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MRSA: A Tale of Three Types

15 years of survey data from AGAR

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AURA
Antimicrobial Use and Resistance in Australia

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Introduction

Staphylococcus aureus (*S. aureus)* is a frequent coloniser of humans and a major human bacterial pathogen. It is the cause of a wide range of infections from benign self-limiting conditions (including boils, bullous impetigo and folliculitis), to more serious infections (including cellulitis, post-surgical wound infection, acute and chronic osteomyelitis, septic arthritis, infections of intravascular lines, and prosthetic joint and other device infections), to life-threatening infections (including septicaemia, meningitis, post-viral pneumonia and endocarditis).[1] It is carried by about 30% of the population at any one time, and for the great majority of people it causes no harm.[2] Nevertheless, it has the capacity to cause outbreaks of infection in hospitals from a common source or through poor hand hygiene practices.

Soon after the introduction of (benzyl) penicillin into clinical medicine in the 1940s, strains of penicillin-resistant *S. aureus* emerged that produced penicillinase – the first β-lactamase enzyme to be described.[3] By the late 1950s, chemists began working on chemical modifications of the penicillin nucleus in the hope of finding a modification that would protect the antimicrobial medicine from degradation by penicillinase. The first successful modification was methicillin, which was marketed for the treatment of staphylococcal infection in 1960 in the United Kingdom. Other modifications followed (such as nafcillin, oxacillin, cloxacillin, flucloxacillin and dicloxacillin), each developed specifically for treating staphylococcal infection caused by penicillinase-producing strains.

Jevons[4] first reported resistance to methicillin in clinical isolates of *S. aureus* (methicillin-resistant *S. aureus* – MRSA) from a London hospital in 1961. Of note, the isolates were also resistant to streptomycin and tetracycline, highlighting the staphylococcal propensity for accumulating resistance to multiple agents. Since that time, and slowly at first, MRSA has become a global phenomenon, and has taken many forms. The first report of MRSA in Australia was from Sydney in 1968.[5] By the late 1970s a particular type of multi-resistant MRSA had become established in public hospitals on the eastern Australian seaboard.[6] That clone, now called Aus-2/3 (multi-locus sequence type ST239-MRSA-III), has now become established in tertiary care hospitals in most parts of Australia. By the mid-1980s, community strains of MRSA started appearing in Western Australia, and since that time have developed into an Australia-wide problem.[6]

The mechanism of resistance to methicillin in staphylococci differs from resistance to penicillin. Rather than being mediated by a β-lactamase, methicillin resistance is due to the production of an additional so-called penicillin-binding protein, pbp-2a, which is encoded by the *mecA* gene. This protein is a variant of one of the essential cell-wall synthetic enzymes, pbp-2 (a transpeptidase). A methicillin-resistant isolate retains its original pbp-2, but also produces pbp-2a, which retains its transpeptidase function but has much lower affinity for β-lactams generally, including penicillins, cephalosporins and carbapenems. Because the resistance mechanism is not that of a β-lactamase, MRSA are also resistant to the combinations of β-lactamase inhibitors with β-lactams.

Treatment of MRSA infections depends on severity. Superficial skin infections can be managed with drainage and/or topical agents. More serious infections will require systemic antimicrobials: vancomycin is most commonly used when intravenous therapy is needed, and only a limited range of agents is effective when oral therapy is needed. Recent evidence has confirmed that vancomycin is suboptimal treatment for staphylococcal infection compared to β-lactams when the infection is caused by strains susceptible to methicillin.[7] The implication is that vancomycin is

suboptimal therapy for MRSA infections, but unfortunately there is no evidence that any alternative intravenous agent is superior.

Tracking MRSA emergence and spread through typing

There have been several systems for typing strains of *S. aureus*. Prior to the advent of multi-locus sequence typing (MLST), the most popular system was phage typing, a system that used a collection of different viruses (called bacteriophages) that attack and kill specific strains of this bacterial species. The patterns of killing by the different phages defined the 'phage type'. Phage typing was supplanted by pulsed-field gel electrophoresis (PFGE) in the 1980s, a technique that created a 'bar code' of the bacterial DNA after fragmenting it with specific enzymes. PFGE was valuable at the local level, but due to technical variation, could not easily be used to compare results from different laboratories locally or internationally.

MLST was developed in the late 1990s, and applied to a range of bacterial species, including *S. aureus*, soon after. MLST involves the DNA sequencing of seven so-called housekeeping genes, which are found in all strains of the species, and whose sequences are known not to vary significantly over time. Each unique gene sequence is called an 'allele', and the combination of the seven allelic sequences defines the allelic profile, which is considered to be a distinct clone. MLST has the advantage of being stable and readily portable, meaning that sequences are stored and can then be compared from anywhere in the world (MLST online database and analysis website). It can also provide information about the evolution of individual clones. The sequence type is designated by a number, preceded by 'ST'. Related sequence types belong to families called 'clonal complexes'.

The sequence type provides the base information of a clone, but an additional piece of genetic typing is required to identify an MRSA clone. This additional information is called the 'SCC*mec*' type (Staphylococcal Cassette Chromosome *mec*). It is a piece of mobile DNA (meaning it can be transferred to other staphylococci) that has been acquired by a staphylococcus and inserted into its chromosome. Possession of SCC*mec* makes the staphylococcus resistant to methicillin because it contains the *mec* gene, which codes for the additional penicillin-binding protein pbp2a, and the *mec* gene's associated regulatory genes. There are at least 12 varieties of SCC*mec*, which vary in size and content, and each type is designated by an upper case roman numeral. This is added to the sequence type to provide the full designation of a clone – for example, the Aus-2/3 clone is ST239-III, meaning it is sequence type 239 and SCC*mec* type III. Larger SCC*mecs* possess additional resistance genes besides *mec,* and are the main contributors to multi-resistance. The acquisition of SCC*mec* converts a methicillin-susceptible clone of *S. aureus* into an MRSA clone.

PFGE still plays a role in discriminating specific genetic lineages amongst strains with the sequence and SCC*mec* type. It forms the basis of the Western Australian typing nomenclature that has wide currency across Australia. For instance, at least five different clones have been identified in the ST5-IV type, only one of which (PFGE pattern WA-3) has become more common in recent years.

As costs come down, whole genome sequencing (WGS) is now being used with increasing frequency for tracking clones of resistant bacteria. Within a few years, it is likely that the additional information generated by WGS will refine *S. aureus* typing.

AGAR surveillance

The Australian Group on Antimicrobial Resistance (AGAR) has been tracking MRSA infections across the country since 1985 (AGAR website). While participation in AGAR has been voluntary, the group has managed to maintain contributions from at least 24 laboratories, with almost all

states and territories regularly represented. With the introduction of MLST, the activities of AGAR have greatly enhanced our understanding of MRSA epidemiology, or more correctly, epidemiologies. We now recognise MRSA comes in three 'types': healthcare-associated, community-associated and livestock-associated, and each with a range of different clones. Table 1 below shows the key features of the healthcare-associated and the community-associated types and clones that have been tracked in Australia since 2000.

From 2000−12, AGAR conducted period prevalence surveys on all types of *S. aureus* infections (see note below about AGAR data for figures). In 2001, isolates from hospital emergency departments were also included. From 2013, AGAR switched to continuous surveillance of blood culture isolates, and included those with community-onset (from blood cultures collected prior to or within 48 hours of admission), and hospital-onset (from blood cultures collected more than 48 hours after admission) infections.

Figures 1 and 2 show the combined incidence of the major clones since 2000 in hospital-onset and community-onset infections respectively. The vertical blue dotted line in these figures indicates where the sampling method changed. There has been a noticeable decline in the proportion of hospital-onset *S. aureus* infections that are MRSA since 2009 (Figure 1). This trend appears to have continued despite the change in sampling method. By contrast, the prevalence of MRSA in community-onset infections has remained reasonably stable since 2008 (Figure 2).

Note about AGAR data for figures

Community-onset infection:
For the biennial AGAR surveys from 2000–12, each participating institution contributed 100 consecutive clinical isolates causing infection of any type from outpatients and those attending emergency departments.

Hospital-onset infection:
For the biennial AGAR surveys from 2001–11, each participating institution contributed 100 consecutive clinical isolates causing infection of any type from patients who had been hospitalised for at least 48 hours. In 2001 and 2003, the sample also included clinical isolates from patients attending an emergency department.

From 2013 onwards:
The AGAR survey method changed in 2013 to the continuous collection of isolates from blood cultures (invasive disease). Both community-onset and hospital-onset episodes were included, defined by the '48-hour rule' (onset > 48h after admission = hospital-onset, otherwise community-onset).

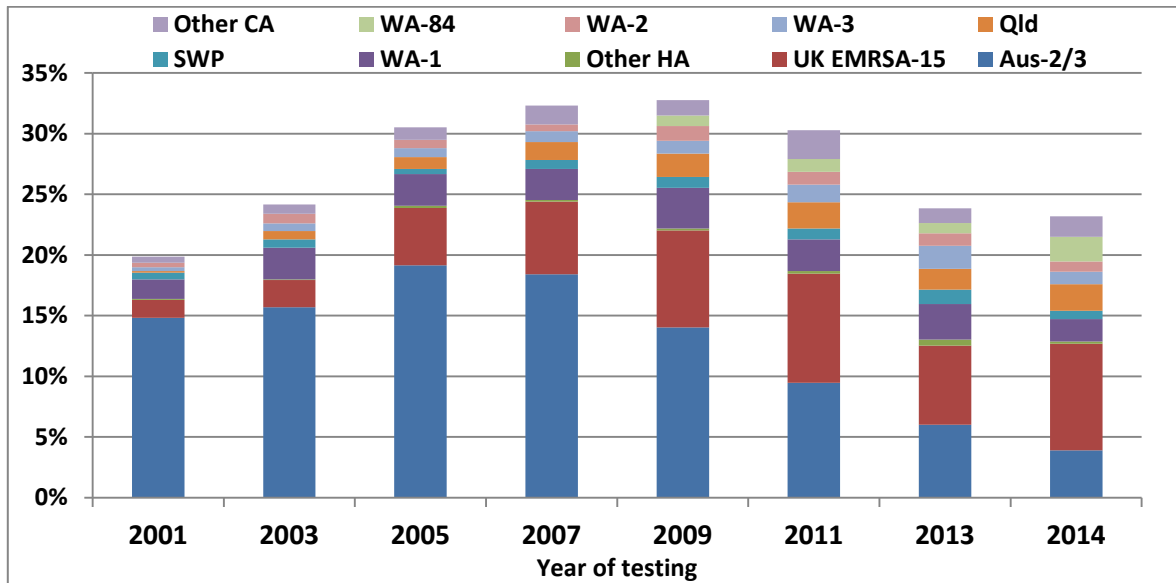**Figure 1:** **Hospital-onset MRSA, all clones, 2001–2014; percentage of all *S. aureus***

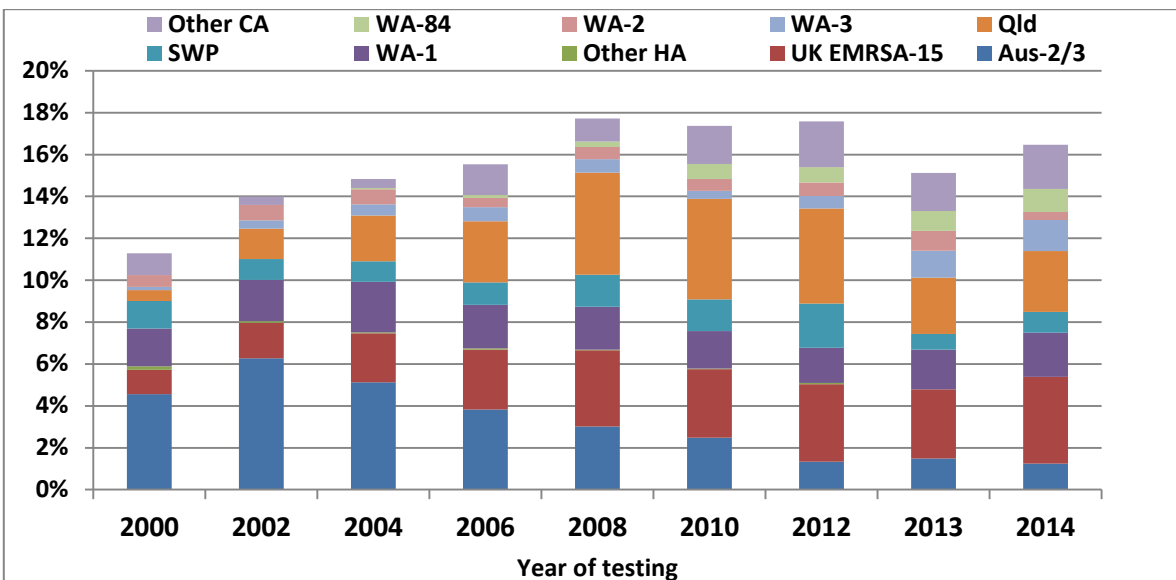**Figure 2:** **Community-onset MRSA, all clones, 2000–2014; percentage of all *S. aureus***

Table 1:   Important MRSA clones that have been identified in Australia 2000–14

Variety	Type – common names (MLST type & SCC*mec** type)	Origin (year) [references]	First detected in Australia [reference]	Typical resistance pattern†	Panton-Valentine leucocidin	Major reservoir	Prevalence
Healthcare-associated	Aus-2/3‡ (ST239-III)	Australia or USA (1976)[8,9,10]	1976[9]	Macrolides/Lincosamides Tetracyclines Trimethoprim-sulfamethoxazole Gentamicin Fluoroquinolones	Negative	Hospital 'frequent flyers'	Was common in many countries around the world Was very common in NSW, Qld, Vic. and SA, now diminishing
	UK EMRSA-15 (ST22- IV)	England (1991)[11]	1997[12]	Fluoroquinolones Macrolides/Lincosamides variable	Negative	Long-term care facilities[13]	Increasingly common
	New York / Japan or USA100 (ST5-II)	Japan (1982)[14]	2005[15]	Macrolides/Lincosamides Fluoroquinolones	Negative	None	Very common in the USA, Japan and Korea Rare and sporadic in Australia
	UK EMRSA-16 or USA200 (ST36-II)	Southern England (1991)[16]	2002[17]	Macrolides/Lincosamides Fluoroquinolones Mupirocin	Negative	None	Rare and sporadic
Community-associated	WA-1 (ST1-IV)	Northern Western Australia[18,19]	1989[18]	Typically no additional resistances Macrolides/Lincosamides variable Fusidic acid variable	Negative	Community	Common
	Queensland (ST93-IV)	South-eastern Queensland (2000)[20]	2000[20]	Typically no additional resistances	Positive	Community	Common
	Oceania/Southwest	New Zealand	1997[22]	Typically no additional	Positive	Community	Common

Variety	Type – common names (MLST type & SCC*mec** type)	Origin (year) [references]	First detected in Australia [reference]	Typical resistance pattern†	Panton-Valentine leucocidin	Major reservoir	Prevalence
	Pacific (ST30-IV)	(1992)[21]		resistances			
	WA-3 (ST5-IV)	Western Australia	1999[19]	Macrolides/Lincosamides variable	Negative	Community	Increasing
	WA-2 (ST78-IV)	Western Australia	≤ 2000 [AGAR studies]	Macrolides/Lincosamides (variable)	Negative	Community	Increasing
	WA-84 (ST45-V)	Victoria	≤ 2004 [AGAR studies]	Fluoroquinolones Macrolides/Lincosamides, Tetracyclines (variable)	Negative	Community	Increasing
	USA300 (ST8-IV)	United States (2000)[23]	2000[23]	Macrolides/Lincosamides Fluoroquinolones (variable)	Positive	Community	Rare and sporadic

*Staphylococcal Cassette Chromosome *mec*
†Apart from β-lactams
‡The 2/3 designation refers to different pulsed field electrophoresis types.

TYPE 1 MRSA – healthcare-associated (HA-MRSA)

Two healthcare-associated clones have dominated healthcare-acquired *S. aureus* infections in Australia: Aus-2/3 and EMRSA-15 – the first possibly 'home-grown' and the second imported.

Aus-2/3 – the first major multi-resistant clone in Australian hospitals

The current evidence suggests that the first strains of Aus-2/3 originated in Australia or possibly the USA;[8,9,10] the earliest known Australian strain was isolated in 1976.[9] By the late 1970s this clone had become established in many Melbourne teaching hospitals.[24] By the time of the first surveys conducted by the AGAR in 1985, Aus-2/3 was found to cause 12–25% of all *S. aureus* infections in large public capital-city hospitals along the eastern seaboard, in Brisbane, Sydney, Canberra and Melbourne, and to a lesser extent in Adelaide.[25] Ultimately, the only state not to become a reservoir for Aus-2/3 was Western Australia, which introduced intensive efforts at screening and segregating patients and staff coming from eastern states hospitals.[26] It remains very uncommon there.[27]

Recent detailed studies of the Aus-2/3 sequence and SCC*mec* type in Australia (ST239-III) using detailed genomic and phenotypic methods have shown that what is currently identified as Aus-2/3 may actually represent a mixture of two clades.[28] One clade represents the long-established (many decades) Aus-2/3 HA-MRSA, while in 2001 a new clade appeared in Victoria which appears to have originated in Asia. Whether this explains the boost in the prevalence of Aus-2/3 between 2001 and 2005 in Victoria, New South Wales and Queensland (see Figure 9 in the geographic section), in an otherwise previously well-established clone, is not clear.

A decline of Aus-2/3 in hospital-onset infections began 2009, and has continued rapidly (Figure 3). Aus-2/3 has also contributed to community-onset infections but almost always occurs in patients who have been previously hospitalised in facilities where the clone is known to be prevalent (Figure 4).[29]

It is believed that the decline in hospital-onset Aus-2/3 reflects improving infection control efforts in all hospitals, and especially the introduction of a national hand hygiene program in June 2008,[30] supported by the national pubic reporting of healthcare-associated *S. aureus* bacteraemia.[31] These initiatives would have been boosted by the 2012 implementation of the National Safety and Quality Health Service (NSQHS) Standards, linked to accreditation, released by the Australian Commission on Safety and Quality in Health Care, and in particular Standard 3: Preventing and Controlling Healthcare Associated Infections.[32]

Figure 3:   Healthcare-associated (HA) clones of MRSA, hospital onset infections, 2001–2014; percentage of all *S. aureus*
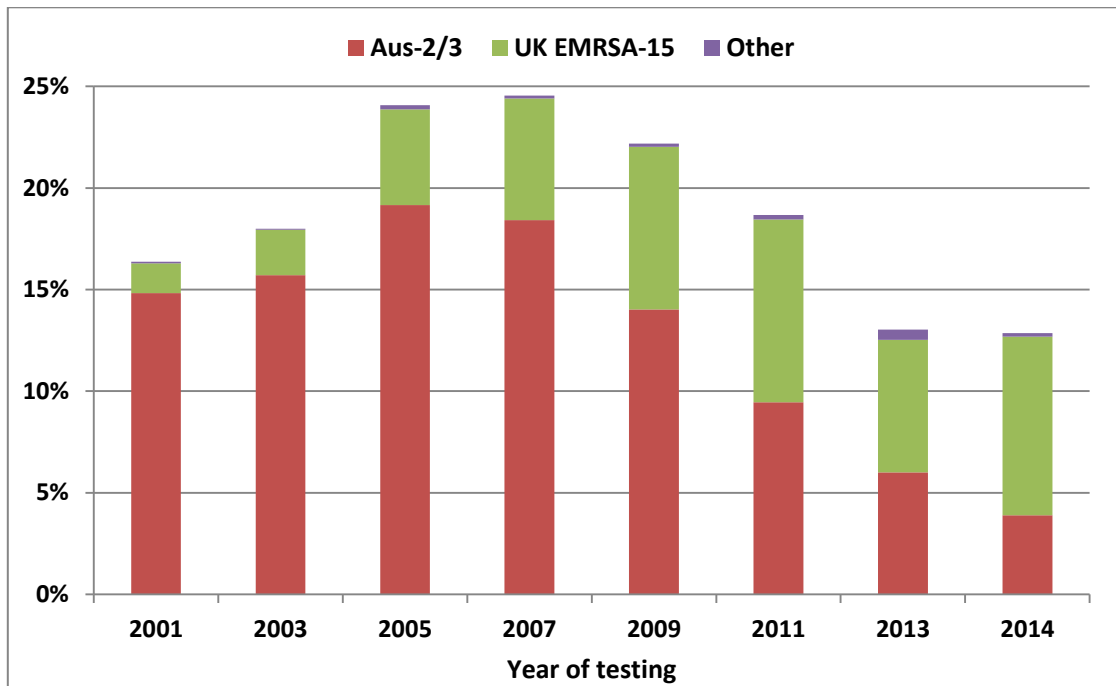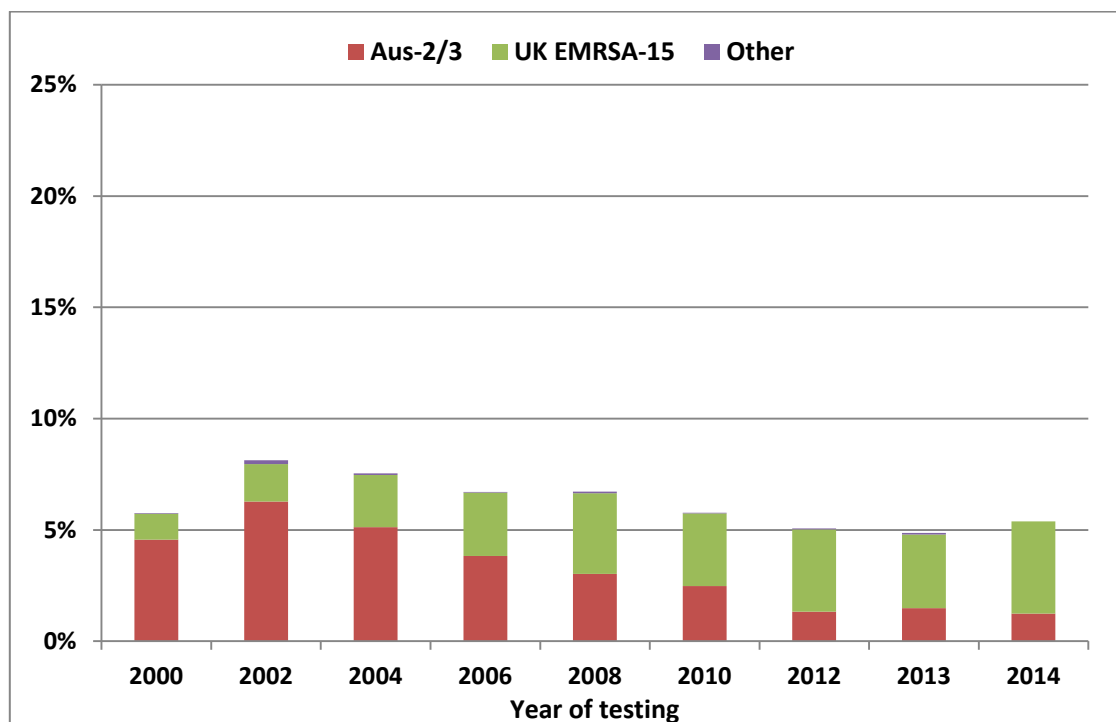

Figure 4:   Healthcare-associated (HA) clones of MRSA, community-onset infections, 2000–2014; percentage of all *S. aureus*

One of the major problems in treating Aus-2/3 is that it is multi-resistant. Typically, it harbours resistance to macrolides, lincosamides, tetracyclines (genes located within SCC*mec* III), as well as trimethoprim and trimethoprim-sulfamethoxazole, plus gentamicin,

and frequently acquired resistance to ciprofloxacin and rifampicin. Few agents are available for treatment.

UK EMRSA-15 – the first imported healthcare-associated clone to spread widely

The EMRSA-15 clone emerged in the United Kingdom in 1991. It has a distinct resistance profile, being resistant consistently to ciprofloxacin and often to macrolides/lincosamides but typically to no other classes of antimicrobial beyond the β-lactams. It was first documented in Western Australia in 1997, in British healthcare workers who were screened as part of that state's MRSA containment policy.[12] By 2000, it was seen nationally in AGAR surveys, most prominently in Sydney.[17] Since that time its prevalence has continued to grow steadily. In the AGAR 2014 survey, EMRSA-15 comprised 30% of all MRSA and 5% of all *S. aureus* isolates, was more than twice as common as Aus-2/3, and was the most frequently identified type of MRSA overall. It contributed significantly to both hospital- and community-onset bacteraemia (Figures 3 and 4).[29]

The EMRSA-15 clone appears to have a significant reservoir in residential aged-care facilities.[13,27] At one tertiary hospital in Melbourne, 33% of EMRSA-15 infections occurred in patients admitted from residential aged-care facilities, compared to only 5% of cases caused by Aus-2/3.[13] Apart from the first detection in UK healthcare workers in Western Australia, the link between the foreign healthcare workers and the repeated introduction of EMRSA-15 remains speculative. Medical and nursing staff born in the UK made up 13% and 26% of all those who were foreign-born in 2011, falling from 2001 levels of 20% and 36% respectively.[33] Nevertheless, they are still the largest group of foreign-born healthcare workers in both categories, and active recruitment from the UK continues.

Another feature of EMRSA-15 contributing to its ongoing spread is its capacity to colonise healthcare workers, being four-fold more likely to colonise healthcare workers in an outbreak than Aus-2/3.[34] It is likely therefore that the reservoir for EMRSA-15 has components in frequently hospitalised patients, in residents of residential aged-care facilities, and in some healthcare workers. The increasing prevalence of EMRSA-15 is occurring in Australia at a time when it has declined significantly in England.[35]

Other healthcare-associated clones

Other healthcare-associated clones have remained rare in Australia. The AGAR surveys have regularly detected the New York / Japan clone (ST5-II and also called USA100) at very low levels since 2005 (1-3 isolates annually). It has been isolated in four states so far. The New York / Japan clone was first described in Australia in an outbreak in Western Australia that could traced to an Australian healthcare worker who had been previously hospitalised in New York. However, this clone has remained uncommon afterwards in that state.[15] Despite its high prevalence in the United States, Japan and Korea,[36] consistent with a high capacity for spread, ST5-II has not become established in Australia. The picture is one of intermittent introduction from overseas, but without local spread. The New York / Japan clone has a similar resistance profile to EMRSA-15, including to macrolides/lincosamides and ciprofloxacin, but is less multi-resistant than Aus-2/3.

A similar story applies to UK EMRSA-16 (ST36-II and also called USA200). This is second only to EMRSA-15 in prevalence in the United Kingdom. It has been seen intermittently in AGAR surveys, but shows no signs of becoming established.

Other healthcare-associated clones that have been found in the AGAR surveillance include ST250-I (so-called classical MRSA), ST247-I (UK EMRSA-17), ST8-VI (Irish 2), and ST228-I (Southern German). These fit the pattern of sporadic introduction into Australia, with no or very limited spread.

TYPE 2 – community-associated MRSA (CA-MRSA)

Community-associated MRSA clones first emerged in Australia in the 1980s and since that time have both diversified and increased in prevalence. They now exceed HA-MRSA as a cause of community-onset infection and rival them as a cause of hospital-onset infections. CA-MRSA clones are totally different from those found to cause cross-infection in healthcare settings. They tend not to be resistant to the non-beta-lactam antibiotics, although with the passage of time, some CA-MRSA clones are accumulating more resistances. A characteristic frequently associated with *some* clones of CA-MRSA is the possession of the Panton-Valentine Leucocidin (PVL) toxin – details are provided in the next section. CA-MRSA now play a substantial role in hospital-onset *S. aureus* infections. This is not surprising, as a significant proportion of healthcare-associated staphylococcal infections are caused by strains that are carried by the patient at the time of the intervention that led to the infection.[37] In 2014, almost half of CA-MRSA (48%) bacteraemias were hospital-onset, and CA-MRSA rivalled HA-MRSA as a cause of hospital-onset MRSA infection (45% CA-MRSA).

WA-1 – the first established CA-MRSA in Australia

Community-associated strains of MRSA were first noted in Western Australia in 1984, and became a particular problem in the Kimberley region by 1989.[38] By 2004, it had become clear that a number of new clones of CA-MRSA had emerged over the years in Western Australia, and that one particular clone, WA-1 (ST1-IV), had come to dominate the CA-MRSA picture there, and that it had spread to almost all other states and territories.[17,19] WA-1 is still one of the three most important CA-MRSA clones isolated across Australia (Figures 5 and 6).

WA-1 is usually susceptible to non-β-lactam agents. Around half of the strains harbour at least one additional resistance mechanism, most commonly to macrolides/lincosamides and/or fusidic acid. WA-1 does not usually produce PVL, although 10% of ST1-IV isolates possess this toxin.[29]

Figure 5: AGAR Surveys: Community-associated clones of MRSA, community-onset infections, 2000–2014; percentage of all *S. aureus*
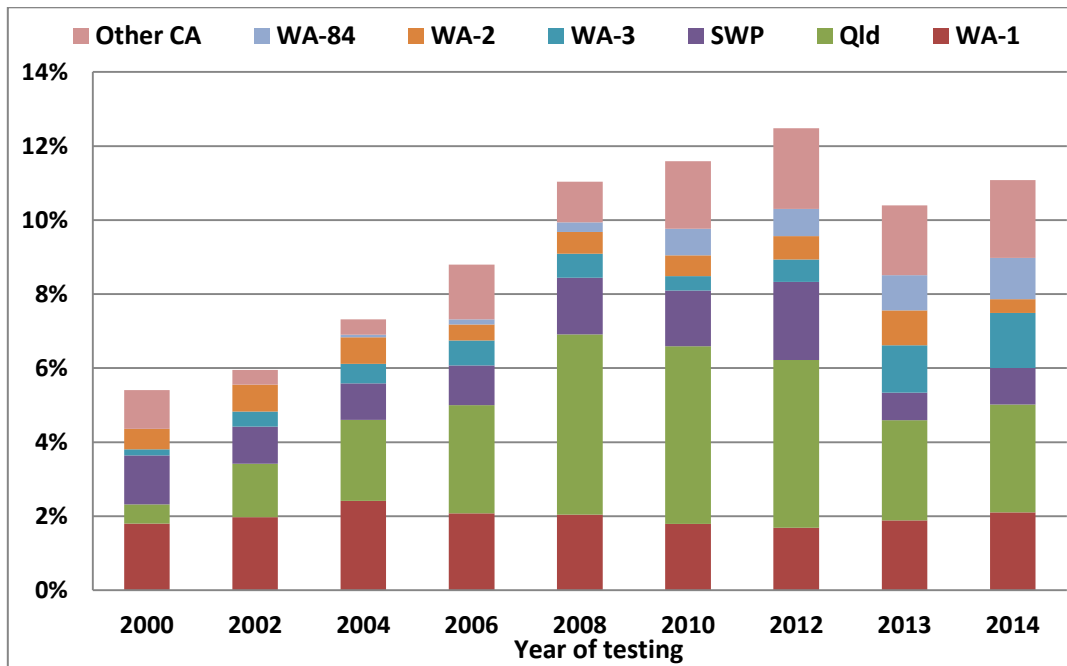

Figure 6: AGAR Surveys: Community-associated clones of MRSA, hospital-onset infections, 2001–2014; percentage of all *S. aureus*
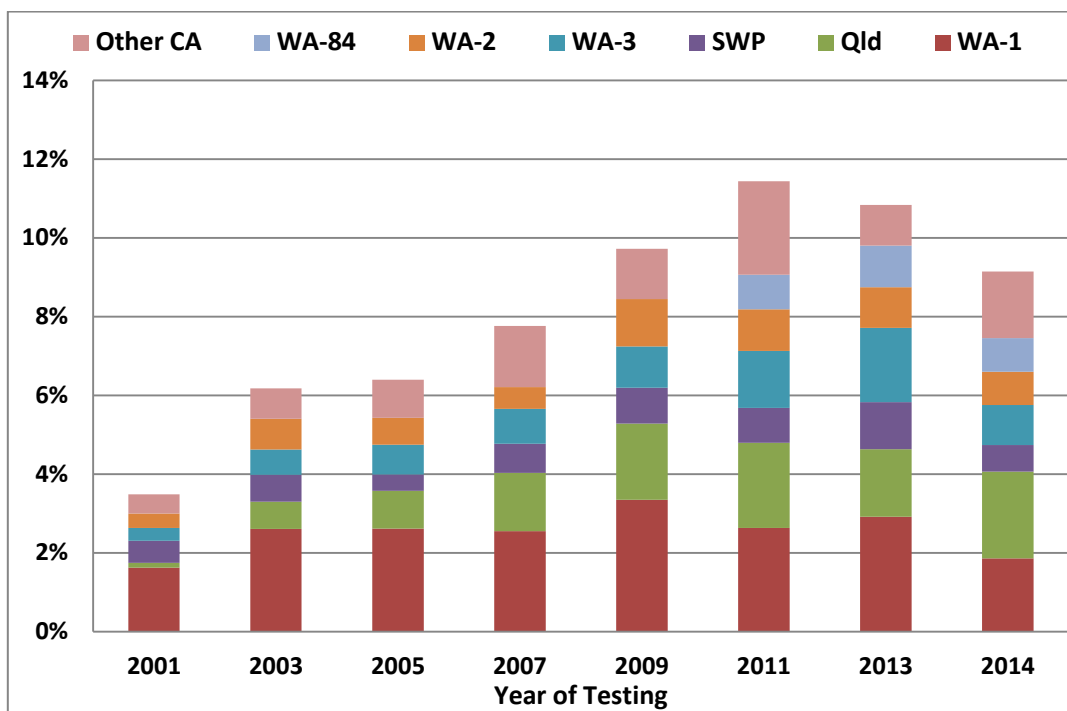
Figure 7: AGAR Surveys: Community-associated MRSA, trends of the three dominant clones in community-onset infections, 2000–2014; percentage of all *S. aureus*
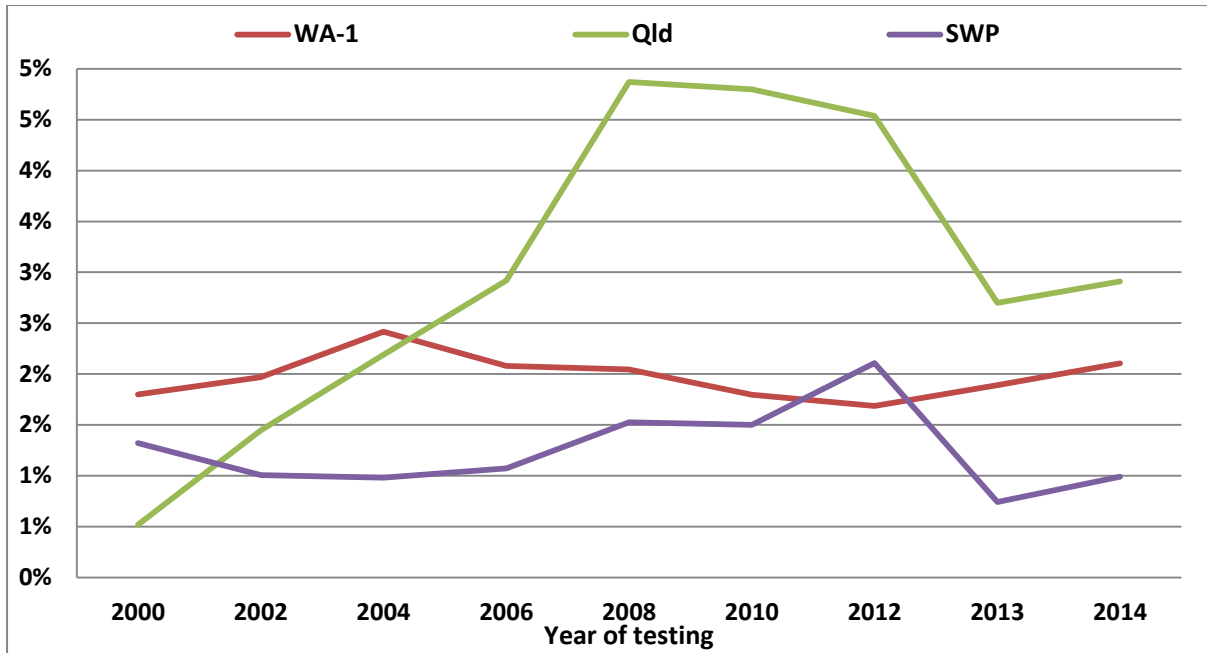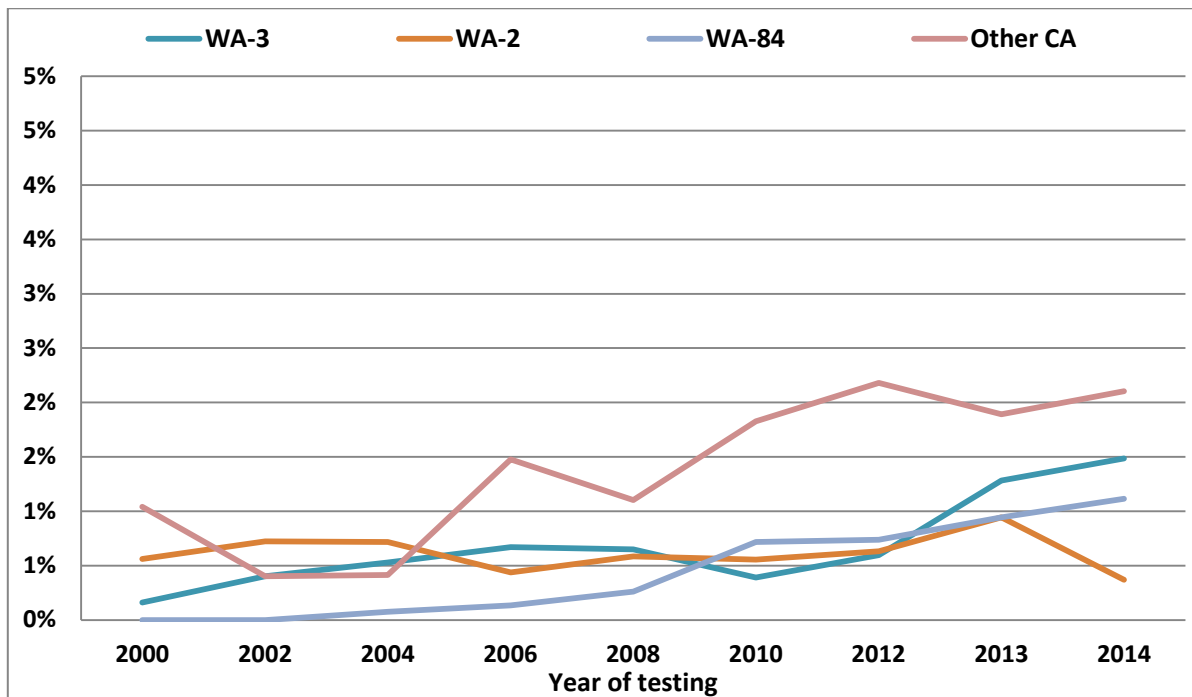

Figure 8: AGAR Surveys: Community-associated MRSA, trends of other clones in community-onset infections, 2000–2014; percentage of all *S. aureus*

The Southwest Pacific (SWP) clone – an introduced CA-MRSA

The SWP clone (ST30-IV) first appeared in Auckland, New Zealand, and was frequently isolated from patients of Western Samoan origin, leading to its designation initially as WSPP (Western Samoan phage pattern).[39] The first descriptions were in 1998.[40] Soon after it was recognised that ST30-IV was also present in Australia; again people of Pacific Island nation origin in the southwest Pacific (Western Samoa and Tonga) were disproportionally affected.[22,41] More recent studies have shown that the SWP clone had its origins as far back as 1953,[42] when its methicillin-susceptible and PVL-producing ancestor, then called 'phage type 80/81', was associated with major outbreaks of infections in neonatal nurseries in Australia[43] and subsequently many other parts of the world.

The SWP clone is almost always susceptible to non-β-lactam classes of antimicrobial – approximately 10% have additional resistance(s). Most notably, SWP produces PVL (see next section 'The importance of Panton-Valentine leucocidin').

The Queensland (Qld) clone – a home-grown and increasing problem

The Queensland clone (ST93-IV) has become the dominant CA-MRSA in Australia (see Figure 7). First recognised amongst Caucasians (and not Pacific Islanders) in southern Queensland in 2000,[20] it has since spread to become the dominant CA-MRSA in Queensland, Northern Territory, and South Australia, on equal terms with WA-1 in New South Wales, and Victoria, and second only to WA-1 in Western Australia.[29] AGAR surveys show that it was actually first detected in five states/territories in 2000, mostly notably in New South Wales.

Like the SWP clone, the Queensland clone tends to be susceptible to non-β-lactam classes of antimicrobial, and importantly it also produces PVL (see 'The importance of Panton-Valentine leucociden'). The reasons for its success remain unclear despite extensive molecular studies, and it harbours very few virulence factors besides the genes encoding PVL.[44]

It is noticeable that the proportion of the PVL-producing clones, the Queensland and SWP clones, decreased with the change to bacteraemia-only surveillance in 2013 (Figure 7). This is consistent with the observation that PVL-producing strains are less likely to cause invasive infection.[45,46]

Other CA-MRSA clones – ever increasingly diversity

Following the introduction of molecular typing of MRSA, the AGAR surveys have witnessed an ever increasing number of new CA-MRSA clones across Australia. A few have gained a foothold and are seen regularly (Figure 8). These include:

- WA-3 (ST5-IV): first documented in New South Wales and South Australia in 2000,[17] but now seen Australia wide;[47] largely PVL negative
- WA-2 (ST78-IV): first documented in 2000, predominantly in Western Australia,[17] but since spread Australian-wide; [47] largely PVL negative

- the Victorian clone (WA-84, ST45-V): first documented in Victoria in 2004 and increasingly prominent there ever since;[47] PVL negative and multi-resistant.

More than 100 clones on CA-MRSA have now been detected in Australia since the year 2000. These are a mixture of both locally arising and international clones. For the locally arising clones, it suggests that although SCC*mec* is not believed to spread easily from MRSA to other methicillin-susceptible *S. aureus* clones, it does happen with some frequency. This increasing diversity is reflected in Figure 8 which shows that 'other CA-MRSA' have collectively outnumbered WA-1, SWP and Queensland since 2006. In 2014 for instance, there were 17 clones (community- plus hospital-onset) detected in addition to the common three clones. Thus, while SCC*mec* has the ability to be inserted into many chromosomal backgrounds, most of the resulting clones are not particularly well adapted for transmission and carriage compared to the dominant clones. Nevertheless, there are two clones – WA-3 (ST5-IV) and the Victorian clone (WA-84, ST45-V) – which appear to be on the rise (Figure 8).

Another clone of interest is USA300 (ST8-IV). This is a clone of CA-MRSA that has become a major cause of *S. aureus* infection in the community in the USA, accounting for up to 50% of all community infections in many parts of country.[48] It was first recognised in 1999, and after spread across the US community, is an important cause of infection in at least some parts of the USA.[49] This clone has been detected in AGAR surveys from at least 2000. However, its numbers remain low, and present another example of the sporadic introduction of a clone that has failed to become established yet in Australia, despite success elsewhere.[50] Like the Southwest Pacific and Queensland clones, USA300 produces PVL (see 'The importance of Panton-Valentine leucociden').

There have also been sporadic appearances of CA-MRSA from other countries, including the Taiwan clone (ST59-V), the Bengal Bay clone (ST772-V), and the European clone (ST80-IV)). Again, none of these are showing signs of becoming established.

The importance of Panton-Valentine leucocidin

Panton-Valentine leucocidin (PVL) was first described in 1932 by Panton and Valentine in *S.aureus* causing purulent infections.[51] Its importance was unrecognised until 2003 when a strong association was noted between certain clones of CA-MRSA and PVL[52] by French and other international investigators. Both the SWP and Queensland clones, as well as USA300, were identified as carrying PVL in that study. It has been shown subsequently that PVL is not confined to CA-MRSA, but can be found in methicillin-susceptible strains.[53]

PVL-producing strains of *S. aureus* are associated with a variety of distinctive clinical manifestations: excessively purulent skin and soft tissue infections that frequently require drainage/surgical intervention,[54] recurrent furunculosis (boils),[56] multifocal osteomyelitis associated with early bone necrosis and deep vein thrombosis,[57] and necrotising pneumonia.[58] By contrast, PVL-producing strains are less likely to cause bacteraemia or other invasive disease and the same or lower mortality than that caused by PVL negative *S. aureus*.[45,59] Overall, PVL-producing *S. aureus* are not more life-threatening than other *S. aureus* but cause more morbidity, hospitalisation and infections that require surgical intervention. They appear to be over-represented in skin and soft tissue infections requiring hospital care, when compared to PVL-negative strains.[45,59] The high degree of purulence of these infections may contribute to higher densities of organisms on the skin available for transmission to other susceptible individuals.

Infections caused by PVL-producing MRSA strains are more challenging to treat in the community, not just because of the frequent need for surgical invention, but also because the availability of effective antimicrobials in the community is limited.

TYPE 3 MRSA – livestock-associated

There have been sporadic isolates of MRSA internationally for many years, but the first major problem emerged in Europe in 2003, with the description of ST398 in pigs and subsequently other livestock.[61] To date, this livestock-associated clone has not been detected in any AGAR surveys. In 2013, it was detected in a nasal swab from an Australian pig veterinarian,[62] and subsequently detected at very low levels in pig herds across Australia.[63] A distinctive clone often carried by equine veterinarians in Australia (WA-20 – ST612-IV),[64] has been found only once in the 2013 AGAR survey causing community-onset bloodstream infection.

Geographic variation

The geographic features of Australia have had a notable impact in the distribution of both HA- and CA-MRSA clones.

Figures 9–14 show the comparative changes in proportions of the five major clones (two HA and three CA) in the states and territories. For example, as noted above, Aus-2/3 has never become established in Western Australia because of intensive infection control strategies (Figure 9). Figure 10 shows that UK EMRSA-15 has been a greater problem in New South Wales, and that this clone is increasing in prevalence in all states and territories except the Northern Territory. The fluctuations seen in Tasmania reflect the small numbers from this state. Figure 11 emphasises EMRSA-15's increasing role in infections arising in the community, which included residential aged care. Amongst the CA-MRSA clones, the

Queensland clone has been a greater problem in New South Wales, Queensland and the Northern Territory than in the other states and territories. It is in decline in New South Wales and Queensland but is on the increase elsewhere, particularly in the Northern Territory (Figure 12). The WA-1 clone has mainly been a problem in Western Australia, the Northern Territory and South Australia and has been more or less stable elsewhere since 2004 (Figure 13). For the Southwest Pacific clone, Queensland and the Northern Territory have had higher rates than other states, and overall the rates across the other states and territories have been greatly different or have not varied much over time (Figure 14).

Figure 9: Trends of Aus-2/3 clone in hospital-onset infections across states and territories, 2001–2014; percentage of all *S. aureus*
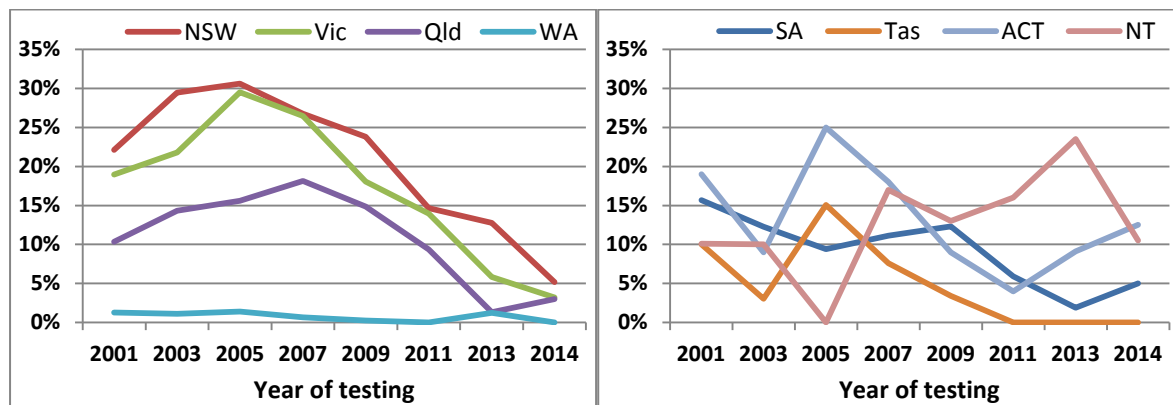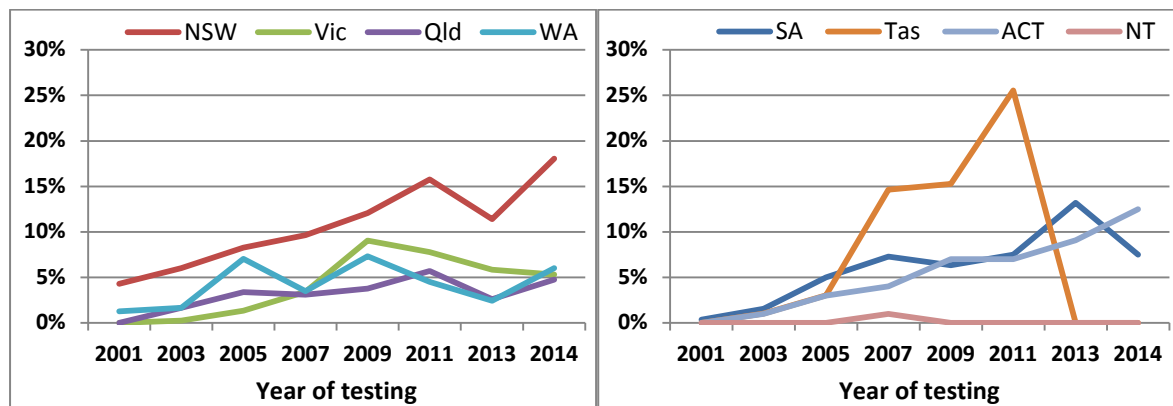

Figure 10: Trends of UK EMRSA-15 clone in hospital-onset infections across states and territories*, 2001–2014; percentage of all *S. aureus*

*The percentage for Tasmania in 2011 was 25.6%

Figure 11: Trends of UK EMRSA-15 clone in community-onset infections across states and territories*, 2001–2014; percentage of all *S. aureus*
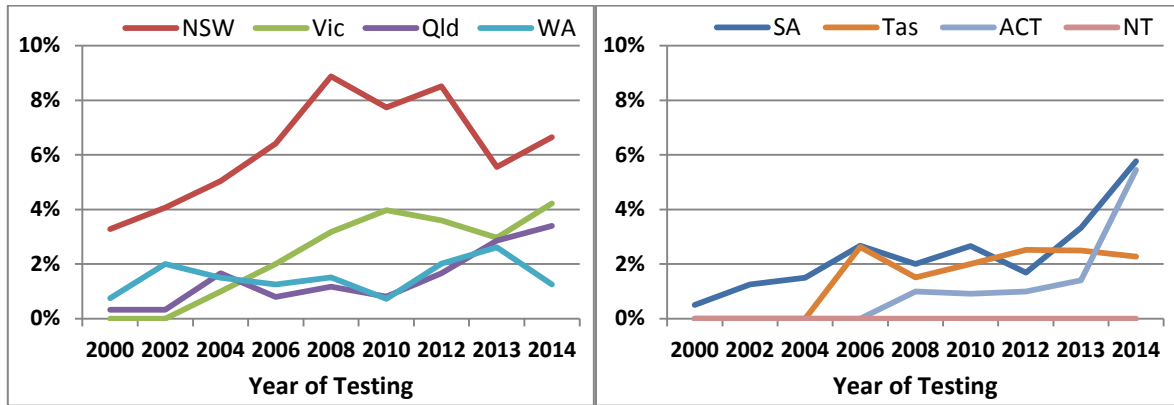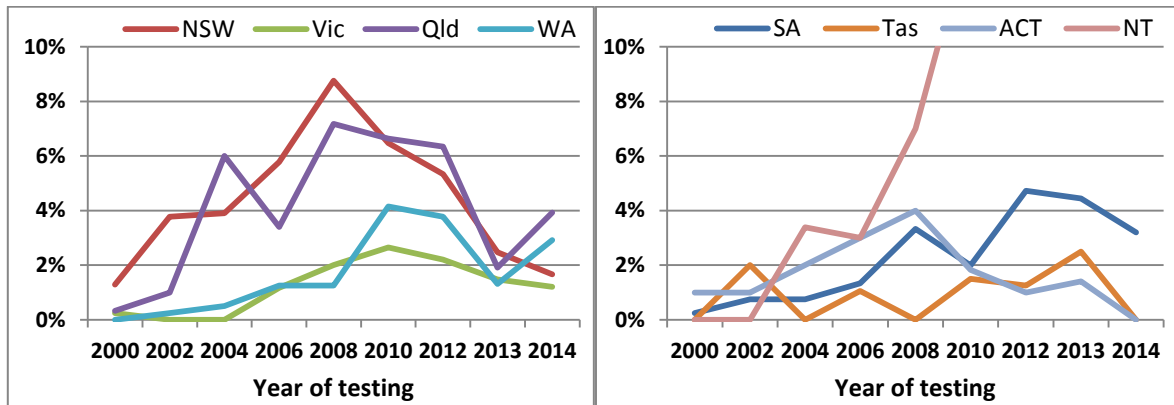

Figure 12: Trends of Queensland clone in community-onset infections across states and territories*, 2001–2014; percentage of all *S. aureus*

*The percentages for NT in 2010, 2012, 2013 and 2014 were 14.4, 11.0, 17.0 and 22.2 respectively

Figure 13: Trends of WA-1 clone in community-onset infections across states and territories, 2001–2014; percentage of all *S. aureus*
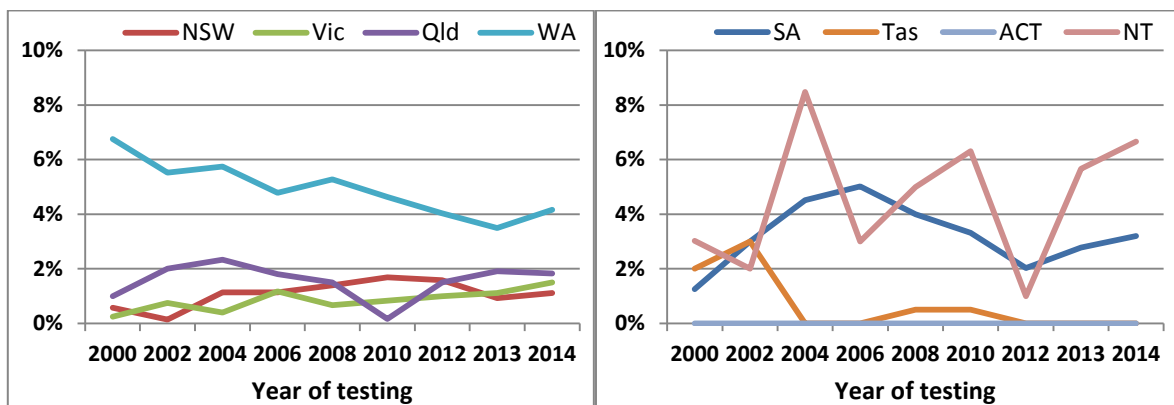
Figure 14: Trends of Southwest Pacific clone in community-onset infections across states and territories, 2001–2014; percentage of all *S. aureus*

Figure 15: Trends of the WA-3 clone in community-onset infections across states and territories, 2001–2014; percentage of all *S. aureus*

Figure 16: Trends of the WA-2 clone in community-onset infections across states and territories, 2001–2014; percentage of all *S. aureus*
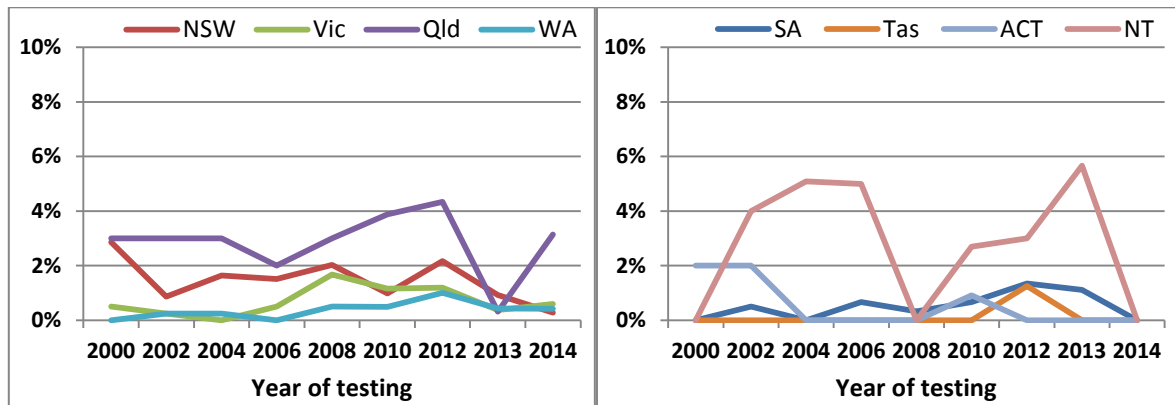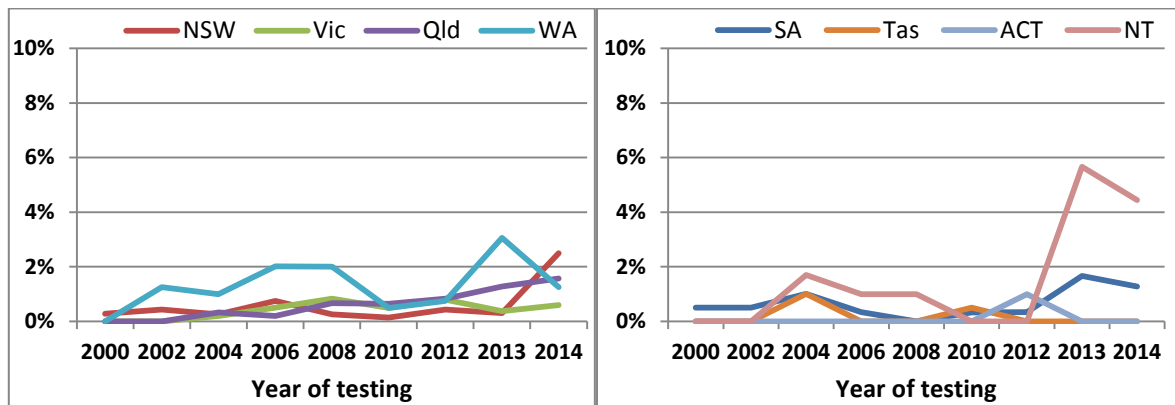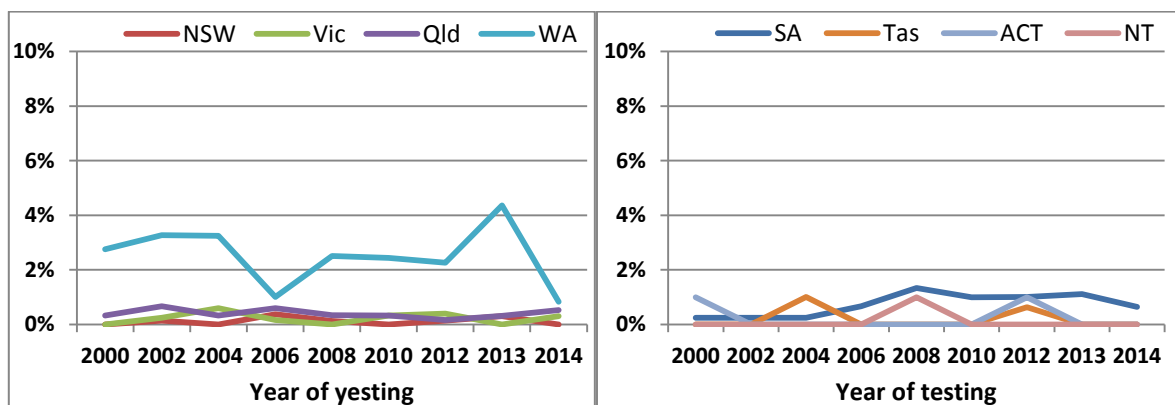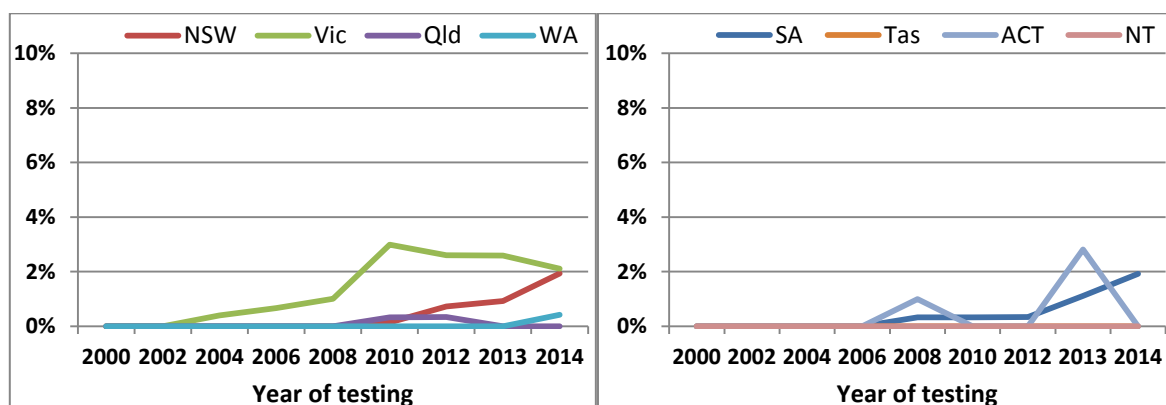
Figure 17: Trends of the WA-84 clone in community-onset infections across states and territories, 2001–2014; percentage of all *S. aureus*

Commentary

As this analysis has shown, the situation with MRSA in Australia in the 15 years from 2000 to 2014 has been changing significantly. Importantly, the hospital burden has grown and then decreased, while that in the community has continued to grow steadily. The main implication of these changes is the potential impact on empirical treatment of *S. aureus* infections, accounting for whether they arise in patients who are hospitalised, come from residential aged care, or come from the community. For serious infections, vancomycin is the mainstay of treatment. With the now significant prevalence of CA-MRSA in the community, the empirical treatment of common minor infections is not as certain, due to the variable number of additional resistances in the CA-MRSA clones. Oral options for treatment in the community include the macrolides and clindamycin, tetracyclines (expect in young children), or trimethoprim-sulfamethoxazole (except in the elderly) if the local clones are susceptible.

The good news is the rapid decline in the prevalence of the multi-resistant Aus-2/3 HA-MRSA clone after so many decades. This is despite the introduction of a related clade in 2001. The reasons for this decline, as mentioned above, may have been a combination of improvements in infection-control measures and the introduction of a national hand hygiene program. A further factor in reducing the importance in *S. aureus* infections may have been a decline in virulence as measured *in vitro* and *in vivo*.[28]

By contrast, the expansion of the UK EMRSA-15 clone continues and is concerning. It is hypothesised that this is due in part to increased rates of colonisation rates in residential aged care.[13] A recent survey undertaken by the National Centre for Antimicrobial Stewardship in residential aged-care facilities, and supported by the Commission, shows high rates of antimicrobial use,[54] much of it inappropriate, which could act as a driver to colonisation and subsequent infection.

The most notable feature of CA-MRSA between 2000 and 2014 has been the emergence and spread of the Queensland clone. It was already present in most states and territories in very low numbers in the 2000 survey, mostly in New South Wales. By 2008 it had become dominant in New South Wales and Queensland but since then has subsequently declined in those states. In the other states and territories, it started off more slowly but has steadily

increased in prevalence. It has been suggested that part of the success of this clone can be attributed to the possession of Panton-Valentine leucocidin, analogous to the great success of the USA300 clone in the United States. However, if this were the case, then the Southwest Pacific clone, which also possesses this toxin and preceded the emergence of the Queensland clone, might have been expected to become more prominent earlier. Other factors such as different accessory gene content may have played a part.

There have been no overall significant trends in the SWP clone of CA-MRSA over the same time period. It is most common in Queensland and the Northern Territory. Its prevalence in New Zealand by contrast, where it was first described, is slowly declining ([Annual Survey of MRSA, 2013 online](#))

The WA-1 clone has been present in Australia since 1989. It was identified first in Western Australia, and has since slowly expanded eastwards, and still remains important in South Australia and the Northern Territory. Since 2000, its role has been declining in Western Australia, but it is still the commonest CA-MRSA there. All states except Tasmania see this clone on a regular basis (Figure 13).

Although dominated by three clones, community-associated MRSA are continuing to diversify. Three clones are gaining prominence in parts of Australia: WA-3 (ST5-IV), WA-2 (ST78-IV) and the Victorian clone (WA-84 – ST45-V) (Figures 15–17). The WA-3 clone has a similar distribution to WA-1, being most common in Western Australia and to a lesser extent South Australia and the Northern Territory. It is now found throughout Australia except for the Australian Capital Territory. By contrast, WA-2 has remained prominent, mainly in Western Australia, although it is slowly increasing in South Australia. Again, it is found across Australia now, except for the Australian Capital Territory. The Victorian clone is the newest of the three additional CA-MRSA clones. It first emerged in Victoria in 2004 and subsequently in New South Wales and South Australia. It is seen intermittently in the Australian Capital Territory, Queensland and South Australia.

To date, the livestock-associated clone of MRSA, ST398, has not been detected in any AGAR surveys. The ST398 MRSA clone emerged in Europe in 2003, initially associated with pigs and pig farmers, and subsequently in other livestock.[61] In 2013, it was detected in a nasal swab from an Australian pig veterinarian,[62] and subsequently detected at very low levels in pig herds across Australia.[63] A distinctive clone often carried by equine veterinarians in Australia, (WA-20 – ST612-IV),[64] has been found only once in the 2013 survey, causing a community-onset bloodstream infection.

There is no doubt that MRSA types and clones will continue to evolve in Australia. SCC*mec* is transmitted between strains of *S. aureus*, and probably between all staphylococcal species including the many species of coagulase-negative staphylococci that colonise humans.[60] Each clone varies in its ability to spread and become a problem, and each requires specific measures for control. Control of HA-MRSA is possible through effective infection control, hand hygiene and antimicrobial stewardship programs in hospitals and aged care facilities. More challenging is finding effective control measures for the spread of CA-MRSA.

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