

The Australian Group on Antimicrobial Resistance

<http://antimicrobial-resistance.com>

***Staphylococcus aureus* Programme 2008 (SAP 2008)
Community Survey
Antimicrobial Susceptibility Report**

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1 Executive Summary

The Australian Group on Antimicrobial Resistance (AGAR) performs regular multicentre period-prevalence studies to monitor changes in antimicrobial resistance. In 2008, 31 laboratories participated in national surveillance of *Staphylococcus aureus* resistance with a focus on community isolates. Three thousand and seventy five isolates of *S. aureus* were collected prospectively from hospital outpatients, emergency departments and general practice patients. Susceptibility testing was performed by the Vitek[®] 2 automated system and Etest[®]. Biennial community-based *S. aureus* antimicrobial surveillance programmes have been performed in Australia by AGAR since 2000.

In the 2008 programme the percentage of *S. aureus* identified as MRSA ranged from 3.0% in Tasmania to 27.2% in New South Wales. The proportion of MRSA was similar in non-invasive isolates compared with invasive isolates (18.1% and 14.0% respectively). The proportion of *S. aureus* that were MRSA varied by patient type with long-term care residents having the highest proportion (72%). Outpatients and emergency department patients had approximately 18% whilst 11% of general practitioner patients with a *S. aureus* had an MRSA.

Approximately 45% of all MRSA were resistant to erythromycin and ciprofloxacin and approximately 17% were resistant to tetracycline, gentamicin and trimethoprim-sulphamethoxazole. Resistance to fusidic acid, mupirocin and rifampicin was uncommon. No resistance was detected to vancomycin, teicoplanin, quinupristin-dalfopristin, daptomycin or linezolid. Significant differences in resistance across regions were evident for all antimicrobials except rifampicin and mupirocin. These differences are explained by the different MRSA clones in circulation in each region (refer to the SAP 2008 MRSA Typing and Epidemiology report, www.antimicrobial-resistance.com). Hospital outpatients had higher rates of resistance, compared with general practitioner and emergency department patients, for the majority of the non- β -lactam antimicrobials.

Over the five biennial AGAR community surveys (2000 to 2008) a significant decrease in resistance in MRSA to all the non- β -lactams except mupirocin and rifampicin was observed in Australia. In the same time period the percentage of *S. aureus* identified as MRSA increased significantly from 11.5% in 2000 to 18.0% in 2008 ($p < 0.0001$). This is due to the emergence and expansion of non-multiresistant clones in the community.

Resistance to non- β -lactams among the MSSA in 2008 was uncommon except for erythromycin (10.3%). Over the five AGAR surveys, no national trends for either an increase or decrease in resistance were evident for clindamycin, tetracycline, gentamicin, ciprofloxacin or rifampicin. Erythromycin resistance decreased significantly from 12.2% in 2000 to 10.3% in 2008 ($p = 0.0025$). Fusidic acid increased from 3.7% in 2000 to 4.6% ($p = 0.011$) in 2008. Trimethoprim-sulphamethoxazole and mupirocin were tested in the last two survey only; no significant trends were detected.

2 Introduction

2.1 Objective of the Program

The objective of the 2008 surveillance program was to determine the prevalence of antimicrobial resistance throughout Australia in clinical isolates of *Staphylococcus aureus* causing infections with their onset in the community in general practice patients and in hospital outpatients (excluding day-only patients but including 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 beta-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) was 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 (Aus 2/3, ST239-III), 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 MRSA strain responsible for the latter epidemic was ST30-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-IV), it is also PVL positive¹². It has been responsible for deaths due to necrotising pneumonia in previously healthy young adults^{14, 15}. This clone is now detected in most regions of Australia and is increasing in prevalence¹⁶.

The Australian Group for Antimicrobial Resistance (AGAR) has conducted surveillance of antimicrobial resistance in *S. aureus* for 25 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 hypervirulent community MRSA strains, AGAR changed its methodology in 2000 to conduct surveys of community isolates biennially. The community-based surveys performed from 2000 to 2006 have been reported previously^{16, 21}. These reports

document the emergence and spread of a number of community MRSA strains including the hypervirulent SWP and Queensland strains.

Evidence has emerged of the intercontinental spread of major hypervirulent community-associated MRSA clones. The USA300 clone (ST8-IV) 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, Japan and Europe^{24, 25, 26}. It was first detected in Australia in 2003 and in retrospect three isolates from South Australia, Western Australia and Queensland collected as part of the 2005 AGAR Hospital Survey have been shown to belong to USA300. Other international PVL positive clones detected in Western Australia through the Western Australian surveillance programme (www.public.health.wa.gov.au) include the Taiwan clone (ST59-V_T), the European Clone (ST80-IV) and the Bengal Bay clone (ST772-V). Both the Taiwan and European clones were detected in the AGAR 2006 Community survey. The Bengal Bay clone has not been detected in any AGAR survey to date. MRSA from AGAR surveys are typed by phenotypic and molecular methods and results are published on the AGAR website (www.antimicrobial-resistance.com).

The susceptibility results of the fifth community-based survey of *S. aureus* infection conducted in 2008 is reported here.

3 Methods

Up to 100 clinically significant consecutive isolates of *S. aureus* from different patients were collected by each institution. Isolates were collected from non-inpatients. Day surgery and dialysis patients were excluded. Isolates from nursing homes, long-term care facilities and hospice patients were included. Each *S. aureus* isolate was from an individual patient and was judged to have come from a potentially infected site.

3.1 Identification

At least two of the following three tests for the identification of *S. aureus* were used and were positive: slide coagulase test; tube coagulase test; and demonstration of deoxyribonuclease production. Additional tests such as *nuc* gene PCR, 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-P579 card (bioMérieux) (Table 1). Penicillin susceptible strains were tested for β -lactamase production using nitrocefin. Daptomycin and

tigecycline MICs were determined by Etest[®] (AB Biodisk, Solna, Sweden) as was the MIC of mupirocin resistant strains.

Table 1: Vitek[®] 2 AST-P579 card

Antibiotic	MIC Range (mg/L)
Benzylpenicillin	0.03 – 0.5
Oxacillin	0.25 – 4
Cefoxitin screen	+/-
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
Nitrofurantoin	16 – 152
Mupirocin	2 – 8
Chloramphenicol	4 – 64

3.3 Quality Control

ATCC 29213 was the control organism for the AST-P579 card. ATCC 29212 and ATCC 29213 were the QC organisms for the daptomycin and tigecycline Etests respectively. All participating laboratories are NATA accredited.

3.4 Statistical Analysis

P values were calculated using Fischer's exact test or chi-squared 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

Sydney South West Pathology Service – Liverpool
Westmead Hospital

Northern Territory (1)

Royal Darwin Hospital

Queensland (6)

Pathology Queensland - Princess Alexandra Hospital

Pathology Queensland Central Laboratory

Pathology Queensland – Prince Charles Hospital

Pathology Queensland – Gold Coast Hospital

Pathology Queensland – Cairns Base Hospital

Sullivan Nicolaides Pathology

South Australia (3)

SA Pathology, Flinders Medical Centre

SA Pathology, Royal Adelaide Hospital

SA Pathology, 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, WA

4 Demographics

4.1 Regional source of isolates

3,075 *S. aureus* were tested by the 31 institutions. Each state and mainland territory of Australia was represented. The contributions to the 3,075 isolates from six states and two territories ranged from 3.3% from the Northern Territory to 25.6% from NSW ($p < 0.0001$) (Table 2).

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

Region	Number of Institutions	Total	%
Australian Capital Territory (ACT)	1	100	3.3
New South Wales (NSW)	8	786	25.6
Northern Territory (NT)	1	100	3.3
Queensland (Qld)	6	598	19.4
South Australia (SA)	3	300	9.8
Tasmania (Tas)	2	198	6.4
Victoria (Vic)	6	597	19.4
Western Australia (WA)	4	396	12.9
Total	31	3,075	100.0

4.2 Age

Few isolates were received from patients 0 years to 16 years (Table 3) with more isolates contributed by patients 17 years and older ($p < 0.0001$).

Table 3. Age range of patients

Age Range (years)	n	%
0-1	160	5.2
2-16	384	12.5
17-40	903	29.4
41-61	701	22.8
62-101	927	30.1
Total	3,075	100.0

5 Specimen Source

The majority (97.0%) of isolates were from non-invasive infections predominantly skin and soft tissue infections (Table 4). Blood culture isolates contributed only 2.1% of the total.

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

Specimen Source	n	%
Skin and Soft Tissue	2,669	86.8
Respiratory	157	5.1
Urine	69	2.2
Blood	65	2.1
Eye	54	1.8
Sterile Site	28	0.9
Ear	27	0.9
Sinus	4	0.1
Unknown	2	<0.1
Total	3,075	
Invasive	93	3.0
Non-Invasive	2,980	97.0

6 Susceptibility Testing Results

6.1 Methicillin-resistant *S. aureus*

The proportion of MRSA was 18.0% nationally (Table 5); a significant increase from the proportion identified in 2006 (16.0%) ($p=0.0445$). At a regional level, all states/territories showed small non-significant increases in the proportions of MRSA identified in 2006 and 2008 except Tasmania where a small drop was recorded (6.8% in 2006 to 3.0% in 2008, $p=0.1007$).

The proportion of invasive isolates (blood/sterile sites) that were MRSA was 14.0% overall and did not vary significantly ($p=0.0795$) between regions.

The proportion of specimen types with MRSA was variable with the ear having the highest proportion (25.9%) but differences between groups were not significant (Table 6).

The proportion of *S. aureus* that were MRSA varied between patient types with nursing home/long term care facility patients having the highest rates (71.9%) (Table 7).

Resistance in MRSA to non- β -lactam antimicrobials with the exception of mupirocin and rifampicin varied significantly between states (Table 8). Of the mupirocin resistant isolates, 7 (88%) had high-level resistance (MIC >256mg/L).

Resistance to clindamycin, ciprofloxacin, gentamicin, tetracycline and trimethoprim-sulphamethoxazole was highest in Victoria. The high proportion of AUS-2/3 MRSA (ST239-III) was responsible for the high proportion of resistance to these agents observed in most regions. Western Australia and South Australia record few episodes of ST239-III and rates of resistance to gentamicin, tetracycline and trimethoprim-sulphamethoxazole were 5% or less. Resistance to these agents is rare in other clones in Australia.

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

	% [n/N]									
	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aus	X ² P*
All	7.0 [7/100]	27.2 [214/786]	21.0 [21/100]	17.4 [104/598]	14.0 [42/300]	3.0 [6/198]	16.8 [100/597]	14.6 [58/396]	18.0 [552/3075]	92.58 <0.0001
Invasive	-	23.3 [7/30]	100 [1/1]	7.1 [1/14]	0.0 [0/9]	0.0 [0/2]	7.1 [2/28]	22.2 [2/9]	14.0 [13/93]	11.30 0.0795
Non-invasive	7.0 [7/100]	27.5 [207/754]	20.2 [20/99]	17.6 [103/584]	14.4 [42/291]	3.1 [6/196]	17.2 [98/569]	14.5 [56/387]	18.1 [539/2980]	89.70 <0.0001

* Difference across regions

Table 6. Proportion of *S. aureus* that are MRSA by Source

Specimen Source	MRSA
Skin and Soft Tissue	18.3 [488/2669]
Respiratory	15.9 [25/157]
Urine	18.8 [13/69]
Blood	12.3 [8/65]
Eye	11.1 [6/54]
Sterile Site	17.9 [5/28]
Ear	25.9 [7/27]
Sinus	0.0 [0/4]
X ²	5.835
P	p=0.5592

Table 7. Proportion of *S. aureus* that are MRSA by Patient Type

Patient Type	MRSA
Emergency Dept	19.3 [251/1268]
General Practitioner	11.1 [101/912]
Outpatient	18.0 [123/684]
Long-term Care Facility	71.9 [23/32]
Other/Unknown	30.2 [54/179]
χ^2	97.50
P	p<0.0001

Table 8. Proportion [and number] of MRSA non-susceptible to non- β -lactams

Drug	ACT [n=7]	NSW [n=214]	NT [n=21]	Qld [n=104]	SA [n=42]	Tas [n=6]	Vic [n=100]	WA [n=58]	Aus [n=552]	Difference across regions χ^2 P
Erythromycin	28.6 [2]	48.6 [104]	47.6 [10]	30.8 [32]	28.6 [12]	66.7 [4]	59.0 [59]	32.8 [19]	43.8 [242]	27.28 0.0003
Clindamycin*	0.0 [0]	18.2 [39]	23.8 [5]	11.5 [12]	2.4 [1]	16.7 [1]	24.0 [24]	1.7 [1]	15.0 [83]	24.77 0.0008
Tetracycline	14.3 [1]	17.8 [38]	28.6 [6]	11.5 [12]	4.8 [2]	16.7 [1]	42.0 [42]	5.2 [3]	19.0 [105]	52.52 <0.0001
Trimethoprim- Sulphamethoxazole	14.3 [1]	16.4 [35]	28.6 [6]	11.5 [12]	4.8 [2]	16.7 [1]	38.0 [38]	1.7 [1]	17.4 [96]	48.75 <0.0001
Ciprofloxacin	42.9 [3]	52.3 [112]	28.6 [6]	22.1 [23]	23.8 [10]	66.7 [4]	69.0 [69]	19.0 [11]	43.1 [238]	76.46 <0.0001
Gentamicin	14.3 [1]	16.4 [35]	28.6 [6]	9.6 [10]	0.0 [0]	16.7 [1]	36.0 [36]	0.0 [0]	16.1 [89]	54.20 <0.0001
Fusidic Acid	0.0 [0]	1.4 [3]	9.5 [2]	5.8 [6]	14.3 [6]	0.0 [0]	3.0 [3]	8.6 [5]	4.5 [25]	18.56 0.0097
Mupirocin	0.0 [0]	0.9 [2]	0.0 [0]	2.9 [3]	0.0 [0]	0.0 [0]	2.0 [2]	1.7 [1]	1.4 [8]	3.272 0.8587
Rifampicin	0.0 [0]	0.9 [2]	4.8 [1]	1.9 [2]	2.4 [1]	0.0 [0]	2.0 [2]	0.0 [0]	1.4 [8]	3.701 0.8135

* 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, ciprofloxacin, gentamicin, tetracycline, clindamycin and trimethoprim-sulphamethoxazole (Table 9). MRSA isolated from hospital outpatients had the highest level of resistance for clindamycin, tetracycline, trimethoprim-

sulphamethoxazole and gentamicin which is consistent with their having a higher proportion of healthcare-related acquisition. Erythromycin and ciprofloxacin resistance was highest in the nursing home/long-term care facility patients. No resistance was detected to vancomycin, teicoplanin, quinupristin-dalfopristin, daptomycin or linezolid.

Table 9. Proportion [and number] of non-susceptible MRSA by patient type (Australia)

Drug	ED [n=251]	OP [n=123]	GP [n=101]	NH/LTCF [n=23]	Others or not specified [n=54]	Difference between type of patients X ² P
Erythromycin	39.4 [99]	62.6 [77]	30.7 [31]	69.6 [16]	35.2 [19]	34.47 <0.0001
Clindamycin*	11.6 [29]	27.6 [34]	9.9 [10]	13.0 [3]	13.0 [7]	20.02 0.0005
Tetracycline	17.1 [43]	30.1 [37]	13.9 [14]	13.0 [3]	14.8 [8]	13.25 0.0101
Trimethoprim- Sulphamethoxazole	15.1 [38]	30.1 [37]	9.9 [10]	13.1 [3]	14.8 [8]	19.17 0.0007
Ciprofloxacin	42.2 [106]	55.3 [68]	25.7 [26]	82.6 [19]	35.2 [19]	35.95 <0.0001
Gentamicin	14.7 [37]	26.0 [32]	9.9 [10]	13.0 [3]	13.0 [7]	12.71 0.0128
Fusidic Acid	4.0 [10]	5.7 [7]	3.0 [3]	4.3 [1]	7.4 [4]	2.161 0.7063
Rifampicin	0.8 [2]	3.3 [4]	0.0 [0]	0.0 [0]	3.7 [2]	7.292 0.1212
Mupirocin	1.6 [4]	3.3 [4]	0.0 [0]	0.0 [0]	0.0 [0]	5.453 0.2439

6.2 Trends in Proportion of *S. aureus* that are MRSA 2000-2008

Table 10. Trend data for proportion of *S. aureus* that are MRSA, 2000-2008.

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aus
2000	5.0 [5/100]	19.7 [138/700]	7.0 [7/100]	7.7 [23/300]	7.5 [30/400]	2.0 [2/100]	9.6 [45/469]	11.5 [46/400]	11.5 [296/2569]
2002	8.0 [8/100]	25.4 [175/689]	21.0 [21/100]	12.3 [37/300]	9.0 [36/400]	6.0 [6/100]	11.5 [46/399]	13.8 [55/398]	15.4 [384/2486]
2004	6.0 [6/100]	22.6 [159/703]	28.8 [17/59]	18.0 [54/300]	10.3 [41/399]	3.0 [3/99]	12.2 [61/500]	13.0 [52/400]	15.4 [393/2560]
2006	5.0 [5/100]	25.3 [201/795]	20.0 [20/100]	13.8 [69/500]	12.0 [36/299]	6.8 [13/190]	14.5 [87/598]	11.3 [45/397]	16.0 [476/2979]
2008	7.0 [7/100]	27.2 [214/786]	21.0 [21/100]	17.4 [104/598]	14.0 [42/300]	3.0 [6/198]	16.8 [100/597]	14.6 [58/396]	18.0 [552/3075]
X ²	0.1720	9.059	4.788	12.66	9.493	0.1108	13.87	0.5153	38.30
P for trend	0.8957	0.0026	0.0287	0.0004	0.0021	0.7393	0.0002	0.4728	<0.0001

A significant increase in the proportion of *S. aureus* that are MRSA occurred nationally (from 11.5% in 2000 to 18.0% in 2008) and in New South Wales, the Northern Territory, Queensland, South Australia and Victoria.

6.3 Trends in MRSA non-susceptibility 2000-2008

Erythromycin

Table 11. Trend data for non-susceptibility to erythromycin in MRSA, 2000-2008.

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aus
2000	20.0 [1/5]	70.3 [97/138]	57.1 [4/7]	52.2 [12/23]	66.7 [20/30]	0.0 [0/2]	93.3 [42/45]	45.7 [21/46]	66.6 [197/296]
2002	62.5 [5/8]	72.6 [127/175]	61.9 [13/21]	40.5 [15/37]	36.1 [13/36]	33.3 [2/6]	89.1 [41/46]	60.0 [33/55]	64.8 [249/384]
2004	66.7 [4/6]	61.6 [98/159]	41.2 [7/17]	31.5 [17/54]	41.5 [17/41]	33.3 [1/3]	83.6 [51/61]	48.1 [25/52]	56.0 [220/393]
2006	60.0 [3/5]	53.2 [107/201]	25.0 [5/20]	40.6 [28/69]	30.6 [11/36]	53.9 [7/13]	60.9 [53/87]	37.8 [17/45]	48.5 [231/476]
2008	28.6 [2/7]	48.6 [104/214]	47.6 [10/21]	30.8 [32/104]	28.6 [12/42]	66.7 [4/6]	59.0 [59/100]	32.8 [19/58]	43.8 [242/552]
X ²	0.01538	30.43	1.898	2.682	8.851	3.325	31.44	5.421	64.45
P for trend	0.9013	<0.0001	0.1684	0.1015	0.0029	0.0682	<0.0001	0.0199	<0.0001

The proportion of MRSA that were non-susceptible to erythromycin over the five test periods declined significantly ($p < 0.0001$) in Australia (Table 11). This trend occurred in New South Wales, South Australia, Victoria and Western Australia. A downwards trend also occurred in Queensland but this was not statistically significant. As only 100 isolates are collected in each of the territories, rates fluctuate markedly from year to year and no significant trends were detected.

Clindamycin

Table 12. Trend data for non-susceptibility to clindamycin in MRSA, 2000-2008.

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aus
2000	0.0 [0/5]	32.6 [45/138]	0.0 [0/7]	17.4 [4/23]	13.3 [4/30]	0.0 [0/2]	80.0 [36/45]	2.2 [1/46]	30.4 [90/296]
2002	12.5 [1/8]	52.6 [92/175]	47.6 [10/21]	16.2 [6/37]	2.8 [1/36]	16.7 [1/6]	50.0 [23/46]	7.3 [4/55]	35.9 [138/384]
2004	0.0 [0/6]	32.7 [52/159]	17.6 [3/17]	9.3 [5/54]	7.3 [3/41]	0.0 [0/3]	32.8 [20/61]	5.8 [3/52]	21.9 [86/393]
2006	20.0 [1/5]	22.4 [45/201]	5.0 [1/20]	17.4 [12/69]	0.0 [0/36]	33.8 [4/13]	24.1 [21/87]	2.2 [1/45]	17.9 [85/476]
2008	0.0 [0/7]	18.2 [39/214]	23.8 [5/21]	11.5 [12/104]	2.4 [1/42]	16.7 [1/6]	24.0 [24/100]	1.7 [1/58]	15.0 [83/552]
X ²	0.001131	34.76	0.991	0.3356	4.039	0.5747	44.05	0.6505	58.61
P for trend	0.9732	<0.0001	0.3195	0.5624	0.0445	0.4484	<0.0001	0.4199	<0.0001

The proportion of MRSA that were non-susceptible to clindamycin over the five test periods declined significantly ($p < 0.0001$) in Australia from 30.4% to 15.0%

(Table 12). Significant downward trends occurred in New South Wales, South Australia and Victoria.

Tetracycline

Table 13. Trend data for non-susceptibility to tetracycline in MRSA, 2000-2008.

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aus
2000	0.0 [0/5]	52.9 [73/138]	14.3 [1/7]	30.4 [7/23]	53.3 [16/30]	0.0 [0/2]	71.1 [32/45]	2.2 [1/46]	43.9 [130/296]
2002	62.5 [5/8]	53.7 [94/175]	52.4 [11/21]	35.1 [13/37]	19.4 [7/36]	33.3 [2/6]	87.0 [40/46]	5.5 [3/55]	45.6 [175/384]
2004	50.0 [3/6]	41.5 [66/159]	23.5 [4/17]	14.8 [8/54]	14.6 [6/41]	33.3 [1/3]	70.5 [43/61]	0.0 [0/52]	33.3 [131/393]
2006	40.0 [2/5]	30.8 [62/201]	20.0 [4/20]	20.3 [14/69]	2.8 [1/36]	46.2 [6/13]	42.5 [37/87]	0.0 [0/45]	26.5 [126/476]
2008	14.3 [1/7]	17.8 [38/214]	28.6 [6/21]	11.5 [12/104]	4.8 [2/42]	16.7 [1/6]	42.0 [42/100]	5.2 [3/58]	19.0 [105/552]
X ²	0.1315	69.53	0.8744	8.817	28.51	0.1034	30.48	0.0278	95.66
P for trend	0.7169	<0.0001	0.3497	0.0030	<0.0001	0.7477	<0.0001	0.8676	<0.0001

The proportion of MRSA that were non-susceptible to tetracycline over the five test periods declined significantly ($p < 0.0001$) in Australia from 43.9% to 19.0% (Table 13). The national downward trend was a reflection of the stable low rate in WA and significant decreases in New South Wales, Queensland, South Australia and Victoria.

Table 14. Trend data for non-susceptibility to trimethoprim-sulphamethoxazole MRSA, 2006-2008.

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aus
2006	40.0 [2/5]	27.4 [55/201]	15.0 [3/20]	20.3 [14/69]	2.8 [1/36]	38.5 [5/13]	42.5 [37/87]	0.0 [0/45]	24.6 [117/476]
2008	14.3 [1/7]	16.4 [35/214]	28.6 [6/21]	11.5 [12/104]	4.8 [2/42]	16.7 [1/6]	38.0 [38/100]	1.7 [1/58]	17.4 [96/552]
P	0.5227	0.0085	0.4537	0.1315	1.0000	0.6047	0.5525	1.0000	0.0054

Trimethoprim-sulphamethoxazole was not tested in 2000, 2002 and 2004. Over the two test periods resistance declined significantly ($p = 0.0054$) in Australia from 24.6% to 17.4% (Table 14). New South Wales was the only region to show a significant decrease whereas rates increased (but not significantly) in the Northern Territory, South Australia and Western Australia.

Ciprofloxacin

Table 15. Trend data for non-susceptibility to ciprofloxacin in MRSA, 2000-2008.

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aus
2000	0.0 [0/5]	68.1 [94/138]	14.3 [1/7]	26.1 [6/23]	56.7 [17/30]	0.0 [0/2]	68.9 [31/45]	8.7 [4/46]	51.7 [153/296]
2002	62.5 [5/8]	70.3 [123/175]	52.4 [11/21]	37.8 [14/37]	33.3 [12/36]	16.7 [1/6]	84.8 [39/46]	23.6 [13/55]	56.8 [218/384]
2004	50.0 [3/6]	66.0 [105/159]	29.4 [5/17]	35.2 [19/54]	39.0 [16/41]	66.7 [2/3]	90.2 [55/61]	19.2 [10/52]	54.7 [215/393]
2006	40.0 [2/5]	55.7 [112/201]	20.0 [4/20]	26.1 [18/69]	27.8 [10/36]	76.9 [10/13]	63.2 [55/87]	11.1 [5/45]	45.4 [216/476]
2008	42.9 [3/7]	52.3 [112/214]	28.6 [6/21]	22.1 [23/104]	23.8 [10/42]	66.7 [4/6]	69.0 [69/100]	19.0 [11/58]	43.1 [238/552]
X ²	0.4486	17.70	0.9636	2.6620	7.339	6.764	2.840	0.1849	17.03
P for trend	0.5030	<0.0001	0.3263	0.1027	0.0067	0.0093	0.0919	0.6672	<0.0001

The proportion of MRSA that were non-susceptible to ciprofloxacin declined in Australia from 51.7% in 2000 to 43.1% in 2008 ($p < 0.0001$) (Table 15). Resistance increased in Tasmania ($p = 0.0093$).

Gentamicin

Table 16. Trend data for non-susceptibility to gentamicin in MRSA, 2000-2008

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aus
2000	0.0 [0/5]	50.0 [69/138]	14.3 [1/7]	17.4 [4/23]	36.7 [11/30]	0.0 [0/2]	80.0 [36/45]	2.2 [1/46]	41.2 [122/296]
2002	62.5 [5/8]	54.9 [96/175]	47.6 [10/21]	32.4 [12/37]	16.7 [6/36]	0.0 [0/6]	80.4 [37/46]	3.6 [2/55]	43.8 [168/384]
2004	50.0 [3/6]	42.1 [67/159]	23.5 [4/17]	14.8 [8/54]	17.1 [7/41]	33.3 [1/3]	68.9 [42/61]	0.0 [0/52]	33.6 [132/393]
2006	40.0 [2/5]	28.4 [57/201]	20.0 [4/20]	24.6 [17/69]	2.8 [1/36]	38.5 [5/13]	39.1 [34/87]	0.0 [0/45]	25.2 [120/476]
2008	14.3 [1/7]	16.4 [35/214]	28.6 [6/21]	8.7 [10/104]	0.0 [0/42]	16.7 [1/6]	36.0 [36/100]	0.0 [0/58]	16.1 [89/552]
X ²	0.1315	73.46	0.4971	4.327	21.93	1.574	45.56	2.906	102.1
P for trend	0.7169	<0.0001	0.4808	0.0375	<0.0001	0.2096	<0.0001	0.0883	<0.0001

The proportion of MRSA that were non-susceptible to gentamicin over the five test periods declined significantly ($p < 0.0001$) in Australia from 41.2% to 16.1% (Table 16). A significant decrease was achieved in New South Wales, Queensland, South Australia and Victoria.

Fusidic acid

Table 17. Trend data for non-susceptibility to fusidic acid in MRSA, 2000-2008.

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aus
2000	0.0 [0/5]	2.9 [4/138]	28.6 [2/7]	17.4 [4/23]	16.7 [5/30]	50.0 [1/2]	8.9 [4/45]	15.2 [7/46]	9.1 [27/296]
2002	0.0 [0/8]	4.6 [8/175]	4.8 [1/21]	5.4 [2/37]	25.0 [9/36]	50.0 [3/6]	2.2 [1/46]	5.5 [3/55]	7.0 [27/384]
2004	0.0 [0/6]	4.4 [7/159]	11.8 [2/17]	5.6 [3/54]	9.8 [4/41]	33.3 [1/3]	1.6 [1/61]	13.5 [7/52]	6.4 [25/393]
2006	0.0 [0/5]	3.0 [6/201]	10.0 [2/20]	8.7 [6/69]	11.1 [4/36]	0.0 [0/13]	2.3 [2/87]	11.1 [5/45]	5.3 [25/476]
2008	0.0 [0/7]	1.4 [3/214]	9.5 [2/21]	5.8 [6/104]	14.3 [6/42]	0.0 [0/6]	3.0 [3/100]	8.6 [5/58]	4.5 [25/552]
X ²		1.75	0.2461	1.172	0.9596	9.31	1.717	0.2486	7.935
P for trend	-	0.01858	0.6198	0.2790	0.3273	0.0023	0.1901	0.6180	0.0048

The proportion of MRSA that were non-susceptible to fusidic acid over the five test periods declined significantly (p=0048) around Australia from 9.1% to 4.5% (Table 17). Tasmania was the only region to record a significant shift (50.0% in 2000 to 0.0% in 2006 and 2008).

Mupirocin

Table 18. Trend data for non-susceptibility to mupirocin in MRSA, 2000-2008.

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aus
2006	0.0 [0/5]	1.0 [2/201]	0.0 [0/20]	8.7 [6/69]	0.0 [0/36]	0.0 [0/13]	3.4 [3/87]	0.0 [0/45]	2.3 [11/476]
2008	0.0 [0/7]	0.9 [2/214]	0.0 [0/21]	2.9 [3/104]	0.0 [0/42]	0.0 [0/6]	2.0 [2/100]	1.7 [1/58]	1.4 [8/552]
P	-	1.0000	-	0.1585	-	-	0.6650	1.0000	0.3569

A mupirocin breakpoint of 2mg/L was first utilized in the 2006 survey. The proportion of MRSA that were non-susceptible to mupirocin over the two test periods remained stable in all regions. Mupirocin resistance was not detected in the ACT, the Northern Territory, South Australia or Tasmania in either survey.

Rifampicin

Table 19. Trend data for non-susceptibility to rifampicin in MRSA, 2000-2008.

Year	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aus
2000	0.0 [0/5]	2.9 [4/138]	0.0 [0/7]	0.0 [0/23]	3.3 [1/30]	0.0 [0/2]	8.9 [4/45]	0.0 [0/46]	3.0 [9/296]
2002	12.5 [1/8]	2.3 [4/175]	0.0 [0/21]	10.8 [4/37]	0.0 [0/36]	0.0 [0/6]	4.3 [2/46]	3.6 [2/55]	3.4 [13/384]
2004	0.0 [0/6]	4.4 [7/159]	0.0 [0/17]	3.7 [2/54]	0.0 [0/41]	33.3 [1/3]	1.6 [1/61]	0.0 [0/52]	2.8 [11/393]
2006	0.0 [0/5]	2.5 [5/201]	0.0 [0/20]	7.3 [5/69]	0.0 [0/36]	0.0 [0/13]	2.3 [2/87]	0.0 [0/45]	2.5 [12/476]
2008	0.0 [0/7]	0.9 [2/214]	4.8 [1/21]	1.9 [2/104]	2.4 [1/42]	0.0 [0/6]	2.0 [2/100]	0.0 [0/58]	1.4 [8/552]
X ²	0.5599	1.1315	1.712	0.687	0.0176	0.1784	3.907	1.114	3.331
P for trend	0.4543	0.2515	0.1908	0.4072	0.8943	0.6728	0.0481	0.2912	0.068

The proportion of MRSA that were non-susceptible to rifampicin over the five test periods declined significantly ($p=0.0481$) in Victoria (Table 16). Rifampicin resistance is found in approximately 13% of Aus-3 strains (ST239-III with a SCC $_{merc}$) and rarely in other clones. The decline in rifampicin resistance in Victoria mirrors the decline of Aus-3 in that region.

6.3 Methicillin-susceptible *S. aureus*

Results of susceptibility testing of MSSA are shown in Table 20. Resistance to non- β -lactam agents remains uncommon. All isolates were susceptible to vancomycin, teicoplanin, quinupristin-dalfopristin, daptomycin and linezolid. There was a significant difference in the proportion of resistance across regions identified in the 2008 survey for erythromycin, fusidic acid and mupirocin. Of the mupirocin resistant isolates, 27 (77%) exhibited high level resistance (MIC >256mg/L). Resistance to penicillin was high ranging from 78.5% to 89.9% across regions. Resistance to the non- β -lactam antimicrobials in MSSA associated with various patient types was often difficult to establish due to low levels of resistance. Where significant differences were noted (for clindamycin, ciprofloxacin and rifampicin) rates of resistances was higher for outpatients than other patient groups (Table 21).

Table 20. Proportion [and number] of MSSA Non-Susceptible

Drug	ACT [n=93]	NSW [n=572]	NT [n=79]	Qld [n=494]	SA [n=258]	Tas [n=192]	Vic [n=497]	WA [n=338]	Aus [n=2,523]	Difference across regions χ^2 P
Penicillin	78.5 [73]	87.9 [503]	89.9 [71]	82.4 [407]	86.8 [224]	81.3 [156]	83.5 [415]	85.5 [289]	84.7 [2,138]	14.46 0.0435
Erythromycin	6.5 [6]	10.0 [57]	8.9 [7]	14.6 [72]	11.2 [29]	4.2 [8]	10.3 [51]	9.2 [31]	10.3 [261]	19.96 0.0057
Clindamycin*	0.0 [0]	1.8 [10]	0.0 [0]	1.2 [6]	1.2 [3]	0.0 [0]	1.6 [8]	0.3 [1]	1.1 [28]	9.437 0.2228
Tetracycline	3.2 [3]	4.0 [23]	1.3 [1]	2.4 [12]	4.3 [11]	4.7 [9]	4.2 [21]	1.8 [6]	3.4 [86]	8.475 0.2926
Trimethoprim- Sulphamethoxazole	2.2 [2]	3.3 [19]	0.0 [0]	2.6 [13]	2.7 [7]	1.6 [3]	3.6 [18]	0.9 [3]	2.6 [65]	10.24 0.1755
Ciprofloxacin	1.1 [1]	2.3 [13]	0.0 [0]	3.9 [19]	1.9 [5]	1.6 [3]	3.0 [15]	0.6 [2]	2.3 [58]	13.89 0.0532
Gentamicin	0.0 [0]	1.4 [8]	0.0 [0]	1.0 [5]	1.2 [3]	0.5 [1]	1.4 [7]	0.0 [0]	1.0 [24]	7.735 0.3565
Fusidic Acid	7.5 [7]	7.2 [41]	3.8 [3]	4.0 [20]	2.7 [7]	2.6 [5]	3.8 [19]	4.4 [15]	4.6 [117]	15.28 0.0325
Rifampicin	0.0 [0]	0.3 [2]	0.0 [0]	0.0 [0]	0.0 [0]	0.5 [1]	0.2 [1]	0.0 [0]	0.2 [4]	4.973 0.6633
Mupirocin	0.0 [0]	1.7 [10]	1.3 [1]	3.4 [17]	0.0 [0]	1.0 [2]	0.8 [4]	0.3 [1]	1.4 [35]	25.07 0.0007

* Constitutive resistance

Table 21. Proportion and number of MSSA Non-Susceptible by Patient Type (Australia)

Drug	ED [n=1017]	GP [n=811]	OP [n=561]	NH/LTCF [n=9]	Others or not specified [n=125]	Difference across regions χ^2 P
Penicillin	86.0 [875]	83.6 [678]	83.6 [469]	55.6 [5]	88.8 [111]	10.22 0.0368
Erythromycin	10.4 [106]	9.2 [75]	12.3 [69]	0.0 [0]	8.8 [11]	4.730 0.3161
Clindamycin*	1.0 [10]	0.5 [4]	2.3 [13]	0.0 [0]	0.8 [1]	10.62 0.0312
Tetracycline	3.7 [38]	3.3 [27]	3.2 [18]	0.0 [0]	2.4 [3]	1.120 0.8912
Trimethoprim- Sulphamethoxazole	2.9 [30]	2.0 [16]	2.9 [16]	0.0 [0]	2.4 [3]	2.615 0.7054
Ciprofloxacin	2.2 [22]	1.2 [10]	4.6 [26]	0.0 [0]	0.0 [0]	20.96 0.0003
Gentamicin	0.9 [9]	0.6 [5]	1.6 [9]	0.0 [0]	0.8 [1]	3.668 0.4528
Fusidic Acid	4.0 [41]	5.1 [41]	4.6 [26]	0.0 [0]	7.2 [9]	3.459 0.4842
Rifampicin	0.0 [0]	0.0 [0]	0.5 [3]	0.0 [0]	0.8 [1]	11.18 0.0246
Mupirocin	1.4 [14]	0.6 [5]	2.5 [14]	0.0 [0]	1.6 [2]	8.728 0.0683

6.4 Trends in MSSA non-susceptibility 2000-2008

In spite of some survey to survey variability there were no long term trends for either an increase or decrease in resistance to the non- β -lactams either within regions or nationally for clindamycin, trimethoprim-sulphamethoxazole, gentamicin, ciprofloxacin or rifampicin. Erythromycin resistance decreased in all regions except Queensland where it increased, but not significantly, from 11.9% in 2000 to 14.6% in 2008. Significant decreases were seen nationally (12.2% to 10.3%, $p=0.0025$) in the ACT (18.9% to 6.5%, $p=0.0007$) and in Tasmania (11.2% to 4.2%, $p=0.0347$). Tetracycline resistance decreased in Victoria (7.1% to 4.2%, $p=0.0229$). Mupirocin decreased significantly in Western Australia from 2.6% in 2006 to 0.3% in 2008 ($p=0.0208$) and fusidic acid increased nationally from 3.7% in 2000 to 4.6% in 2008 ($p=0.011$) and in New South Wales from 2.8% to 7.2% over the same time period ($p=0.0018$) (raw data not shown).

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. 16/2,977 (0.5%) isolates were classified as resistant using the US FDA and EUCAST breakpoint of 0.5mg/L.

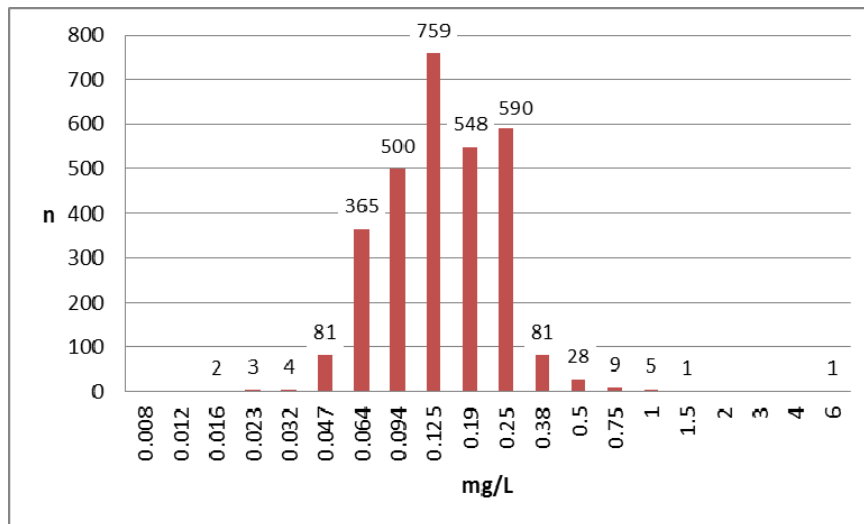


Figure 1. MIC distribution for all isolates against tigecycline

6.6 Daptomycin MIC distribution

Daptomycin is a cyclic lipopeptide antimicrobial. Isolates with an MIC >1mg/L are considered to be non-susceptible by CLSI guidelines. One isolate (1/3,075, 0.03%) had an MIC of 1.5mg/L by Etest but broth microdilution confirmed the MIC as 1mg/L.

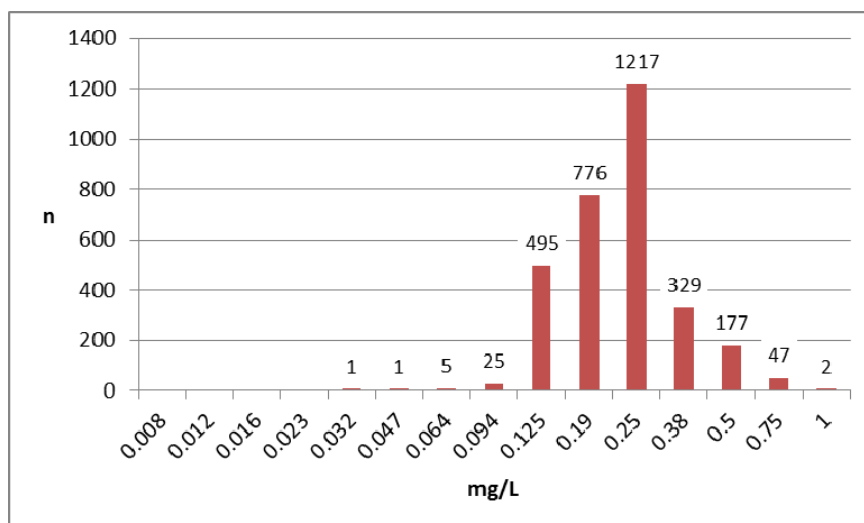


Figure 2. MIC distribution for all isolates against daptomycin

7 Discussion

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

In the 2008 programme the percentage of *S. aureus* identified as MRSA ranged from 3.0% in Tasmania to 27.2% in New South Wales.

Resistance in MRSA to the non- β -lactams was: erythromycin 43.8%, ciprofloxacin 43.1%, tetracycline 19.0%, trimethoprim-sulphamethoxazole 17.4%, gentamicin 16.1%, clindamycin 15.0%, fusidic acid 4.5%, mupirocin 1.4% and rifampicin 1.4%. No resistance was detected to vancomycin, teicoplanin, quinupristin-dalfopristin or linezolid. Significant differences in resistance across regions were evident for all antimicrobials except mupirocin and rifampicin. These differences may be explained by the different MRSA clones in circulation in each region, for example Aus 2/3 EMRSA (ST239-III) which are reliably resistant to gentamicin, erythromycin, tetracycline, ciprofloxacin and trimethoprim-sulphamethoxazole are commonly found in all regions except South Australia and Western Australia.

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

Over the five biennial AGAR community surveys (2000 to 2008) a significant decrease in resistance to all the non- β -lactams except mupirocin and rifampicin was observed in Australia. In the same time period the percentage of *S. aureus* identified as MRSA increased significantly from 11.5% in 2000 to 18.0% in 2008 ($p < 0.0001$). This increase in MRSA is due to non-multiresistant clones emerging in the community.

Resistance to non- β -lactams among the MSSA in 2008 was: erythromycin 10.3%, fusidic acid 4.6%, tetracycline 3.4%, trimethoprim-sulphamethoxazole 2.6%, ciprofloxacin 2.3%, mupirocin 1.4%, clindamycin 1.1%, gentamicin 1.0% and rifampicin 0.2%. As for MRSA, resistance was higher among outpatients than other hospital groups although this did not reach statistical significance except for clindamycin, ciprofloxacin and rifampicin. Over the five AGAR surveys, no trends for either an increase or decrease in resistance were evident for clindamycin, trimethoprim-sulphamethoxazole, gentamicin, ciprofloxacin or rifampicin. Erythromycin resistance decreased significantly from 12.2% in 2000 to 10.3% in 2008. Fusidic acid increased from 3.7% in 2000 to 4.6% in 2008.

In summary, methicillin resistance is increasing in the Australian community. General Practitioners can expect one in ten, and emergency department and outpatient physicians can expect one in five patients infected with *S. aureus* to

have MRSA and therefore be unresponsive to treatment with the β -lactam antimicrobials.

Resistance in MRSA appears dynamic due to the success or decline of MRSA clones circulating in Australia. Resistance in MSSA remains uncommon except for erythromycin.

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