

SHORT REPORT

Progressive increase in community-associated methicillin-resistant *Staphylococcus aureus* in Indigenous populations in northern Australia from 1993 to 2012

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SUMMARY

Hospital-based studies have determined high rates of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) in Indigenous populations. However, there is a paucity of community-based data. We obtained 20 years (1993–2012) of data on *S. aureus* isolates ($N = 20\ 210$) collected from community clinics that provide services for Indigenous communities in the Northern Territory, Australia. Methicillin resistance increased from 7% to 24%, resistance to macrolides remained stable at ~25%, and there was a slight increase in resistance to trimethoprim-sulfamethoxazole. The increase in methicillin resistance is concerning for the Indigenous communities represented by this data, but it is also of significance if virulent MRSA clones emerge and spread more widely from such settings.

Key words: Antibiotic resistance, community epidemics, methicillin-resistant *S. aureus* (MRSA), trimethoprim-sulfamethoxazole.

The progressive global threat of a rise in antimicrobial-resistant bacteria has been highlighted by the World Health Organization (WHO) [1]. One key pathogen is *Staphylococcus aureus*, which causes clinical infections ranging from skin and soft tissue infections (SSTIs) to invasive bloodstream infections [2]. Methicillin-resistant *S. aureus* (MRSA) that are resistant to β -lactam antibiotics have been common in hospitals since the 1970s. However, at least in industrialized world settings, improved infection control efforts have resulted in reductions in rates of nosocomial MRSA [2].

By contrast, the past 20 years has seen a new wave of resistance in community-associated (CA) *S. aureus* [3].

Most evident in the USA with the rapid rise of the USA300 clone, CA-MRSA has also been widely reported globally [3]. The first reports of CA-MRSA were in Australian Indigenous populations in the early 1990s [4] and subsequent studies have noted the continued prevalence of CA-MRSA in Australian Indigenous populations [5]. Hospital-based surveillance studies of Australian community-onset *S. aureus* have consistently found that rates of CA-MRSA are highest in regions with large proportions of Indigenous people [6]. However, there is a paucity of longitudinal community-based data. The reliance on hospital-based resistance data has been identified by the WHO as a key limitation of surveillance reports [1].

We gathered 20 years of data on *S. aureus* isolations from the main community-based pathology provider for the Northern Territory (NT), Australia. The NT is 1 349 129 km² (520 902 square miles) and has a

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current population of ~220 000 of whom ~30% are Indigenous. We aimed to describe trends in *S. aureus* resistance to methicillin and other antibiotics used for treatment of community *S. aureus* infections.

This study was approved by the Human Research Ethics Committee of the NT Department of Health (HREC 13–2031).

We obtained data through a query of the microbiology database from Western's Diagnostic Pathology (the key provider of pathology services for community clinics) for all isolates of *S. aureus* from the NT from 1993 to 2012 inclusive. Antibiotic susceptibility testing was performed for flucloxacillin, cephalexin, erythromycin, doxycycline and trimethoprim-sulfamethoxazole (SXT) according to Calibrated Dichotomous Sensitivity test methods and criteria [7]. We defined methicillin resistance or susceptibility, respectively, as concordant resistance or susceptibility to flucloxacillin and cephalexin. Additional variables obtained were age and sex of the individuals, and the date and geographical community of origin of samples. Communities were classified into local government areas (LGAs) as defined by the Australian Bureau of Statistics (<http://www.abs.gov.au/>).

The outcomes of interest were the proportion of isolates resistant to methicillin, erythromycin, doxycycline and SXT. We built random-effects logistic regression models for resistance as the dependent variable and took into account community of origin, year of isolation, age and sex. We used Stata v. 13 (StataCorp LP, USA) for statistical analysis.

There were 20 210 unique isolates from 1993 to 2012 from 93 communities in 13 LGAs across the NT. Most isolates were from remote community areas where >90% of the population are Indigenous, and isolates from the city of Darwin were exclusively from clinics that serve Indigenous patients. The median number of isolates from each LGA was 1522 (range 176–3499). There was a steady increase in submitted isolates over the time period [numbers per year for 1993–2012: 65 (1993), 60, 100, 107, 89, 165, 255, 353, 327, 388, 638, 912, 1076, 1195, 1436, 1599, 1925, 2526, 3097, 3897 (2012)] partly as a result of more communities being represented [isolates were received from 20 communities in the first 5-year period (1993–1997) and 80 communities in the final 5-year period (2008–2012)]. The increase in the number of isolates is not explained by an increase in the population over 2001–2011 (accurate population denominator figures are available from Australian census counts in 2001, 2006, 2011: <http://www.abs.gov.au/>

websites/censushome.nsf/home/census). Taken at face value, the calculated population incidence of *S. aureus* isolations in the NT Indigenous population was 6.4/1000 in 2001, 22.3/1000 in 2006, and 54.5/1000 in 2011. Fifty percent of isolates came from females, the median age was 27 years (range 0–100 years), and 35% of isolates were recovered from children (<16 years). Isolates were almost all from skin and soft tissue sites (19 876/20 210, 98%) and were recovered from clinical specimens; there were no documented carriage or colonization specimens. There was no difference in the number of isolates recovered during the wet season (1 November to 30 April; $N = 7730$) compared to the dry season (1 May to 30 October; $N = 7818$) for the five LGAs situated in the tropical north of the NT.

Resistance to both flucloxacillin and cephalexin was reported in 4054 isolates and thus defined as MRSA (21%), and 15 467 isolates were reported as susceptible to both flucloxacillin and cephalexin and thus defined as methicillin-susceptible *S. aureus* (MSSA) (79%). Overall rates of resistance to erythromycin were 24% (missing data 64 isolates), doxycycline 2% (missing 35), and SXT 1% (missing 686).

Proportions of MRSA increased from 7% in the first 5-year period (1993–1997) to 24% in the final 5-year period (2008–2012) (Fig. 1). Similar increases in MRSA rates were seen in the subgroup of 17 clinics that had >30 isolates available both before and after 1 January 2003 (data not shown). MRSA rates increased in all LGAs. For the 5-year periods, the proportion of MRSA that were multi-resistant decreased from 7/22 (32%) in 1993–1997, to 11/87 (13%) in 1999–2002, to 31/915 (3%) in 2003–2007, and 37/3019 (1%) in 2008–2012. The calculated population incidence of MRSA isolations in the NT Indigenous population was 0.3/1000 in 2001, 4.2/1000 in 2006, and 13.0/1000 in 2011.

There was no increase in rates of erythromycin resistance and a decrease in doxycycline resistance (Fig. 2). For SXT resistance, after remaining stable during 2000–2011 at ~1%, there was a rise to 2% in 2012 (Fig. 2). The majority of SXT-resistant isolates were multi-resistant MRSA isolates in the first three time periods (49/65, 75%). However, for 2008–2012, only 37/105 (30%) of SXT-resistant isolates were multi-resistant MRSA. Taken together, these data show that the higher rates of SXT resistance in the 1990s were primarily due to multi-resistant MRSA strains, with a drop in rates of SXT resistance in the 2000s due to an increase in prominence of

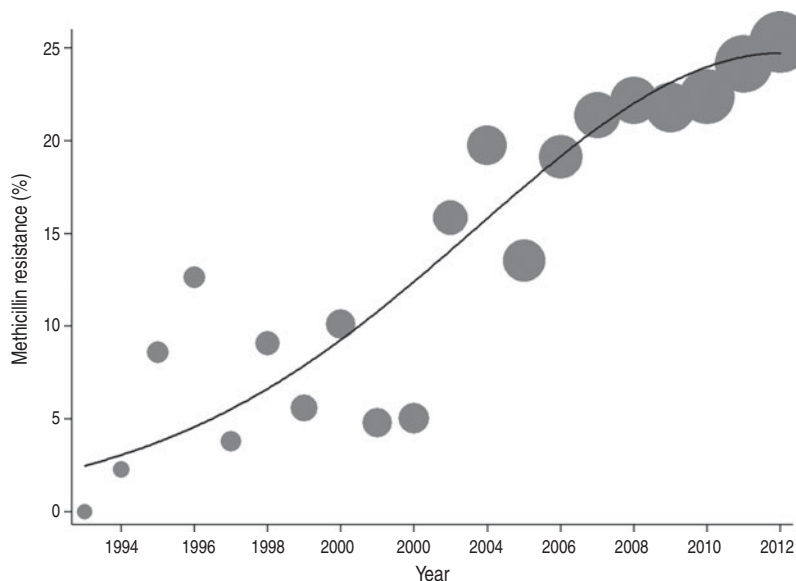


Fig. 1. Rates (%) of resistance to methicillin over the period 1993–2012. The size of the circles reflects the total number of isolates for each year. The modelled line is from a random-effects logistic regression model taking into account community of origin, year of isolation (cubic), age (quadratic) and sex.

CA-MRSA (and thus a dilution of multi-resistant MRSA), followed by a rise in SXT resistance in CA-MRSA strains in 2010–2012. Doxycycline resistance rates initially followed a similar pattern to that of SXT with reducing rates as multi-resistant MRSA decreased, but without evidence of a rise in doxycycline resistance from 2010 onwards. Erythromycin resistance has remained stable over time, with only a small proportion attributed to multi-resistant MRSA strains (6%, 3%, 3%, and 1% for each successive 5-year period). Over the 20-year period, the majority of erythromycin-resistant isolates were MSSA (3797/4730, 80%) compared to 38/200 (19%) for SXT and 111/234 (47%) for doxycycline.

Female sex was associated with an 11% (relative) increased odds of MRSA. Previously we had hypothesized that CA-MRSA was more common in women as they are more likely to be involved in child-caring activities [5]. To investigate this hypothesis further we included age <16 and age \geq 16 years as an interaction term with gender for the logistic regression model. This revealed that there was no female predominance in children aged <16 years [adjusted odds ratio (aOR) 0.96, 95% confidence interval (CI) 0.85–1.08], but that in those aged \geq 16 years, MRSA was more likely in females (aOR 1.19, 95% CI 1.09–1.30). Thus the increased odds of MRSA in females is restricted to adults in whom there are likely to be gender differences with regards to proximity and contact time with children.

Our data demonstrate an ongoing rise in rates of MRSA in community-based *S. aureus* in a predominantly Indigenous population. The increase is apparent across different geographical regions within the sparsely populated NT, suggesting that similar antibiotic selection pressures may be present in disparate communities. High rates of scabies, skin, respiratory and ear infections, and the severity of these infections result in frequent courses of β -lactam antibiotics [8]. Combined with domestic crowding within households and poor levels of functioning health hardware (e.g. working showers, baths, washing machines) for skin hygiene, this represents a potent mix for the ongoing selection for antibiotic resistance. Whether the increase in MRSA is principally due to ongoing *de novo* resistance arising in a variety of MSSA clones [9, 10], or to clonal expansion of a single or a few MRSA clones such as the virulent ST93 MRSA is yet to be determined [11]. With community levels of MRSA now at \sim 25% in the NT, empirical therapy for severe staphylococcal infections in this setting should clearly include targeting of MRSA.

Azithromycin has been used in trachoma control programmes, broadly for sexually transmitted infections, and increasingly for chronic suppurative lung disease [12]. Indigenous children with chronic suppurative lung disease randomized to long-term azithromycin were more likely to carry azithromycin-resistant bacteria than those on placebo [12]. The lack of an increase

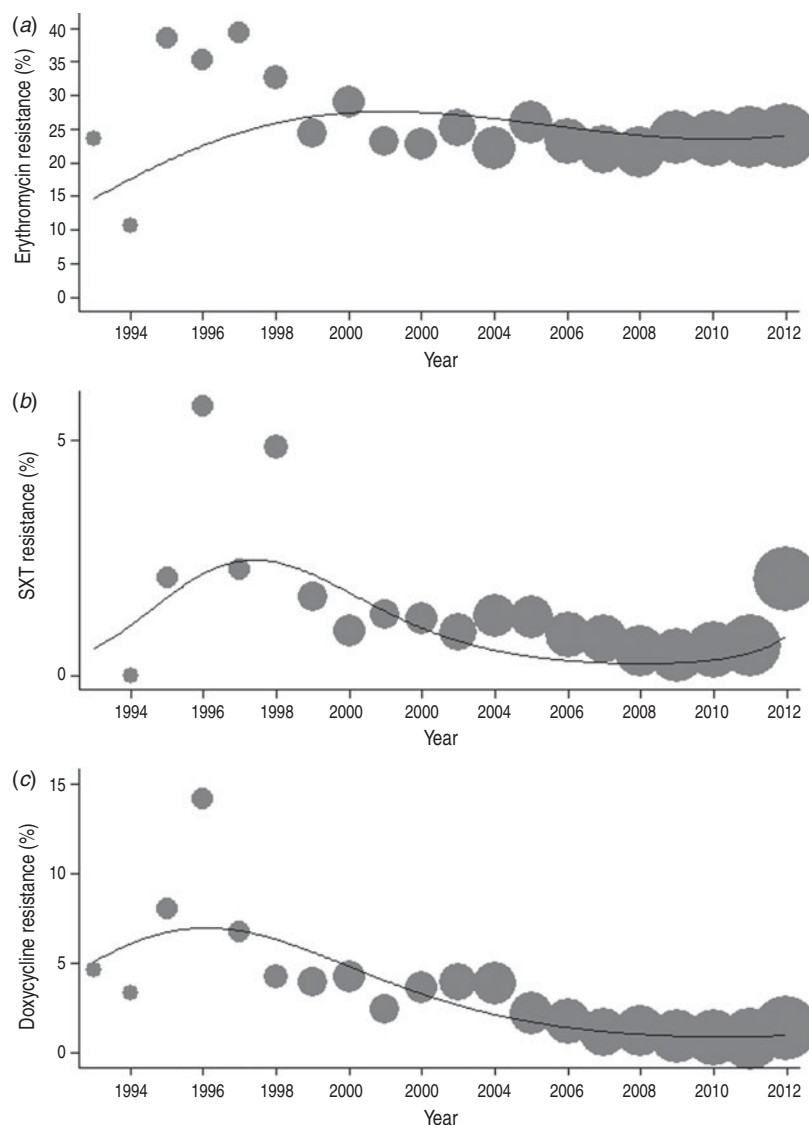


Fig. 2. Rates (%) of resistance to (a) erythromycin, (b) trimethoprim-sulfamethoxazole (SXT) and (c) doxycycline over the period 1993–2012 for all *Staphylococcus aureus* isolates. The size of the circles reflects the total number of isolates for each year. The modelled lines are from random-effects logistic regression models taking into account community of origin, year of isolation (cubic), age (quadratic) and sex.

in erythromycin resistance in the current study is therefore surprising, but may be related to macrolides not being used for SSTIs.

By contrast, SXT is now recommended for use in SSTIs, and particularly for impetigo following a randomized controlled trial demonstrating the non-inferiority of SXT to benzathine penicillin for impetigo [13]. SXT resistance was principally attributed to multi-resistant MRSA in the 1990s, but the increase in SXT resistance from 2010 is due to resistance in CA-MRSA isolates rather than multi-resistant MRSA. The notable increase in rates of SXT

resistance in 2012 is potentially concerning and warrants close monitoring.

Strengths of this study include the longitudinal community-based dataset and large numbers. A limitation is that despite discussions with the primary-care providers, it is unclear as to why the number of isolates has increased at a faster rate than population growth over time. Thus we cannot determine whether the increases in numbers of isolates and the calculated population incidences are principally related to an increase in disease burden or to a change in testing patterns. We also do not have genotyping data to

determine if there has been clonal expansion of particular lineages. Future studies are planned to address these limitations and at this stage we highlight that the calculated population incidence figures may not reflect a true increase in disease burden.

While the ongoing rise of MRSA is directly important for Indigenous populations, it has broader implications. There is evidence of the spread of ST93 MRSA from northwestern Australia to the rest of Australia [11]. Similarly, virulent MRSA and multidrug-resistant Gram-negatives have spread from the Indian subcontinent [14]. It will become increasingly important to address issues in under-privileged populations where the emergence and amplification of antimicrobial resistance is facilitated by poverty linked to high rates of infectious diseases and antimicrobial use.

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DECLARATION OF INTEREST

None.

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