Annual survey of methicillin-resistant *Staphylococcus aureus* (MRSA), 2014

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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 2014 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 2014 to ESR. The Microbiology Laboratory, Whangarei Hospital; Microbiology Laboratory, Hutt Hospital; and Canterbury Southern Community Laboratories referred isolates during a 31-day period between mid-August and mid-October 2014. All remaining laboratories referred MRSA during August 2014.

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 6.6 (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 6.6 and sequence types (STs) were assigned using the *S. aureus* database accessible at http://www.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.9.3 (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.

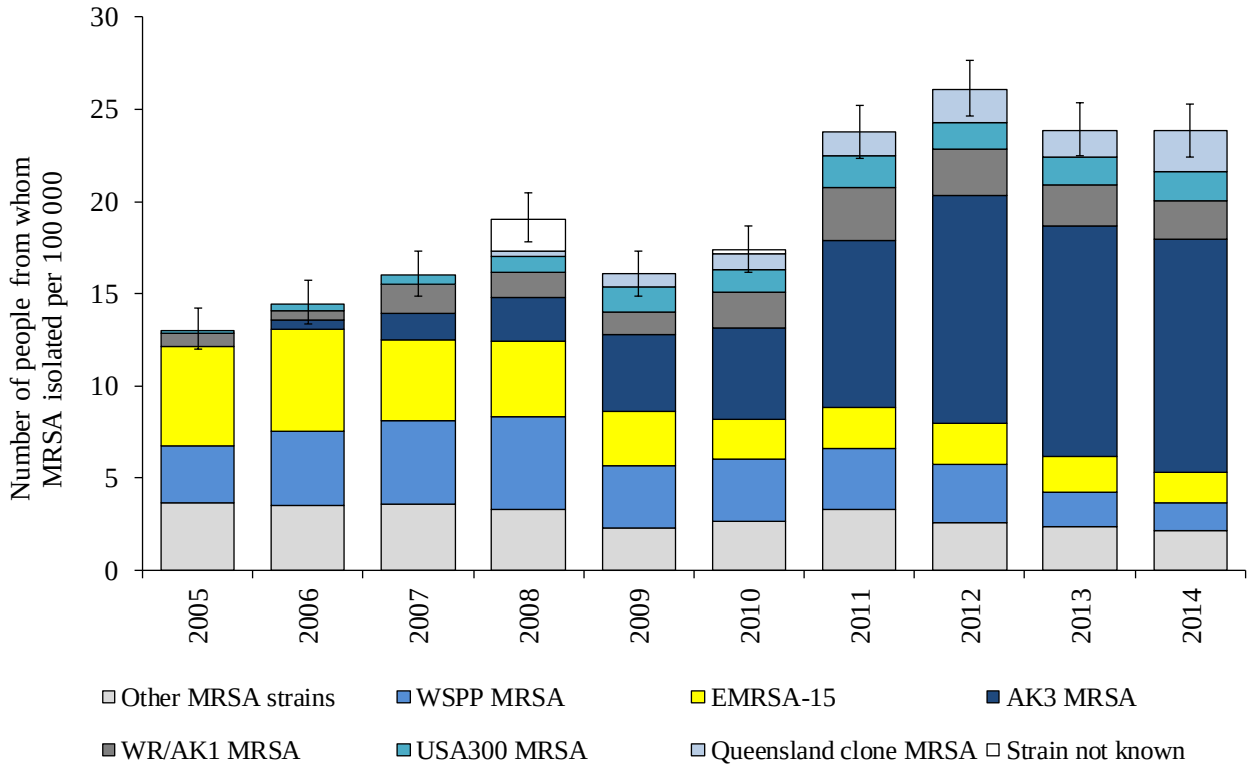
Results

During the period of the 2014 MRSA survey, confirmed MRSA were isolated from 1076 people, 1067 of whom were patients and 9 of whom were staff. All methicillin resistance was mediated by *mecA* with no *mecC* genes detected.

National period-prevalence rates of MRSA, 2005-2014

The MRSA period-prevalence rate in 2014, 23.8 per 100 000 population, was very similar to the rate of 23.9 recorded for the 2013 survey. While over the last 10 years, 2005 to 2014, the period-prevalence rate has increased 85% from 12.9 to 23.8 per 100 000, there has been little change since 2011 (Figure 1).

Figure 1. MRSA period-prevalence rates, 2005-2014



95% confidence intervals indicated by error bars. The category 'Strain not known' for 2008 and 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 2014, of the 1067 patients with MRSA, 61.4% were categorised as community patients and 38.6% as hospital patients. 68.9% of the MRSA isolated from patients were from skin and soft tissue infection (SSTI) and 21.1% were from screening swabs. Less than 1% of MRSA were isolated from an invasive site.

Six MRSA strains (AK3 MRSA, Queensland clone MRSA, WR/AK1 MRSA, EMRSA-15, USA300 MRSA and WSPP MRSA) were predominant in 2014 and collectively represented 91.2% of all MRSA isolations (Table 1). The dominance of the community-associated AK3 MRSA strain evident in recent years continued in 2014 with this strain accounting for 53.2% of all MRSA included in the survey. Conversely, the decline of the former most prevalent community-associated MRSA (CA-MRSA) strain in New Zealand, WSPP MRSA, continued in 2014 with this strain representing just 6.4% of MRSA in the 2014 survey (Figure 1).

Table 1. MRSA strain prevalence, association with healthcare facilities versus community, and association with patient age, 2014

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]	53.2	33.0	67.0	17.4
Queensland clone MRSA [ST93, SCC*mec* type IV]	9.2	33.3	66.7	12.1
WR/AK1 MRSA [ST1, SCC*mec* type IV]	8.9	46.9	53.1	37.2
EMRSA-15 MRSA [ST22, SCC*mec* type IV]	6.9	62.2	37.8	83.8
USA300 MRSA [ST8, SCC*mec* type IV]	6.6	52.1	47.9	56.3
WSPP MRSA [ST30, SCC*mec* type IV]	6.4	40.6	59.2	20.3

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 8.8% of MRSA.
c Age distribution for patients only, staff not included.
d ST, multilocus sequence type; SCC*mec*, staphylococcal cassette chromosome *mec*.

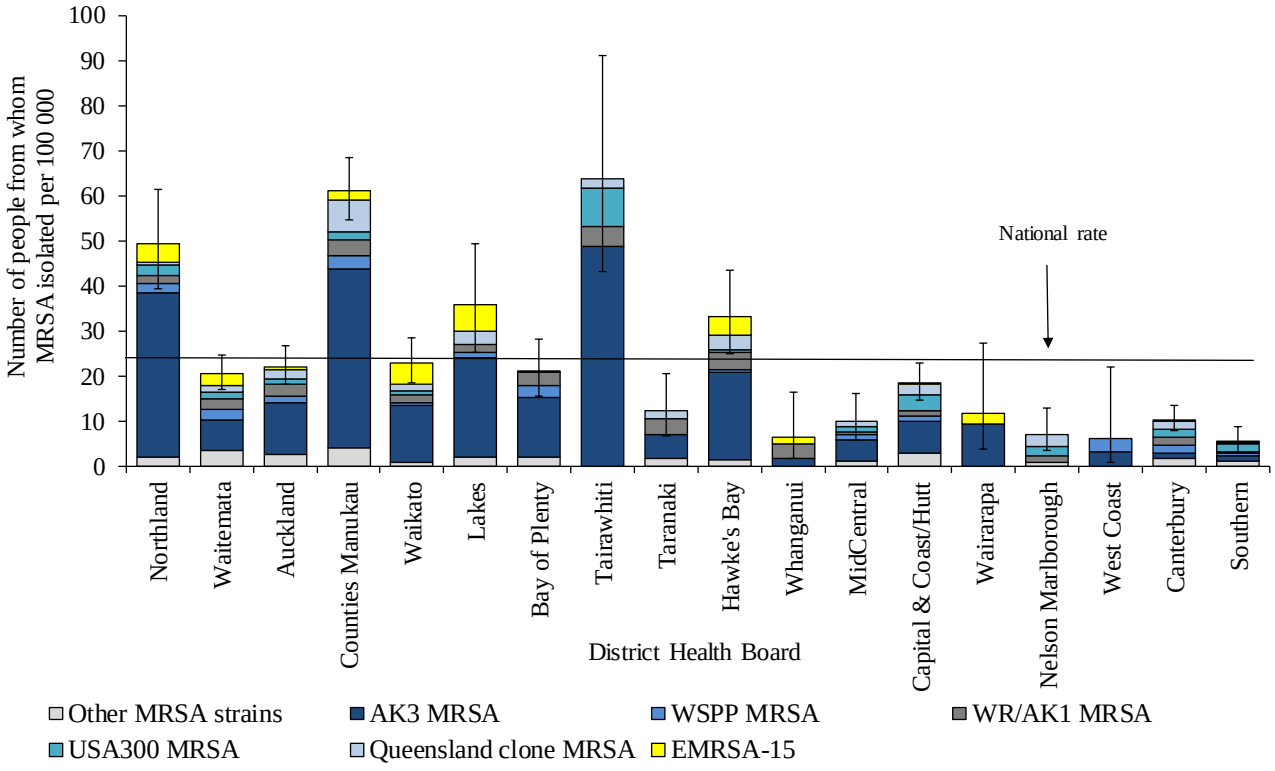
Geographic distribution of MRSA

There were significant geographical differences in the period-prevalence rates of MRSA isolations in 2014. Rates exceeded the national rate of 23.8 people with MRSA per 100 000 population in five district health boards (DHBs): Tairawhiti (63.7 per 100 000), Counties Manukau (61.1), Northland (49.4), Lakes (35.7) and Hawke's Bay (33.2) (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 five DHBs being significantly higher than the national period-prevalence rate of 18.7 people with MRSA from a clinical specimen per 100 000 population: Tairawhiti (59.4 per 100 000), Northland (44.6), Counties Manukau (33.8), Lakes (31.9) and Hawke's Bay (29.5) (Figure 3).

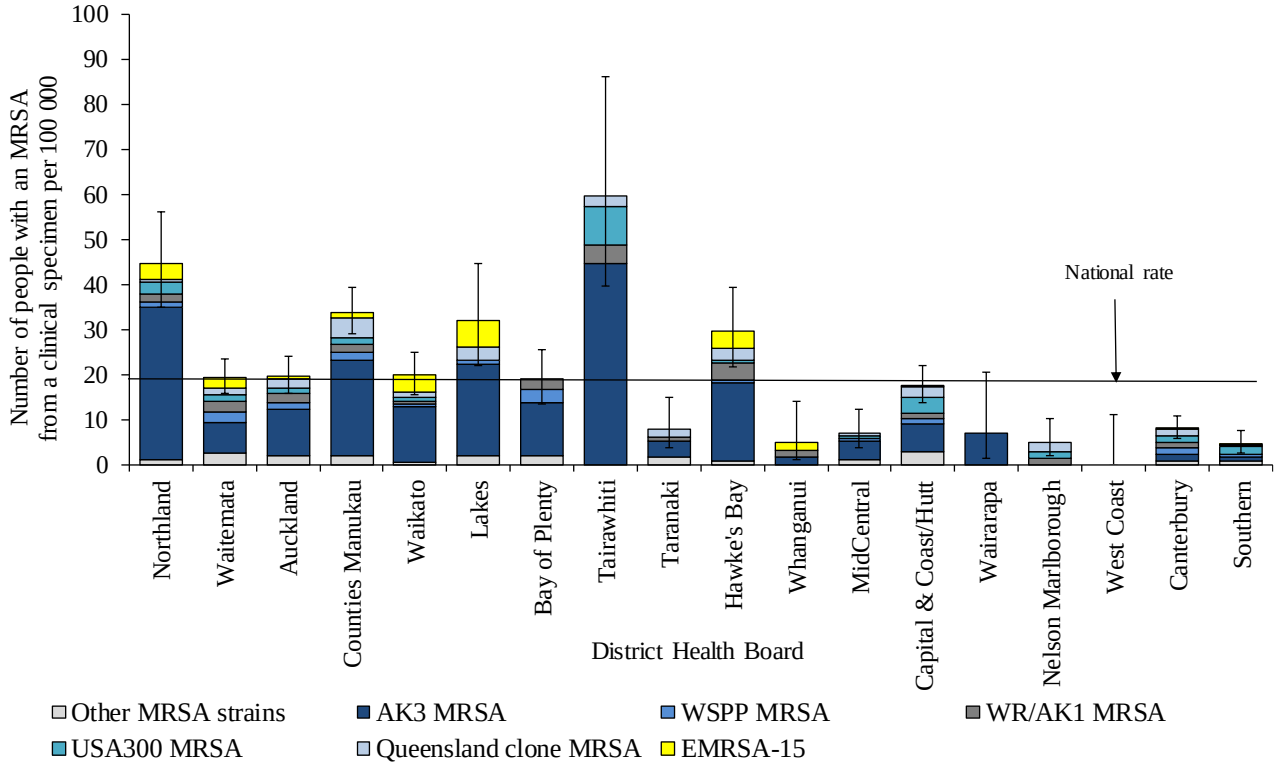
AK3 MRSA was the most prevalent MRSA strain in all North Island DHBs except Whanganui.

Figure 2. MRSA period-prevalence rates by district health board, 2014



95% confidence intervals indicated by error bars. 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'.

Figure 3. Period-prevalence rates for MRSA from clinical specimens, by district health board, 2014

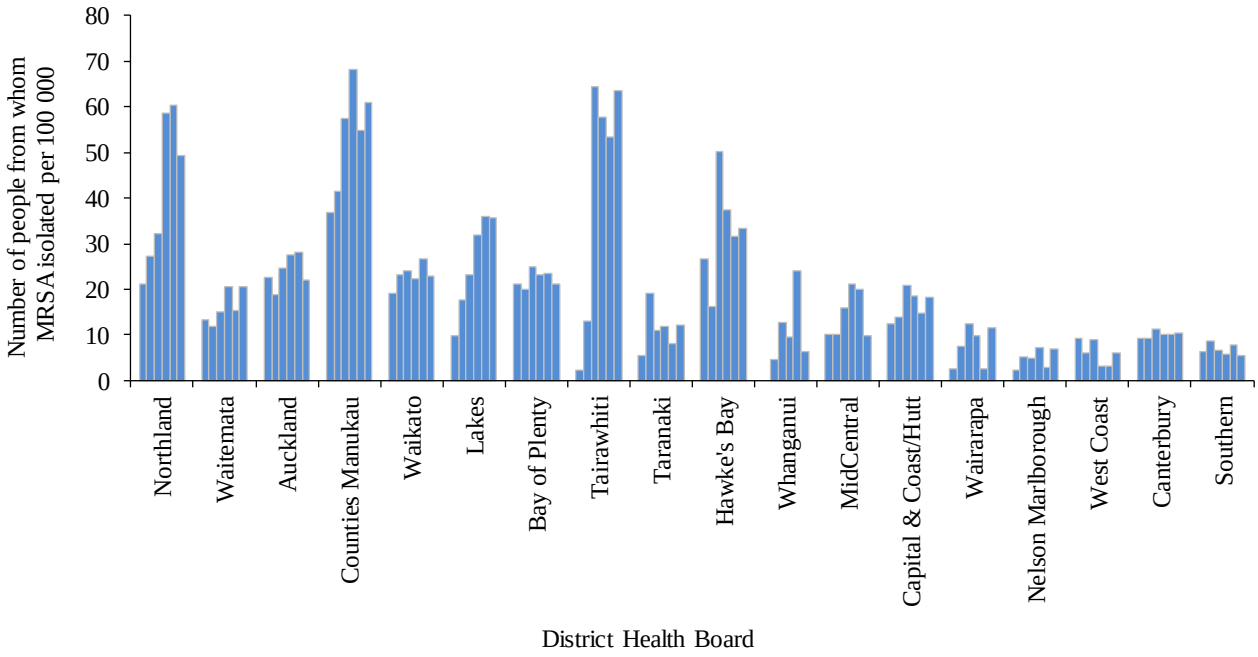


95% confidence intervals indicated by error bars. Data for the Capital & Coast and Hutt DHBs are combined as 'Capital & Coast/Hutt', and data for the Canterbury and South Canterbury DHBs are combined as 'Canterbury'.

Period-prevalence rates of MRSA by DHB, 2009-2014

Over the six-year period 2009 to 2014, there were statistically significant increases in MRSA period-prevalence rates in 6 of the 18 DHBs/DHB combinations analysed. These DHBs were, ordered from the DHB with the largest increase to that with the smallest increase: Tairawhiti, Northland, Lakes, Counties Manukau, Whanganui and Waitemata (Figure 4).

Figure 4. MRSA period-prevalence rates by district health board, 2009-2014



The series of bars for each DHB represent the individual years 2009 to 2014 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, the Queensland clone MRSA with t3949, WR/AK1 MRSA with t127, EMRSA-15 with t032, USA300 MRSA with t008 and WSPP MRSA with t019 (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 most six most prevalent MRSA strains in 2014

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]	570[c]	Spa-CC002	t002	479
			t548	15
			t045	10
			t5213	6
			t088	5
			t306	5
			t311	5
			t242	4
			t6787	4
			t062	3
			t214	3
			t1062	3
			t010	2
			t067	2
			t539	2
			t1265	2
		Excluded[d]	t535	2
			t1781	2
Queensland clone MRSA [ST93, SCC*mec* type IV]	99	Spa-CC202	t3949	74
			t202	15
			t4699	4
			t6487	2
			t11037	2
WR/AK1 MRSA [ST1, SCC*mec* type IV]	96	Spa-CC127	t127	73
			t267	9
			t359	2
Alternative name: Western Australia (WA) MRSA-1			t591	2
			t1418	2
		Spa-CC008	t701	4

Table 2 continued next page

Table 2. *spa* types of the most six most prevalent MRSA strains in 2014 *continued*

Strain	Number of isolates of the strain	*spa* clonal cluster	*spa* type[a]	Number of isolates of the *spa* type
EMRSA-15 [ST22, SCC*mec* type IV]	70[e]	Spa-CC032	t032	43
			t5538	5
			t005	3
			t022	3
			t309	2
			t646	2
			t852	2
			t3107	2
USA300 MRSA [ST8, SCC*mec* type IV]	70[f]	Spa-CC008	t008	61
			t024	6
			t1767	2
WSPP MRSA [ST30, SCC*mec* type IV]	69	Spa-CC019	t019	53
			t021	4
Alternative names: Southwest Pacific clone and Oceania clone			t138	2
			t1752	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: t179, t586, t668, t688, t856, t1084, t1154, t2069, t4323, t5607, t6398, t7348, t10308, t13228, t14303 and t14305;

among the Queensland clone MRSA isolates there was also 1 isolate of each of the following *spa* types: t4178 and t14035;

among the WR/AK1 MRSA isolates there was also 1 isolate of each of the following *spa* types: t386, t1236, t2279 and t14302;

among the EMRSA-15 MRSA isolates there was also 1 isolate of each of the following *spa* types: t020, t628, t1370, t1401, t1433, t2159, t5501 and t7428;

among the USA300 MRSA isolates there was also 1 isolate of *spa* type t1627; and

among the WSPP MRSA isolates there was also 1 isolate of each of the following *spa* types: t122, t975, t2208, t3812, t4224, t4672, t5783 and t14307.

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

c The total number of AK3 MRSA isolates was 572, but the *spa* type of 2 isolates could not be determined and therefore these isolates were 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 EMRSA-15 isolates was 74, but the *spa* type of 4 isolates could not be determined and therefore these isolates were identified solely by PFGE typing.

f The total number of USA300 MRSA isolates was 71, 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:

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

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.

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 a family connections, with this region.

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.

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. Neither of the two CC398 MRSA isolates identified in the 2014 survey were from people who had direct contact with farm animals in New Zealand or overseas. However, one patient lived on a rural Canterbury property, and the other patient was a chef who handled raw meat, including pork, most days and whose MRSA was isolated from a finger wound.

There were 85 isolates that were not associated with a recognized MRSA strain, and the most common *spa* types among these isolates were t1853 (11 isolates) and t976 (6 isolates). There were <3 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 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 t005, t309 and t3107.

The prevalence of PVL was significantly lower among MRSA from patients <5 years of age than among MRSA from older patients (14.7 vs 33.1%, p <0.001). This difference was in large part due to the fact that the PVL-negative AK3 MRSA strain was most prevalent among MRSA isolated from <5 year olds, accounting for 76.4% 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 (34.6 vs 21.3%, 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 20.1%, p <0.001).

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

	Percent (number) PVL positive	
All isolates (n=1076)	29.7	(319)
MRSA strain		
AK3 MRSA (n=572)	0.4	(2)
Queensland clone MRSA (n=99)	100	(99)
WR/AK1 MRSA (n=96)	59.4	(57)
EMRSA-15 (n=74)	14.9	(11)
USA300 MRSA (n=71)	97.2	(69)
WSPP MRSA (n=69)	91.3	(63)
Patient age group (years)[a]		
<5 (n=191)	14.7	(28)
5-14 (n=139)	25.9	(36)
15-24 (n=110)	38.2	(42)
25-64 (n=374)	38.2	(143)
≥65 (n=252)	27.4	(69)
Hospitalisation history of patients		
Hospital patient (n=412)	30.6	(126)
Community patient (n=655)	29.3	(192)
Site of isolation[b]		
SSTI (n=735)	34.6	(254)
Other non-screening sites (n=107)	15.0	(16)
Screening site (n=225)	21.3	(48)

a The age of 1 patient was not known.
b Only MRSA from patients included, that is, MRSA from staff excluded.

Discussion

Based on data from New Zealand's annual MRSA surveys, the period-prevalence rate of MRSA isolation has remained relatively stable over the past four years: 23.7 per 100 000 population in 2011 and 23.8 per 100 000 in 2014. The AK3 ST5-IV clone, which is characterised by a high rate of fusidic acid resistance,[11,12] has been the most common MRSA clone in New Zealand for the last six years and in 2014 accounted for over half of all MRSA.

The 2014 survey provided some additional molecular information about MRSA in New Zealand. For the first time isolates included in an annual MRSA survey were tested for the presence of the *mecC* gene. Methicillin resistance in *S. aureus* is generally conferred by an altered penicillin-binding protein (PBP2a) encoded by the *mecA* gene which is located on a mobile genetic element, known as the staphylococcal chromosome cassette (SCC*mec*).[13] Although several different SCC*mec* types have been described, *mecA* was thought to be highly conserved. However in 2011, a new SCC*mec* type (type XI) was described and it contained a novel *mec* gene, now designated *mecC*.[14] This new gene shares only about 70% nucleotide homology with *mecA*. MRSA with *mecC* 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.[15] Characteristically, MRSA with *mecC* will test as oxacillin susceptible but cefoxitin resistant in standard antimicrobial susceptibility tests. We did not identify any MRSA isolates harbouring *mecC*, but this will be monitored in future annual surveys.

This survey was also the first annual MRSA survey in which all isolates were tested for the presence of the genes that encode the PVL toxin. However, the association between PVL and each of the common MRSA strains in New Zealand has been well established previously. The overall rate of PVL-positive MRSA in this survey (29.7%) is in keeping with the rate found among MRSA included in a recent national survey of all *S. aureus* isolates (25.2%).[11] Interestingly, we found that approximately 15% of EMRSA-15 isolates were PVL positive. While most EMRSA-15 are PVL negative, PVL-positive EMRSA-15, including *spa* type t005, are well described from overseas.[16] Future MRSA surveys will continue to test for PVL genes.

Finally, although the AK3 MRSA strain continues to predominate in our setting, there were some notable changes in the relative prevalence of other MRSA clones. Notably, the WSPP MRSA strain, which was the most common CA-MRSA in New Zealand for nearly two decades, now accounts for only 6% of MRSA. In addition, the ST93 Queensland clone is now the second most common MRSA in New Zealand, accounting for approximately 9% of MRSA. Previous work has suggested that this clone may be more virulent than other common MRSA clones,[17] and consideration should be given to better understanding the emergence and spread of this clone in New Zealand, including high-resolution molecular typing.

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