



CARAlert
THE NATIONAL ALERT
SYSTEM FOR CRITICAL
ANTIMICROBIAL RESISTANCE



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Introduction

The Australian Commission on Safety and Quality in Health Care (the Commission) established the National Alert System for Critical Antimicrobial Resistances (CARAlert) in March 2016 as part of the Antimicrobial Use and Resistance in Australia (AURA) Surveillance System. CARAlert collects surveillance data on priority organisms with critical resistance to last-line antimicrobial agents.

Primary responsibility for clinical response to critical resistances lies with local health organisations and the state and territory health departments. The role of CARAlert includes collecting and analysing data to identify trends and timely communication of information concerning critical resistances to states and territories, to complement current local reporting of results. It is intended that states and territories will use the data to identify local problems, and respond to potential and proven multi-site outbreaks of critical antimicrobial resistances (CARs).

Over time, the data will increasingly be useful to inform safety and quality improvement programs.

CARs are defined as resistance mechanisms, or profiles, known to be a serious threat to the effectiveness of last-line antimicrobial agents. CARs have been detected across Australia. They may result in significant morbidity and mortality in healthcare facilities, and in the community.

The monthly organisms reported under CARAlert are listed in Table 1; they were drawn from the list of high priority organisms and antimicrobials which are the focus of the AURA Surveillance System. The scope of organisms and CARs will be regularly reviewed, based on the latest available evidence on critical resistances which emerge in Australia and overseas. The most recent review in October 2016 did not result in any change to the list.

Table 1 – List of Critical Antimicrobial Resistances

Species	Critical Resistance
<i>Enterobacteriaceae</i>	Carbapenemase-producing strains, or ribosomal methylase-producing strains
<i>Enterococcus</i> species	Linezolid non-susceptible
<i>Mycobacterium tuberculosis</i>	Multidrug-resistant – at least rifampicin- and isoniazid-resistant strains
<i>Neisseria gonorrhoeae</i>	Ceftriaxone non-susceptible or azithromycin non-susceptible strains
<i>Salmonella</i> species	Ceftriaxone non-susceptible strains
<i>Shigella</i> species	Multidrug-resistant strains
<i>Staphylococcus aureus</i>	Vancomycin, linezolid or daptomycin non-susceptible
<i>Streptococcus pyogenes</i>	Penicillin reduced susceptibility

Under existing testing processes, originating laboratories perform routine tests of an isolate to identify whether it is potentially a CAR. If suspected as a CAR, the isolate is referred to one of the 28 confirming laboratories currently participating in CARAlert.

The confirming laboratory advises the originating laboratory of the result of the test for reporting back to the general practice or hospital which cared for the patient from whom the specimen was collected. These reports occur before the confirming laboratory enters the details of the resistance and organism into the CARAlert web portal. Alerts are reported to the Commission and to nominated state and territory health personnel weekly.

The data in this report are based on the date that the CAR was confirmed. The majority of CARs are submitted within seven days of confirmation. However, some batch testing occurs for isolates referred to the National Neisseria Network (NNN) and the Australian Mycobacterium Reference

Laboratory Network (AMRLN) laboratories. This may result in the outcome of testing being entered into the CARAlert database in the following month.

This report includes CARs submitted between 17 March 2016 and 31 December 2016, and complements the individual alerts sent to the nominated state and territory contacts.

Critical antimicrobial resistances – Summary

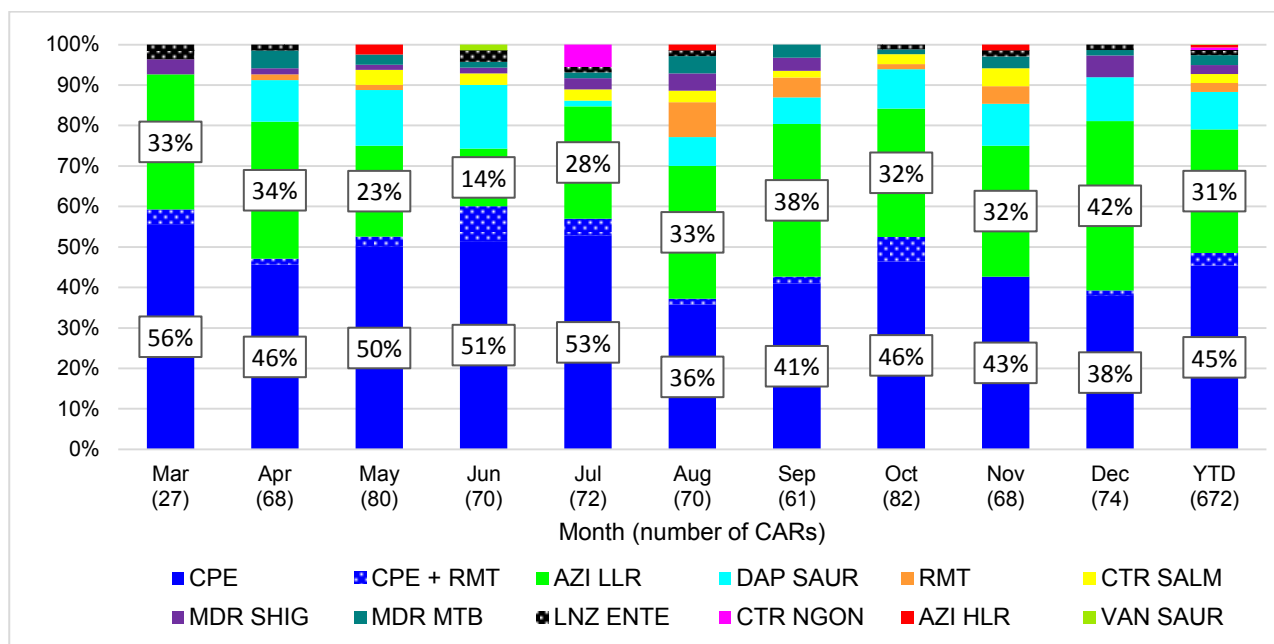
From 17 March 2016 to 31 December 2016, 672 results were entered in the CARAlert system, with an average of 71 per month (range 61-82) from April to December (Figure 1). Isolates for these reports were referred from 70 originating laboratories across Australia. The proportion of CARs associated with priority organisms is shown in Figure 1. The number of CARs reported by species and month is shown in Figure 2.

Carbapenemase-resistant *Enterobacteriaceae* (CPE) were the most frequently recorded CAR of all CARs reported to date (n=326, 48%); either alone (305, 45%), or in combination with ribosomal methyltransferases (RMT) (21, 3%). The differences in the proportion of CPE per month were not statistically significant (χ^2 for trend, p=0.0502).

The next most frequently reported CAR was azithromycin non-susceptible *Neisseria gonorrhoeae* (n=209, 31%). As confirmation of this CAR is often performed in batches, this influences the numbers seen per month. Only four of the 209 (2%) azithromycin-resistant *N. gonorrhoeae* were reported to have high-level resistance (HLR) – that is, the minimum inhibitory concentration (MIC) \geq 256 mg/L. There was a significant increase in the differences in the proportion of *N. gonorrhoeae* per month (χ^2 for trend, p=0.0194).

The previous CARAlert report was for the period 17 March 2016 to 31 October 2016.¹ From 31 October 2016 to 31 December 2016, 142 new CAR records were entered. CPE continued to be the most frequently reported CAR (n=58, 41%), followed by azithromycin non-susceptible *N. gonorrhoeae* with low-level resistance (LLR) [MIC < 256 mg/L] (n=53, 37%) and daptomycin non-susceptible *S. aureus* (n=15, 11%).

Figure 1: Critical antimicrobial resistances (CARs), as a percentage of all CARs, reported by month, March–December 2016

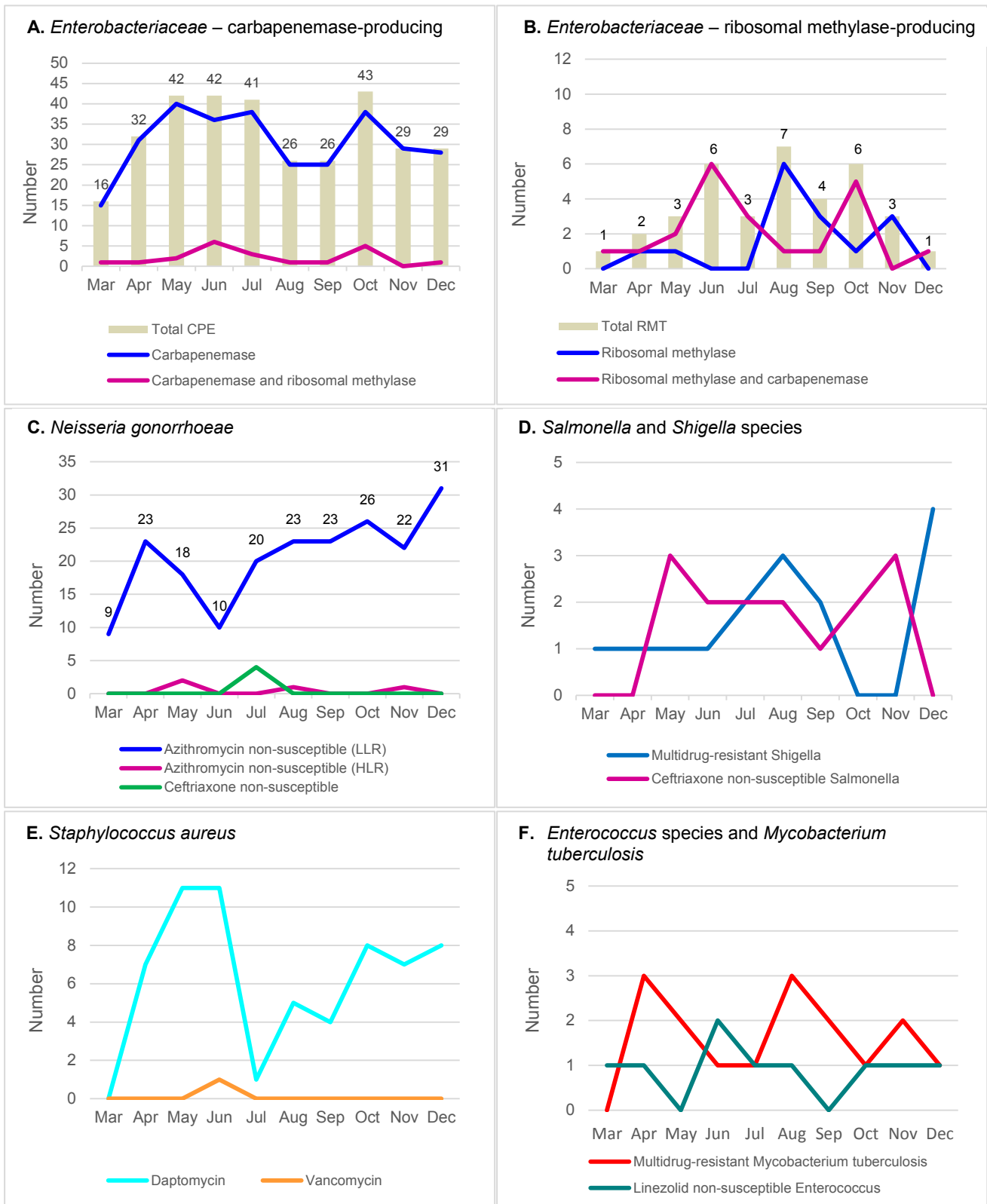


CPE = carbapenemase-producing-*Enterobacteriaceae*; RMT = ribosomal methylase-producing *Enterobacteriaceae*; CPE+RMT = carbapenemase- and ribosomal methylase-producing *Enterobacteriaceae*; LNZ ENTE = linezolid non-susceptible *Enterococcus* species; AZI (LLR) = azithromycin non-susceptible (LLR, MIC < 256 mg/L) *Neisseria gonorrhoeae*; AZI (HLR) = azithromycin non-susceptible (HLR, MIC > 256 mg/L) *Neisseria gonorrhoeae*; CTR NGON = ceftriaxone non-susceptible *Neisseria gonorrhoeae*; DAP SAUR = daptomycin non-susceptible *Staphylococcus aureus*; VAN SAUR =

¹ Australian Commission on Safety and Quality in Health Care. CARAlert Summary Report: 17 March – 31 October 2016. Sydney: ACSQHC, 2016

vancomycin non-susceptible *Staphylococcus aureus*; CTR SALM = ceftriaxone non-susceptible *Salmonella* species; MDR SHIG = multidrug-resistant *Shigella* species; MDR MTB = multidrug-resistant *Mycobacterium tuberculosis*

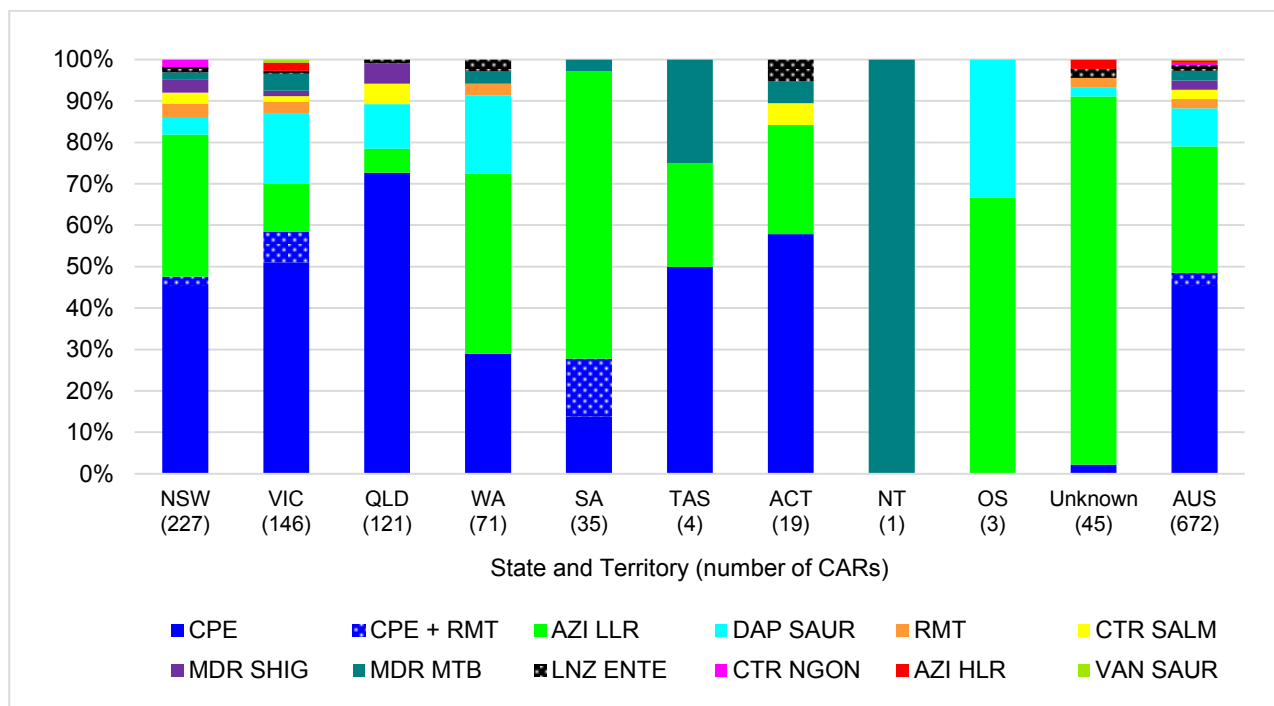
Figure 2: Critical antimicrobial resistances, number reported by species and month, March–December 2016



Critical Antimicrobial Resistances by state and territory

Seventy-four per cent of all CARs were from the three most populous states, New South Wales (34%), Victoria (22%) and Queensland (18%). Only one report was received from the Northern Territory and four from Tasmania. Half of all CARs submitted were for CPE, either alone (46%) or in combination with RMT (3%). Lower incidences of CPE were reported from South Australia (26%) and Western Australia (30%), with Queensland (73%) reporting the highest prevalence (Figure 3).

Figure 3: Critical antimicrobial resistances, percentage reported by state and territory, March–December 2016



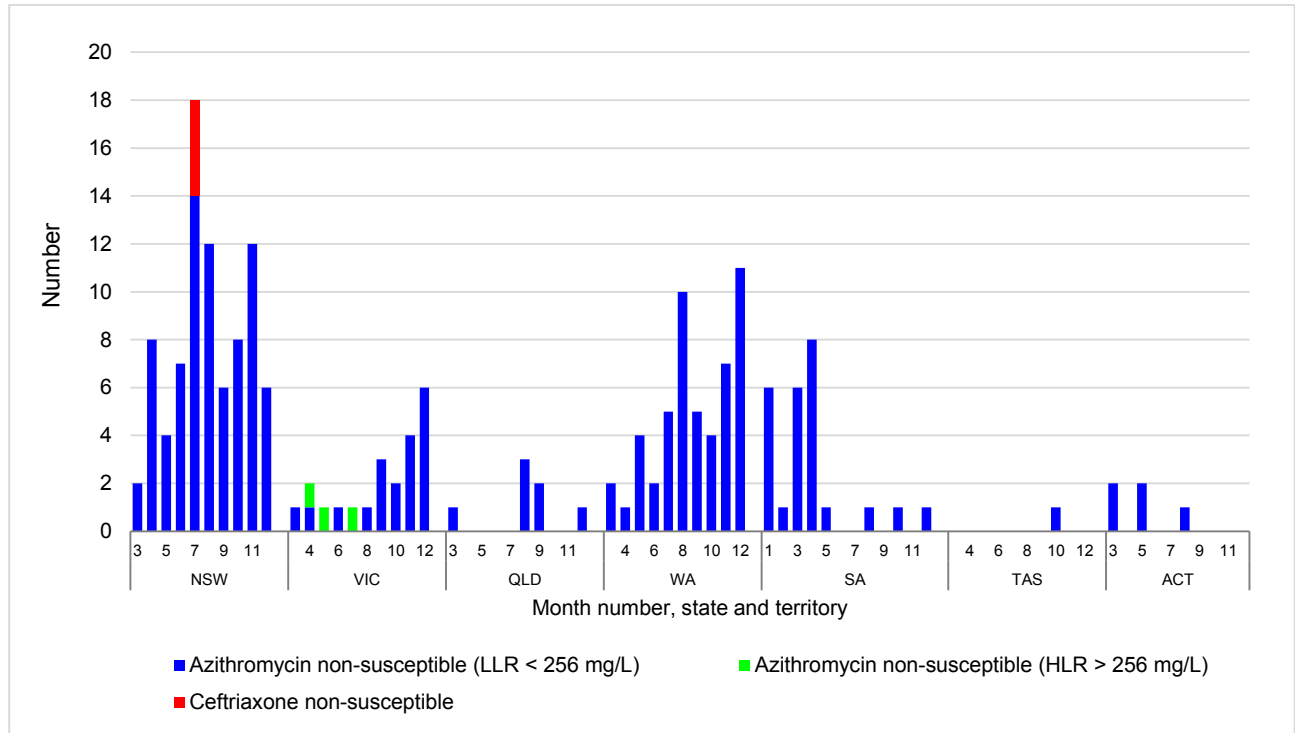
CPE = carbapenemase-producing *Enterobacteriaceae*; RMT = ribosomal methylase-producing *Enterobacteriaceae*; CPE+RMT = carbapenemase- and ribosomal methylase-producing *Enterobacteriaceae*; LNZ ENTE = linezolid non-susceptible *Enterococcus* species; AZI (LLR) = azithromycin non-susceptible (LLR, MIC < 256 mg/L) *Neisseria gonorrhoeae*; AZI (HLR) = azithromycin non-susceptible (HLR, MIC > 256 mg/L) *Neisseria gonorrhoeae*; CTR NGON = ceftriaxone non-susceptible *Neisseria gonorrhoeae*; DAP SAUR = daptomycin non-susceptible *Staphylococcus aureus*; VAN SAUR = vancomycin non-susceptible *Staphylococcus aureus*; CTR SALM = ceftriaxone non-susceptible *Salmonella* species; MDR SHIG = multidrug-resistant *Shigella* species; MDR MTB = multidrug-resistant *Mycobacterium tuberculosis*

There was a significant number of entries of azithromycin non-susceptible (low-level resistance [LLR] MIC < 256 mg/L) *N. gonorrhoeae* from South Australia in March 2016. As batch testing of this CAR is common, reports were analysed by date of collection, rather than date of confirmation (Figure 4). There were isolates from South Australia collected in January 2016 with LLR, and only small numbers of strains were confirmed with a collection date after April 2016. There was a sharp increase in reports of this CAR in April 2016 from New South Wales, with a peak during July 2016. Although the number of LLR strains has declined in a number of states and territories, both Western Australia and Victoria have seen significant increases from September to December 2016. Four strains with high-level azithromycin resistance (MIC ≥ 256 mg/L) were confirmed, three from Victoria, collected in April, May, and July 2016; and one in October 2016, from unknown place of residence, but originating from South Australia. Ceftriaxone non-susceptible strains collected in July 2016 were also confirmed from New South Wales.

State or territory of residence was not available for 51 reports (41 azithromycin-resistant [LLR MIC < 256 mg/L] of *N. gonorrhoeae*, four CPE, two CPE+RMT, and one each of RMT alone, azithromycin-resistant [HLR MIC ≥ 256 mg/mL] *N. gonorrhoeae*, linezolid non-susceptible *Enterococcus* species and daptomycin non-susceptible *S. aureus*). For *N. gonorrhoeae*, this is due to the isolates being collected from patients that attended sexual health clinics, where postcode of residence is not always sought. Five reports were from overseas residents, one daptomycin non-susceptible *S. aureus*, one linezolid non-susceptible *Enterococcus* species, and three azithromycin-resistant (LLR, MIC < 256 mg/L) *N. gonorrhoeae*.

Daptomycin non-susceptible *S. aureus* were reported from four states/territories, with 41% (25/61) from Victoria, and 21% (13/61) from both Queensland and Western Australia. Multidrug-resistant *Mycobacterium tuberculosis* were reported from patients from all states and territories except Queensland.

Figure 4: Critical antimicrobial resistances, *Neisseria gonorrhoeae*, number reported by state and territory and month of collection, March–December 2016

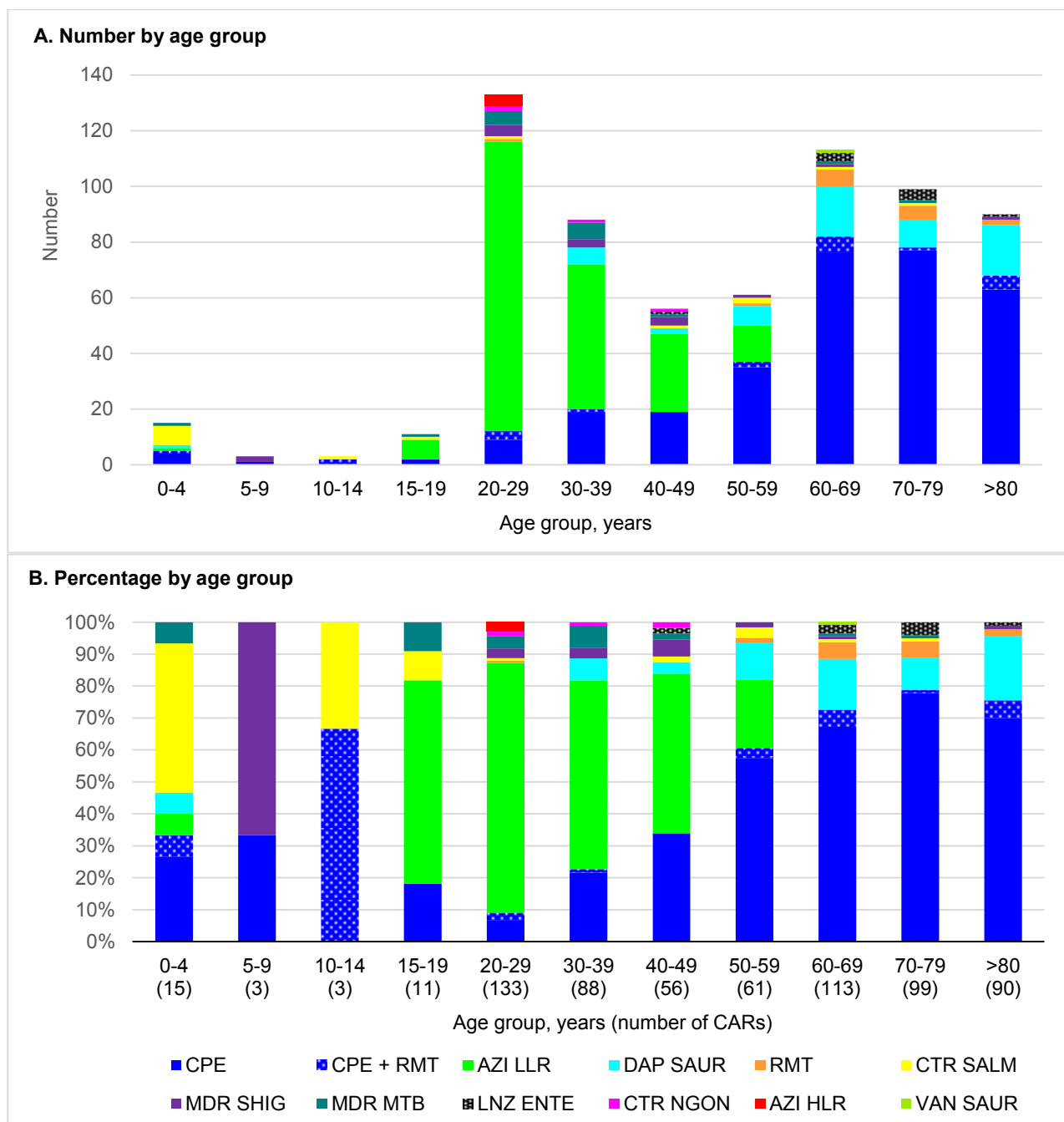


Month number – 3=March; 4=April; 5=May; 6=June; 7=July; 8=August; 9=September; 10=October; 11=November; 12=December

Critical antimicrobial resistances by age group

Seventy per cent (228/326) of CPE were from people aged 60 years and older. The age range was 0-4 to >80 years, with a median age of 60-69 years (see Figure 5). Azithromycin-resistant *N. gonorrhoeae* were the predominant CAR reported among the age groups of 15-19, 20-29, 30-39 and 40-49. Only 3.1% (21/672) of all CARs were reported in children aged less than 15 years; CPE and ceftriaxone non-susceptible *Salmonella* species were common (76%).

Figure 5: Critical antimicrobial resistances, number (A) and percentage (B) reported by age group, March-December 2016



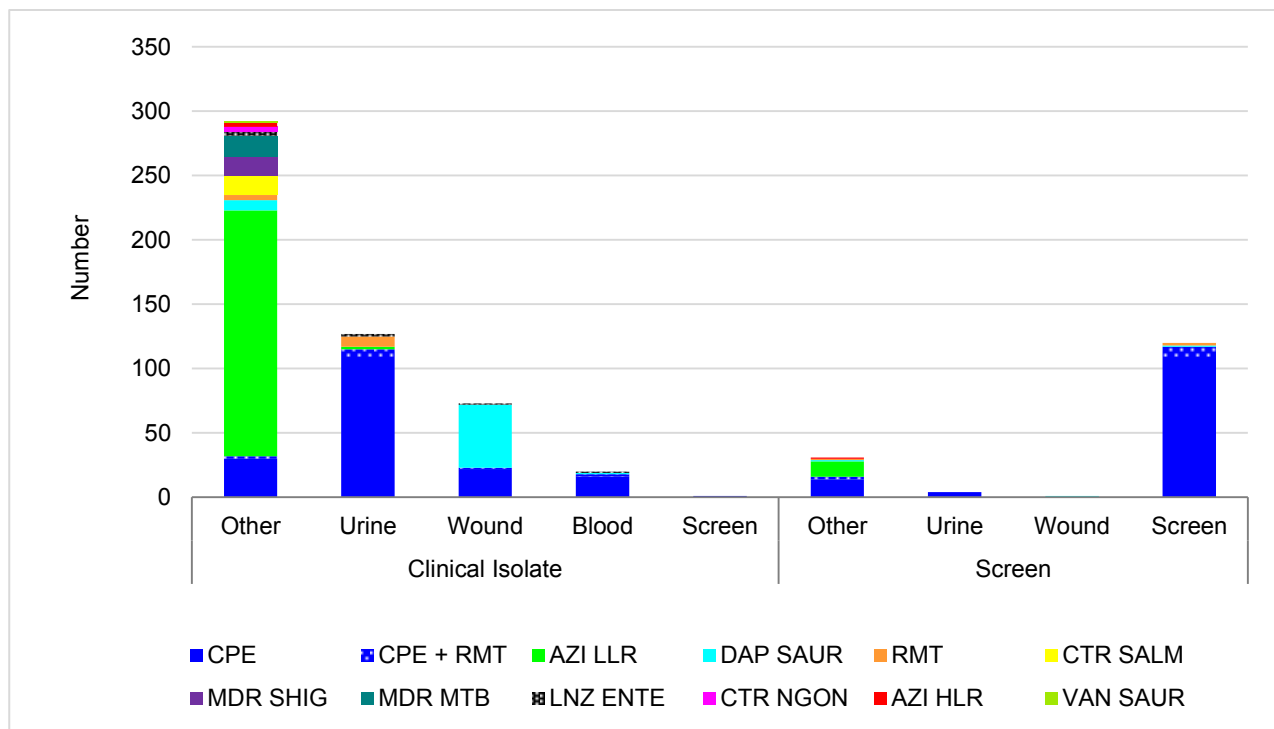
CPE = carbapenemase-producing *Enterobacteriaceae*; RMT = ribosomal methylase-producing *Enterobacteriaceae*; CPE+RMT = carbapenemase- and ribosomal methylase-producing *Enterobacteriaceae*; LNZ ENTE = linezolid non-susceptible *Enterococcus* species; AZI (LLR) = azithromycin non-susceptible (LLR, MIC < 256 mg/L) *Neisseria gonorrhoeae*; AZI (HLR) = azithromycin non-susceptible (HLR, MIC > 256 mg/L) *Neisseria gonorrhoeae*; CTR NGON = ceftriaxone non-susceptible *Neisseria gonorrhoeae*; DAP SAUR = daptomycin non-susceptible *Staphylococcus aureus*; VAN SAUR = vancomycin non-susceptible *Staphylococcus aureus*; CTR SALM = ceftriaxone non-susceptible *Salmonella* species; MDR SHIG = multidrug-resistant *Shigella* species; MDR MTB = multidrug-resistant *Mycobacterium tuberculosis*

Critical antimicrobial resistances by specimen type

Over 76% of all CARs were from clinical specimens (specimens collected for diagnostic purposes, as opposed to those taken for screening). These include urine, wound, blood and other (such as genital or respiratory) specimens (Figure 6).

Fifty-eight per cent (189/326) of CPE isolates were from clinical specimens; 61% (115/189) of these were from urine, and 10% (18/189) from blood cultures. One linezolid non-susceptible *E. faecalis*, and one daptomycin non-susceptible *S. aureus* were from blood culture. Urine is an important specimen for certain CARs such as CPE and the urinary tract is a common site of infection.

Figure 6: Critical antimicrobial resistances, number reported by specimen type, March–December 2016



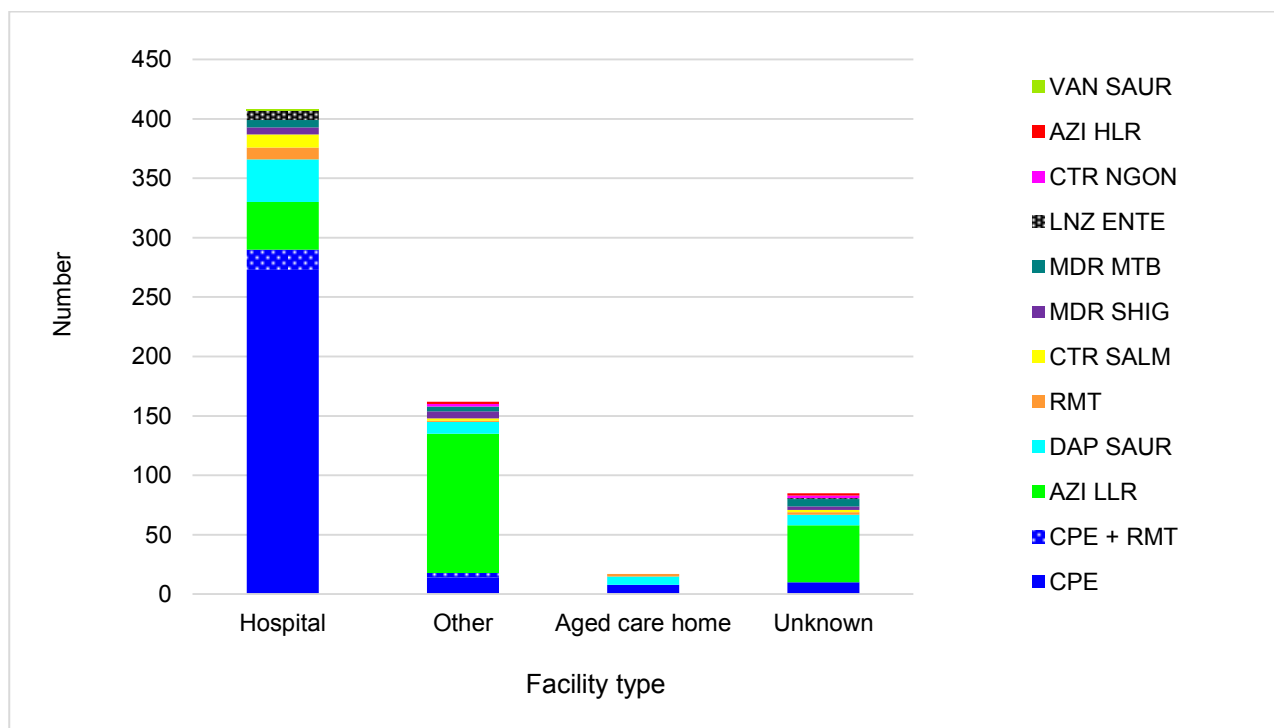
Other specimen type: Not-urine, wound, or blood (e.g. genital, faecal, respiratory)

CPE = carbapenemase-producing *Enterobacteriaceae*; RMT = ribosomal methylase-producing *Enterobacteriaceae*; CPE+RMT = carbapenemase- and ribosomal methylase-producing *Enterobacteriaceae*; LNZ ENTE = linezolid non-susceptible *Enterococcus* species; AZI (LLR) = azithromycin non-susceptible (LLR, MIC < 256 mg/L) *Neisseria gonorrhoeae*; AZI (HLR) = azithromycin non-susceptible (HLR, MIC > 256 mg/L) *Neisseria gonorrhoeae*; CTR NGON = ceftriaxone non-susceptible *Neisseria gonorrhoeae*; DAP SAUR = daptomycin non-susceptible *Staphylococcus aureus*; VAN SAUR = vancomycin non-susceptible *Staphylococcus aureus*; CTR SALM = ceftriaxone non-susceptible *Salmonella* species; MDR SHIG = multidrug-resistant *Shigella* species; MDR MTB = multidrug-resistant *Mycobacterium tuberculosis*

Critical antimicrobial resistances by facility type

While most CARs were detected in either hospitalised patients or hospital outpatients (61%, 408/672), some were found in the community (24%, 162/672) and in aged care homes (formerly referred to as residential aged care facilities) – see Figure 7. Facility type for azithromycin-resistant *N. gonorrhoeae* was difficult to obtain as most isolates are referred to a public health laboratory for confirmation, and as such may reflect the facility from which the isolate was sent rather than the facility that the patient attended.

Figure 7: Critical antimicrobial resistances, number reported by facility type, March–December 2016



Other: Community (non-hospital and non-aged care home)

CPE = carbapenemase-producing-*Enterobacteriaceae*; RMT = ribosomal methylase-producing *Enterobacteriaceae*; CPE+RMT = carbapenemase- and ribosomal methylase-producing *Enterobacteriaceae*; LNZ ENTE = linezolid non-susceptible *Enterococcus* species; AZI (LLR) = azithromycin non-susceptible (LLR, MIC < 256 mg/L) *Neisseria gonorrhoeae*; AZI (HLR) = azithromycin non-susceptible (HLR, MIC > 256 mg/L) *Neisseria gonorrhoeae*; CTR NGON = ceftriaxone non-susceptible *Neisseria gonorrhoeae*; DAP SAUR = daptomycin non-susceptible *Staphylococcus aureus*; VAN SAUR = vancomycin non-susceptible *Staphylococcus aureus*; CTR SALM = ceftriaxone non-susceptible *Salmonella* species; MDR SHIG = multidrug-resistant *Shigella* species; MDR MTB = multidrug-resistant *Mycobacterium tuberculosis*

Carbapenemase-producing *Enterobacteriaceae* type by state and territory

Six different carbapenemase types (IMP, NDM, OXA-48-like, KPC, VIM, and SME) were reported throughout Australia; significant regional differences were noted (see Figure 8). Two carbapenemase types, IMP (64%, 208/326) and NDM (20%, 65/326), accounted for 84% of all *Enterobacteriaceae* with a confirmed carbapenemase.

IMP type carbapenemases comprised the majority (>70%) of CPE in New South Wales (80%, 86/108), Queensland (89%, 78/88) and the Australian Capital Territory (73%, 8/11). No IMP-producing *Enterobacteriaceae* were reported from South Australia or Tasmania. All the strains that have been genetically sequenced to date (41%, 85/208) are *bla*_{IMP-4}.

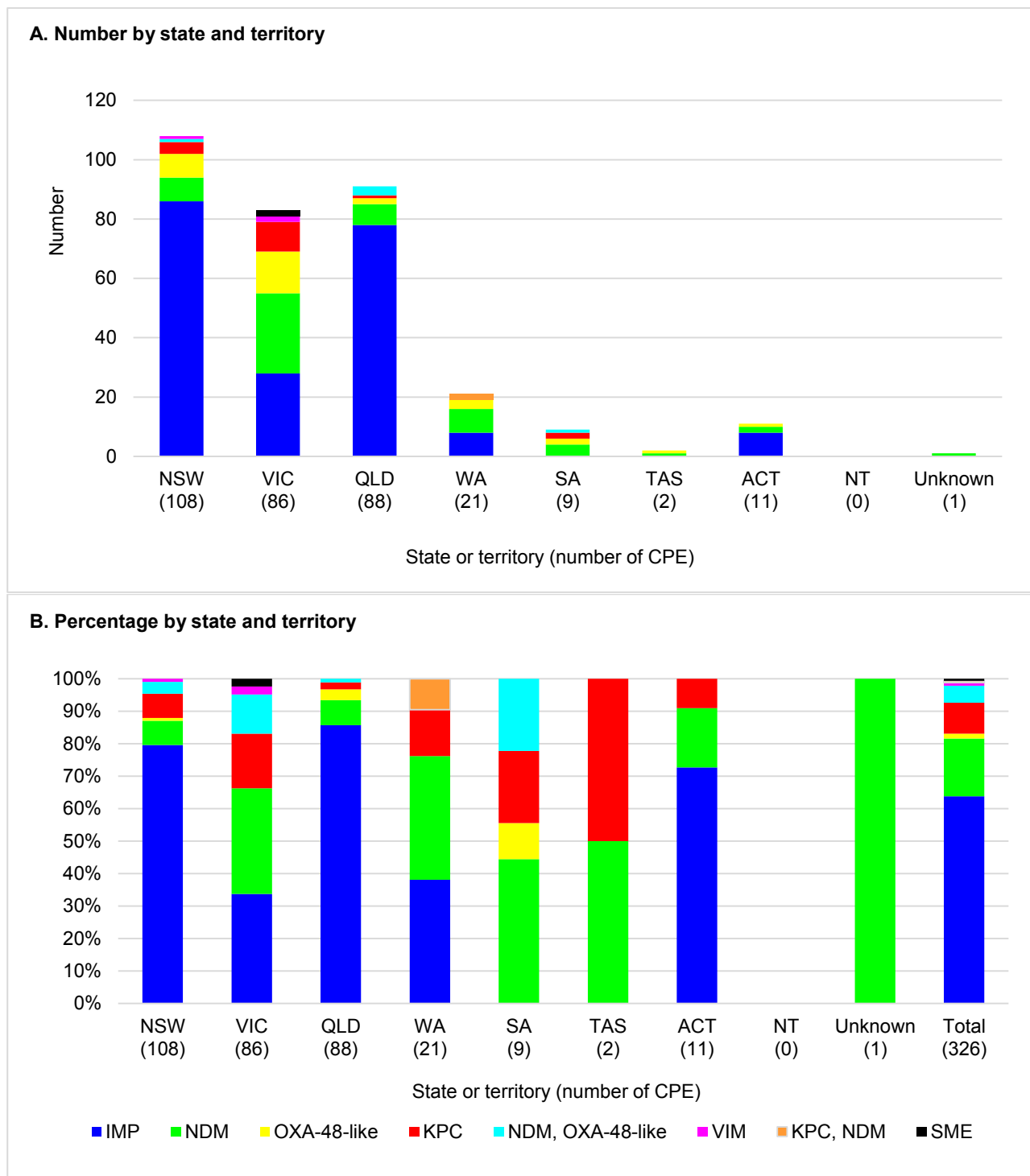
NDM types were found in all states and territories where CPE were detected. NDM+OXA-48-like (5/65) and NDM+KPC (n=2/65), were reported. Four different genes were found in the strains sequenced to date: *bla*_{NDM-5} (39%, 14/36), *bla*_{NDM-1} (42%, 15/36), *bla*_{NDM-4} (11%, 4/36), and *bla*_{NDM-7} (8%, 3/36). NDM types contributed to 31% (27/86) of all types found in Victoria and 48% (10/21) of all types found in Western Australia.

Ribosomal methylases were often detected among isolates containing NDM types (29%, 19/65; *rmtB* [14], *armA* [3], *rmtB+rmtF* [1] and *rmtB+rmtE* [1]).

Klebsiella pneumoniae carbapenemase (KPC) types were mostly confined to Victoria (53%, 10/19), although reports were noted in four other states (New South Wales, n=4; South Australia, n=2; Western Australia, n=2; and Queensland, n=1).

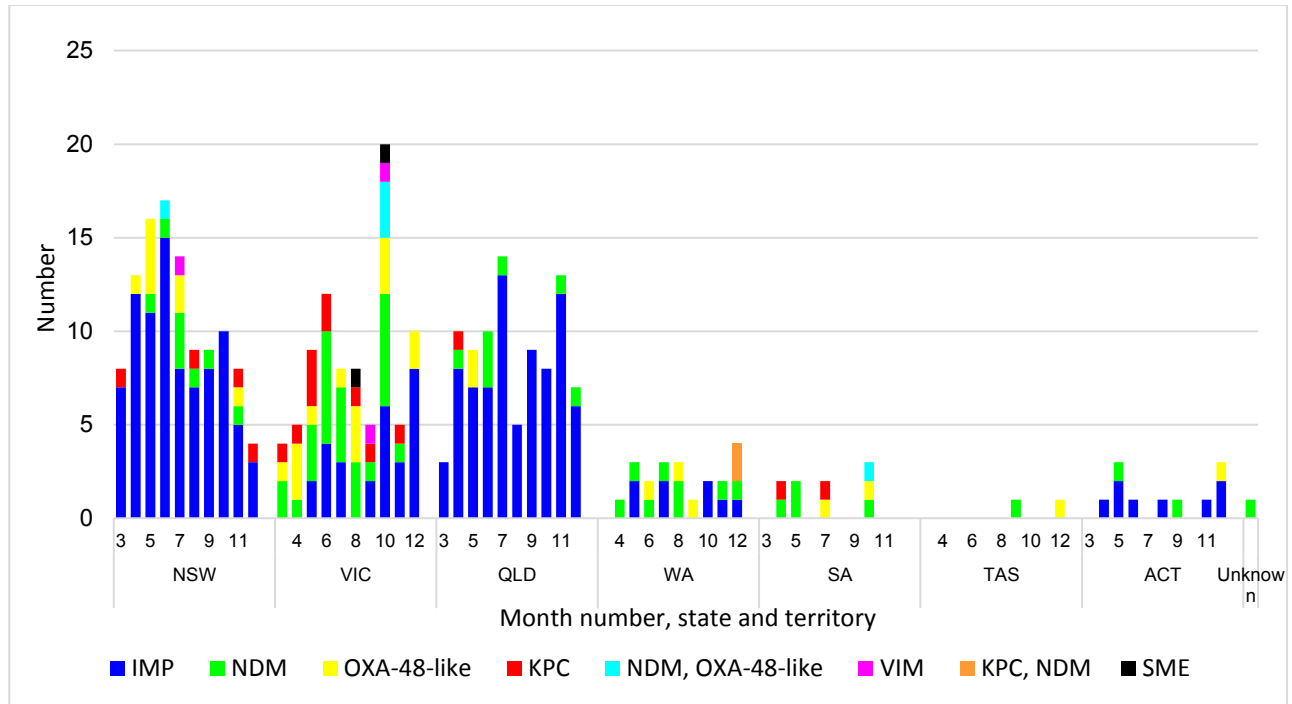
No CPE have been reported from the Northern Territory to date.

Figure 8: Carbapenemase types as a proportion of all carbapenemases, number (A) and percentage (B) reported by state and territory, March–December 2016



The distribution of carbapenemase types by state and territory and month of confirmation is shown in Figure 9. There was a peak in reports during June and July 2016 in New South Wales, Queensland and Victoria. The sharp increase noted in October 2016 for Victoria reflects several isolates that were collected in September 2016. Of interest is the emergence of two *Serratia marcescens* with SME type in Victoria. There have been increasing numbers of SME carbapenemases reported globally especially in the Americas.

Figure 9: Carbapenemase types, number reported by month and state and territory, March–December 2016

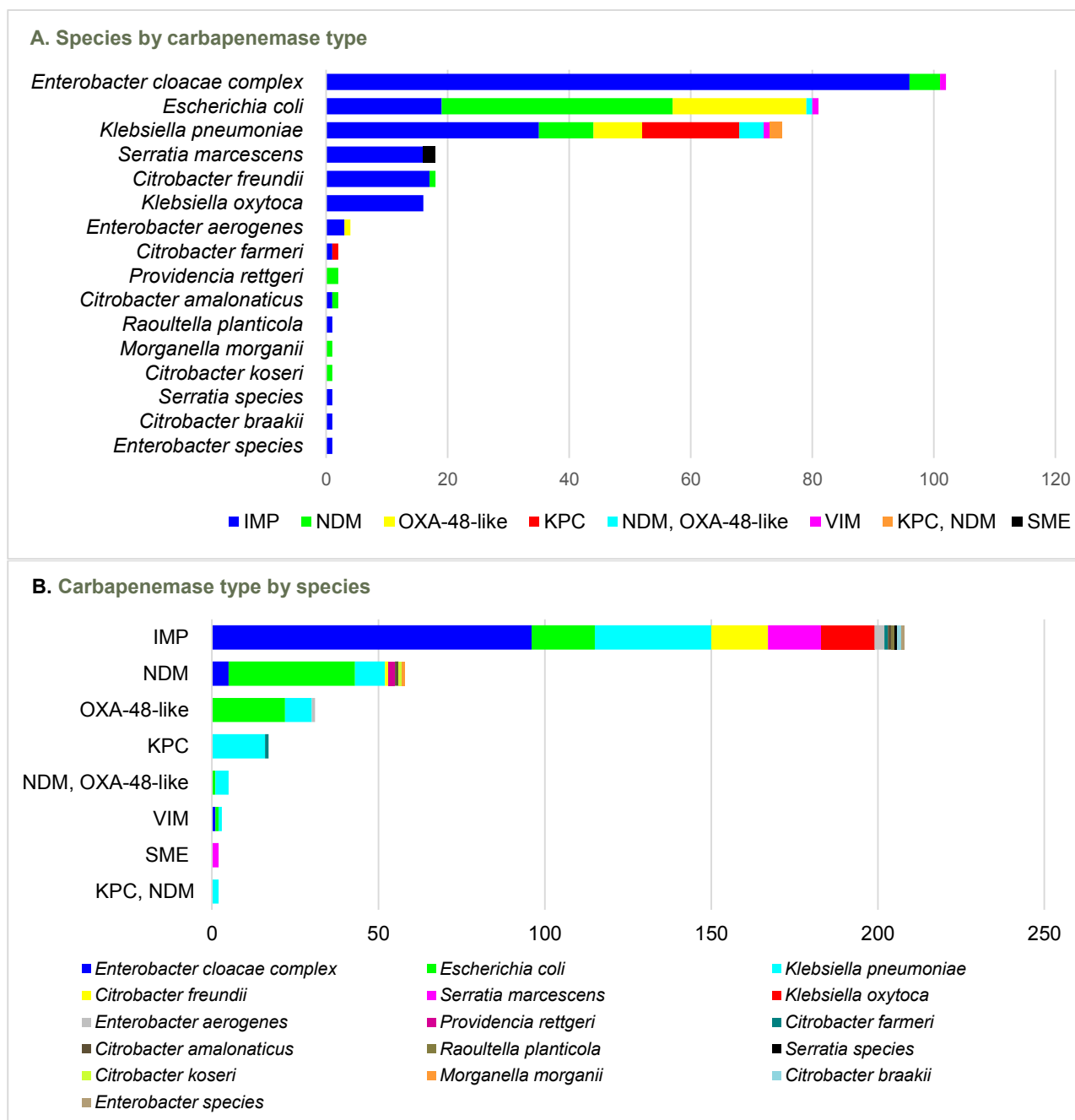


Month number – 3=March; 4=April; 5=May; 6=June; 7=July; 8=August; 9=September; 10=October; 11=November; 12=December

Organism by carbapenemase-producing *Enterobacteriaceae* type

Carbapenemases were found in 16 species of *Enterobacteriaceae*. IMP type carbapenemase accounted for 64% (208/326) of all carbapenemases, and was found in 13 different species (Figure 10). *Enterobacter cloacae* complex accounted for 46% (96/208) of all IMP type carbapenemases and 29% (96/326) of all CPE. However, in Queensland 55% (48/87) of all CPE reported were *E. cloacae* complex containing IMP types. NDM and OXA-48-like carbapenemase types were found mainly in *E. coli* (60%, 39/65; 64%, 23/36, respectively); however, when both NDM and OXA-48-like or KPC types were found together, they were mainly in *K. pneumoniae* (86%, 6/7). One KPC (5%, 1/19) was found in *Citrobacter farmeri*.

Figure 10: Carbapenemase-producing *Enterobacteriaceae*, number reported by species (A) and carbapenemase type (B), March–December 2016



Other Critical Antimicrobial Resistance types

Ceftriaxone non-susceptible *N. gonorrhoeae* were reported from NSW, and contributed to 17% (4/24) of all *N. gonorrhoeae* in July 2016.

For *S. aureus*, 98% were daptomycin non-susceptible strains (62/63). One vancomycin non-susceptible (vancomycin-intermediate) strain was reported in June 2016 from Victoria. No linezolid non-susceptible *S. aureus* strains were reported.

Ribosomal methylases were detected in 36 *Enterobacteriaceae*, representing seven different species; 58% (21/36) of which also had a carbapenemase. Ribosomal methylases are not always associated with a carbapenemase gene. Five genes were found; *rmtB* (61%, 22/36), *armA* (28%, 10/36), *rmtC* (8%, 3/36), *rmtF* (3%, 1/36). Two isolates had multiple genes; *Providencia rettgeri* (*rmtB*, *rmtE*, and NDM) and *K. pneumoniae* (*rmtB*, *rmtF*, and NDM+OXA-48-like).

Conclusion

For this reporting period, 70 originating laboratories contributed CARs. All states and territories have had at least one CAR reported.

The Commission will continue to monitor records from the CARAlert System, and prepare summary reports on a regular basis; the volume of CARs will inform the frequency of reports. The Commission will provide ad hoc reports to the nominated jurisdictional contacts, as required. However, the direct access to CARAlert now available to authorised state and territory officers has reduced the need for ad-hoc reports.

The relatively small number of records in the database to date means that it is not yet possible to draw specific conclusions from the analyses. As the data collection develops and numbers of reports increase sufficiently to enable meaningful analyses of trends and their implications, it is anticipated that the data will inform quality improvement initiatives and antimicrobial resistance reduction policies.

The CARAlert Handbook is currently under review. During this process, all CARs will be examined for suitability to remain on the list, and additional CARs will be considered for inclusion, such as colistin-resistance, carbapenemase-producing *Pseudomonas* species and *Acinetobacter* species. The revised CARAlert Handbook will be issued mid-2017.

Enquiries regarding either this report or the CARAlert System should be submitted to CARAlert@safetyandquality.gov.au.

Glossary of Terms and Abbreviations

Term/Abbreviation	Definition
Clinical specimen	Clinical specimens are collected for diagnostic purposes. They include urine, wound, blood and other (e.g. genital or respiratory) specimens
Screen specimen	Specimens taken for the purpose of screening for resistances
Confirming laboratory	The laboratory which performs the necessary confirmatory tests for a CAR. Confirming laboratories: <ul style="list-style-type: none"> notify the originating laboratory of test outcomes through the usual communication channels, regardless of whether a CAR is confirmed or not. enter data for each confirmed CAR into the CARAlert web-portal. State and territory health authorities and the Public Health Laboratory Network have contributed to identification of confirming laboratories for the purpose of CARAlert.
Critical Antimicrobial Resistances (CARs)	CARs are resistance mechanisms, or profiles, known to be a serious threat to the effectiveness of last-line antimicrobial agents
Originating laboratory	The laboratory to which a specimen is initially referred by a general practice or hospital for routine testing of isolates. If an originating laboratory identifies an isolate that may have the potential to be a CAR, it: <ul style="list-style-type: none"> notifies the requesting clinician of the test results, and the suspected CAR sends the suspected isolate onto a confirming laboratory for confirmation.
Abbreviation	Critical antimicrobial resistance
CPE	carbapenemase-producing <i>Enterobacteriaceae</i>
RMT	ribosomal methylase-producing <i>Enterobacteriaceae</i>
CPE+RMT	carbapenemase- and ribosomal methylase-producing <i>Enterobacteriaceae</i>
LNZ ENTE	linezolid non-susceptible <i>Enterococcus</i> species
AZI (LLR)	Azithromycin-resistant (LLR, MIC < 256 mg/L) <i>Neisseria gonorrhoeae</i>
AZI (HLR)	Azithromycin-resistant (HLR, MIC > 256 mg/L) <i>Neisseria gonorrhoeae</i>
CTR NGON	ceftriaxone non-susceptible <i>Neisseria gonorrhoeae</i>
DAP SAUR	daptomycin non-susceptible <i>Staphylococcus aureus</i>
VAN SAUR	vancomycin non-susceptible <i>Staphylococcus aureus</i>
CTR SALM	ceftriaxone non-susceptible <i>Salmonella</i> species
MDR SHIG	multidrug-resistant <i>Shigella</i> species
MDR MTB	multidrug-resistant <i>Mycobacterium tuberculosis</i>