Original Article

Invasive *Staphylococcus aureus* Infections in Children in Tropical Northern Australia

Daniel Engelman,[1,2] Alexandra Hofer,[1] Joshua S. Davis,[1,3] Jonathan R. Carapetis,[3,4] Robert W. Baird,[1] Philip M. Giffard,[3] Deborah C. Holt,[3] and Steven Y. C. Tong[1,3]

[1]Royal Darwin Hospital, Darwin, Australia; [2]Centre for International Child Health, University of Melbourne, Australia; [3]Menzies School of Health Research, Darwin, Australia; and [4]Telethon Institute for Child Health Research, University of Western Australia, Perth

Corresponding Author: Steven Tong, MBBS, PhD, Menzies School of Health Research, PO Box 41096, Casuarina NT 0811 Australia. E-mail: steven.tong@menzies.edu.au.

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Background. Despite a high burden of staphylococcal skin disease in children and high incidence of *Staphylococcus aureus* bacteremia in adult Indigenous populations in northern Australia, there are few studies describing incidence or clinical information of invasive *S aureus* (ISA) infections in children.
Methods. We conducted a retrospective review for all cases of *S aureus* bacteremia and sterile site infections, for children under 15 years, in northern Australia over a 4-year period (2007–2010). Cases were categorized as neonatal (<28 days) and pediatric (≥28 days).
Results. Forty-four cases (9 neonatal, 35 pediatric) were identified. The annual incidence of ISA was 27.9 cases per 100 000 population. Among pediatric cases, the annual incidence was significantly higher in the Indigenous (46.6) compared with the non-Indigenous (4.4) population (IRR: 10.6 [95% confidence interval, 3.8–41.4]). Pediatric infections were predominantly community-associated (86%). Clinical infection sites included osteoarticular (66%), pleuropulmonary (29%), and endocarditis (9%), and multifocal disease was common (20%). Eighty-three percent of pediatric cases presented with sepsis; 34% resulted in intensive care admission. Neonatal cases were all born prematurely; 89% were late-onset infections. Overall, 27% of infections were due to methicillin-resistant *S aureus* (MRSA). Compared with methicillin-sensitive *S aureus* (MSSA), there was no difference in severity or presentation in pediatric MRSA cases, but a higher proportion of MRSA cases were readmitted.
Conclusions. The annual incidence of ISA infection in this study is among the highest described, largely due to a disproportionate burden in Indigenous children. Infections are frequently severe and infection with MRSA is common. Children presenting with suspected ISA in this region should be treated empirically for MRSA.

Key words. bacteremia; indigenous; neonatal; pediatric; *Staphylococcus aureus*.

Skin infections due to *Staphylococcus aureus* commonly affect children living in tropical settings [1]. Northern Australia is a tropical region with a large Indigenous population, and it has among the highest burden of bacterial skin disease in the world [2, 3]. There is a high incidence of *S aureus* bacteremia in adult Indigenous populations in this region [4, 5], with overrepresentation of community-associated methicillin-resistant *S aureus* (MRSA) [6].

Although *S aureus* is one of the most frequent causes of pediatric bacteremia [7, 8], there are few studies describing clinical features [9–12] or estimating population-based incidence [13–18] of invasive *S aureus* (ISA) infections in pediatric populations. Therefore, we aimed to describe the incidence, clinical presentation, and antibiotic susceptibility patterns of ISA infections in children in northern Australia.

METHODS

Setting

The Top End of the Northern Territory of Australia is a large tropical region with an estimated population of 170 000 over an area of 500 000 km^2. The population includes 39 000 (23%) children less than 15 years of age, and 42% of children are Indigenous Australians [19].

The Royal Darwin Hospital is the sole referral hospital for the entire region, servicing 3 district hospitals (Gove

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and Katherine) and more than 70 remote communities. This centralized healthcare system makes it possible to undertake population-based surveillance of severe diseases in this region, particularly as patients have a unique identification number consistent across all health services. There are 2 pediatric wards and a tertiary neonatal unit at the Royal Darwin Hospital. Children who require complex surgery or oncology treatment are transferred to interstate hospitals.

Case Identification and Review

Cases were identified by searching the microbiological database for ISA isolates from all 3 hospitals in the region, for all patients less than 15 years of age, over a 4-year period (January 2007–December 2010).

Invasive infection was defined as isolation of *S aureus* from a normally sterile site (including blood, cerebrospinal fluid, pleura, bone, joint and deep visceral abscesses). Specimens from nonsterile sites, including skin and soft tissue infections, or labeled only as "swab" or "tissue" were not included.

We then performed a retrospective review of medical records. Only the initial presentation of a patient with ISA was included. Information collected included demographics, details of hospital admissions, microbiological culture, susceptibility results, comorbidities and healthcare-associated risk factors, clinical presentation and observations, investigation results, and details of medical and surgical treatment.

Laboratory Methods

Staphylococcus aureus isolates were identified using standard methods. Susceptibility testing was performed with an automated system (Vitek 2 V4.01; bioMérieux) and Kirby-Bauer disk diffusion method in accordance with guidelines of the Clinical and Laboratory Standards Institute (2007–2011). Genotyping was performed with a high-resolution melting method to assign isolates to multilocus sequence typing-based clonal complexes [20].

Definitions

Cases were divided into 2 populations based on age and corresponding hospital wards. Neonatal infections were defined as patients aged less than 28 days (corrected for prematurity) at time of infection. These cases were managed in the neonatal unit and were classified as either early-onset if they occurred in the 48 hours after birth or late-onset if they occurred after 48 hours [21].

Pediatric infections were defined as patients aged from 28 days to 15 years, and these cases included patients admitted to the pediatric wards or intensive care unit. Patients older than 15 years of age were managed on adult wards and therefore were excluded. Cases were classified as hospital-onset if the index isolate was taken more than 2 days after hospital admission and community-associated if it was less than 2 days; and healthcare-associated community-onset if patients had at least 1 of the following: hospitalization, surgery or dialysis in the previous 12 months; or an indwelling venous catheter [22].

Isolates were considered contaminants and excluded from analysis if the clinical history was not consistent with infection, repeated cultures were negative, and the patient recovered without anti-staphylococcal antibiotics. For an episode to be classified as a contaminant, agreement was required from 3 investigators.

Focus of infection was based on recorded clinical diagnoses; infections were considered multifocal if more than 2 sterile sites were involved. Severe infections were defined a priori as those requiring admission to the intensive care unit, as well as those requiring 3 or more surgical procedures for management (chosen as a proxy for complicated infections that did not require intensive care). Sepsis and the systemic inflammatory response syndrome (SIRS) were defined by previously published criteria, using observations and investigations from the 12 hours before and after culture collection [23]. Infective endocarditis was defined as per the modified Duke's criteria [24]. During the study period, there was no standard protocol for echocardiography in children with bacteremia and the decision to perform echocardiography was left to individual clinicians. Malnutrition was defined as weight-for-age less than 2 standard deviations below the median. Relapse was defined as readmission due to infection with an *S aureus* isolate with the same antibiogram.

Methicillin-resistant isolates were classified as multiresistant (mMRSA) if they demonstrated reduced susceptibility to $\geq$3 classes of non-β-lactam antibiotics, otherwise they were classified as non-multiresistant (nmMRSA) [4].

Incidence Rates

Crude incidence rates were calculated using denominator data from the Australian Census, averaged over the study period [19]. Live births, hospital admissions, and categorization of urban or rural and remote dwelling were derived from government publications [25, 26].

Statistical Analyses

Incidence rate ratios (IRRs) were calculated with 95% confidence intervals (CIs). Fisher's exact test was used for comparison of proportions. Nonparametric data were compared with the Mann-Whitney *U* test. A *P* value of <.05 was considered significant. Results were analyzed using Stata 12 (StataCorp, College Station, TX).

This study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research.

RESULTS

There were 44 episodes of ISA in children <15 years old during the 4-year study period. Two additional isolates were excluded as contaminants. This sum represents 1.3% of total pediatric and neonatal admissions to Royal Darwin Hospital. Table 1 shows the demographic information and risk factors.

Incidence

The overall annual incidence of ISA in the Top End was 27.9 cases per 100 000 population aged under 15 years. Table 2 shows the incidence stratified by age, ethnicity, and place of residence. The incidence was higher in Indigenous versus non-Indigenous pediatric-aged population, with an IRR of 10.7 (95% CI, 3.8–41.4); but it was similar between Indigenous and non-Indigenous neonates (IRR, 1.7; 95% CI, 0.3–7.7). The incidence was higher in the pediatric population from rural and remote areas than from urban areas (IRR, 2.3; 95% CI, 1.1–4.8).

Table 1. Characteristics of Children With Invasive *Staphylococcus aureus* Infections

Characteristic	Total (%)	Indigenous (%)	Nonindigenous (%)
Neonatal (0 to <28 days)	9	4	5
Male	5 (55)	3 (75)	2 (40)
Rural/remote	4 (44)	3 (75)	1 (20)
Risk factors			
Prematurity	9 (100)	4 (100)	5 (100)
IUGR	3 (33)	2 (50)	1 (20)
Medical comorbidities*	8 (89)	4 (100)	4 (80)
Vascular device	6 (66)	2 (50)	4 (80)
Pediatric (28 days to <15 years)	35	31	4
Age			
28 days to 1 year	5 (14)	5 (16)	0
1 to 4 years	7 (20)	5 (16)	2 (50)
5 to 9 years	12 (34)	11 (35)	1 (25)
10 to <15 years	11 (31)	10 (32)	1 (25)
Male	23 (66)	20 (65)	3 (75)
Rural/remote	21 (60)	19 (61)	2 (50)
Risk factors			
Total comorbidities	9 (26)	8 (26)	1 (25)
Malnutrition	5 (14)	5 (16)	0
Medical comorbidities*	6 (17)	5 (16)	1 (25)
Vascular device	2 (6)	2 (6)	0

Abbreviation: IUGR, intrauterine growth restriction.
*Neonatal comorbidities (not exclusive): hyaline membrane disease/bronchopulmonary dysplasia: 8; patent ductus arteriosus: 2; anemia of prematurity: 2; necrotizing enterocolitis: 1; pediatric comorbidities (not exclusive): congenital heart disease: 2; rheumatic heart disease, bronchiectasis, bronchopulmonary dysplasia, malrotation of gut, cerebral palsy, severe eczema: 1 each.

Pediatric Wards

Clinical Details. There were 35 pediatric cases (28 days to 15 years age). The median age was 6.3 years (interquartile range [IQR], 2.5–11.6). Twenty-three (66%) cases were male, and 31 (88%) were Indigenous. Nine (26%) cases had comorbidities, including 5 (14%) with malnutrition. Two (6%) cases were related to vascular devices, both in infants <6 months of age.

Thirty infections (86%) were community-associated, 2 cases (6%) were healthcare-associated community-onset, and 3 infections (9%) were hospital-onset.

Thirty-three (94%) patients had bacteremia. One case did not have an identifiable clinical focus. Thirty-seven percent of patients had infections affecting more than 1 site (in addition to bacteremia), with considerable overlap between pleuropulmonary, bone and joint, and skin and soft tissue infections (Figure 1).

Table 3 shows the site and severity of infection. Forty percent of infections were severe (34% admitted to intensive care unit; 11% required 3 or more surgical procedures). Eighty-three percent of patients presented with sepsis (fulfilled SIRS criteria). Fifty-seven percent required surgical management. Those with pleuropulmonary or multifocal infections had particularly high rates of severity (90% and 71%, respectively). There were no recorded cases of toxic shock syndrome.

Echocardiography was performed on 21 of 35 (60%) cases: (transthoracic, 21; transoesophageal, 4). Three patients (9%) were diagnosed with infective endocarditis—2 had underlying cardiac disease (rheumatic and congenital heart disease: 1 each).

Table 2. Cases and Estimated Incidence of Invasive *Staphylococcus aureus* Infection in Children the Top End of Australia, 2007–2010

Age Group	Cases (4 years)	Annual Incidence (per 100 000)	95% CI	IRR (95% CI)
Total (0 to < 15 years)	44	27.9	20.3, 37.5	
Indigenous	35	52.7	36.7, 73.2	IRR 5.3 (2.5, 12.6)
Nonindigenous	9	9.9	4.5, 18.8	
Neonatal (0 to < 28 days)	9	80.2	36.7, 152.2	
Indigenous	4	109.8	29.9, 280.8	IRR 1.7 (0.3, 7.7)
Nonindigenous	5	66.0	21.4, 153.9	
Pediatric (28 days to < 15 years)	35	22.2	15.5, 30.9	
Indigenous	31	46.6	31.7, 66.2	IRR 10.7 (3.8, 41.4)
Nonindigenous	4	4.4	1.2, 11.2	
Rural	21	33.3	20.6, 51.0	IRR 2.3 (1.1, 4.8)
Urban	14	14.8	8.1, 24.9	

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

Antibiotic Management. The median duration of intravenous antibiotic treatment was 22 days, and median total treatment (intravenous and oral) was 45 days. An anti-MRSA treatment (vancomycin) was administered as a first-line antibiotic (on first day of treatment) in only 6 (17%) pediatric cases. Twenty-three (65%) patients were treated with vancomycin at some time during admission; 16 of these had a serum vancomycin trough concentration measured. Of the initial levels, 15 (94%) were below the hospital's target range of 12–18 mg/L. All 9 cases with nmMRSA were treated with vancomycin as the main intravenous therapy (median duration 16 days). Oral continuation therapy was with trimethoprim-sulfamethoxazole (SXT) for 8 of the nmMRSA cases; 1 patient was treated with oral clindamycin and rifampicin.

Outcome. The median length of hospital stay for pediatric patients with ISA was 23 days (IQR, 16–36 days). The median hospital stay was longer for those with severe infections (29.5 days) versus non-severe (21 days), but the difference was not statistically significant ($P = .56$). There were 4 (11%) related readmissions in the 12 months after discharge. Two cases were readmitted with relapse of infection. Both of these patients had nmMRSA that was treated with SXT as the oral continuation therapy. All readmitted children had a pleuropulmonary focus, and the proportion readmitted was significantly higher among cases with a pleuropulmonary infection ($P = .004$). Two (6%) patients required transfer interstate for specialist surgical care. There were no deaths.

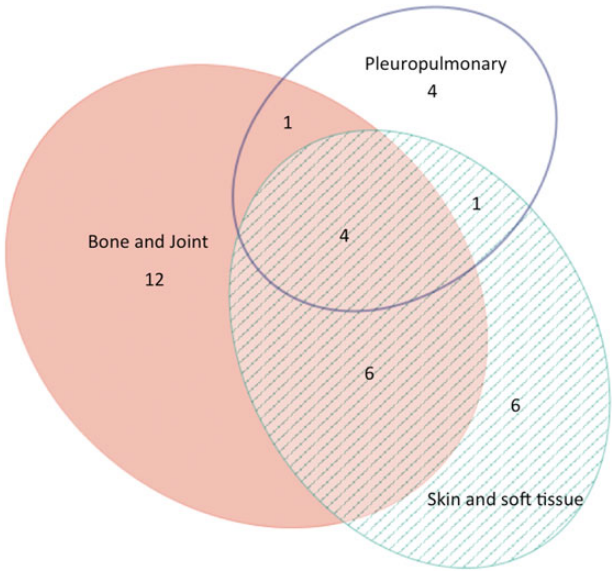

Figure 1. Clinical infection syndromes for pediatric, invasive *Staphylococcus aureus* infections in the Top End of Australia.

Comparison of MRSA and Methicillin-Sensitive *S aureus* Infections. There was no significant difference in clinical presentation or severity of pediatric infections caused by MRSA compared with methicillin-sensitive *S aureus* (MSSA) (Table 4). The median hospital stay was longer for MRSA (33 days; IQR, 19–36 days) than MSSA (21.5 days; IQR, 11–33 days), but this difference in length of stay was not statistically significant ($P = .265$). A significantly higher proportion of patients with MRSA infections were readmitted in the following 12 months (33% compared with 4%; $P = .044$).

Neonatal Unit

There were 9 cases in neonates admitted to the neonatal unit. All were born prematurely (median, 29 weeks; IQR, 25–29; less than 30 weeks gestation [78%]). Eight cases (89%) had significant comorbidities, particularly related to prematurity. Six (67%) neonates developed ISA at the time a vascular device was in situ (long-line: 3; umbilical venous catheter: 2; unspecified: 1).

There was one early-onset infection (isolated day 2 of life). Of the 8 late-onset infections, the median time from birth to positive culture was 18.5 days (IQR, 10.0–33.5 days). All neonatal cases involved bacteremia. In 7 (78%) cases, there was no clinical focus identified.

The median duration of intravenous antibiotic treatment was 9 days (IQR, 8–12 days). Vancomycin was administered on first day of treatment in 6 (67%) cases. Five of these had a serum vancomycin trough concentration measured, and all were outside the hospital's target range (three <12 mg/L; two >18 mg/L).

Table 3. Clinical Site and Severity of Pediatric Invasive *Staphylococcus aureus* Infections

Site of Infection*	n (%)	ICU	Surgery ≥ 3†	Severe	Sepsis
All	35	12 (34)	4 (11)	14 (40)	29 (83)
Bacteremia	33 (94)	11 (33)	3 (75)	12 (36)	27 (82)
Bone/joint	23 (66)	6 (26)	4 (100)	8 (35)	20 (87)
Pleuropulmonary	10 (29)	9 (90)	1 (25)	9 (90)	9 (90)
Skin and soft tissue	17 (49)	4 (24)	3 (75)	6 (35)	15 (88)
Multifocal	7 (20)	5 (71)	2 (50)	5 (71)	6 (86)

Abbreviation: ICU, intensive care unit.
*Not mutually exclusive.
†Number of patients requiring 3 or more surgical procedures for management.

Table 4. Comparison of Pediatric Infections Caused by MSSA and MRSA *Staphylococcus aureus*

Clinical Feature	MRSA n (%)	MSSA n (%)	*P* Value
All	9	26	
Severe	6 (67)	15 (57)	.712
Clinical presentation			
Bone/joint	7 (78)	16 (62)	.450
Pleuropulmonary	4 (44)	6 (23)	.393
Skin and soft tissue	4 (44)	13 (50)	1.000
Multifocal	2 (22)	5 (19)	1.000
Length of stay (median, days)	33	21.5	.265
Related readmissions	3 (33)	1 (4)	.044

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

Three (33%) neonates were investigated with echocardiography, and there were no diagnoses of endocarditis. There was 1 death, on day 40 of life, in an infant born at 24 weeks gestation, birth weight 680 g, with multiple comorbidities. The median length of stay for neonates with ISA was 76 days (IQR, 55–105). There were no related readmissions in the 12 months after discharge.

Microbiological Epidemiology

Overall, 12 infections (27%) were caused by MRSA (pediatric, 26%; neonatal, 33%). All 9 pediatric MRSA isolates were classified non-multiresistant: 2 of 9 (22%) with available information demonstrated reduced susceptibility to erythromycin; 1 of 8 (13%) demonstrated reduced susceptibility to clindamycin; and 4 of 7 (43%) demonstrated reduced susceptibility to fusidic acid.

In contrast, 0 of 3 neonatal MRSA isolates were sensitive to erythromycin or clindamycin. Two were non-multiresistant (susceptible to fusidic acid) and 1 isolate was multiresistant, demonstrating reduced susceptibility to gentamicin, doxycycline, ciprofloxacin, and SXT. The multiresistant MRSA was isolated from the neonatal mortality case. All 44 study isolates were susceptible to vancomycin, rifampicin, and linezolid.

Eighteen isolates were available for typing (13 pediatric, 5 neonatal). The genes *lukS-PV* and *lukF-PV* for Panton-Valentine leukocidin (PVL) were present in 6 (46%) pediatric isolates (2 of 3 MRSA; 4 of 10 MSSA) but none of the neonatal isolates. High-resolution melting genotyping revealed 8 different clonal complexes (most common: CC1 and CC93 [n = 4 each]; CC8 [n = 3]). Clonal complexes of hospital-onset isolates were CC1, CC8, and CC25; all were late-onset neonatal infections.

DISCUSSION

We report a pediatric population where there is both a high incidence of ISA and disease of considerable severity. The overall annual incidence of 28 per 100 000 is higher than the incidence from the United States (3 per 100 000; only community-onset reported) [13], Denmark (8 per 100 000) [14], Spain (21 per 100 000) [18], and New Zealand (17 per 100 000) [15]. The rates are similar to those reported in Kenya (27 per 100 000 in children under 5 years) [16] and Mozambique (48 per 100 000) [17]. However, although most infections in the African studies occurred in neonates and infants (in Mozambique the incidence of bacteremia in children >5 years age was only 1 per 100 000), more than half of cases in the Top End involved children older than 5 years age.

We found a disproportionate burden of disease in Indigenous children, with an incidence rate of 52.7 per 100 000. This rate is 10 times greater than non-Indigenous children, and it equates to 1 in every 2000 Indigenous children in the region presenting with ISA each year. Higher incidence of ISA has also been described in Maori and Pacific Islander children in New Zealand [15] and black children in the United States [27].

The difference in incidence between Indigenous and non-Indigenous children was only seen in older children, not neonates. Although we cannot exclude a genetic predisposition resulting in susceptibility later in life, it is likely that environmental exposures during childhood play a more significant role. In particular, staphylococcal skin disease, often secondary to scabies infestation, is highly prevalent in Indigenous communities [3, 28]. Half of the pediatric patients with invasive disease in our study also had documented skin and soft tissue infection. Social and environmental factors such as overcrowding, inadequate housing [29–31], and socioeconomic status [6] are likely to be important predisposing factors for frequent skin infection and subsequent risk of invasive disease.

In addition to a high incidence, we report a high severity of ISA infections in this population. Eighty-three percent presented with sepsis, 34% required intensive care, and 57% required surgical management. Multifocal infections involving deep-seated pleuropulmonary, osteoarticular, and multisite abscesses were common.

Rates of readmission related to ISA were high, particularly in those with MRSA, severe, and pleuropulmonary or multifocal infections. The 2 children readmitted with evidence of relapse had been treated with oral SXT. Concerns have been raised regarding the efficacy of SXT in severe infections, in which high organism burden and tissue damage lead to release of thymidine [32]. Results of a study from the United States showed an increased risk of treatment failure for skin and soft tissue infections treated with SXT compared with clindamycin [33]. Most patients treated with oral SXT in our study did not relapse, and further investigation of the risk factors for recurrence would

require a larger sample size. We recommend close monitoring of all patients during and after completion of oral antibiotics.

The proportion of MRSA in our study (27%) is higher than pediatric results from the rest of Australia (12%) [34], New Zealand (6%) [15], Mozambique (9%) [17], Denmark (0.5%) [14], and Spain (0%) [18] and comparable to rates in the United States (10%–33%) [10, 12, 13]. The high proportion of MRSA is in keeping with adult studies from this region [35, 36]. Multiresistant MRSA infections are uncommon. The estimated overall incidence of invasive MRSA in our study overall was 7.5 per 100 000. The incidence in infants <12 months was similar to incidence in the United States (Top End: 19.0 per 100 000; compared to United States: 23.1 per 100 000), but the incidence in young children (Top End 1–4 years: 5.0 per 100 000; compared to United States: 2.3–3.8 per 100 000) and older children (Top End 5–14 years: 13.1 per 100 000; compared to United States: 1.4 per 100 000) was higher in our study [27, 37]. Whereas most infections in the United States [10, 22, 37] and Europe [18, 38] are hospital-onset or healthcare-associated, most infections in the Top End are community-associated.

Based on these findings, we recommend children presenting with suspected ISA (ie, those with bone and joint infections, severe pneumonia, endocarditis, or sepsis with skin infection) be treated empirically with antibiotics active against MRSA. Vancomycin is the drug of choice for invasive MRSA infection, but it is inferior to β-lactams for treatment of MSSA bacteremia [39, 40] and has variable tissue penetration to bone [41] and lung [42]. Therefore, we recommend vancomycin in addition to standard antistaphyloccocal antibiotics (eg, flucloxacillin) until antibiotic susceptibility is known. Use of rapid molecular testing methods for MRSA could increase the proportion of cases receiving early appropriate vancomycin and avoid unnecessary treatment in others [43]. Furthermore, almost all children treated with vancomycin had initial trough levels outside the recommended target range [44], and new protocols are required to direct vancomycin therapy in the pediatric population [45]. Clindamycin should not be used as a sole agent because of resistance, but it can be added for theoretical action against toxin production (including PVL) [46] in patients with severe infection.

Genotyping results were consistent with other studies from the region [47]. Notably, PVL-positive infections due to CC93, CC121, and CC30 were common, and PVL was noted to be present in both MRSA and MSSA isolates.

The incidence of neonatal infection in our study was 0.8 per 1000 live births, similar to the reported rate in the only other comparable study [48], which reported an incidence of 0.6 per 1000 live births in the United Kingdom. Similar risk factors of extreme prematurity and low birth weight are reported in developed settings [21, 48–51]. Neonatal infections frequently occur without specific clinical features and are often associated with indwelling vascular devices. This differentiation between infections in neonates and older children has been observed in other settings [38, 52]. Active infection control strategies remain important for prevention.

This study has some limitations. Our study population is small, with unique demographics, and may not be generalizable to other areas. Culture-negative cases of empyema, osteomyelitis, and septic arthritis have not been included, but a proportion of these are due to *S aureus*. The genotyping profile of isolates is incomplete, because several isolates were unavailable. However, these limitations are balanced by the detailed review of cases and availability of regional demographic data, allowing estimation of incidence over a large geographic area and providing insight into a tropical pediatric population with a high burden of disease.

The incidence of invasive infection due to *S aureus* in children in the Top End of Australia is among the highest in the world, largely due to the disproportionate burden in Indigenous children. Infections are frequently severe. Empiric treatment for children presenting with suspected invasive *S aureus* in this region should include treatment for MRSA.

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Potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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