Annual survey of methicillin-resistant *Staphylococcus aureus* (MRSA), 2015

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Introduction

ESR conducts annual surveys of methicillin-resistant *Staphylococcus aureus* (MRSA). Each year, all hospital and community microbiology laboratories in New Zealand are asked to refer all MRSA isolated during a one-month period to ESR. Laboratories provide epidemiological information with each isolate referred. At ESR, MRSA are typed to identify MRSA strains. The purpose of these annual surveys is to provide information on the epidemiology of MRSA in New Zealand and to monitor changes over time.

The results of the 2015 MRSA survey are presented in this report, along with the trends in MRSA prevalence.

Previous reports on the annual MRSA surveys are available at http://www.surv.esr.cri.nz/antimicrobial/mrsa_annual.php.

Methods

MRSA isolates and data collection

Hospital and community diagnostic microbiology laboratories in New Zealand were asked to refer all MRSA isolated during August 2015 to ESR.

When referring MRSA isolates, laboratories were asked to supply selected epidemiological data, including the patient's date of birth, geographic location, hospitalisation status and history, MRSA isolation site, infection or colonisation status, and if the MRSA was obtained from a screen or a diagnostic specimen. Laboratories also provided information on the susceptibility of the MRSA isolates to non-β-lactam antibiotics.

People were classified as hospital patients or hospital staff if (i) they were inpatients or outpatients in a healthcare facility when MRSA was isolated, or had been in the previous three months; (ii) they were in a residential-care facility when MRSA was isolated, or had been in the previous three months; or (iii) they were employed in a healthcare or residential-care facility when MRSA was isolated. Patients or staff were classified as people in the community if (i) MRSA was isolated from patients while in the community and the patients had no history of being in a healthcare or residential-care facility in the previous three months; (ii) MRSA was isolated from healthcare or residential-care facility admission-screening of patients who had no history of being in such facilities in the previous three months; or (iii) MRSA was isolated from pre-employment swabs of healthcare staff with no employment history supplied.

PCR for mecA, mecC, nuc *and* lukS-*PV genes*

A real-time PCR assay was used to detect *mecA; mecC;* the *S. aureus* species-specific thermostable nuclease gene, *nuc;* and one of the two genes encoding Panton-Valentine leukocidin (PVL), *lukS*-PV.[1] Only isolates that were confirmed as MRSA by the detection of *nuc* and either *mecA* or *mecC* were included in the survey.

While only the *lukS*-PV gene was targeted in the PVL PCR assay used, any isolates in which *lukS*-PV was detected were assumed to have both PVL genes. For convenience, isolates positive for the *lukS*-PV gene are termed 'PVL positive' in this report and isolates in which the *lukS*-PV gene was not detected are termed 'PVL negative'.

spa *typing and based upon repeat pattern (BURP) analysis*

The polymorphic X region of the staphylococcal protein A gene (*spa*) was amplified as previously described.[2] PCR products were sequenced by the Sequencing Laboratory at ESR using an ABI 3130XL Sequencer. *spa* sequences were analysed using Ridom StaphType software version 2.2.1 (Ridom GmbH, Würzburg, Germany). Sequences were automatically assigned repeats and *spa* types using the software. Clustering of clonal complexes of related *spa* types (Spa-CCs) was performed using the based upon repeat pattern (BURP) algorithm of the Ridom StaphType software and the default settings of the software which exclude *spa* types with less than five repeats and allow a maximum four costs to cluster *spa* types into the same Spa-CC.[3]

Pulsed-field gel electrophoresis (PFGE) and profile analysis

Where necessary to identify strains, PFGE of *Sma*I-digested genomic DNA was performed as previously described.[4] PFGE banding patterns were analysed using BioNumerics software version 7.6 (Applied Maths, St-Martens-Latem, Belgium), with the Dice coefficient and unweighted-pair group method with arithmetic averages, at settings of 0.5% optimisation and 1.5% position tolerance. PFGE banding patterns were interpreted using the criteria proposed by Tenover et al.[5]

Multilocus sequence typing (MLST) and sequence analysis

Where necessary to characterise strains, MLST was performed as previously described.[6] Sequences were analysed using BioNumerics software version 7.6 and sequence types (STs) were assigned using the *S. aureus* database accessible at http://saureus.mlst.net/.

Antibiotic susceptibility testing

Antibiotic susceptibility testing was performed where necessary to identify strains and to supplement the susceptibility information provided by referring laboratories. Disc susceptibility testing was performed according to the methods of the Clinical and Laboratory Standards Institute (CLSI).[7] Except for fusidic acid and mupirocin, zones of inhibition were interpreted according to CLSI criteria.[8] Fusidic acid zones of inhibition were determined with a 10 µg disc and interpreted as ≥21 mm susceptible, 20 mm intermediate and ≤19 mm resistant.[9] Mupirocin zones of inhibition were determined with a 5 µg disc and interpreted as ≥14 mm susceptible and ≤13 mm resistant.[10]

Assigning MRSA strains

Isolates were characterised primarily based upon *spa* types and antibiotic susceptibility patterns, with PFGE as a supplementary typing tool where *spa* typing was inconclusive. There were three situations in which *spa* typing was considered inconclusive: (i) when a *spa* type correlated to a known MRSA strain but the antibiotic susceptibility pattern did not; (ii) when an isolate had a novel *spa* type; and (iii) when an isolate had a *spa* type ESR had not yet correlated to an MRSA strain.

Epidemiological analyses

Epidemiological data and test results were entered into ESR's laboratory information management system. Statistical analyses were performed with SAS software v.9.4 (SAS Institute Inc, Cary, NC, United States). Period-prevalence rates were calculated based on the number of MRSA isolated per 100 000 population during the period of the survey. Mid-year New Zealand population estimates were used to calculate these prevalence rates. The chi-square test was used to determine the significance of any observed differences and a *p* value of ≤0.05 was considered significant. 95% confidence intervals were calculated based on Poisson distribution. The statistical significance of time trends was calculated at a 95% confidence level using Poisson regression and the Mantel-Haenszel test for linear trend.

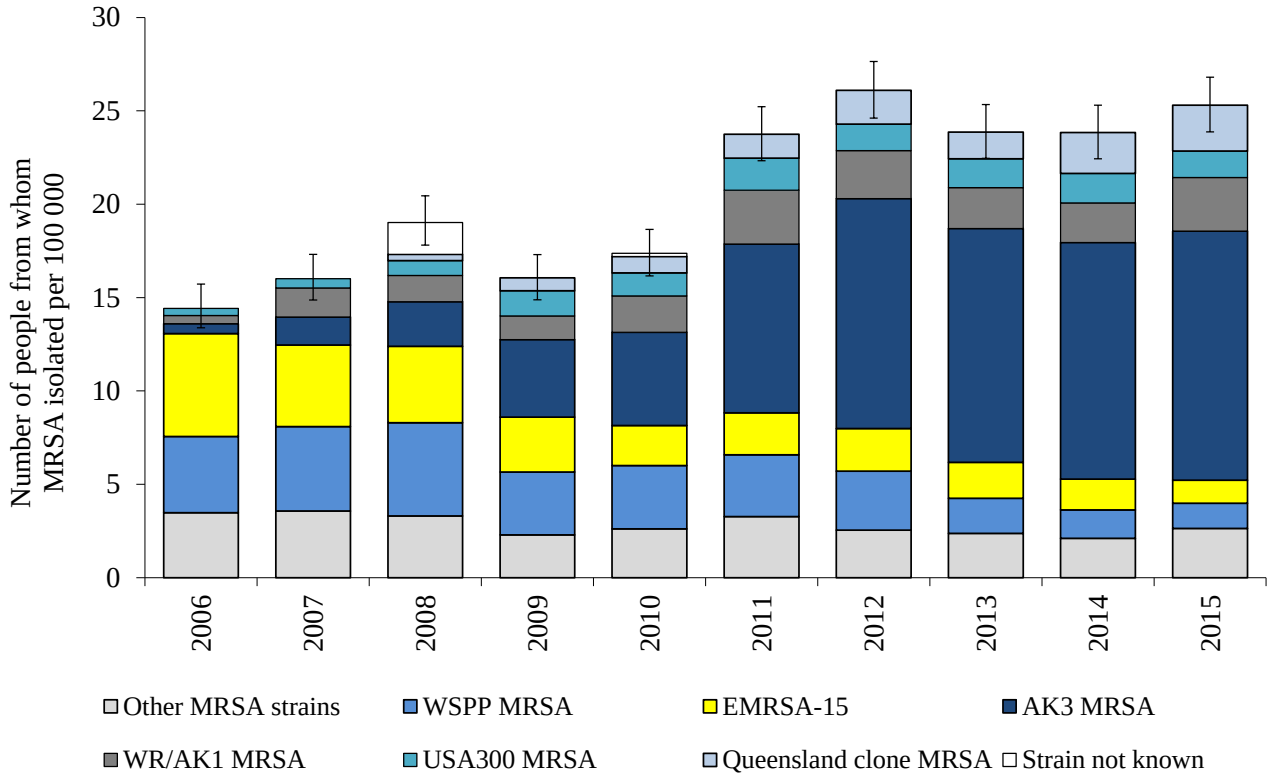
Results

During the period of the 2015 MRSA survey, confirmed MRSA were isolated from 1163 people, 1151 of whom were patients and 12 of whom were staff. All methicillin resistance was mediated by *mecA* with no *mecC* genes detected.

National period-prevalence rates of MRSA, 2006-2015

The MRSA period-prevalence rate in 2015 was 25.3 per 100 000 population, compared with a rate of 23.8 recorded for the 2014 survey. While over the last 10 years, 2006 to 2015, the period-prevalence rate has increased 77% from 14.3 to 25.3 per 100 000, there has been little change since 2011 (Figure 1).

Figure 1. MRSA period-prevalence rates, 2006-2015



95% confidence intervals indicated by error bars. The category 'Strain not known' for 2008 and 2010 (the latter barely visible at the top of the bar for 2010) represents people identified with MRSA during the survey period but from whom no isolate was referred for strain identification.

MRSA infection status, strain prevalence, and strain association with healthcare facilities versus the community and with patient age

In 2015, of the 1151 patients with MRSA, 69.3% were categorised as community patients and 30.7% as hospital patients. 73.4% of the MRSA isolated from patients were from skin and soft tissue infection (SSTI) and 18.5% were from screening swabs. Just 1.1% of MRSA were isolated from an invasive site.

Six MRSA strains (AK3 MRSA, WR/AK1 MRSA, Queensland clone MRSA, USA300 MRSA, WSPP MRSA and EMRSA-15) were predominant in 2015 and collectively represented 89.6% of all MRSA isolations (Table 1).

The dominance of the community-associated AK3 MRSA strain evident in recent years continued in 2015. This strain has accounted for around 50% (range 47.2-53.2%) of the MRSA included in each survey since 2012 (Figure 1). Conversely, the decline of the former most prevalent community-associated MRSA (CA-MRSA) strain in New Zealand, WSPP MRSA, has continued with this strain representing just 5.3% of MRSA in 2015 compared with 28.5% a decade ago (Figure 1). Similarly the healthcare-associated EMRSA-15 strain has been in decline over the last 10 years, decreasing from 38.4% of MRSA in 2006 to just 4.9% in 2015 (Figure 1).

Table 1. MRSA strain prevalence, association with healthcare facilities versus community, and association with patient age, 2015

Strain[a]	Proportion (%) of all MRSA isolations[b]	Proportion (%) of each strain isolated from:		
		hospital patients or staff	people in the community	patients ≥60 years of age[c]
AK3 MRSA [ST5, SCC*mec* type IV][d]	52.7	27.2	72.8	19.9
WR/AK1 MRSA [ST1, SCC*mec* type IV]	11.4	31.8	68.2	26.0
Queensland clone MRSA [ST93, SCC*mec* type IV]	9.7	31.0	69.0	10.6
USA300 MRSA [ST8, SCC*mec* type IV]	5.6	38.5	61.5	44.6
WSPP MRSA [ST30, SCC*mec* type IV]	5.3	27.4	72.6	13.1
EMRSA-15 [ST22, SCC*mec* type IV]	4.9	54.4	45.6	74.1

a Further information on each of these strains is available at: http://www.esr.cri.nz/assets/HEALTH-CONTENT/Images-and-PDFs/MRSAdescriptions.pdf.

b Other strains accounted for the remaining 10.4% of MRSA.

c Age distribution for patients only, staff not included.

d ST, multilocus sequence type; SCC*mec*, staphylococcal cassette chromosome *mec*.

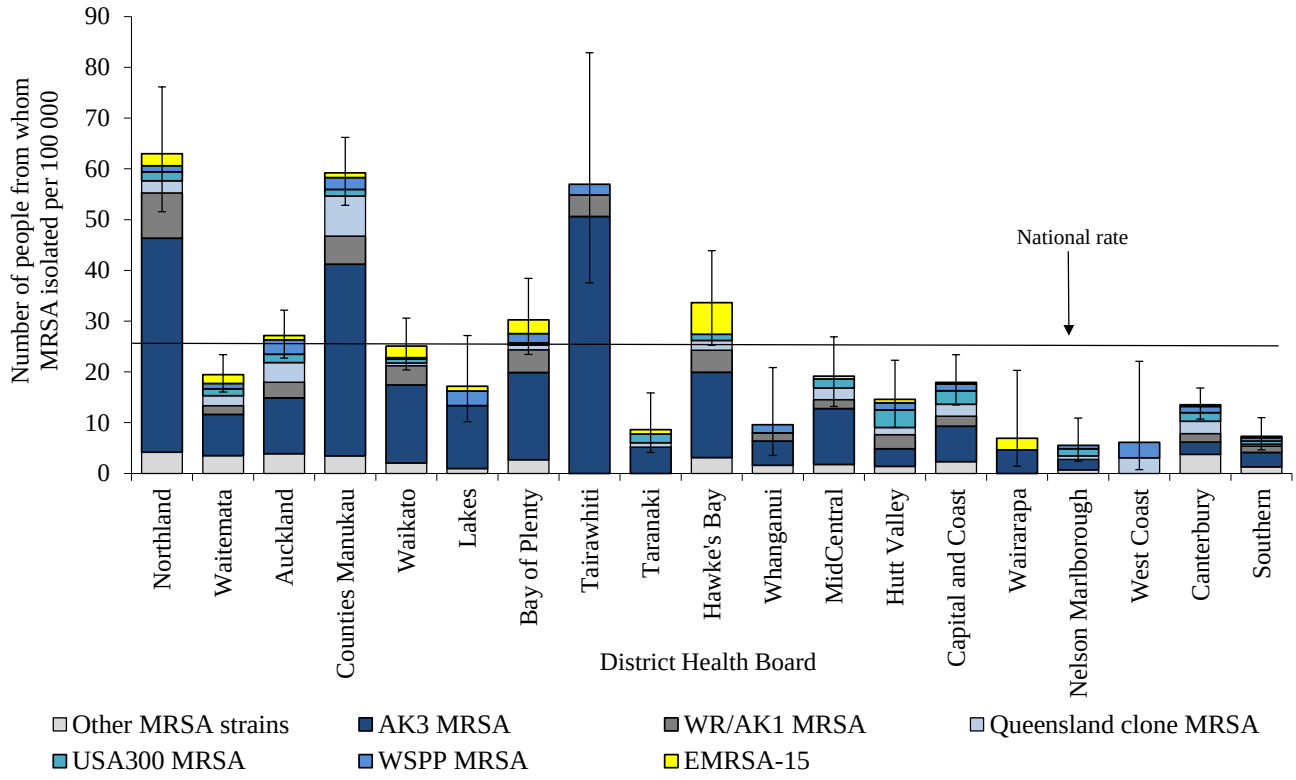
Geographic distribution of MRSA

There were significant geographical differences in the period-prevalence rates of MRSA isolations in 2015. Rates exceeded the national rate of 25.3 people with MRSA per 100 000 population in six district health boards (DHBs): Northland (63.0 per 100 000), Counties Manukau (59.2), Tairawhiti (57.0), Hawke's Bay (33.6), Bay of Plenty (30.2) and Auckland (27.1) (Figure 2).

When MRSA isolated from clinical specimens only were analysed (ie, screening specimens were excluded), similar geographical differences in the period-prevalence rates were evident, with rates in the same six DHBs, and one additional DHB (Waikato), being higher than the national period-prevalence rate of 20.4 people with MRSA from a clinical specimen per 100 000 population: Northland (55.9 per 100 000), Counties Manukau (38.7), Tairawhiti (38.0), Hawke's Bay (28.0), Bay of Plenty (26.6), Auckland (24.5) and Waikato (21.8) (Figure 3).

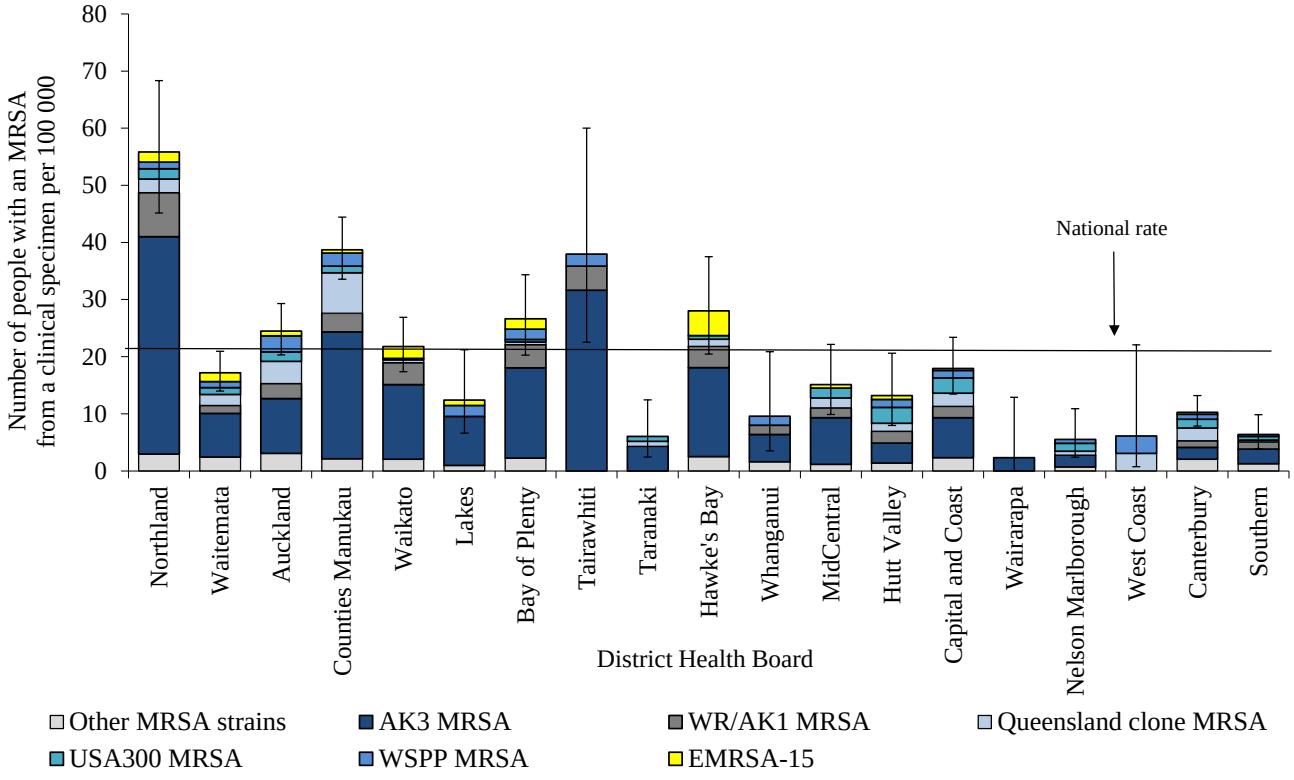
AK3 MRSA was the most prevalent MRSA strain in all DHBs except Hutt Valley, West Coast and Canterbury. In Hutt Valley DHB, AK3 MRSA and USA300 MRSA were the two equal most prevalent strains, and in the Canterbury region, AK3 MRSA and Queensland clone MRSA were the two equal most prevalent strains.

Figure 2. MRSA period-prevalence rates by district health board, 2015



95% confidence intervals indicated by error bars. Data for the Canterbury and South Canterbury DHBs are combined as 'Canterbury'.

Figure 3. Period-prevalence rates for MRSA from clinical specimens, by district health board, 2015

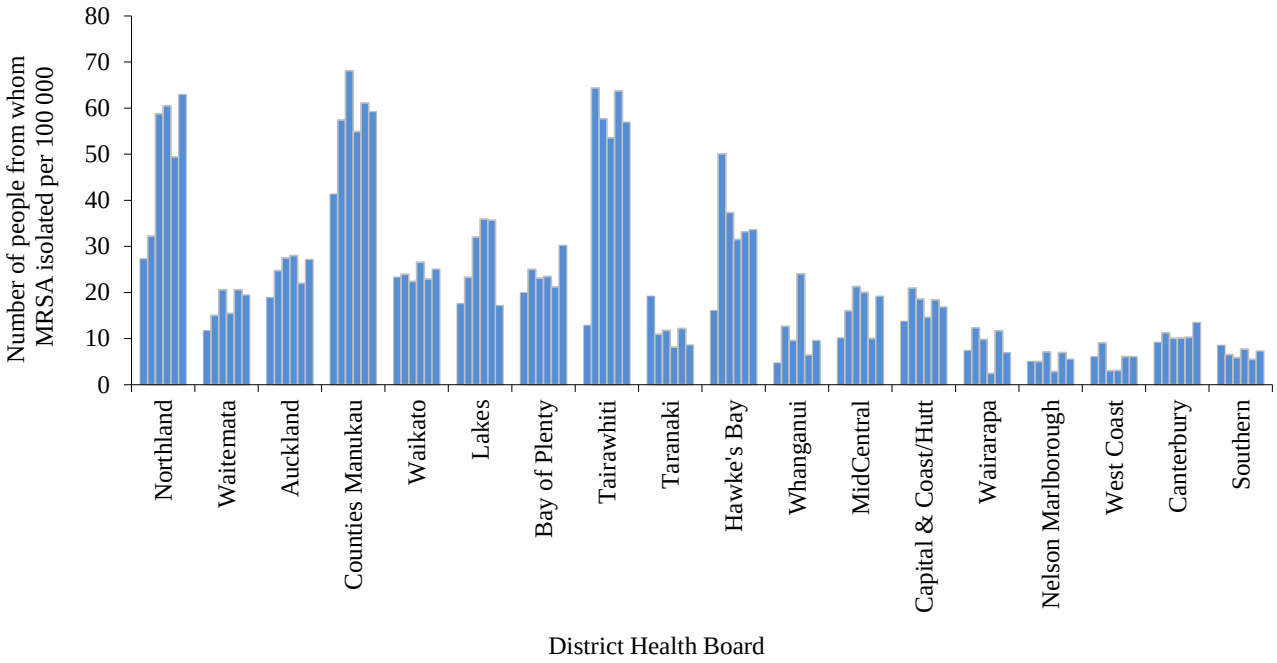


95% confidence intervals indicated by error bars. Data for the Canterbury and South Canterbury DHBs are combined as 'Canterbury'.

Period-prevalence rates of MRSA by DHB, 2010-2015

Over the 6-year period 2010 to 2015, there was a statistically significant trend of increasing MRSA prevalence in the Northland DHB and increases of borderline statistical significance in the Waitemata, Counties Manukau and Tairawhiti DHBs (Figure 4).

Figure 4. MRSA period-prevalence rates by district health board, 2010-2015



The series of bars for each DHB represent the individual years 2010 to 2015 from left to right. Data for the Capital & Coast and Hutt DHBs are combined as 'Capital & Coast/Hutt', and data for the Canterbury and South Canterbury DHBs are combined as 'Canterbury'.

MRSA strain association with spa *types*

The AK3 MRSA strain was most commonly associated with *spa* type t002, WR/AK1 MRSA with t127, the Queensland clone MRSA with t3949, USA300 MRSA with t008, WSPP MRSA with t019, and EMRSA-15 with t032 (Table 2). However, several other *spa* types were also identified among isolates of each of these MRSA strains. The *spa* types associated with any one strain usually belonged to the same *spa* clonal cluster, which indicates that they are closely related when analysed by the BURP algorithm.

Table 2. *spa* types of the six most prevalent MRSA strains in 2015

Strain	Number of isolates of the strain	*spa* clonal cluster	*spa* type[a]	Number of isolates of the *spa* type
AK3 MRSA [ST5, SCC*mec* type IV][b]	612[c]	Spa-CC002	t002	522
			t045	16
			t548	9
			t088	7
			t6787	6
			t105	4
			t062	3
			t179	3
			t214	3
			t306	3
			t311	3
			t1265	3
			t1781	3
			t010	2
			t509	2
			t688	2
			t856	2
			t1062	2
			t2069	2
			t5213	2
		Excluded[d]	t1781	3
WR/AK1 MRSA [ST1, SCC*mec* type IV]	131[e]	Spa-CC127	t127	94
			t267	24
Alternative name: Western Australia (WA) MRSA-1			t359	4
Queensland clone MRSA [ST93, SCC*mec* type IV]	113	Spa-CC202	t3949	81
			t202	23
			t4178	3
USA300 MRSA [ST8, SCC*mec* type IV]	65	Spa-CC008	t008	50
			t024	5
			t1767	3

Table 2 continued next page

Table 2. *spa* types of the six most prevalent MRSA strains in 2015 *continued*

Strain	Number of isolates of the strain	*spa* clonal cluster	*spa* type[a]	Number of isolates of the *spa* type
WSPP MRSA [ST30, SCC*mec* type IV]	62	Spa-CC019	t019	51
			t021	3
Alternative names: Southwest Pacific clone and Oceania clone			t1752	2
EMRSA-15 [ST22, SCC*mec* type IV]	57	Spa-CC032	t032	37
			t022	4
			t020	3
			t852	2

a The *spa* types are only listed in the table if there were ≥2 isolates of the type. In addition to the *spa* types listed in the table:

among the AK3 MRSA isolates there was also 1 isolate of each of the following *spa* types: t067, t242, t539, t568, t570, t1107, t2065, t2066, t5607, t8428, t9197, t15447 and t15504;

among the WR/AK1 MRSA isolates there was also 1 isolate of each of the following *spa* types: t386, t559, t591, t693, t701, t1175, t3636, t14122 and t15058;

among the Queensland clone MRSA isolates there was also 1 isolate of each of the following *spa* types: t4699, t11037, t14922, t15361, t15446 and t15506;

among the USA300 MRSA isolates there was also 1 isolate of each of the following *spa* types: t955, t2063, t2229, t2849, t4919, t15180 and t15465;

among the WSPP MRSA isolates there was also 1 isolate of each of the following *spa* types: t975, t1749, t2208, t5045, t14599 and t15364; and

among the EMRSA-15 MRSA isolates there was also 1 isolate of each of the following *spa* types: t223, t309, t379, t891, t1214, t1733, t1821, t3151, t5785, t12550 and t15362.

b ST, multilocus sequence type; SCC*mec*, staphylococcal cassette chromosome *mec*.

c The total number of AK3 MRSA isolates was 613, but the *spa* type of 1 isolate could not be determined and therefore this isolate was identified solely by PFGE typing.

d An excluded *spa* type does not have sufficient repeat sequences (ie, <5 repeats) to validly include it in the based upon repeat pattern (BURP) cluster analysis.

e The total number of WR/AK1 MRSA isolates was 132, but the *spa* type of 1 isolate could not be determined and therefore this isolate was identified solely by PFGE typing.

In addition to the six most prevalent MRSA strains listed in Table 2, isolates of several other recognized MRSA strains were identified. These included:

- 13 isolates of the Bengal Bay MRSA clone (ST772, SCC*mec* type V);
- 5 isolates of the CC398 MRSA clone (CC398, SCC*mec* type V);
- 1 isolate of the AKh4 MRSA strain (ST239, SCC*mec* type III); and
- 1 isolate of the WA MRSA-2 strain (ST78, SCC*mec* type IV).

The Bengal Bay MRSA clone is a multiresistant MRSA, typically resistant to ciprofloxacin, erythromycin and gentamicin. It also carries the genes for several virulence factors including the PVL genes and the enterotoxin gene cluster. The Bengal Bay clone is usually isolated from people who have travelled to India or Bangladesh, or have other associations, such as family connections, with this region.

CC398 MRSA is a livestock-associated MRSA which was originally identified in pigs in Northern European countries and first identified in New Zealand during the 2011 MRSA survey. Since then, CC398 MRSA has been isolated from several people involved in pig farming or the abattoir industry in the Canterbury region. All the isolates from these people have been *spa* type t011. The other common *spa* type among CC398 MRSA in New Zealand is t034, with isolates of this *spa* type mainly identified from people who appear to have acquired this MRSA strain overseas, especially in Asia. None of the five CC398 MRSA isolates identified in the 2015 survey were from people known to have direct contact with farm animals in New Zealand. One of the five isolates was *spa* type t034 and was from a person who had recently travelled in Asia. The other four isolates were all *spa* type t011 and from North Island patients, but no risk factor information was received for any of these patients.

The AKh4 MRSA is a healthcare-associated MRSA (HA-MRSA) strain that is multiresistant to ciprofloxacin, clindamycin, co-trimoxazole, erythromycin, gentamicin and tetracycline. This strain is a common cause of HA-MRSA infections in many parts of the world including some states of Australia. Its prevalence in New Zealand has decreased in recent years, but it still occasionally causes small outbreaks in healthcare facilities.

WA MRSA-2 is a non-multiresistant, typically PVL-negative, CA-MRSA strain. It was originally recognized in Western Australia, where is still accounts for an appreciable proportion of CA-MRSA.[11]

There were 101 isolates that were not associated with a recognized MRSA strain, and the most common *spa* type among these isolates was t437 (19 isolates). There were ≤6 isolates of any other *spa* type not associated with a known MRSA strain.

PVL prevalence and association with MRSA strains and spa *types*

Among the common MRSA strains, isolates of the Queensland clone, USA300 and WSPP MRSA strains were usually PVL positive, whereas isolates of AK3 MRSA were usually PVL negative (Table 3). In contrast, PVL was very variable among isolates of the WR/AK1 MRSA strain and to a lesser extent among isolates of the EMRSA-15 strain. Notably any PVL-positive EMRSA-15 isolates belonged to *spa* types that were exclusively associated with isolates that were PVL positive, and these *spa* types included t309, t852, t891 and t1821.

The prevalence of PVL was significantly lower among MRSA from patients <5 years of age than among MRSA from older patients (14.7 vs 34.0%, p <0.001) (Table 3). This difference was in large part due to the fact that the usually PVL-negative AK3 MRSA strain was most prevalent among MRSA isolated from <5 year olds, accounting for 74.2% of MRSA in this age group.

The prevalence of PVL among MRSA isolated from SSTI was significantly higher than among MRSA isolated from screening swabs (35.5 vs 16.0%, p <0.001) (Table 3). Similarly, MRSA from infected sites were more likely to be PVL positive than those from colonised sites (34.3 vs 16.4%, p <0.001).

Table 3. PVL prevalence by MRSA strain, patient demographics and site of isolation

	Percent (number) PVL positive	
All isolates (n=1163)	30.1	(350)
MRSA strain		
AK3 MRSA (n=613)	0.7	(4)
WR/AK1 MRSA (n=132)	61.4	(81)
Queensland clone MRSA (n=113)	98.2	(111)
USA300 MRSA (n=65)	93.8	(61)
WSPP MRSA (n=62)	93.5	(58)
EMRSA-15 (n=57)	8.8	(5)
Patient age group (years)		
<5 (n=225)	14.7	(33)
5-14 (n=150)	22.7	(34)
15-24 (n=127)	44.1	(56)
25-64 (n=409)	40.3	(165)
≥65 (n=240)	25.0	(60)
Hospitalisation history of patients		
Hospital patient (n=353)	28.9	(102)
Community patient (n=798)	30.8	(246)
Site of isolation[a]		
SSTI (n=845)	35.5	(300)
Other non-screening sites (n=93)	15.1	(14)
Screening site (n=213)	16.0	(34)

a Only MRSA from patients included, that is, MRSA from staff excluded.

Discussion

Based on data from these annual national MRSA surveys, the period-prevalence rate of MRSA isolation has remained relatively stable over the past 5 years: 23.7 per 100 000 population in 2011 and 25.3 per 100 000 in 2015. Similarly, data collected by ESR from diagnostic laboratories in New Zealand, indicates that the proportion of *S. aureus* that are MRSA has been stable over this same time period, ranging between 10.1% and 10.4% during the years 2011 to 2014 (the latest year data is currently available for).[12] However, as has been consistently recorded, there are significant geographic variations in MRSA prevalence throughout New Zealand.

The AK3 ST5-IV clone, which is characterised by a high rate of fusidic acid resistance,[13,14] has been the most common MRSA clone in New Zealand for the last 7 years, and in 2015 accounted for over half of all MRSA. Interestingly a national survey of antimicrobial susceptibility among clinical isolates of *S. aureus* undertaken by ESR in 2014 also found there was a high rate of 95% fusidic acid resistance among the most common methicillin-susceptible *S. aureus* clone (MLST CC1, *spa* type t127) in New Zealand.[13]

While the AK3 MRSA strain continues to predominate in New Zealand, there have been some notable changes in the relative prevalence of other MRSA clones. The prevalence of the healthcare-associated EMRSA-15 strain has now shrunk to 5%, after consistently accounting for over a third of the MRSA in the surveys conducted each year between 2001 and 2006. Correspondingly, the proportion of patients categorised as community patients as opposed to hospital patients, according to the definitions we have consistently used for these surveys, has been increasing in recent years from about 50% in the mid-2000s to 69% in 2015. MRSA clones recognised first and foremost as CA-MRSA accounted for 85% of the MRSA in this year's survey.

The 2014 MRSA survey provided for the first time some additional molecular information about MRSA in New Zealand, with all isolates included in the survey being screened for the *mecC* gene and PVL toxin.[15] This testing was repeated again in the 2015 survey with very similar results.

MRSA with *mecC*-encoded, rather than the usual *mecA*-encoded, methicillin resistance have now been reported in many European countries, from a diverse range of human and animal hosts, and from a range of *S. aureus* clonal lineages but predominantly CC130.[16] Recently the first identification of *mecC* in *S. aureus* in Australia was reported.[17] The isolate was from a specimen taken from a domestic cat in 2013 in the state of Victoria. As for the 2014 MRSA survey, we did not identify any MRSA isolates harbouring *mecC* in this year's survey, and, to the best of our knowledge, *mecC* has not been identified among *S. aureus* in New Zealand to date. Characteristically MRSA with *mecC* will test as oxacillin susceptible but cefoxitin resistant in standard antimicrobial susceptibility tests, and will be negative in tests for PBP2a.

The overall prevalence of PVL found in this survey (30.1%) was very similar to that found among the MRSA included in the 2014 MRSA survey (29.7%).[15] The association between the presence of PVL genes and each of the common MRSA strains was as previously established, although there was a little more variation within a strain than previously found. For example in 2014, all isolates of the Queensland clone MRSA were PVL positive whereas two isolates in this year's survey were PVL negative. Of note, MRSA isolated from SSTI

were significantly more likely to be PVL positive than MRSA isolated from screening specimens.

In conclusion, the prevalence and molecular epidemiology of MRSA in New Zealand has been relatively stable in recent years.

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