

The Australian Group on Antimicrobial Resistance

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***Staphylococcus aureus* Programme 2006 (SAP 2006)
Community Survey
Antimicrobial Susceptibility Report**

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On behalf of the Australian Group for Antimicrobial Resistance (AGAR).

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Contents

1	Executive Summary.....	3
2	Introduction.....	4
2.1	Objective of the Program.....	4
2.2	Importance of Staphylococcus aureus.....	4
3	Methods.....	5
3.1	Identification.....	5
3.2	Antimicrobial Susceptibility Testing.....	6
3.3	Quality Control.....	6
3.4	Statistical Analysis.....	6
3.5	Participating Laboratories.....	7
4	Demographics.....	8
4.1	Regional source of isolates.....	8
4.2	Age.....	8
5	Specimen Source.....	9
6	Susceptibility Testing Results.....	9
6.1	Methicillin-resistant <i>S. aureus</i>	9
6.2	Trends in MRSA non-susceptibility 2000-2006.....	13
6.3	Methicillin-susceptible <i>S. aureus</i>	21
6.4	Trends in MSSA non-susceptibility 2000-2006.....	22
6.5	Tigecycline MIC distribution.....	28
7	Discussion.....	29
8	References.....	31
9	Acknowledgements.....	33

1 Executive Summary

The Australian Group on Antimicrobial Resistance (AGAR) performs regular multicentre period-prevalence studies to monitor changes in antimicrobial resistance. In 2006, 30 laboratories participated in national surveillance of *Staphylococcus aureus* resistance. Two thousand nine hundred and seventy nine isolates of *S. aureus* were collected prospectively from hospital outpatients and general practice patients and tested by Vitek[®] 2, disc diffusion and Etest. Biennial community-based *S. aureus* antimicrobial surveillance programmes have been performed in Australia by AGAR since 2000.

In the 2006 programme the percentage of *S. aureus* identified as MRSA ranged from 11.3% in WA to 23.0% in ACT/NSW. The proportion of MRSA for non-invasive isolates and invasive isolates (16.2% and 10.4% respectively) did not differ significantly (P=0.0970).

Approximately half of all MRSA were resistant to erythromycin and ciprofloxacin and approximately a quarter were resistant to tetracycline, gentamicin and trimethoprim-sulphamethoxazole. Fusidic acid, mupirocin and rifampicin resistance was uncommon. No resistance was detected to vancomycin, teicoplanin, quinupristin-dalfopristin or linezolid. Significant differences in resistance across regions were evident for all antimicrobials except rifampicin. These differences may be explained by the different MRSA clones in circulation in each region. For a more detailed account of the MRSA clones detected in Australia in the 2006 survey refer to the SAP 2006 Epidemiology and MRSA Typing Report (.antimicrobial-resistance.com).

Over the four AGAR community surveys (2000, 2002, 2004 and 2006) a significant decrease in resistance to all the non- β -lactam antimicrobials except mupirocin and rifampicin was observed in Australia in MRSA. In the same time period the percentage of *S. aureus* identified as MRSA increased significantly from 11.6% in 2000 to 16.0% in 2006 (P<0.0001). This suggests that the increase in MRSA is due to the emergence and expansion of non-multiresistant clones in the community.

Resistance to non- β -lactam antimicrobials among the MSSA in 2006 was uncommon except for erythromycin (11.1%). Over the four AGAR surveys, no trends for either an increase or decrease in resistance were evident for penicillin, erythromycin, tetracycline, ciprofloxacin, gentamicin or fusidic acid. Small but significant increases in constitutive clindamycin resistance occurred in WA and in rifampicin resistance in Qld/NT. Mupirocin resistance increased significantly in three regions (Qld/NT, Vic/Tas and WA) and nationally but levels remain below 3%.

2 Introduction

2.1 Objective of the Program

The objective of the 2006 surveillance program was to determine the prevalence of antimicrobial resistance throughout Australia in clinical isolates of *S. aureus* causing infections with their onset in the community in general practice patients, hospital outpatients (excluding day-only patients) and emergency department patients.

2.2 Importance of *Staphylococcus aureus*

S. aureus continues to cause a wide range of community-acquired infections ranging from relatively minor skin and soft tissue infections to systemic sepsis with a high mortality¹. Strains circulating in the community acquired resistance to penicillin soon after its introduction in the 1940s and these β -lactamase producing strains soon became predominant in both healthcare and community settings. However, resistance to methicillin and related anti-staphylococcal penicillins², while appearing early after the introduction of methicillin, remained limited to a relatively few hospital-acquired strains for many years. In Australia, methicillin-resistant *S. aureus* (MRSA) were first detected in Sydney in the 1960s³, but really became an endemic problem in hospitals, in the Eastern states in particular with the appearance of a multiresistant strain, eastern-Australian MRSA (now divided into AUS-2 and AUS-3), in the 1970s and 80s^{4,5}. Community MRSA strains, less resistant to antibiotics and associated with skin and soft tissue sepsis, emerged in the 1990s, initially in Western Australia^{6,7} and the Northern Territory⁸, and subsequently in the Eastern states⁹⁻¹¹. The strain responsible for the latter epidemic was ST30-MRSA-IV or the southwest Pacific clone (SWP). It differed from the strains causing infections in WA and the NT in possessing a potent necrotising toxin, Panton-Valentine leukocidin (PVL)¹². PVL is associated with furunculosis and more severe infections including osteomyelitis, septicaemia and necrotising pneumonia. Subsequently, another hypervirulent community MRSA strain was detected in Queensland¹³. Dubbed the Queensland clone (ST93-MRSA-IV), it is also PVL positive¹². It has been responsible to deaths due to necrotising pneumonia in previously healthy young adults^{14,15}. This clone is now detected throughout Australia and is increasing in prevalence¹⁶.

The Australian Group for Antimicrobial Resistance (AGAR) has conducted surveillance of antimicrobial resistance in *S. aureus* for over 20 years¹⁷. This surveillance role is very important given the ability of *S. aureus* strains to acquire new resistance and virulence determinants and to undergo rapid clonal expansion. Since the 1960s multiple waves of MRSA have occurred in Australia. Results of previous AGAR surveys provide the only longitudinal record of the epidemiology of MRSA at a national level¹⁸⁻²⁰. Given the emergence of community MRSA strains, AGAR changed its methodology in 2000 to conduct surveys of community isolates biennially. The community-based surveys performed in 2000, 2002 and 2004 have been reported

previously^{16,21}. These reports document the emergence and spread of a number of community-associated MRSA strains including hypervirulent strains such as the SWP and Queensland clones.

Evidence has emerged of the intercontinental spread of major hypervirulent community-associated MRSA clones. The USA300 clone, which is PVL positive, has caused major epidemics of community and healthcare-associated infection in the USA^{22,23}. The spread of a hypervirulent community strain into healthcare institutions is a major cause for concern. Furthermore, USA300 has spread to Canada and Europe^{24,25}. More recently reports have been received of its spread to Western Australia and in retrospect one isolate from Queensland collected as part of the 2005 Hospital Survey has been shown to belong to USA300.

The fourth community-based survey of *S. aureus* infection conducted in 2006 is reported here.

Note: This report should be read in conjunction with the SAP 2006 Epidemiology and Typing Report (.antimicrobial-resistance.com) as MRSA antimicrobial susceptibility profiles may be indicative of some MRSA clones.

3 Methods

Thirty laboratories from the each state and two territories of Australia participated in the *S. aureus* AGAR survey. Starting in June 2006, each laboratory collected up to 100 consecutive significant clinical isolates from outpatients. Isolates from nursing homes, long-term care facilities and hospice patients were included. Day surgery and dialysis patients were excluded as were specimens received for the purpose of gathering surveillance data.

3.1 Identification

The minimum tests for identification of *S. aureus* were two positive test results from the following:

1. Slide coagulase test
2. Tube coagulase test
3. Demonstration of deoxyribonuclease production

Additional tests such as fermentation of mannitol or growth on mannitol-salt agar may have been performed for confirmation.

3.2 Antimicrobial Susceptibility Testing

Participating laboratories performed antimicrobial susceptibility tests using the Vitek[®] 2 AST-P545 card (bioMérieux) (Table 1). Penicillin susceptible strains were tested for β -lactamase production using nitrocefin. Mupirocin and cefoxitin were tested by disc diffusion using the CLSI or CDS methods²⁶⁻²⁷. Tigecycline MIC was determined by Etest[®] as was the MIC of mupirocin resistant isolates (AB Biodisk, Solna, Sweden). CLSI breakpoints²⁸ were utilised for all antimicrobials excluding mupirocin²⁹, fusidic acid³⁰ and tigecycline³¹.

Table 1. Vitek[®] 2 AST-P545 card

Antibiotic	MIC Range (mg/L)
Benzylpenicillin	0.03 – 0.5
Oxacillin	0.25 – 4
Cefazolin	4 – 64
Vancomycin	1 - 32
Rifampicin	0.5 – 32
Fusidic acid	0.5 – 32
Gentamicin	0.5 – 16
Erythromycin	0.25 – 8
Clindamycin	0.25 – 8
Tetracycline	1 – 16
Trimethoprim/Sulphamethoxazole	10 - 320
Ciprofloxacin	0.5 – 8
Quinupristin/dalfopristin (Synercid [®])	0.25 – 16
Teicoplanin	0.5 – 32
Linezolid	0.5 – 8
Imipenem	1 – 16
Nitrofurantoin	16 - 152

3.3 Quality Control

Additional quality control was not performed for this survey. As all participating laboratories are NATA accredited, routine QC testing of antimicrobial susceptibility test methods is an integral part of routine procedures.

3.4 Statistical Analysis

P values were calculated using Fisher's exact test (GraphPad[®] Prism Software).

3.5 Participating Laboratories

Australian Capital Territory (1)

The Canberra Hospital

New South Wales (8)

Concord Hospital

Douglass Hanley Moir

John Hunter Hospital

Nepean Hospital

Royal North Shore Hospital

Royal Prince Alfred Hospital

South Western Area Pathology Service

Westmead Hospital

Northern Territory (1)

Royal Darwin Hospital

Queensland (5)

Pathology Queensland - Princess Alexandra Hospital

Pathology Queensland Central Laboratory

Pathology Queensland – Prince Charles Hospital

Pathology Queensland – Gold Coast Hospital

Sullivan Nicolaides Pathology

South Australia (3)

Flinders Medical Centre

Institute of Medical and Veterinary Science

Women's and Children's Hospital

Tasmania (2)

Royal Hobart Hospital

Launceston General Hospital

Victoria (6)

Alfred Hospital

Austin Health

Monash Medical Centre

Gribbles Pathology

Royal Women's and Children's Hospital

St Vincent's Hospital

Western Australia (4)

PathWest Laboratory Medicine WA, Fremantle Hospital

PathWest Laboratory Medicine WA, QEII Medical Centre

PathWest Laboratory Medicine WA, Royal Perth Hospital

Saint John of God Pathology

4 Demographics

4.1 Regional source of isolates

Both public (26) and private laboratories (4) participated in the study. Participants included New South Wales (8), Victoria (6), Queensland (5), Western Australia (4), South Australia (3), Tasmania (2), ACT (1) and Northern Territory (1). There were 2,979 isolates from 30 institutions. To ensure institutional anonymity data from NSW and ACT, from Tasmania and Victoria and from Queensland and Northern Territory have been combined.

The contributions to the 2,979 isolates from six States and two Territories ranged from 10.0% to 30.0% with NSW/ACT contributing more ($P < 0.001$) (Table 2).

Table 2. Number of institutions and *S. aureus* isolates collected in state/territory

Region	Number of Institutions	Total	%
New South Wales (NSW)	9	895	30.0
Australian Capital Territory (ACT)			
Queensland (Qld)	6	600	20.1
Northern Territory (NT)			
South Australia (SA)	3	299	10.0
Victoria (Vic)	8	788	26.5
Tasmania (Tas)			
Western Australia (WA)	4	397	13.3
Total	30	2,979	100.0

4.2 Age

Of the 2,970 isolates with the age provided, few were received from patients 0 years to 16 years (Table 3) with more isolates contributed by patients 17 years and older ($P < 0.001$).

Table 3. Age range of patients

Age Range (years)	n	% (95%CI)
0-1	137	4.6 (3.9-5.4)
2-16	332	11.1 (10.1-12.4)
17-40	855	28.7 (27.2-30.4)
41-61	677	22.7 (21.3-24.3)
62-101	969	32.5 (30.9-34.3)
Total	2,970	100.0

5 Specimen Source

Of the 2,978 specimens which provided the specimen type, the majority (95.5%) were non-invasive (Table 4). Skin and soft tissue infections specimens contributed the majority (81.0%, 95%CI 79.6-82.4%) of isolates followed by respiratory specimens (5.9%, 95%CI 5.1%-6.9%) while blood culture isolates contributed only 3.6% (95%CI 2.9%-4.3%) of the total.

Table 4. Number and proportion of isolates associated with specimen types

Specimen Source	n	% (95%CI)
Skin and Soft Tissue	2,414	81.0 (79.6-82.4)
Respiratory	177	5.9 (5.1-6.9)
Ear	109	3.7 (3.0-4.4)
Blood	106	3.6 (2.9-4.3)
Urine	96	3.2 (2.6-3.9)
Eye	48	1.6 (1.2-2.1)
Sterile Site	28	0.9 (0.96-1.4)
Total	2,978	
Invasive	134	4.5 (3.8-5.3)
Non-Invasive	2,844	95.5 (94.7-96.2)

6 Susceptibility Testing Results

6.1 Methicillin-resistant *S. aureus*

The proportion of MRSA was 16.0% (95%CI 14.7% -17.3%) nationally (Table 5), which is not significantly different from the proportion identified in 2004 (15.3%) (P=0.55). At a regional level the proportions of MRSA identified in 2004 and 2006 were stable in NSW/ACT (19.8% in 2004 to 23.0%, P=0.1066), SA (10.3% to 12.0%, P=0.4666) and Vic/Tas (10.7% to 12.7%, P=0.2754) and WA (13.0% to 11.3%, P=0.5162) while Qld/NT showed a significant decrease (19.8% to 14.8%, P= 0.0494). Any significance of the proportions of isolates will be clarified in the companion epidemiology and typing report where the relative contributions of healthcare-associated clones and community-associated clones are detailed. (As healthcare-associated risk factors for MRSA acquisition are not collected as part of this survey, the proportion of the MRSA infections in this outpatient survey that are in reality healthcare-associated will remain undefined. Some estimate of this can be made by separating MRSA into healthcare-associated and community-associated clones.)

The proportion of invasive isolates (blood/sterile sites) that were MRSA was 10.4% overall and did not vary significantly (P=0.6563) between regions. On examination of the proportions of MRSA isolates from various specimen types,

urinary isolates included significantly ($P < 0.0001$, $X^2 = 42.59$) more (33.3%, 95%CI 24.2% - 43.8%) MRSA than any other specimen (Table 6).

Resistance in MRSA to non- β -lactam antimicrobials with the exception of rifampicin varied significantly between states (Table 7). Gentamicin, tetracycline and trimethoprim-sulphamethoxazole resistance was highest in Vic/Tas, followed by NSW/ACT, Qld/NT, SA and WA. The proportion of AUS-2/3 MRSA may have caused the high proportion of resistance to these agents observed in these regions. Gentamicin, tetracycline and trimethoprim-sulphamethoxazole resistance is rare in other clones in Australia. This explanation is confirmed in the companion epidemiology and typing report.

Table 5. Proportion of *S. aureus* that are MRSA by Region and Source

	% (95% Confidence Interval) [n/N]						Difference across regions
	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus	X^2
							P
All	23.0 (20.3-25.9) [206/895]	14.8 (12.1-18.0) [89/600]	12.0 (8.7-16.4) [36/299]	12.7 (10.5-15.3) [100/788]	11.3 (8.5-15.0) [45/397]	16.0 (14.7-17.3) [476/2979]	49.79 <0.0001
Invasive	15.4 (5.0-35.7) [4/26]	12.5 (4.1-29.9) [4/32]	0.0 (0.0-40.2) [0/8]	10.9 (4.5-22.9) [6/55]	0.0 (0.0-28.3) [0/13]	10.4 (6.0-17.2) [14/134]	3.284 0.6563
Non-invasive	23.2 (20.5-26.2) [202/869]	15.0 (12.2-18.2) [85/568]	12.4 (8.9-16.8) [36/291]	12.8 (10.5-15.5) [94/733]	11.5 (8.6-15.2) [44/383]	16.2 (14.9-17.6) [461/2844]	47.95 <0.0001

Table 6. Proportion of *S. aureus* that are MRSA by Source (where known)

Specimen Source	MRSA	95% CI
Skin and Soft Tissue	16.0 [387/2414]	14.6 - 17.6
Respiratory	19.8 [35/177]	14.3 - 26.6
Ear	3.7 [4/109]	1.2 - 9.7
Blood	11.3 [12/106]	6.2 - 19.3
Urine	33.3 [32/96]	24.2 - 43.8
Eye	6.3 [3/48]	1.5 - 17.5
Sterile Site	7.1 [2/28]	1.9 - 23.7

Table 7. Proportion [and number] of MRSA non-susceptible to non-β-lactam antimicrobials

Drug	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus	Difference across regions X ² P
Erythromycin	53.4 [110/206]	37.1 [33/89]	30.6 [11/36]	60.0 [60/100]	37.8 [17/45]	48.5 [231/476]	18.63 0.0022
Clindamycin*	22.3 [46/206]	14.6 [13/89]	0.0 [0/36]	25.0 [25/100]	2.2 [1/45]	17.9 [85/476]	22.34 0.0005
Tetracycline	31.1 [64/206]	20.2 [18/89]	2.8 [1/36]	43.0 [43/100]	0.0 [0/45]	26.5 [126/476]	44.64 <0.0001
Trimethoprim-Sulphamethoxazole	27.7 [57/206]	19.1 [17/89]	2.8 [1/36]	42.0 [42/100]	0.0 [0/45]	24.6 [117/476]	42.77 <0.0001
Ciprofloxacin	55.3 [114/206]	24.7 [22/89]	27.8 [10/36]	65.0 [65/100]	11.1 [5/45]	45.4 [216/476]	64.92 <0.0001
Gentamicin	28.6 [59/206]	23.6 [21/89]	2.8 [1/36]	39.0 [39/100]	0.0 [0/45]	25.2 [120/476]	36.27 <0.0001
Fusidic Acid	2.9 [6/206]	9.0 [8/89]	11.1 [4/36]	2.0 [2/100]	11.1 [5/45]	5.3 [25/476]	12.48 0.0288
Mupirocin	1.0 [2/206]	7.9 [7/89]	0.0 [0/36]	4.0 [4/100]	0.0 [0/45]	2.7 [13/476]	14.11 0.0149
Rifampicin	2.4 [5/206]	5.6 [5/89]	0.0 [0/36]	2.0 [2/100]	0.0 [0/45]	2.5 [8/473]	5.686 0.3380

* Constitutive resistance

There were significant differences in the proportion of resistance to non-β-lactam antimicrobials in MRSA associated with various patient types for erythromycin, clindamycin, tetracycline, trimethoprim-sulphamethoxazole and rifampicin (Table 8). MRSA isolated from hospital outpatients had the highest level of resistance for these four antimicrobials which is consistent with their having a higher proportion of healthcare-related acquisition.

No resistance was detected to vancomycin, teicoplanin, quinupristin-dalfopristin or linezolid.

Table 8. Proportion [and number] of non-susceptible MRSA by patient type (Australia)

Drug	GP	NH/LTCF	ED	OP	All	Difference between type of patients χ^2 P
Erythromycin	37.5 [33/88]	46.7 [7/15]	45.2 [94/208]	68.6 [70/102]	48.5 [231/476]	23.20 <0.0001
Clindamycin*	10.2 [9/88]	13.3 [2/15]	14.9 [31/208]	27.5 [28/102]	17.9 [85/476]	11.57 0.0089
Tetracycline	14.8 [13/88]	20.0 [3/15]	26.4 [55/208]	34.3 [35/102]	26.5 [126/476]	9.79 0.02
Trimethoprim-Sulphamethoxazole	14.8 [13/88]	13.3 [2/15]	24.5 [51/208]	31.4 [32/102]	24.6 [117/476]	8.16 0.043
Ciprofloxacin	36.4 [32/88]	60.0 [9/15]	43.3 [90/208]	52.9 [54/102]	45.4 [216/476]	6.87 0.076
Gentamicin	18.2 [16/88]	13.3 [2/15]	23.6 [49/208]	33.3 [34/102]	25.2 [120/476]	7.32 0.062
Fusidic Acid	3.4 [3/88]	6.7 [1/15]	3.8 [8/208]	9.8 [10/102]	5.3 [25/476]	5.65 0.13
Rifampicin	0.0 [0/88]	6.7 [1/15]	1.4 [3/208]	6.9 [7/102]	1.7 [8/473]	11.47 0.009
Mupirocin	1.1 [1/88]	0.0 [0/15]	2.9 [6/208]	5.9 [6/102]	2.5 [8/473]	4.21 0.24

GP: general practitioner; NH/LTCF: nursing home/long-term care facility, ED: emergency department, OP: outpatient

6.2 Trends in MRSA non-susceptibility 2000-2006

Note: Trimethoprim-sulphamethoxazole testing commenced in 2006, therefore trend data is not available.

Erythromycin

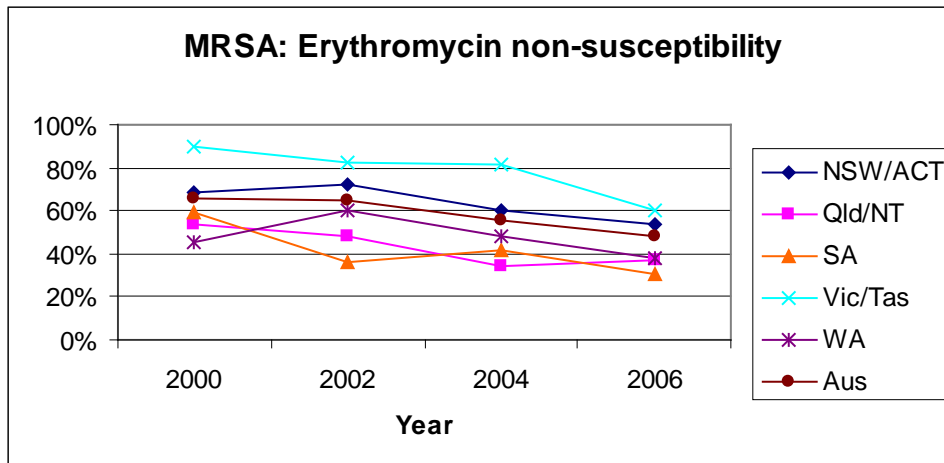


Figure 1. Non-susceptibility to erythromycin in MRSA, 2000-2006

Table 9. Trend data for non-susceptibility to erythromycin in MRSA, 2000-2006.

Year	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2000	68.5 [98/143]	53.3 [16/30]	59.4 [19/32]	89.4 [42/47]	45.7 [21/46]	65.8 [196/298]
2002	72.1 [132/183]	48.3 [28/58]	36.1 [13/36]	82.6 [38/46]	60.0 [33/55]	64.6 [244/378]
2004	60.5 [107/177]	33.8 [24/71]	41.5 [17/41]	81.3 [52/64]	48.1 [25/52]	55.6 [225/405]
2006	53.4 [110/206]	37.1 [33/89]	30.6 [11/36]	60.0 [60/100]	37.8 [17/45]	48.5 [231/476]
χ^2	76.97	3.63	4.39	16.65	0.263	30.42
P for trend	<0.0001	0.0569	0.0362	<0.0001	0.261	<0.0001

The proportion of MRSA that were non-susceptible to erythromycin over the four test periods declined significantly ($P < 0.0001$) around Australia (Table 9, Figure 1). Significant trends occurred in all regions other than WA and Qld/NT. Vic/Tas had an impressive decline from 89.4% in 2000 to 60.0% by 2006.

Clindamycin

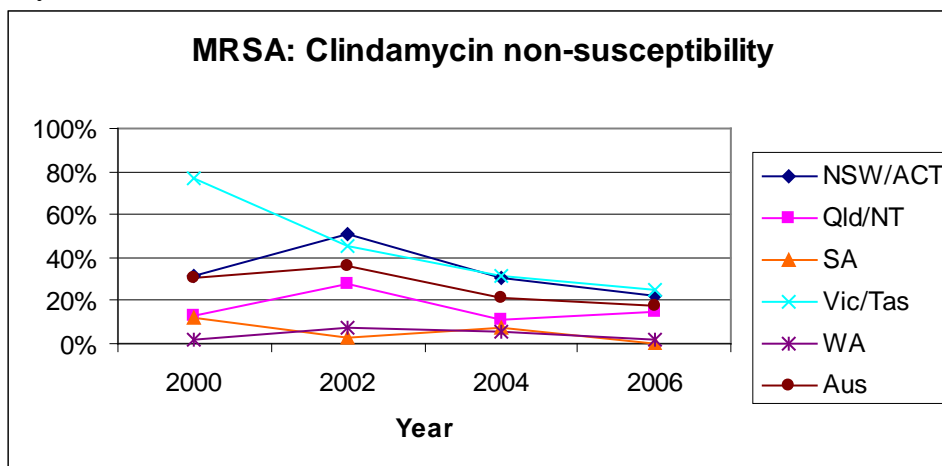


Figure 2. Non-susceptibility to clindamycin in MRSA, 2000-2006

Table 10. Trend data for non-susceptibility to clindamycin (constitutive resistance) in MRSA, 2000-2006.

Year	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2000	31.5 [45/143]	13.3 [4/30]	12.5 [4/32]	76.6 [36/47]	2.2 [1/46]	30.2 [90/298]
2002	50.8 [93/183]	27.6 [16/58]	2.8 [1/36]	45.7 [21/46]	7.3 [4/55]	35.7 [135/378]
2004	30.5 [54/177]	11.3 [8/71]	7.3 [3/41]	31.3 [20/64]	5.8 [3/52]	21.7 [88/405]
2006	22.3 [46/206]	14.6 [13/89]	0.0 [0/36]	25.0 [25/100]	2.2 [1/45]	17.9 [85/476]
χ^2	12.33	1.06	3.34	34.63	0.01	29.38
P for trend	0.0004	0.3035	0.0676	<0.0001	0.9086	<0.0001

The proportion of MRSA that were non-susceptible to clindamycin over the four test periods declined significantly ($P < 0.0001$) around Australia from 30.2% to 17.9% (Table 10, Figure 2). Significant decreases occurred in NSW/ACT and Vic/Tas.

Tetracycline

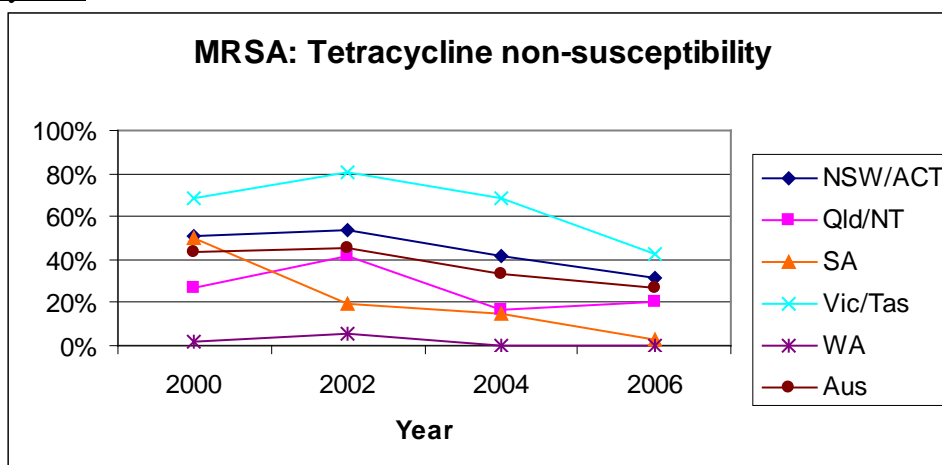


Figure 3. Non-susceptibility to tetracycline in MRSA, 2000-2006

Table 11. Trend data for non-susceptibility to tetracycline in MRSA, 2000-2006.

Year	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2000	51.0 [73/143]	26.7 [8/30]	50.0 [16/32]	68.1 [32/59]	2.2 [1/46]	43.6 [130/298]
2002	54.1 [99/183]	41.4 [24/58]	19.4 [7/36]	80.4 [32/47]	5.5 [3/55]	45.0 [170/378]
2004	41.8 [74/177]	16.9 [12/71]	14.6 [6/41]	68.8 [44/64]	0.0 [0/52]	33.6 [136/405]
2006	31.1 [64/206]	20.2 [18/89]	2.8 [1/36]	43.0 [43/100]	0.0 [0/45]	26.5 [126/476]
X ²	20.51	4.40	21.75	14.54	1.89	35.47
P for trend	<0.0001	0.0359	<0.0001	0.0001	0.1697	<0.0001

The proportion of MRSA that were non-susceptible to tetracycline over the four test periods declined significantly ($P < 0.0001$) around Australia from 43.6% to 26.5% (Table 11, Figure 3). The national downward trend was a reflection of the stable low rate in WA and significant decreases in the other regions; NSW/ACT 51.0% to 31.1% ($P < 0.0001$), SA from 50.0% to 2.8% ($P < 0.0001$), Vic/Tas 68.1% to 43.0% ($P = 0.0001$) and Qld/NT from 26.7% to 20.2% ($P = 0.0359$).

Ciprofloxacin

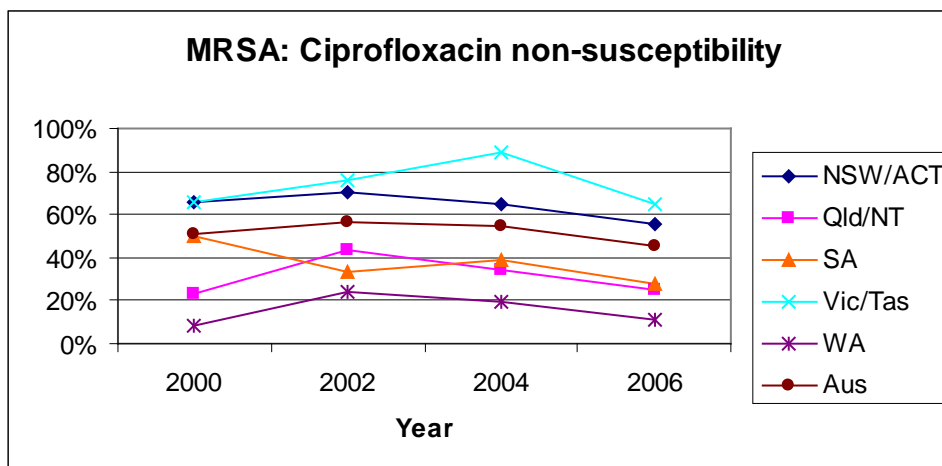


Figure 4. Non-susceptibility to ciprofloxacin in MRSA, 2000-2006

Table 12. Trend data for non-susceptibility to ciprofloxacin in MRSA, 2000-2006.

Year	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2000	65.7 [94/143]	23.3 [7/30]	50.0 [16/32]	66.0 [31/47]	8.7 [4/46]	51.0 [152/298]
2002	69.9 [128/183]	43.1 [25/58]	33.3 [12/36]	76.1 [35/46]	23.6 [13/55]	56.3 [213/378]
2004	64.4 [114/177]	33.8 [24/71]	39.0 [16/41]	89.1 [57/64]	19.1 [10/52]	54.6 [221/405]
2006	55.3 [114/206]	24.7 [22/89]	27.8 [10/36]	65.0 [65/100]	11.1 [5/45]	45.4 [216/476]
χ^2	6.14	1.09	2.57	0.12	0.01	4.20
P for trend	0.0132	0.2960	0.1086	0.7328	0.9310	0.0404

The proportion of MRSA that were non-susceptible to ciprofloxacin remained high in all regions with significant decreases nationally (51.0% to 45.4%, $P=0.0404$) and in NSW/ACT (65.7% to 55.3%, $P=0.0132$). Resistance in SA decreased from 50.0% to 27.8% but this did not reach significance (Table 12, Figure 4).

Gentamicin

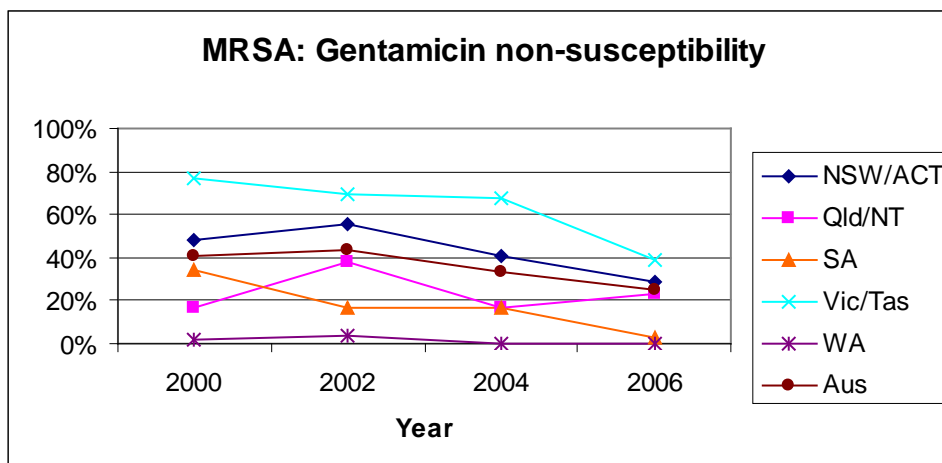


Figure 5. Non-susceptibility to gentamicin in MRSA, 2000-2006

Table 13. Trend data for non-susceptibility to gentamicin in MRSA, 2000-2006

Year	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2000	48.3 [69/143]	16.7 [5/30]	34.4 [11/32]	76.6 [36/47]	2.2 [1/46]	40.9 [122/298]
2002	55.2 [101/183]	37.9 [22/58]	16.7 [6/36]	69.6 [32/46]	3.6 [2/55]	43.1 [163/378]
2004	41.2 [73/177]	16.9 [12/71]	17.1 [7/41]	67.2 [43/64]	0.0 [0/52]	33.3 [135/405]
2006	28.6 [59/206]	23.6 [21/89]	2.8 [1/36]	39.0 [39/100]	0.0 [0/45]	25.2 [120/476]
χ^2	21.89	0.33	10.40	21.78	1.74	30.56
P for trend	<0.0001	0.5667	0.0013	<0.0001	0.1866	<0.0001

The proportion of MRSA that were non-susceptible to gentamicin over the four test periods declined significantly ($P < 0.0001$) around Australia from 40.9% to 25.2% (Table 13, Figure 5). A significant decrease was achieved in three regions; NSW/ACT 48.3% to 28.6% ($P < 0.0001$), SA from 34.4% to 2.8% ($P = 0.0013$), and Vic/Tas 76.6% to 39.0% ($P < 0.0001$). The only region to achieve an increase in resistance was Qld/NT, 16.7% to 23.6%, although this did not reach significance.

Fusidic acid

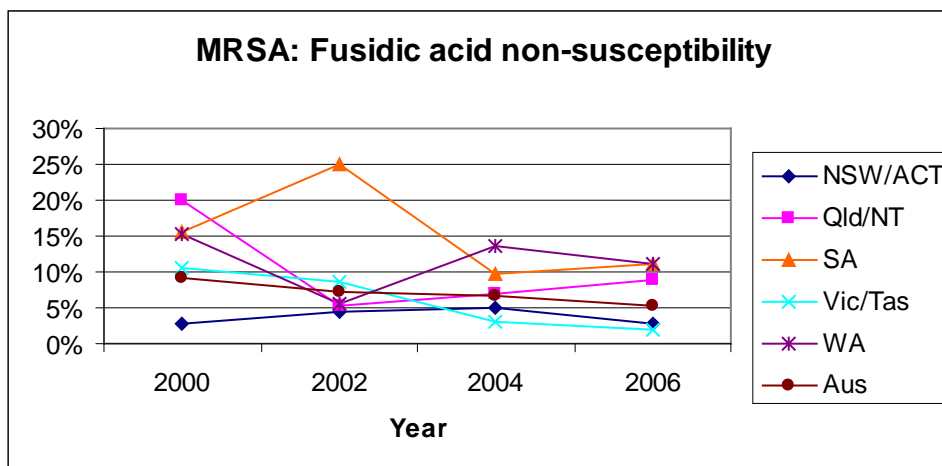


Figure 6. Non-susceptibility to fusidic acid in MRSA, 2000-2006

Table 14. Trend data for non-susceptibility to fusidic acid in MRSA, 2000-2006.

Year	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2000	2.8 [4/143]	20.0 [6/30]	15.6 [5/32]	10.6 [5/47]	15.2 [7/46]	9.1 [27/298]
2002	4.4 [8/183]	5.2 [3/58]	25.0 [9/36]	8.7 [4/46]	5.5 [3/55]	7.1 [27/378]
2004	5.1 [9/177]	7.0 [5/71]	9.8 [4/41]	3.1 [2/64]	13.5 [7/52]	6.7 [27/405]
2006	2.9 [6/206]	9.0 [8/89]	11.1 [4/36]	2.0 [2/100]	11.1 [5/45]	5.3 [25/476]
χ^2	0.00	0.92	1.27	6.32	0.02	4.08
P for trend	0.9978	0.3375	0.2606	0.0119	0.8891	0.0434

The proportion of MRSA that were non-susceptible to fusidic acid over the four test periods declined significantly ($P=0.0434$) around Australia from 9.1% to 5.3% (Table 14, Figure 6). Decreases were seen in all regions except NSW/ACT although the only region to experience a significant decrease was Vic/Tas (10.6% to 2.0%, $P=0.0119$).

Mupirocin

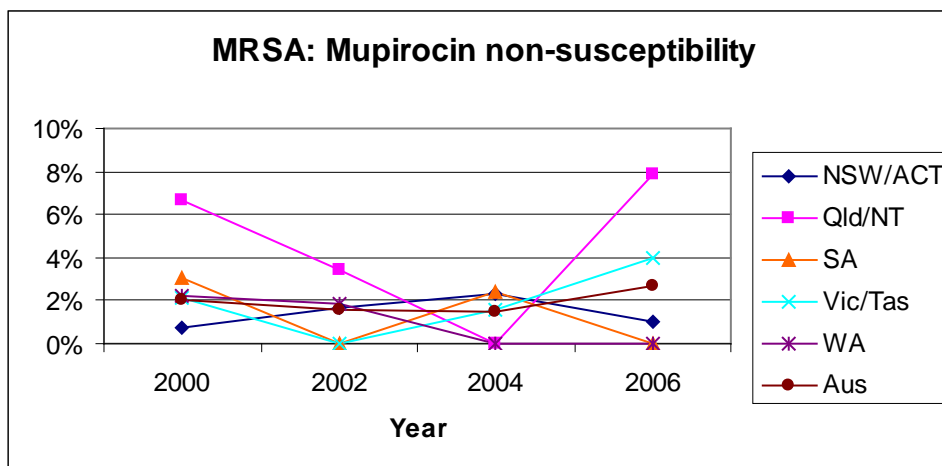


Figure 7. Non-susceptibility to mupirocin in MRSA, 2000-2006

Table 15. Trend data for non-susceptibility to mupirocin in MRSA, 2000-2006.

Year	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2000	0.7 [1/143]	6.7 [2/30]	3.1 [1/32]	2.1 [1/47]	2.2 [1/46]	2.0 [6/298]
2002	1.6 [3/183]	3.4 [2/58]	0.0 [0/36]	0.0 [0/46]	1.8 [1/55]	1.6 [6/378]
2004	2.3 [4/177]	0.0 [0/71]	2.4 [1/41]	1.6 [1/64]	0.0 [0/52]	1.5 [6/405]
2006	1.0 [2/206]	7.9 [7/89]	0.0 [0/36]	4.0 [4/100]	0.0 [0/45]	2.7 [13/476]
χ^2	0.04	0.47	0.53	1.15	1.68	0.6646
P for trend	0.8378	0.4940	0.4648	0.2832	0.1954	0.4149

The proportion of MRSA that were non-susceptible to mupirocin over the four test periods remained stable in most regions. Small increases were observed for Qld/NT and Vic/Tas and small decreases for SA and WA (Table 15, Figure 7).

Rifampicin

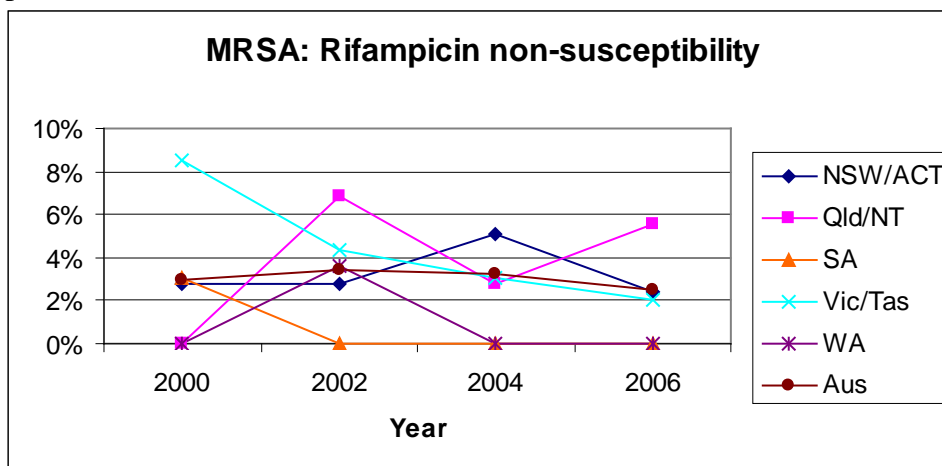


Figure 8. Proportion and number of non-susceptibility to rifampicin in MRSA, 2000-2006

Table 16. Trend data for non-susceptibility to rifampicin in MRSA, 2000-2006.

Year	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2000	2.8 [4/143]	0.0 [0/30]	3.1 [1/32]	8.5 [4/47]	0.0 [0/46]	3.0 [9/298]
2002	2.7 [5/183]	6.9 [4/58]	0.0 0/36]	4.3 [2/46]	3.6 [2/55]	3.4 [13/378]
2004	5.1 [9/177]	2.8 [2/71]	0.0 [0/41]	3.1 [2/64]	0.0 [0/52]	3.2 [13/405]
2006	2.4 [5/206]	5.6 [5/89]	0.0 [0/36]	2.0 [2/100]	0.0 [0/45]	2.5 [8/473]
χ^2	0.01	0.47	2.06	3.39	0.4063	1.65
P for trend	0.9186	0.4940	0.1507	0.0657	0.5239	0.1991

The proportion of MRSA that were non-susceptible to rifampicin was stable in NSW/ACT, WA and nationally (Table 16, Figure 8). The largest regional trend was a decrease from 8.5% to 2.0% in Vic/Tas although this did not reach significance.

6.3 Methicillin-susceptible *S. aureus*

Results of susceptibility testing of MSSA are shown in Table 17. Resistance to non- β -lactam agents remains uncommon. All isolates were susceptible to vancomycin, teicoplanin, quinupristin-dalfopristin and linezolid. There was no significant difference in the proportion of resistance isolates identified in the 2006 survey to any antimicrobial across regions with the exception of trimethoprim-sulphamethoxazole which ranged from 0.9% in WA to 3.3% in NSW/ACT (P=0.0412). Penicillin resistance was high and in similar proportions, ranging from 84.1% to 87.1%, across all regions. Antimicrobial resistance in MSSA associated with various patient types was often difficult to establish due to small sample sizes. The only significant difference in the proportions found was for erythromycin (P=0.003) which ranged from 0.0% in nursing homes or long term care facilities (NH/LTCF) to 26.1% in outpatients (Table 18).

Table 17. Proportion and number of MSSA non-susceptible to penicillin and the non- β -lactam antimicrobials

Drug	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus	Difference across regions χ^2 P
Penicillin	84.5 [582/689]	87.1 [445/511]	85.2 [224/263]	85.5 [588/688]	84.1 [296/352]	85.3 [2135/2503]	2.104 0.8346
Erythromycin	10.2 [70/689]	12.7 [65/511]	14.8 [39/263]	10.0 [69/688]	9.9 [35/352]	11.1 [278/2503]	6.956 0.2239
Clindamycin*	1.0 [7/689]	0.6 [3/511]	0.0 [0/263]	1.0 [7/688]	1.1 [4/352]	0.8 [21/2503]	3.512 0.6216
Tetracycline	4.2 [29/689]	2.9 [15/511]	1.9 [5/263]	3.9 [27/688]	3.7 [13/352]	3.6 [89/2503]	3.822 0.5752
Trimethoprim-Sulphamethoxazole	3.3 [23/689]	1.2 [6/511]	1.1 [3/263]	2.3 [16/688]	0.9 [3/352]	2.0 [51/2503]	11.57 0.0412
Ciprofloxacin	2.5 [17/689]	1.0 [5/511]	1.1 [3/263]	2.2 [15/688]	0.9 [3/352]	1.7 [43/2503]	6.899 0.2283
Gentamicin	1.3 [9/689]	1.0 [5/511]	0.4 [1/263]	1.0 [7/688]	0.3 [1/352]	0.9 [23/2503]	3.625 0.6046
Fusidic Acid	3.6 [25/689]	5.3 [27/511]	3.4 [9/263]	4.7 [32/688]	3.7 [13/352]	4.2 [106/2503]	2.988 0.7018
Rifampicin	0.6 [4/689]	1.0 [5/511]	0.0 [0/263]	0.1 [1/688]	0.0 [0/352]	0.3 [7/2503]	4.635 0.4620
Mupirocin	1.5 [10/689]	2.5 [13/511]	0.8 [2/263]	0.7 [5/688]	2.6 [9/352]	1.6 [39/2503]	9.770 0.0820

* Constitutive resistance

Table 18. Proportion and number of MSSA Non-Susceptible by Patient Type (Australia)

Drug	GP	NH/LTCF	ED	OP	All	X ² P
Penicillin	83.8 [531/634]	70.0 [7/10]	90.5 [76/84]	93.5 [43/46]	85.3 [2135/2503]	7.05 0.070
Erythromycin	9.5 [60/634]	0.0 [0/10]	10.7 [9/84]	26.1 [12/46]	11.1 [278/2503]	13.84 0.003
Clindamycin*	0.6 [4/634]	0.0 [0/10]	0.0 [0/84]	2.2 [1/46]	0.8 [21/2503]	2.29 0.515
Tetracycline	3.2 [20/634]	0.0 [0/10]	3.6 [3/84]	8.7 [4/46]	3.6 [89/2503]	0.56 0.905
Trimethoprim-Sulphamethoxazole	1.6 [10/634]	0.0 [0/10]	1.2 [1/84]	4.3 [2/46]	2.0 [51/2503]	1.61 0.404
Ciprofloxacin	2.2 [14/634]	0.0 [0/10]	0.0 [0/84]	4.3 [2/46]	1.7 [43/2503]	0.02 0.88
Gentamicin	0.8 [5/634]	0.0 [0/10]	1.2 [1/84]	4.3 [2/46]	0.9 [23/2503]	3.47 0.062
Fusidic Acid	4.3 [27/634]	0.0 [0/10]	1.2 [1/84]	13.0 [6/46]	4.2 [106/2503]	1.41 0.234
Rifampicin	0.2 [1/634]	0.0 [0/10]	0.0 [0/84]	0.0 [0/46]	0.3 [7/2503]	0.22 0.9741
Mupirocin	3.3 [12/634]	0.0 [0/10]	0.0 [0/84]	2.2 [1/46]	1.6 [39/2503]	1.85 0.60

GP: general practitioner; NH/LTCF: nursing home/long-term care facility, ED: emergency department, OP: outpatient

6.4 Trends in MSSA non-susceptibility 2000-2006

In spite of some survey to survey variability there were no long term trends for either an increase or decrease in resistance either within regions or nationally for penicillin (Figure 9), erythromycin (Figure 10), tetracycline (Figure 11), ciprofloxacin (Figure 12), gentamicin (Figure 13) or fusidic acid (Figure 14) (raw data not shown). Clindamycin resistance increased significantly in WA from 0.0% in 2000 to 1.1% in 2006 (P=0.0270) (Figure 15, Table 19). Rifampicin resistance increased significantly in Qld/NT from 0.0% to 1.0% (P=0.0091) (Figure 16, Table 20). Mupirocin resistance increased in Qld/NT from 0.5% to 2.5% (P=0.0057), in Vic/Tas from 0.0% to 0.7% (P=0.0462), in WA from 0.6% to 2.6% (P=0.0078) and nationally from 0.4% to 1.6% (P<0.0001) (Figure 17, Table 21).

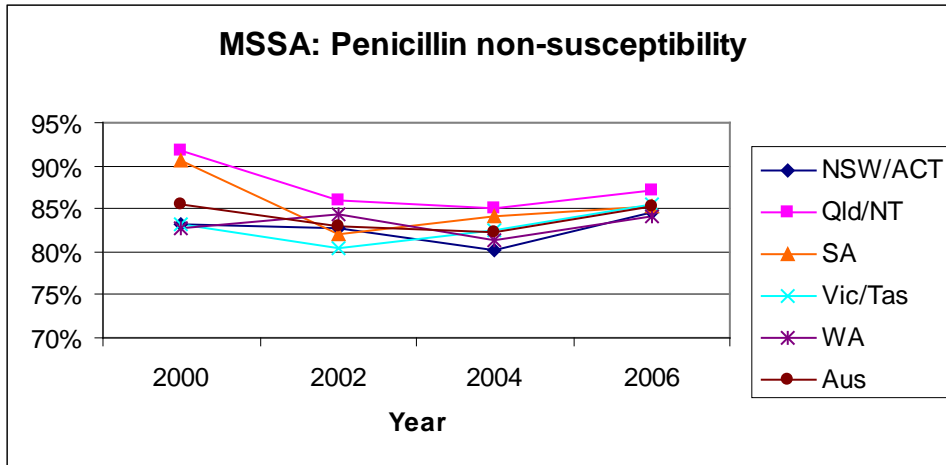


Figure 9. Non-susceptibility to penicillin in MSSA, 2000-2006

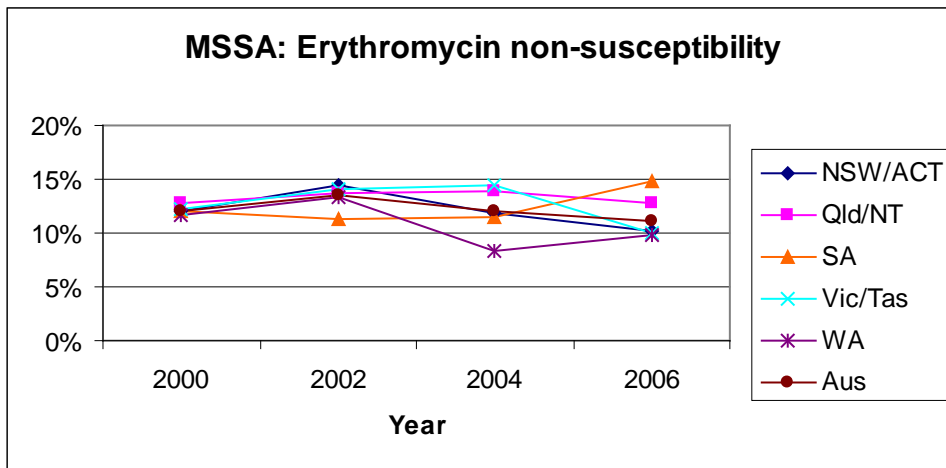


Figure 10. Non-susceptibility to erythromycin in MSSA, 2000-2006

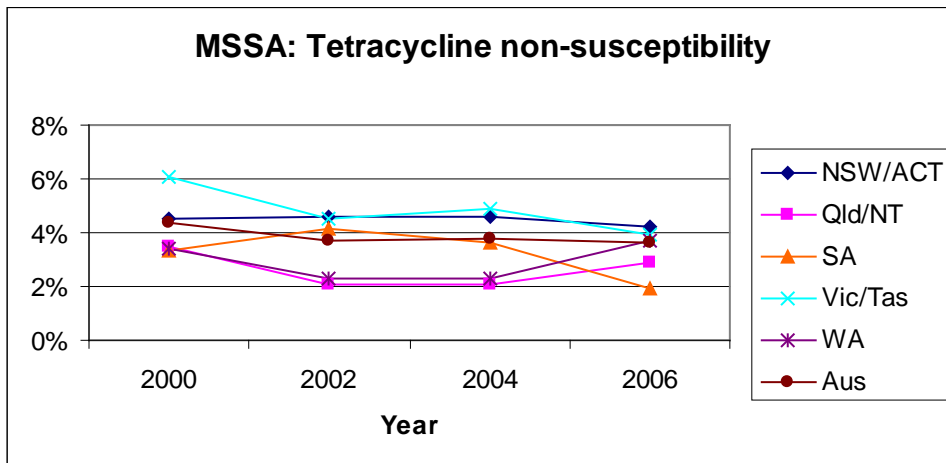


Figure 11. Non-susceptibility to tetracycline in MSSA, 2000-2006

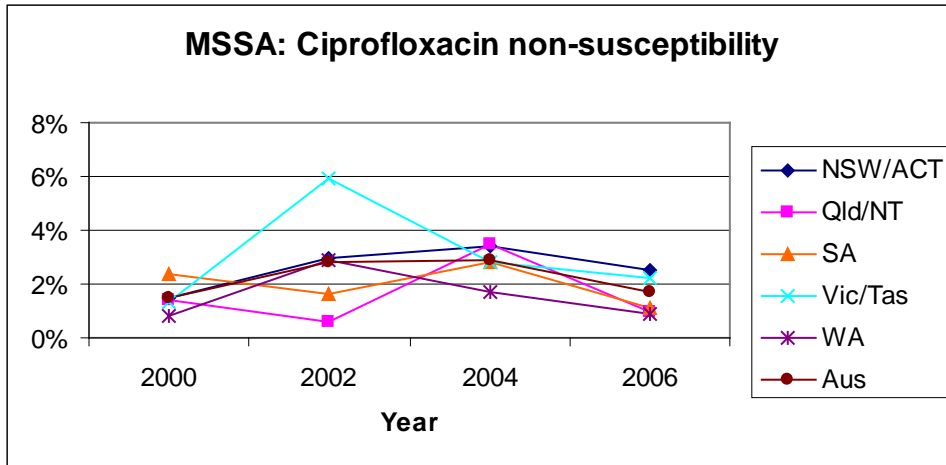


Figure 12. Non-susceptibility to ciprofloxacin in MSSA, 2000-2006

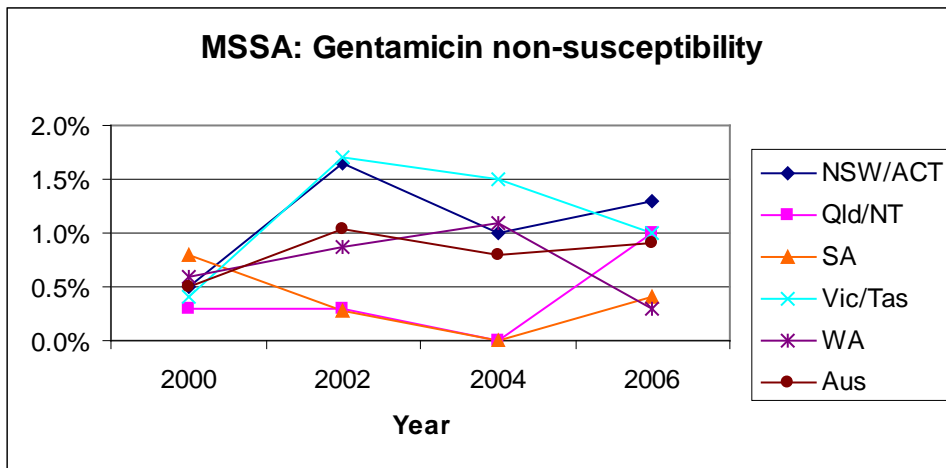


Figure 13. Non-susceptibility to gentamicin in MSSA, 2000-2006

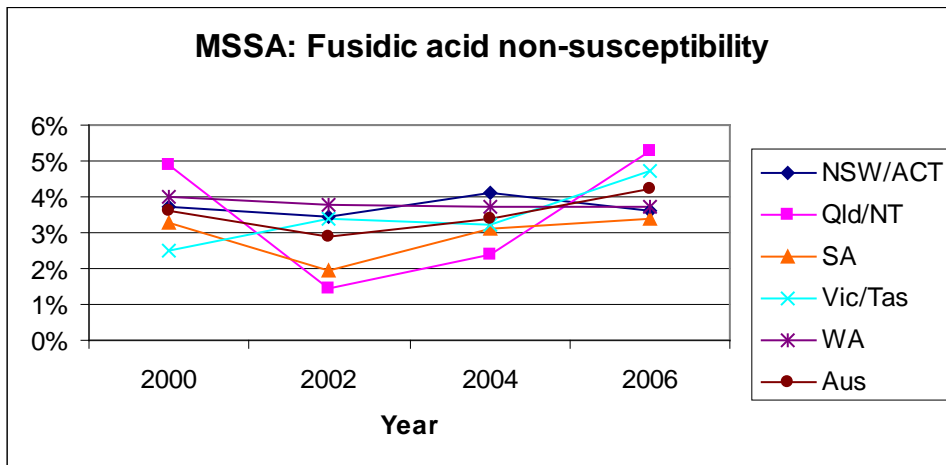


Figure 14. Non-susceptibility to fusidic acid in MSSA, 2000-2006

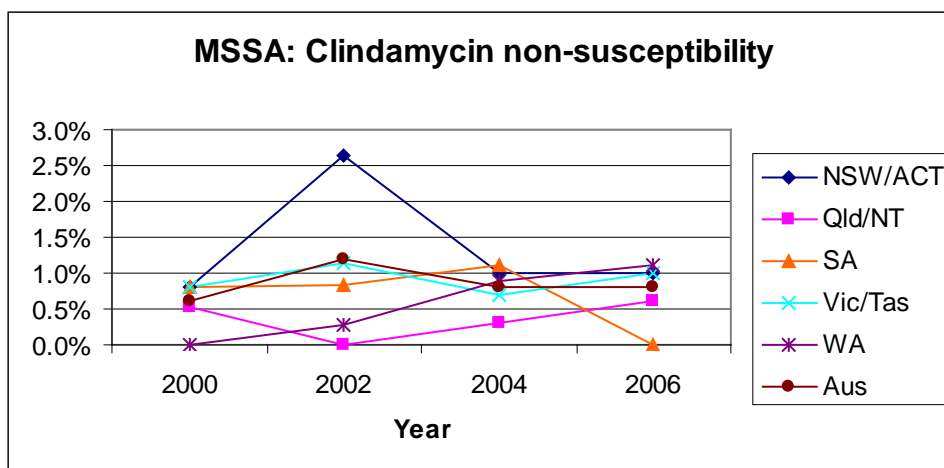


Figure 15. Non-susceptibility to clindamycin (constitutive resistance) in MSSA, 2000-2006

Table 19. Trend data for non-susceptibility to clindamycin (constitutive resistance) in MSSA, 2000-2006.

Year	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2000	0.8 [5/657]	0.5 [2/370]	0.8 [3/368]	0.8 [4/522]	0.0 [0/354]	0.6 [14/2271]
2002	2.6 [6/606]	0.0 [0/342]	0.8 [3/364]	1.1 [4/353]	0.3 [1/343]	1.2 [24/2008]
2004	1.0 [7/716]	0.3 [1/288]	1.1 [4/358]	0.7 [4/535]	0.9 [3/348]	0.8 [19/2245]
2006	1.0 [7/689]	0.6 [3/511]	0.0 [0/263]	1.0 [7/688]	1.1 [4/352]	0.8 [21/2503]
χ^2	0.21	0.19	0.6825	0.08	4.89	0.1369
P for trend	0.6497	0.6614	0.4087	0.7802	0.0270	0.7114

The only significant increase or decrease in clindamycin non-susceptibility was in WA where resistance increased from 0.0% in 2000 to 1.1% in 2006 (P=0.0270).

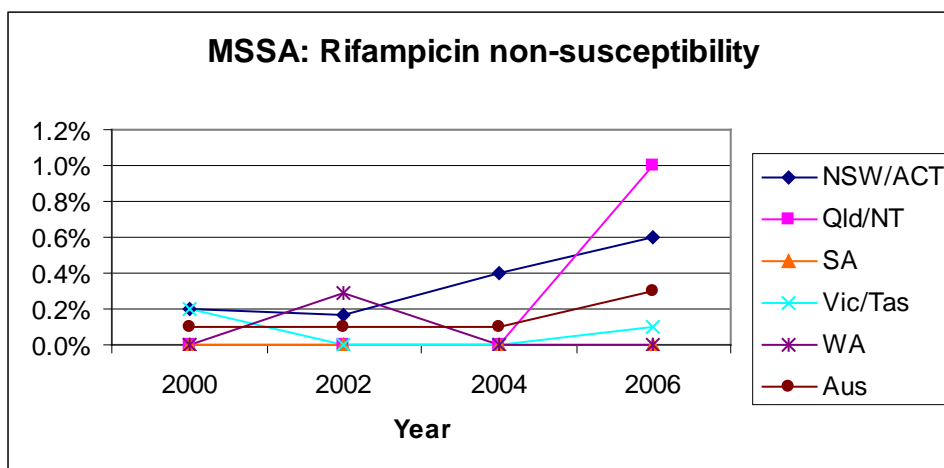


Figure 16. Non-susceptibility to rifampicin in MSSA, 2000-2006

Table 20. Trend data for non-susceptibility to rifampicin in MSSA, 2000-2006.

Year	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2000	0.2 [1/657]	0.0 [0/370]	0.0 [0/368]	0.2 [1/522]	0.0 [0/354]	0.1 [2/2271]
2002	0.2 [1/606]	0.0 [0/342]	0.0 [0/364]	0.0 [0/353]	0.3 [1/343]	0.1 [2/2008]
2004	0.4 [3/716]	0.0 [0/288]	0.0 [0/358]	0.0 [0/535]	0.0 [0/348]	0.1 [3/2245]
2006	0.6 [4/689]	1.0 [5/511]	0.0 [0/263]	0.1 [1/688]	0.0 [0/352]	0.3 [7/2503]
χ^2	2.354	6.80	-	0.04	0.20	2.902
P for trend	0.1250	0.0091	-	0.8451	0.6561	0.0884

The only significant increase or decrease in rifampicin non-susceptibility was in Qld/NT where levels increased from 0.0% in 2000 to 1.0% in 2006 (P=0.0091). Rifampicin non-susceptibility has not been detected in SA in any survey.

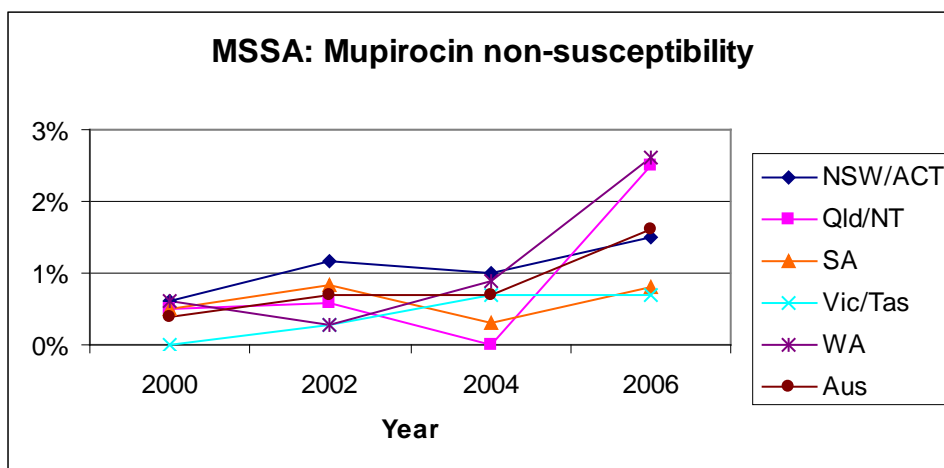


Figure 17. Non-susceptibility to mupirocin in MSSA, 2000-2006

Table 21. Trend data for non-susceptibility to mupirocin in MSSA, 2000-2006.

Year	NSW/ACT	Qld/NT	SA	Vic/Tas	WA	Aus
2000	0.6 [4/657]	0.5 [2/370]	0.5 [2/368]	0.0 [0/522]	0.6 [2/354]	0.4 [10/2271]
2002	1.2 [7/606]	0.6 [2/342]	0.8 [3/364]	0.3 [1/353]	0.3 [1/343]	0.7 [14/2008]
2004	1.0 [7/716]	0.0 [0/288]	0.3 [1/358]	0.7 [4/535]	0.9 [3/348]	0.7 [15/2245]
2006	1.5 [10/689]	2.5 [13/511]	0.8 [2/263]	0.7 [5/688]	2.6 [9/352]	1.6 [39/2503]
χ^2	1.80	7.651	0.00	3.973	7.08	15.83
P for trend	0.1797	0.0057	0.9867	0.0462	0.0078	<0.0001

The significant increase in MSSA non susceptibility to mupirocin from 0.4% to 1.6% ($P < 0.0001$) was contributed by three regions; QLD/NT from 0.5% in 2000 to 2.5% by 2006 ($P = 0.0057$), Vic/Tas from 0.0% in 2000 to 0.7% in 2006 ($P = 0.0462$) and WA from 0.6% to 2.6% ($P = 0.0078$).

6.5 Tigecycline MIC distribution

Tigecycline is the first agent marketed in Australia belonging to a new class of antimicrobials, related to tetracyclines, known as glycylcyclines. 7/2,979 (0.2%) isolates (5 MRSA and 2 MSSA) were classified as resistant using the US FDA and EUCAST breakpoints of 0.5mg/L.

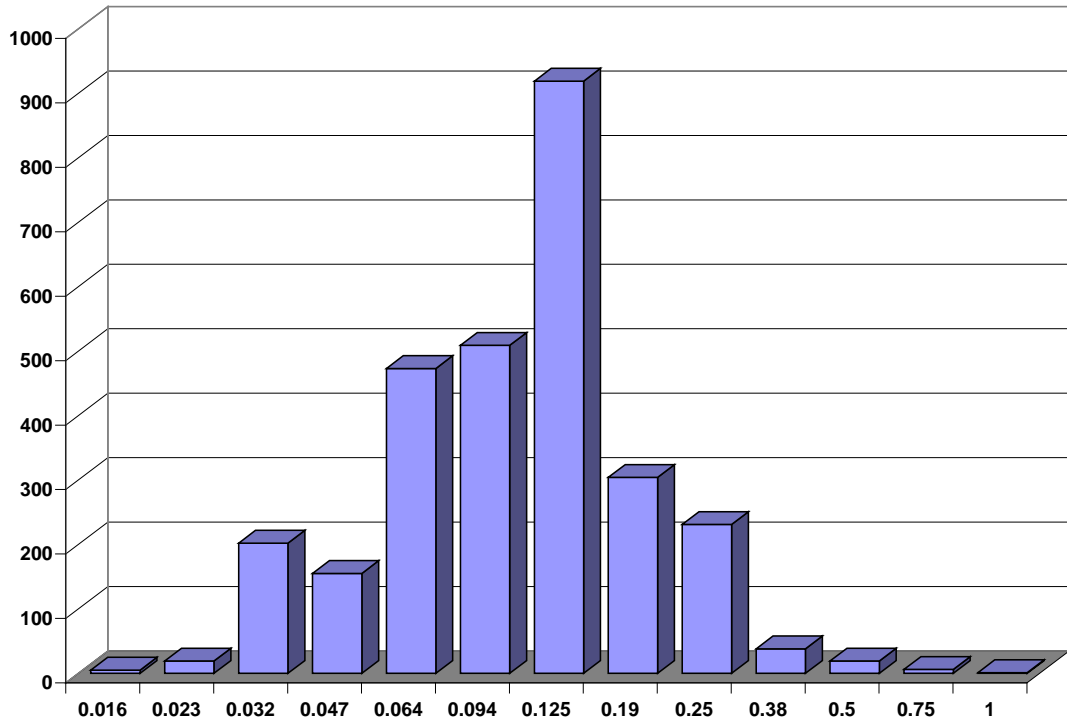


Figure 18. MIC distribution for all isolates against tigecycline

7 Discussion

Biennial community-based *S. aureus* antimicrobial surveillance programmes have been performed in Australia by AGAR since 2000.

In the 2006 programme the percentage of *S. aureus* identified as MRSA ranged from 11.3% in WA to 23.0% in ACT/NSW. The proportion of MRSA in non-invasive isolates and invasive isolates (16.2% and 10.4%) did not differ significantly ($P=0.0970$).

Resistance in MRSA to the non- β -lactam antimicrobials was: erythromycin 48.5%, ciprofloxacin 45.4%, tetracycline 26.5%, gentamicin 25.2%, trimethoprim-sulphamethoxazole 24.6%, clindamycin 17.9%, fusidic acid 5.3%, mupirocin 2.7% and rifampicin 2.5%. No resistance was detected to vancomycin, teicoplanin, quinupristin-dalfopristin or linezolid. Significant differences in resistance across regions were evident for all antimicrobials except rifampicin. These differences may be explained by the different MRSA clones in circulation in each region, for example Aus 2/3 EMRSA (ST239-MRSA-III) which are reliably resistant to gentamicin, erythromycin, tetracycline, ciprofloxacin and trimethoprim-sulphamethoxazole are commonly found in Vic/Tas, NSW/ACT and Qld/NT (40%, 29% and 19% of MRSA respectively). Only 3% of MRSA in SA were AUS 2/3 EMRSA and none were detected in WA.

Resistance in MRSA to the non- β -lactam antimicrobials also varied by patient type. Hospital outpatients had the highest rates of resistance to all the non- β -lactam antimicrobials except ciprofloxacin which was highest in nursing home and long-term care facility residents. Hospital outpatient and NH/LTCF patient groups tend to have recent antimicrobial exposure and recent hospital admissions exposing them to an increased risk of acquiring multi-resistant healthcare-associated MRSA.

Over the four AGAR community surveys (2000, 2002, 2004 and 2006) a significant decrease in resistance to all the non- β -lactam antimicrobials except mupirocin and rifampicin was observed in Australia. In the same time period the percentage of *S. aureus* identified as MRSA increased significantly from 11.6% in 2000 to 16.0% in 2006 ($P<0.0001$). This suggests that the increase in MRSA is due to non-multiresistant clones emerging in the community.

Resistance to non- β -lactam antimicrobials among the MSSA in 2006 was: erythromycin 11.1%, fusidic acid 4.2%, tetracycline 3.6%, trimethoprim-sulphamethoxazole 2.0%, ciprofloxacin 1.7%, mupirocin 1.6%, gentamicin 0.9%, clindamycin 0.8% and rifampicin 0.3%. As for MRSA, the proportion of resistance among hospital outpatients and other patient groups did not reach statistical significance except for erythromycin. Over the four AGAR surveys, no trends for either an increase or decrease in resistance were evident for penicillin, erythromycin, tetracycline, ciprofloxacin, gentamicin or fusidic acid. In Qld/NT rifampicin resistance increased from 0.0% in 2000 to 1.0% in 2006 ($P=0.0091$) and in WA constitutive clindamycin resistance increased from 0.0%

in 2000 to 1.1% in 2006 ($P=0.027$). Mupirocin resistance significantly increased in three regions (Qld/NT, Vic/Tas and WA) and nationally where it increased in resistance from 0.4% in 2000 to 1.6% in 2006 ($P<0.0001$).

In summary, resistance in MSSA remains uncommon except for erythromycin. Resistance in MRSA appears dynamic due to the success or decline of MRSA clones circulating in Australia. From 2000 to 2006, the AUS-2/3 EMRSA (ST239-MRSA-III) declined from 42.0% to 24.8% ($P<0.0001$) of MRSA. As these strains are generally resistant to gentamicin, erythromycin, ciprofloxacin, tetracycline and trimethoprim-sulphamethoxazole, the decrease in this clone explains the decrease in the proportion of MRSA resistant to four out of five of these agents. The relative stability of ciprofloxacin resistance can be explained by the increase of EMRSA-15 (ST22-MRSA-IV) from 11.7% of MRSA in 2000 to 18.3% in 2006 ($P=0.0197$) counterbalancing the decrease in AUS-2/3. EMRSA-15 is reliably resistant to ciprofloxacin (and often erythromycin) but is usually susceptible to the other non- β -lactam antimicrobials. From 2000 to 2006, the proportion of MRSA identified as community-associated MRSA (CA-MRSA) strains increased from 45.9% to 56.7% ($P=0.0064$). CA-MRSA are commonly susceptible to the majority of non- β -lactam antimicrobials with the exception of erythromycin ($\approx 25\%$ resistance) hence the increase in overall prevalence of MRSA without a concurrent increase in resistance to the non- β -lactam antimicrobials.

For a more detailed account of the MRSA clones circulating in Australia refer to the SAP 2006 Epidemiology and MRSA Typing Report ([.antimicrobial-resistance.com](http://antimicrobial-resistance.com)).

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