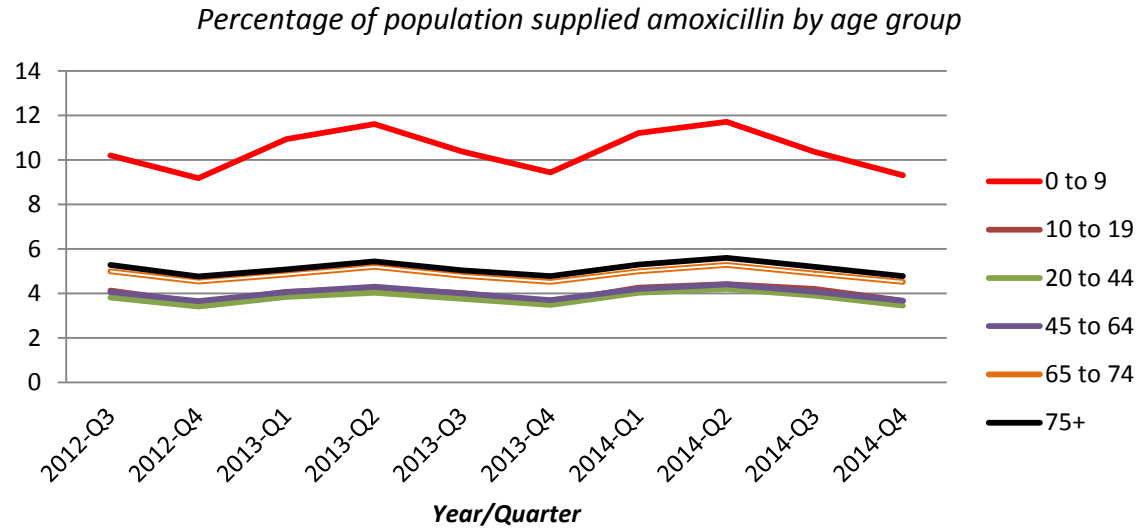
Source: National Antimicrobial Utilisation Surveillance Program 2014

How much is used in the community?

Amoxicillin is widely used in the Australian community. PBS/RPBS data show that it is the third most often dispensed antibacterial. Prescribing of this antibacterial increased by about 3.5%, from 5 665 810 prescriptions (244 prescriptions/1000 people) in 2013 to 5 870 123 prescriptions (249 prescriptions/1000 people) in 2014.[1] Amoxicillin is prescribed most often for people under the age of 10 with more use in the winter months; this may represent inappropriate use for viral upper respiratory tract infections (see Figure 5). Twice the number of children aged 0–9 years were dispensed amoxicillin than for other age groups.[1] The average number of prescriptions dispensed for amoxicillin varied across states and territories, from 15 047 per 100 000 people in the Northern Territory, to 28 347 per 100 000

people in Victoria.[2] After excluding the highest and lowest results, the amoxicillin prescription rate across 301 local areas was 2.7 times higher in one local area compared to another.[2] The acNAPS data from residential aged-care facilities showed that amoxicillin was the sixth most commonly prescribed antibacterial (4.7%).[1]

Figure 5: Amoxicillin dispensing in the community by age group (years) (three-point moving average), Quarter 3 2012 to Quarter 4 2014[3]



Sources: Drug Utilisation Sub-Committee; PBS

How appropriate is the use of extended-spectrum penicillins in hospitals and in the community?

Hospital prescribing of extended-spectrum penicillins was often inappropriate. The NAPS data found that about one in four prescriptions were inappropriate (24.5%).[1] Similarly, amoxicillin prescribing and use in the community is often inappropriate. The number of prescriptions dispensed has consistently increased since 2008.[1] The most common indications for which GPs who contribute to MedicineInsight prescribed antibacterials were upper respiratory tract infections (30%), for which antibacterials are not indicated; and otitis media (15%), for which amoxicillin is indicated in specific circumstances (see Table 11).[8] About one in four amoxicillin prescriptions had one or more repeats and the proportion of repeat prescriptions varied for upper respiratory tract infections (see Table 11).[1] Amoxicillin prescribing did not comply with guidelines for sinusitis, acute otitis media and pneumonia (see Table 12).[1] For example, only about one in three antibacterial prescriptions for sinusitis, about two in three for acute otitis media/myringitis and about one in four for pneumonia were for amoxicillin as recommended by guidelines; all of these results were below the acceptable range (see Table 12).

Table 11: Patterns of use, indications for prescribing, repeat prescribing, and differences between PBS/RPBS and private prescriptions for amoxicillin, 2014[1]

Antibacterial (PBS/RPBS benefit)	Patients issued a prescription (%)[a]	Most common indications (%)	Patient cohort	Repeats prescribed	Differences between PBS/RPBS and private prescriptions
Amoxicillin (general benefit)	12.4	URTIs (30%) Otitis media (15%) Non-respiratory infections (minority of cases)	Highest use in children, and patients with COPD or asthma	27% of prescriptions ordered with one or more repeats Moderate variation between practices in repeats for URTI	Negligible private use

COPD = chronic obstructive pulmonary disease; PBS/RPBS = Pharmaceutical Benefits Scheme/Repatriation Pharmaceutical Benefits Scheme; URTI = upper respiratory tract infection
a Percentage of patients who visited a GP at least once, or had one or more prescriptions in 2014 that were for the specified antimicrobial.
Source: NPS MedicineWise MedicineInsight

Table 12: Percentage of patients prescribed amoxicillin for select conditions, 2014[1]

Condition	Patient	Number	Percentage	95% CI	Acceptable range (%)
Sinusitis (chronic or acute)	Older than 18 years prescribed antibacterials	17 300	86	84–87	0–20
	And prescribed the TG-recommended amoxicillin	5 607	32	29–36	80–100
Acute otitis media/myringitis	Older than 2 years prescribed antibacterials	11 387	91	90–92	0–20
	And prescribed the TG-recommended amoxicillin	7 154	**63**	59–67	80–100
Pneumonia	Aged 18–65 years prescribed antibacterials	607	68	64–71	90–100
	And prescribed the TG-recommended (for mild CAP – amoxicillin or doxycycline)	146	24	19–29	80–100

CAP = community-acquired pneumonia; CI = confidence interval; TG = *Therapeutic Guidelines: antibiotic*; URTI = upper respiratory tract infection
Source: NPS MedicineWise MedicineInsight

β-lactamase inhibitor combinations: piperacillin with tazobactam and amoxicillin with clavulanate

What organisms are they used to treat?

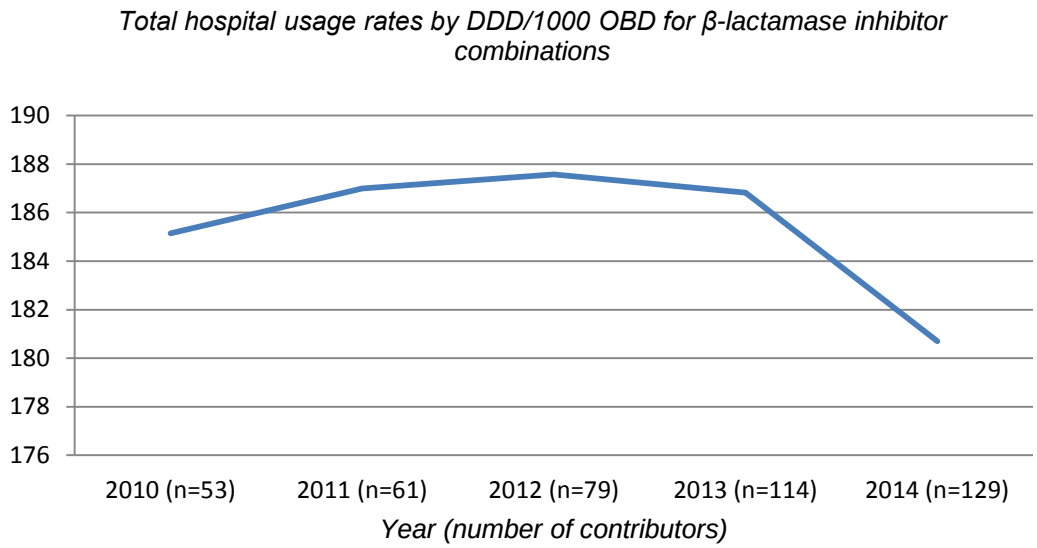
Piperacillin with tazobactam has a broad spectrum and is the only penicillin with reliable activity against *Pseudomonas aeruginosa.*[8] Its use is usually reserved for people who are critically ill, such as those admitted to intensive care and other specialty hospital wards, including haematology and oncology. The addition of tazobactam extends the spectrum of piperacillin's activity.[8] Many hospitals restrict its use and require approval to prescribe from an infectious diseases specialist or an antimicrobial stewardship team or in accordance with hospital prescribing guidelines (for example, febrile neutropenia). Piperacillin with tazobactam is given parenterally, and is often used in preference to third-generation cephalosporins when either would be effective, because it is reputed to have lower capacity for resistance selection.

Amoxicillin with clavulanate has a broad spectrum and is widely used to treat infections in hospitals and the community. The addition of clavulanate significantly extends amoxicillin's spectrum of activity. Use should be reserved for infections caused by organisms that produce β-lactamase enzymes (such as *Staphylococcus aureus*, *Bacteroides fragilis*, *Haemophilus influenza*, some *Escherichia coli* and *Klebsiella* species).[8] In Australia, amoxicillin with clavulanate is only available for oral use in several different formulations.

How much is used in hospitals?

The NAUSP data showed that total use of β-lactamase inhibitor combinations has decreased slightly since 2010 (see Figure 6). In 2014, amoxicillin with clavulanate and piperacillin with tazobactam were the first and seventh most used antibacterials, accounting for 14.5% and 4.7% of total antibacterial use in hospitals.[10] In the same year, the NAPS data showed that piperacillin with tazobactam and amoxicillin with clavulanate were the fourth and fifth most prescribed antibacterials, accounting for 6.1% and 6.0% of all antibacterial prescriptions respectively.[11]

Figure 6: Hospital usage rates, by defined daily dose per occupied bed days (DDD/1000 OBD), for β-lactamase inhibitor combinations: NAUSP contributors, 2010–14[10]

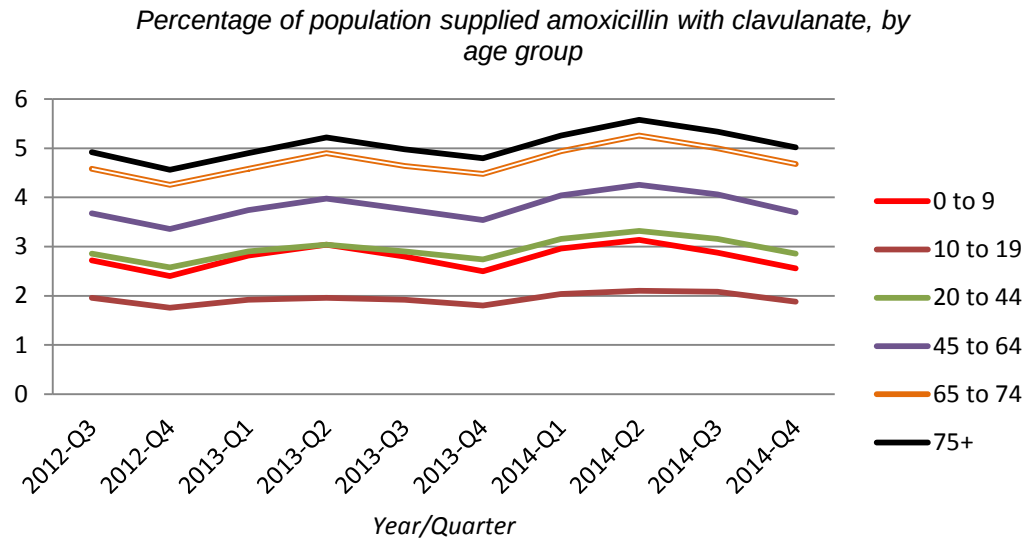


Source: National Antimicrobial Utilisation Surveillance Program 2014

How much is used in the community?

Amoxicillin with clavulanate is one of the most widely used antibacterials in the Australian community. PBS/RPBS data show that it is the third most often dispensed antibacterial and increased by about 8%, from 4 512 149 prescriptions (195 prescriptions/1000 people) in 2013 to 4 897 449 prescriptions (208 prescriptions/1000 people) in 2014.[2] Amoxicillin with clavulanate is prescribed most often for people over the age of 45, with greater use in winter months, which may represent inappropriate use for viral upper respiratory tract infections (see Figure 7). The average number of prescriptions dispensed for amoxicillin with clavulanate varied across states and territories from 13 740 per 100 000 people in Tasmania, to 21 979 per 100 000 people in Queensland.[2] After excluding the highest and lowest results, the amoxicillin with clavulanate prescription rate across 300 local areas was 2.2 times higher in one local area compared with another.[2] The 2015 pilot survey data from residential aged-care facilities show that amoxicillin with clavulanate was the fourth most commonly prescribed antibacterial (6.5%).[4]

Figure 7: Amoxicillin with clavulanate dispensing in the community by age group (three-point moving average), Quarter 3 2012 to Quarter 4 2014[3]



Sources: Drug Utilisation Sub-Committee; PBS

How appropriate is the use of β-lactamase inhibitor combinations in hospitals and in the community

Hospital prescribing of β-lactamase inhibitor combinations is often inappropriate. The NAPS data found that about one in five (19.5%) piperacillin with tazobactam prescriptions and about one in three (31.5%) amoxicillin with clavulanate prescriptions were inappropriate.[11] Similarly, amoxicillin with clavulanate prescribing and use in the community is often inappropriate. The number of prescriptions dispensed has consistently increased since 2008.[1] The most common indications recorded by MedicineInsight GPs were sinusitis and upper respiratory tract infections (see Table 13).[1] Amoxicillin with clavulanate is not indicated for either of these.[8] There was wide variation between practices in the proportion of repeat prescriptions for upper respiratory tract infections (see Table 13).[1]

Table 13: Patterns of use, indications for prescribing, repeat prescribing, and differences between PBS/RPBS and private prescriptions for amoxicillin with clavulanate, 2014[1]

Antibacterial (PBS/RPBS benefit)	Patients issued a prescription (%)[a]	Most common indications (%)	Patient cohort	Repeats prescribed	Differences between PBS/RPBS and private prescriptions
Amoxicillin with clavulanate (restricted to infections resistant to amoxicillin)	7.1	Sinusitis (15%) Acute URTIs (14%) Otitis media (10%) Skin and wound infections (~10%)	Higher use in major cities and patients with COPD or asthma	58% of prescriptions ordered with one or more repeats (often for COPD, sinusitis or bronchitis) Wide variation between practices in repeats for URTIs	Negligible private use

COPD = chronic obstructive pulmonary disease; PBS/RPBS = Pharmaceutical Benefits Scheme / Repatriation Pharmaceutical Benefits Scheme; URTI = upper respiratory tract infection

a Percentage of patients who visited a GP at least once, or had one or more prescriptions in 2014 that were for the specified antimicrobial.

Source: NPS MedicineWise MedicineInsight

Case Study 2: Use amoxicillin with clavulanate only when it is clearly indicated

Amoxicillin is the most commonly dispensed antibacterial in the Australian community[2] and the combination of amoxicillin with clavulanate is the third most commonly dispensed. Combined, these two accounted for more than 10 million prescriptions dispensed under the PBS in 2013–14.[2] Amoxicillin with clavulanate is restricted on the PBS for infections where resistance to amoxicillin is suspected or proven.[12] Amoxicillin is preferred for most upper and lower bacterial respiratory infections.[8] The NPS MedicineWise MedicineInsight program data show that 15% of amoxicillin with clavulanate prescribing was for sinusitis, for which antibacterials are only indicated in specific circumstances (and amoxicillin is recommended),[8] and 14% was for upper respiratory tract infections for which antibacterials are not indicated.[1]

Unnecessary use of amoxicillin with clavulanate increases the risk of resistance (because of its broad spectrum) and exposes people to the risk of drug-induced liver injury. Amoxicillin with clavulanate causes more adverse events than amoxicillin alone[2] and is one of the two medicines that most often cause drug-induced liver injury.[13,14] Unlike most medicines, which only cause one type of liver injury characteristic to that medicine, amoxicillin with clavulanate causes more than one type of liver injury.[16] Concern about inappropriate and unnecessary use of amoxicillin with clavulanate is not new: in 1996 the Adverse Drug Reactions Advisory Committee (ADRAC) bulletin noted that its use grew despite publicity by ADRAC and others about the continuing high number of reports of drug-induced liver injury.[14] In 1996, nine of the 309 reports received had a fatal outcome, five of these were caused by liver failure.[14]

Amoxicillin with clavulanate continues to cause drug-induced liver injury[16] and should only be used when clearly indicated. As primary empirical therapy, amoxicillin with clavulanate should only be prescribed before amoxicillin for specific infections (e.g. lower urinary tract infections). *Therapeutic Guidelines: antibiotic*[8] provides guidance on when amoxicillin with clavulanate is preferred over amoxicillin.[8]

Key message: Use amoxicillin with clavulanate only when it is clearly indicated. Therapeutic Guidelines: Antibiotic[8] provides guidance on when amoxicillin with clavulanate is preferred over amoxicillin alone.

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