Pediatric *Staphylococcus aureus* bacteremia: clinical spectrum and predictors of poor outcome

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Summary: ISAIAH is a large prospective, multi-centre study of *S. aureus* bacteremia (SAB), in children hospitalized in Australia and New Zealand, over 24-months. A deeper understanding of SAB epidemiology, clinical phenotype and pediatric-specific risk factors for poor outcome are provided.

Abstract

Background

Staphylococcus aureus is a common cause of bacteremia, yet the epidemiology, and predictors of poor outcome remain inadequately defined in childhood.

Methods

ISAIAH is a prospective, cross-sectional study of *S. aureus* bacteremia (SAB), in children hospitalized in Australia and New Zealand, over 24-months (2017–2018).

Results

Overall, 552 SABs were identified, (incidence 4.4/100,000/yr [95% confidence interval (CI) 2.2-8.8]), with methicillin-susceptible (84%), community onset (78%) infection predominating. Indigenous children (8.1/100,000/yr [CI 4.8-14.4]), those from lower-socioeconomic areas (5.5/100,000/yr [CI 2.8-10.2]) and neonates (6.6/100,000/yr (CI 3.4-11.7) were over-represented. Although 90-day mortality was infrequent, one-third experienced the composite of: length of stay >30 days (26%), ICU admission (20%), relapse (4%), or death (3%).

Predictors of mortality included prematurity (aOR 16.8 [CI 1.6-296.9]), multifocal infection (aOR 22.6 [CI 1.4-498.5]), necrotizing pneumonia (aOR 38.9 [CI 1.7 – 1754.6]), multiorgan dysfunction (aOR 26.5 [CI 4.1-268.8]) and empiric-vancomycin (aOR 15.7 [CI 1.6-434.4]); whilst Infectious Diseases (ID) consultation (aOR 0.07 [CI 0.004-0.9]) was protective. Neither MRSA nor vancomycin trough-targets impacted survival; however, empiric-vancomycin was associated with significant nephrotoxicity (OR 3.1 [CI 1.3-8.1]).

Conclusions

High SAB incidence was demonstrated, with at-risk populations identified for future prioritized care. For the first time in a pediatric setting, necrotizing pneumonia and multifocal infection were predictors of mortality, whilst ID consultation was protective. The need to re-

evaluate pediatric vancomycin trough-targets and limit unnecessary empiric-vancomycin exposure, to reduce poor outcomes and nephrotoxicity is highlighted. One in three children experienced considerable SAB morbidity, therefore pediatric inclusion in future SAB comparator trials is paramount to improve outcomes.

key words: *Staphylococcus aureus,* pediatrics, bacteremia, outcomes, mortality

Background

Staphylococcus aureus frequently causes childhood bacteremia, and is the most common cause of sepsis requiring pediatric intensive care unit (PICU) admission [1, 2]. It is a principal reason for Infectious Diseases (ID) consultation [3]. Despite this, the epidemiology, and predictors of poor outcomes in children remain inadequately defined.

Fowler *et al.* revolutionised *S. aureus* bacteremia (SAB) adult treatment recommendations by identifying clinical factors associated with complicated disease and mortality [4]. To date, a large, prospective, pediatric SAB dataset with robust outcomes has not been established. The objectives of this study were to provide a deeper understanding of SAB clinical phenotype, identify pediatric-specific markers for severe disease, and establish risk factors for poor outcomes in children.

Methods

ISAIAH (Invasive *Staphylococcus aureus* Infections and Hospitalizations in children) is a prospective, multi-centre, cross-sectional study of pediatric SAB in Australia and New Zealand. Tertiary (n=8) and secondary (n=3) pediatric hospitals and Neonatal Intensive Care Units (NICUs) (n=10) were included. The aims were to identify host, pathogen, and treatment factors predictive of the primary outcome, 90-day all-cause mortality and a composite outcome (defined *a priori* as 90-day all-cause mortality, 90-day relapse, ICU admission or length of stay [LOS] > 30 days).

Children ≤ 18 years with a positive blood culture for *S. aureus,* presenting to study hospital sites were eligible for inclusion and identified by site microbiology or ID services over 24-

months (2017–2018). Children with SAB transferred from peripheral hospitals to study-sites were also included. Polymicrobial bacteraemia's were excluded.

Information on demographics, comorbidities, infection focus, investigations, disease severity, treatment and patient outcomes were prospectively collected from the hospital, laboratory and radiology records onto an electronic database [5]. Antibiotic agent/s, route and duration, along with initial vancomycin dose, frequency and vancomycin trough level obtained within three days of commencing, were also recorded.

Hospital- and community-onset SAB was defined as a positive blood culture/s collected > 48 hours or ≤ 48 hours after presentation, respectively. A healthcare-associated SAB definition was adapted from the National Healthcare Safety Network Centres for Disease Control and Prevention [NHSN CDC] definitions (Supplementary appendix 1)[6]. Multifocal disease was classified as clinical or radiological evidence of infection in more than one non-contiguous site. Indigenous ethnicity (Aboriginal or Torres Strait Islander, hereafter respectively referred to as Aboriginal in Australia, or *Māori* or Pacific peoples in New Zealand) was verified through routinely collected self-identification at hospital admission.

All time points were calculated from date of index SAB sampling (day 1), including peak C-reactive protein (CRP), days of fever and bacteremia (informed by date of first and last SAB). Multiorgan dysfunction was defined as two or more of; 1) alanine aminotransferase (ALT) ≥ 5 times upper limit of normal (ULN); 2) creatinine ≥ 2 times ULN; 3) positive pressure ventilation; or 4) haemodynamic instability requiring inotropic support [7]. Nephrotoxicity was defined as creatinine ≥ 2 times ULN in week one. Antibiotic treatment was defined as empiric (prior to susceptibility results) or targeted (susceptibility results

known). Combination therapy was defined as simultaneous receipt of ≥ 2 antibiotics for ≥ 24 hours. Empiric antibiotics were deemed appropriate by site investigators if *in vitro* susceptibility was demonstrated for beta-lactams (MSSA) and vancomycin, daptomycin, ceftaroline or linezolid (MRSA) [8], and antibiotic(s) were administered ≤48 hours from index SAB.

Multiple positive SAB cultures within 14 days were considered a single SAB episode. Relapse was defined as repeat *S. aureus* sterile site culture/s or hospital representation 15-90-days post SAB and deemed by site investigators to relate to the initial SAB. Seven, 30 and 90-day attributable and 7, 30, 90 and 365-day all-cause mortality were collected for in-hospital deaths. Laboratories used standard commercial blood cultures systems (BACTEC™, BD diagnostics); bacterial identification (MALDI-TOF; Bruker Daltonics, Bremen, Germany) and semi-automated susceptibility platforms (Vitek®2; bioMérieux, France or Phoenix™; BD, USA), with minimum inhibitory concentration (MIC) breakpoints from CLSI M100 [9] or EUCAST [10].

Annual population SAB incidence was calculated by age, country, ethnicity, socioeconomic status (SES) and rural residence using national census statistics for children ≤ 14 years [11, 12]. SES was assigned according to postcode-derived national census decile-rank scales of income; the NZ index of deprivation (NZiDep) [13] and Australian socioeconomic index for areas (SEIFA) [14]. NZiDep was inverted to align with the Australian SEIFA score. Australian urban residence, was defined as children residing in regions with a population > 100,000, determined from postcode-derived population census data [14].

Ethics approval was obtained from each hospital. Statistical analyses were performed using R version 3.6.3 (R Core Team, 2020). Chi-square or Fisher's exact tests were used to compare categorical variables and Student's t-test or Mann-Whitney U test to compare continuous variables. Potentially significant covariates were considered *a priori* (age, sex, country, number of surgeries performed for SAB management, device removal and MRSA) and those with *p-value* <0.1 on univariate analysis included in the multivariable regression model. Pairwise correlation coefficients were examined between variables before inclusion in the multivariable model to avoid collinearity. Stepwise backward elimination was performed and *p*-values <0.05 considered statistically significant. Model performance was assessed using the C-statistic for discrimination and the Hosmer-lemeshow test for calibration.

Results

Epidemiology and clinical characteristics

552 SAB patient-episodes were identified (Figure 1), with an annual incidence of 4.4/100,000 (95% confidence interval [CI 2.2-8.8]); Australia, 4.1/100,000 (CI 2.2-8.8); NZ, 6.4/100,000 (CI 3.4-11.7). Median age was 6.3 years (interquartile range [IQR] 1.0-11.3), with male (342/552, 62%) predominance (Table 1a).

Elevated SAB incidence was observed among Indigenous children (8.1/100,000 [CI 4.8-14.4]), particularly NZ Pacific children 15.2/100,000 (CI 9.9-23.5), compared with other NZ children (IRR of 3.0/100,000 [CI 1.1-9.2]); neonates (6.6/100,000 [CI 3.4-11.7]); and those residing in low SES areas (5.5 per 100,000 [CI 2.8-10.2]) (Supplementary appendix 3).

Methicillin susceptible *S. aureus* (MSSA) bacteremia (465/552, 84%) was the dominant antibiotic susceptibility phenotype, accounting for 78% (363/465) of community-onset

infections. The main preceding factors included furuncles (32/552, 6%), skin trauma (19/552, 3%) and influenza (14/552, 3%) (Table 1b). Underlying comorbidities (232/552, 42%), included immunosuppression (83/552, 15%), congenital heart disease (48/552, 9%) and prematurity (48/552, 9%), of which most (22/48, 46%) were extremely premature (<28 weeks) (Table 1b). Healthcare-associated SAB (159/528, 30%), occurred more frequently in neonates compared with older children (odds ratio [OR] 3.7 [CI 1.9-7.2]), particularly premature neonates (<37 weeks gestation) (24/48, 50%), with device-related infections (15/24, 62%) (Figure 2).

Focus of infection, investigation, and disease severity

Most children were hospitalised (542/552, 98%), had at least one radiological investigation (502/552, 90%), follow-up blood culture (539/552, 98%), and an ID consultation (478/552, 87%). The most frequent foci of SAB were osteoarticular (273/552, 49%), device-related (123/552, 22%), deep soft-tissue infection (122/552, 22%) and SSTI (83/552, 15%; table 1c). Two-thirds had a single focus, whilst 16% (87/552) had multifocal disease (pulmonary and bone most common [35/87, 40%]). Multifocal disease was associated with *endocarditis (OR 12.3, [CI 5.7 – 27.7]*) and MRSA bacteremia (OR 2.6, [CI 1.5-4.4]). No focus was evident in 14% (78/552), more frequently amongst infants versus older children (OR 4.4, [CI 2.7-7.3]), despite imaging (62/78, 79%) and follow-up blood culture/s performed (76/78, 97%). Surgical source control occurred in nearly half (234/552, 42%). In device related infections, central vascular line-related focus predominated (106/123, 86%), and the majority (88/123, 71%) had line removal after a median of 3 days (IQR 2-5) (Table 1c, 1d).

Children spent a median of 4 days febrile (IQR 2-7), and 1-day (IQR 1-3) with bacteremia. CRP peaked on day 2 (IQR 1-3) with a median CRP of 117mg/L (IQR 47-205). Those with MRSA bacteremia had a higher median peak CRP 187 mg/L ([IQR 68-267], p=0.0001),

longer duration of fever (median 5 days; IQR [3-11]; p=0.0002) and bacteremia (median 2 days, IQR [1-3]; p=0.04), than those with MSSA bacteremia.

Antibiotic treatment

Most children (489/539, 91%) commenced appropriate empiric antibiotic therapy. The majority received empiric beta-lactams (516/536, 93%), principally flucloxacillin (362/536, 66%). Half (269/536, 49%) received empiric vancomycin-containing regimens, combined with a beta-lactam in 98% (263/269). Eighty four percent (449/536) received one antibiotic for targeted therapy, with favoured MSSA bacteremia regimens including IV flucloxacillin (305/452, 67%) or IV cefazolin (55/452, 12%). Children with MRSA bacteremia were more likely to receive combination targeted therapy (OR 3.89, [CI 0.06 – 0.19]) than those with MSSA bacteremia, most commonly with vancomycin and clindamycin (20/85, 24%) (Table 1d).

For empiric vancomycin dosed at 60mg/kg/day QID, only 10% (11/108) achieved initial vancomycin troughs of 15-20mg/L. Those receiving empiric vancomycin developed nephrotoxicity more frequently (23/269, 9%) than those who did not (8/259, 3%); OR 3.1, [CI 1.3-8.1]. Approximately half of children received oral antibiotics following their IV course (303/543, 56%) for whom the median duration of IV therapy was 11 days (IQR 8-20), followed by oral 23 days (IQR 14-35). Median total duration of therapy was 26 days (IQR 15-45), and longer for MRSA bacteremia (39 days [IQR 18-48] compared with MSSA bacteremia (23 days [IQR 15-44]; p=0.0005) as well as multifocal SAB (43 days [IQR 26-49]) compared to non-multifocal SAB (20 days [IQR 14-43]; p=<0.0001).

Outcome and predictors of mortality

Median LOS for SAB was 15 days (IQR 9-31), longer for MRSA bacteremia (22 days, [IQR 14-35]), p=0.001). Relapse occurred in 4% (21/531), after a median of 45 days (IQR 38-71). Seven-day, 30-day, 90-day and 12-month all-cause mortality were 1% (5/546), 2% (13/546), 3% (14/542) and 4% (23/542), respectively. Death occurred after a median of 21 days (IQR 9-164). One in three children (186/503, 36%) experienced the composite outcome of 90-day all-cause mortality (14/542, 3%); relapse (21/531, 4%); ICU admission (111/550, 20%); or LOS > 30 days (140/530, 26%).

Significant predictors of 90-day all-cause mortality included prematurity (aOR 16.8 [1.6-296.9], p=0.03), multifocal infection (aOR 22.6 [1.4-498.5], p=0.03), necrotizing pneumonia (aOR 38.9 [1.7-1754.6], p=0.03), multiorgan dysfunction (aOR 26.5 [4.1-268.8], p=0.001), and empiric vancomycin therapy (aOR 15.7 [1.6-434.4], p=0.04) (table 2). Initial vancomycin troughs of <15mg/L (OR 0.6 [0.1-4.2], p=0.5) and MRSA (aOR 0.4 [0.04-3.3], p=0.4) were not predictive of mortality in children. Factors associated with a mortality reduction included ID consultation (aOR 0.07 [0.004-0.9], p=0.05), an osteoarticular focus (aOR 0.01 [0.0002-0.4], p=0.03) and country of origin; Australia compared with NZ (aOR 0.1 [0.01-0.6], p=0.02). No variables were predictive of 90-day relapse, although less frequent relapse was observed in those receiving empiric beta-lactam therapy (aOR 0.17 [0.03-1.3], p=0.05), (Supplementary appendix 2).

A peak CRP > 200mg/L by day three was predictive of the composite outcome (aOR 2.9 [1.5-6.1], p=0.002). Congruent with mortality predictors, prematurity (aOR 4.4 [1.5-14.1], p=0.008), pneumonia (aOR 2.7 [1.1-7.1], p=0.04) and empiric vancomycin (aOR 2.0 [1.0-4.1], p=0.05) were independent risk factors for this composite outcome. The presence of congenital heart disease (aOR 6.2 [1.7-27.6], p=0.009), age ≤ 1-year (aOR 2.3 [1.1-4.8],

p=0.03) ≥ 3 surgeries for SAB management (aOR 5.5 [2.1-14.8], p=0.0006), increasing days of *S. aureus* bacteraemia (aOR1.2 [1.0-1.4], p=0.04) and hospital-onset SAB (aOR 6.6 (2.9-15.5), p=<0.0001) were also predictive (table 3).

Discussion

In one of the largest prospective cohorts of pediatric SAB to date, we report a high annual incidence affecting 4.4/100,000 children with increased burden amongst neonates, Indigenous children, and those from lower SES areas. We identified early markers of poor outcomes in children including multifocal infection, CRP > 200mg/L, prematurity, and congenital heart disease.

Our reported incidence (4.4/100,000), is similar to other high-income countries including Canada (5.9/100,000) [15] and Denmark (8.4/100,000)[16]. The lower incidence compared to the Australian and NZ 2007-2012 cohort (8.3/100,000) [17], likely reflects differences in methodology (postcode-adjusted incidence rates in the former, with unadjusted whole pediatric population incidence rates used here, and some variation in study-sites), rather than a true decline. Over-representation of Indigenous children (8.1/100,000 [CI 4.8-14.4]), has been reported nationally and internationally [17, 18], which may be due to a disproportionate burden of socioeconomic disadvantage [18], as demonstrated in this cohort (supplementary appendix 3). We conclude that SAB is the leading cause of pediatric bacteremia in Australia and NZ, (with reported incidence of *Streptococcus pneumoniae*; 4.1/100,000 [2.2-8.8][19], Group A *Streptococcus*; 2.7/100,000 [CI 2.3-3.2][20] and *Neisseria meningitidis*; 0.9/100,000 [CI 0.1- 4.9] to 2.48/100,000 [CI 1.53–3.78])[21, 22]. Prioritization of further research into prevention strategies, in the absence of an effective vaccine for SAB, is needed.

The youngest children, particularly neonates (6.6/100,000 [CI 3.4-11.7]), had the highest SAB incidence, albeit lower than the incidence previously reported in the literature (13-124/100,000 [15, 23]). This comparatively lower incidence may relate to fewer NICUs included or improvements in intravascular catheter-care bundle use in NICUs [24]. This study demonstrates that the degree of prematurity drives this early lifetime risk, with half (46%) of affected neonates born <28 weeks and prematurity was identified as a predictor of mortality and poor outcomes. This adds to the limited literature available on neonatal SAB [25], that largely focuses on MRSA [26] and neonatal *S. aureus* colonisation risk factors [27]. With a predominance of neonatal healthcare-associated (49%) and device-related (31%) infections, our data support the importance of optimising infection prevention measures in the NICU.

The ninety-day mortality (3%), is congruent with the United Kingdom (2%) and United States (2%) [28] whilst significantly lower than adult SAB (15%-20%) [29]. This is potentially associated with decreased pediatric comorbidities (42% children vs 85% adults) and lower infective endocarditis rates (6% children vs 12% adults) [29]. Lower mortality was confirmed in Australia (2%), compared with NZ (4%). Potential explanations include differences in clonal *S. aureus* virulence, or host factor variations in genetic susceptibility to severe disease [17].

Compared with previous Australian and NZ data (2007-2012), a decline in pediatric 30-day mortality was observed (5% to 2%, p=0.009) [17], with similar findings reported in adult SAB [29]. This is the only contemporary pediatric study to demonstrate this. Improvements are likely attributable to appropriate early antibiotic therapy, sepsis management [29], and ID consultation [30]. ID consult was frequent and protective against mortality in this study,

similar to findings in adult SAB [30], although due to small numbers the size of the effect remains uncertain. Despite improving mortality, one quarter of children required ICU admission and experienced LOS > 30 days. Future comparator trials for children with SAB are critical to improve care and reduce prolonged hospitalizations.

This detailed dataset identified that MRSA bacteremia, compared with MSSA bacteremia, was associated with increased ICU admissions, more days with bacteremia and longer LOS on bivariate analysis (Table 1c and 1d). Despite these differences, on multivariable regression, methicillin resistance was not associated with mortality, relapse, or poor outcomes in children. Our findings are consistent with the global literature when examining children across ages (not just neonates)[31], and when MRSA bacteremia is predominantly community- (in our study 85%) versus hospital-acquired [31-33]. This suggests healthcare-associated *S. aureus* clonal virulence factors may play a role in this mortality risk [31-33]. Recognition of both methicillin-resistant and methicillin-susceptible SAB as a cause of significant morbidity is critical to advancing approaches in prevention and treatment [16].

In this study, empiric vancomycin (given in combination with a beta-lactam in 98% of children) predicted mortality and poor outcomes, even after adjusting for MRSA and disease severity. Increased risk of nephrotoxicity with empiric vancomycin, identified in this study, other pediatric cohorts [34] and a recent adult SAB randomised trial (CAMERA2), reporting increased nephrotoxicity and mortality with combination vancomycin/flucloxacillin therapy for MRSA bacteremia [35] may explain this. In addition, initial vancomycin troughs of less or greater than 15mg/L, did not result in improved survival overall, or for MRSA bacteremia. These data highlight the need for re-evaluation of pediatric vancomycin trough-targets [36], particularly whilst vancomycin remains standard of care for MRSA bacteremia [37]. It also supports the use of rapid diagnostics, coupled with antimicrobial stewardship [38] for SAB, to

limit unnecessary vancomycin exposure in children and the potential harm associated with this.

Multifocal infection is a confirmed mortality risk in adult SAB (OR 2.1-17.0) [4, 29], and a presumptive risk in children [28, 39]. This is the first pediatric cohort to demonstrate multifocal infection (16%) as a significant predictor of mortality (aOR 22.6 [1.4-498.5], p=0.03). In a Danish retrospective study, logistical regression models examining pediatric SAB mortality [16], used narrower definitions for multifocal SAB, excluding osteoarticular and pulmonary foci (most common in our study), which may explain differences in findings. SAB with pulmonary focus is an established predictor of mortality in adults [40] and children [17], and specifically in this cohort; necrotizing pneumonia (aOR 38.9 [1.7-1754.6], p=0.03). Previous case-series of necrotizing pneumonia [41] describe high mortality however are limited by selection bias and lack of adjustment for confounders. These data confirm the need for source-specific management of SAB and with further validation, suggests the utility of multifocal disease as an outcome measure for future pediatric clinical trials.

Limitations of this study include some missing data as it was captured from multiple sources including medical records, however the mortality endpoint, albeit infrequent, was well documented. Most children were cared for in tertiary pediatric hospitals, which may have introduced selection bias. Incidence is likely underestimated as not all secondary hospitals were included. To reduce data collection burden, the only antibiotic dose recorded was initial vancomycin prescription and therefore dose was not incorporated into the definition of appropriate empiric antibiotic therapy. We were not able to determine if empiric antibiotic choice impacted transfer to ICU from an acute care setting, given data on ICU admission was collected as a binary variable. Relapse and death may be underestimated, with community, out-of-hospital or private provider presentations or deaths not recorded,

although this was estimated to be low. Models included adjustment for disease severity, using a definition of pediatric multiorgan dysfunction [7] that has not been rigorously externally validated and may not have accurately accounted for this. Despite this, our analysis of 552 pediatric SAB episodes provides an in-depth description of the clinical phenotype of severe disease, and risk factors for poor outcome.

Conclusion

The incidence of SAB is confirmed to be the highest for invasive bacterial infections in children in the post-conjugate vaccine era. The most vulnerable at-risk populations include NZ-Pacific children, premature neonates and those residing in lower socioeconomic areas. For the first time in a pediatric setting, we demonstrate that necrotizing pneumonia and multifocal infection were independent predictors of death, whilst ID consultation was protective. Given that MRSA and vancomycin trough levels did not impact on survival, further re-evaluation of pediatric vancomycin trough-targets are required. These data support the use of rapid diagnostics and antimicrobial stewardship for SAB, to limit unnecessary vancomycin exposure in children and consequent nephrotoxicity. This contemporary analysis provides the foundation for a collaborative clinician network for future pediatric SAB randomised clinical trials, given one in three children experience SAB morbidity.

NOTES

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Conflicts of interest

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Table 1a: Baseline characteristics of children ≤18 years diagnosed with *Staphylococcus aureus* bacteremia (SAB) across eleven pediatric hospitals in Australia and New Zealand (2017-2018)

Baseline characteristics	**Total *n* (%)**	**MSSA *n* (%)**	**MRSA *n* (%)**	***p* value (MRSA vs MSSA)**
Pediatric SAB *n*=552	552	465 (84) [a]	87 (16) [b]	-
Age in years, median (IQR)	6.3 (1.0-11.3)	6.3 (0.9-11.3)	5.9 (2.1-10.9)	0.522
Female,	210 (38)	175 (38)	35 (40)	0.725
Ethnicity				
Aboriginal and Torres Strait Islander in Australia SAB *n*=356	51/356 (14)	24/296 (8)	27/60 (45)	<0.0001***
Māori + Pacific children in NZ SAB, *n*=129	76/129 (59)	60/107 (56)	16/22 (73)	0.141
Location, *n*=552				
Australia	422 (76)	357 (77)	65 (75)	0.686
New Zealand	130 (24)	108 (23)	22 (25)	0.686
Resides in a rural location (Australia), *n*=417	113/417 (27)	85/352 (24)	28/65 (43)	0.001**
Transferred from a peripheral hospital, *n*=548	148/548 (27)	115/461 (25)	33/87 (38)	0.012*
Hospital admission for SAB, *n*=552	546 (99)	461 (99)	85 (98)	0.424
Classification, *n*=552				
Hospital-onset	115 (21)	102 (22)	13 (15)	0.141
Community-onset	437 (79)	363 (78)	74 (85)	0.141
Healthcare-associated *n*=528	159/528 (30)	138/442 (31)	21/86 (24)	0.195
Device	126/528 (24)	107/442 (24)	19/86 (22)	0.690
Surgery	37/528 (7)	34/442 (8)	3/86 (3)	0.101
Neutropenia	27/528 (5)	24/442 (5)	3/86 (3)	0.422

*** p < 0.001; ** p < 0.01; * p < 0.05.

[a] Penicillin susceptible *S. aureus* *n*=49/465 (10%) (11 beta-lactamase negative out of 16 results available)

[b] Multi-resistant MRSA *n*=3/87 (0.4%)

Abbreviations: SAB, *S. aureus* bacteremia; IQR, interquartile range; MSSA, methicillin susceptible *S. aureus*; MRSA, methicillin resistant *S. aureus*; n, number

Table 1b: Baseline comorbidities and preceding factors for children <18 years diagnosed with *Staphylococcus aureus* bacteremia (SAB) across eleven pediatric hospitals in Australia and New Zealand (2017-2018)

Baseline characteristics	**Total *n* (%)**	**MSSA *n* (%)**	**MRSA *n* (%)**	***p* value (MRSA vs MSSA)**
Pediatric SAB *n*=552	552	465 (84)	87 (16)	-
Comorbidities, *n*=552	232 (42)	201 (43)	31 (36)	0.225
Immune compromise	83 (15)	70 (15)	13 (15)	1
Haematological malignancy	32 (6)	27 (6)	5 (6)	1
Solid organ transplant	30 (5)	26 (6)	4 (6)	1
Other				
Congenital heart disease	48 (9)	45 (10)	3 (3)	0.035*
Premature (< 37wk), *n*=552	48 (9)	40/433 (9)	8/81 (10)	0.871
Extreme prematurity < 28wk	22 (4)	19 (5)	3 (4)	0.701
Moderate prematurity 28- < 32wk	13 (2)	10 (2)	3 (4)	0.272
Prematurity 32- < 37wk	13 (2)	11 (2)	2 (2)	1
Eczema	42 (8)	35 (7)	7 (8)	0.740
Genetic syndrome	15 (3)	12 (3)	3 (3)	1
Chronic neurological disorder	9 (2)	9 (2)	0 (0)	0.184
Chronic renal disease	7 (1)	6 (1)	1 (1)	1
Chronic lung disease	15 (3)	14 (3)	1 (1)	0.289
Chronic liver/GI disease	15 (3)	12 (3)	3 (3)	1
Preceding factors, *n*=552	61 (11)	36 (8)	25 (29)	<0.0001***
Furuncle/s	32 (6)	19 (4)	13 (15)	0.0001***
Skin trauma	19 (3)	11 (2)	8 (9)	0.0006***
Influenza	14 (2)	9 (2)	5 (6)	0.0325*

*** p < 0.001; ** p < 0.01; * p < 0.05.

Abbreviations: SAB, *S. aureus* bacteremia; MRSA, methicillin resistant *S. aureus*; MSSA, methicillin susceptible *S. aureus*; n, number; wk, weeks; GI, gastrointestinal.

Table 1c: Baseline investigations and source of infection for children <18 years diagnosed with *Staphylococcus aureus* bacteremia (SAB) from eleven pediatric hospitals in Australia and New Zealand (2017-2018)

Baseline characteristics	**Total *n* (%)**	**MSSA *n* (%)**	**MRSA *n* (%)**	***p* value (MRSA vs MSSA)**
Pediatric SAB *n*=552	552	465 (84)	87 (16)	-
Investigations for SAB, *n*=552				
Follow up blood culture	539 (98)	453 (97)	86 (99)	0.289
Any imaging performed	502 (90)	419 (90)	83 (95)	0.139
Number of images performed (median, IQR)	3 (2-5)	3 (2-4)	4 (2-6.5)	0.0001***
Skeletal imaging	341 (62)	278 (60)	63 (72)	0.034*
Echocardiogram	269 (49)	211 (45)	58 (67)	0.0002***
Source of infection, *n*= 552				
Osteoarticular	273 (49)	230 (49)	43 (49)	1
Device-related, *n*= 123	123 (22)	103 (22)	20 (22)	1
Central vascular catheter	106 (86)	88 (85)	18 (90)	0.559
Orthopaedic device	6 (5)	5 (5)	1 (5)	1
Cardiac device	6 (5)	6 (6)	0 (0)	0.263
Peripheral IV cannular	5 (4)	4 (4)	1 (5)	0.838
Deep soft tissue infection	122 (22)	97 (21)	25 (29)	0.1
Skin and soft tissue infection	83 (15)	64 (14)	19 (22)	0.057
Pleuropulmonary	80 (14)	56 (12)	24 (27)	0.0003***
No focus	78 (14)	71 (15)	7 (8)	0.083
Endovascular	37 (7)	23 (5)	14 (16)	0.0002***
Infective Endocarditis	31 (6)	22 (5)	9 (10)	0.067
Other	14 (2)	8 (2)	6 (7)	0.009**
Central nervous system	13 (2)	8 (2)	5 (6)	0.032*
Gastrointestinal	6 (1)	6 (1)	0 (0)	0.349
Renal	5 (1)	3 (1)	2 (2)	0.424
Foci of infection, *n*=552				
No focus	78 (14)	71 (15)	7 (8)	0.083
Single site focus	387 (70)	332 (71)	55 (63)	0.136
Multifocal disease	87 (16)	62 (13)	25 (29)	0.0002***

*** p < 0.001; ** p < 0.01; * p < 0.05

Abbreviations: SAB, *S. aureus* bacteremia; IQR, interquartile range; MRSA, methicillin resistant *S. aureus*; MSSA, methicillin susceptible *S. aureus*; n, number.

Table 1d: Severity, management, and outcome of children <18 years diagnosed with *Staphylococcus aureus* bacteremia (SAB) from eleven pediatric hospitals in Australia and New Zealand (2017-2018)

Baseline characteristics	**Total *n* (%)**	**MSSA *n* (%)**	**MRSA *n* (%)**	***p* value (MRSA vs MSSA)**
Pediatric SAB *n*=552	552	465 (84)	87 (16)	-
Severity				
ICU admission for SAB *n*=550	111/550 (20)	86/463 (18)	25/87 (29)	0.0181*
Positive pressure ventilation *n*=550	68/550 (12)	49/464 (10)	19/87 (22)	0.0015**
Inotropic requirement *n*=550	47/550 (9)	35/462 (7)	12/87 (14)	0.0284*
ALT > X5 ULN *n*=512	26/512 (5)	20/430 (5)	6/82 (7)	0.4600
Creatinine > X2 ULN, *n*=541	32/541 (6)	22/455 (5)	10/86 (12)	0.0130*
Multiorgan dysfunction [a], *n*=512	43/512 (8)	31/430 (7)	12/82 (15)	0.0161*
Days febrile *n*=471, median (IQR)	4 (2-7)	4 (2-6)	5 (3-11)	0.0002***
Days of SAB *n*=552, median (IQR)	1 (1-3)	1 (1-3)	2 (1-3)	0.0403 *
Peak CRP (mg/L) ≤7d from SAB, *n*=503, median (IQR)	117 (47-205), day 2 (1-3)	104 (43-192), day 2 (1-3)	187 (68-267), day 2 (1-4)	0.0001***
SAB management				
Empiric antibiotic treatment, *n*=535				
Combination antibiotics	375/535 (70)	303/452 (67)	72/83 (87)	0.0005***
Any antibiotic susceptible	510/535 (95)	444/452 (99)	66/83 (78)	<0.0001***
Appropriate antibiotics [b]	500/535 (94)	434/452 (93)	66/83 (78)	<0.0001***
Targeted antibiotic treatment *n*=536				
Number of different targeted antibiotics, median (IQR)	2 (1-2)	2 (1-3)	2 (2-3)	<0.0001***
Combination antibiotics	87/536 (16)	53/453 (12)	34/83 (41)	<0.0001***
Length IV antibiotic/s, median (IQR)	15 (10-28)	15 (9-15)	19 (12-37)	0.019*
Length oral antibiotic/s median (IQR)	23 (14-35)	22 (14-35)	28 (14-42)	0.008**
Total length of antibiotic/s median (IQR)	26 (15-45)	23 (15-44)	39 (18-48)	0.0005***
Poor antibiotic adherence, *n*=497	16/497 (3)	11/421 (3)	5/76 (7)	0.086
History of antibiotic allergy, *n*= 547	36/547 (7)	33/460 (7)	3/87 (3)	0.161
Vancomycin trough <15mg/L, *n*=179	138/179 (77)	84/111 (76)	54/68 (79)	0.644
Vancomycin trough 15-20mg/L, *n*=179	24/179 (13)	17/111 (15)	7/68 (10)	0.337
Surgical source control performed, *n*=550	234/550 (42)	185/463 (40)	49/87 (56)	0.0057**
Number of surgeries *n*=550, median (IQR)	0 (0-1)	0 (0-1)	1 (0-2)	0.0008**
Device removal, *n*=123	88/123 (71)	73/104 (70)	15/19 (79)	0.427
Infectious Diseases consult, n=545	474/545 (87)	391/458 (84)	83/87 (95)	0.0072**
Hospital-in-the-home usage, n=546	164/546 (30)	143/461 (31)	21/85 (25)	0.268
Length of stay *n*=530, median (IQR)	15 (9-31)	13 (9-30)	21 (12.5-37.5)	0.001**
Outcome				
30-day all-cause mortality *n*=546	13/546 (2.4)	10/461 (2.2)	3/85 (3.5)	0.472
90-day all-cause mortality *n*=542	14/542 (2.6)	11/458 (2.4)	3/84 (3.6)	0.524
12-month all-cause mortality *n*=542	23/542 (4.2)	18/458 (4)	5/84 (6)	0.407
Day of death from SAB n =542, median (IQR)	21 (9.5-164)	22 (12-140)	21 (6-227)	0.912
Relapse within 90 days, n=531	21/531 (3.9)	18/450 (4.0)	3/81 (3.7)	0.899
Day of relapse from SAB *n*=530, median (IQR)	45 (38-71)	52 (41-76)	19 (16.5-29)	0.024*
Composite outcome [c] *n*=503	186 (37)	141/417 (34)	45/86 (52)	0.002**

*** p < 0.001; ** p < 0.01; * p < 0.05

Abbreviations: SAB, *S. aureus* bacteremia; MRSA, methicillin resistant *S. aureus*; MSSA, methicillin susceptible *S. aureus*; n, number; ICU, intensive care unit; ALT, alanine transferase; CRP, C-Reactive Protein; ULN, upper limit of normal; IQR, interquartile range; IV, Intravenous.

[a] Multiorgan dysfunction defined as ≥ 2 of the following: i) alanine aminotransferase ≥ five times the upper limit of normal, ii) creatinine ≥ two times the upper limit of normal, iii) positive pressure ventilation or iv) requiring inotropes for SAB.

[b] Any antibiotic administered testing susceptible using conventional laboratory methods AND commenced ≤2 day from index *S. aureus* bacteremia

[c] Composite outcome defined as any of the following: i) 90-day all-cause mortality, ii) 90-day relapse, iii) ICU admission, or iv) Length of stay > 30 days

Table 2: Univariate and multivariable logistical regression for children ≤ 18 years, diagnosed with *S. aureus* bacteremia, examining 90-day all-cause mortality [a, b]

Variable	*n* (%)	Univariate analysis		Multivariable logistic regression	
		OR (95% CI)	*p* value	aOR (95% CI)	*p* value
Multiorgan dysfunction [c]	43/511 (8)	30.04 (9.28-115.62)	< 0.0001	26.54 (4.06-268.79)	0.001 **
Osteoarticular focus	273/552 (49)	0.16 (0.02-0.60)	0.018	0.01 (.0002-0.41)	0.028 *
Prematurity	48/514 (9)	5.79 (1.71-17.55)	0.002	16.79 (1.60-296.96)	0.028*
Country: Australia	422/552 (76)	0.54 (0.18-1.81)	0.287	0.11 (0.01-0.65)	0.018*
Multifocal SAB	87/552 (16)	3.07 (0.92-9.11)	0.049	22.64 (1.41-498.49)	0.031*
Necrotizing pneumonia	13/552 (2)	14.13 (2.88-54.37)	0.0002	38.99 (1.67-1754.60)	0.034*
Empirical antibiotics inclusive of vancomycin	269/549 (49)	11.43 (2.20-209.78)	0.017	15.70 (1.55-434.39)	0.041*
Infectious diseases consult	474/545 (87)	0.36 (0.12-1.35)	0.094	0.07 (0.004-0.94)	0.048*
Congenital heart disease	48/552 (9)	4.61 (1.22-14.44)	0.013	3.83 (0.36-35.67)	0.233
≥ 2 comorbidities present	49/552 (9)	6.43 (1.90-19.51)	0.001	3.28 (0.39-30.15)	0.267
Age (years) [d]	6.3 (IQR 1.0-11.3)	0.99 (0.99-1.00)	0.274	1.00 (0.99-1.00)	0.226
Sex: male	342/552 (62)	1.10 (0.37-3.61)	0.869	2.41 (0.42-18.39)	0.349
Number of surgeries for SAB management [d]	0 (IQR 0-1)	0.86 (0.46-1.24)	0.555	0.76 (0.28-1.36)	0.474
MRSA	87/552 (16)	1.50 (0.33-4.94)	0.537	0.41 (0.04-3.26)	0.417
Pleuropulmonary focus [e]	80/552 (14)	8.58 (2.90-26.76)	0.0001	-	-
Empiric number antibiotics [d, e]	2 (IQR 1-3)	1.84 (1.15-2.92)	0.01	-	-
Empiric antibiotics inclusive of 3rd generation cephalosporin [e]	134/536 (25)	3.07 (0.94-9.98)	0.056	-	-
Pacific ethnicity (New Zealand) [f]	43/129 (33)	8.51 (1.21-169.51)	0.059	-	-
Chronic renal disease [f]	7/551 (1)	6.69 (0.34-43.28)	0.088	-	-
Aboriginal and Torres Strait Islander ethnicity (Australia) [g]	51/356 (14)	3.05 (0.63-11.98)	0.123	-	-
Targeted antibiotics inclusive of vancomycin [g]	85/539 (16)	2.07 (0.45-7.32)	0.29	-	-
Vancomycin trough <15mg/L [g]	138/179 (8)	0.57 (0.11-4.23)	0.527	-	-
Device removal [g]	88/123 (71)	1.55 (0.34-5.21)	0.511		
Age < 1 year [g]	136/552 (2)	1.22 (0.33-3.73)	0.736	-	-
Māori ethnicity (New Zealand) [g]	33/129 (26)	0.70 (0.04-4.97)	0.757	-	-
Age < 28 days [g]	49/552 (9)	0.79 (0.04-4.09)	0.82	-	-

*** p < 0.001; ** p < 0.01; * p < 0.05

Abbreviations: SAB, *S. aureus* bacteremia; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; MRSA, methicillin resistant *S. aureus*; IQR, interquartile range

[a] Multivariable logistical regression model adjusted for by age, sex, location (by country), number of surgeries performed for SAB source control and methicillin susceptibility

[b] C- statistic: 0.969; Hosmer-Lemeshow Goodness-of-Fit test: Chi-squared: 2.089, df: 8, p-value: 0.978

[c] Multiorgan dysfunction defined as ≥ 2 of the following: alanine aminotransferase ≥ five times the upper limit of normal, creatinine ≥ two times the upper limit of normal, positive pressure ventilation or requiring inotropes for SAB.

[d] Continuous variable, refence is the lowest value

[e] Variables contributing to collinearity in the model, excluded from the model

[f] Wide confidence intervals (a small number of outcome events in the variable), excluded from the model

[g] *p* value on univariate analysis ≥ 0.1, excluded from the model

Table 3: Univariate and multivariable logistical regression for children ≤ 18 years, diagnosed with *S. aureus* bacteremia, examining the composite outcome of: 90-day all-cause mortality, 90-day relapse, ICU admission or length of stay > 30 days [a, b]

Variable	*n* (%)	Univariate analysis		Multivariable logistic regression	
		OR (95% CI)	*p* value	aOR (95% CI)	*p* value
Hospital-onset SAB	115/552 (21)	9.51 (5.91-15.80)	<0.0001	6.57 (2.88-15.47)	<0.0001 ***
≥ 3 surgeries for SAB management	0 (IQR 0-1)	3.10 (1.71-5.77)	0.0002	5.47 (2.08-14.80)	0.0006***
Peak CRP >200mg/L ≤ 7d from SAB	121/470 (26)	2.81 (1.84-4.31)	<0.0001	2.99 (1.47-6.15)	0.002**
Empiric antibiotic/s inclusive vancomycin	269/549(49)	2.73 (1.90-3.93)	<0.0001	2.01 (1.00-4.10)	0.049*
Prematurity	48/514 (9)	7.48 (3.77-16.23)	<0.0001	4.45 (1.53-14.06)	0.008**
Congenital heart disease	48/552 (9)	9.74 (4.69-22.85)	<0.0001	6.21 (1.66-27.63)	0.009**
Pleuropulmonary focus	80/552 (14)	4.50 (2.73-7.60)	<0.0001	2.74 (1.06-7.09)	0.036*
≤ 1 year of age	136/552 (2)	3.28 (2.20-4.91)	<0.0001	2.31 (1.09-4.85)	0.027*
Number of days of SAB [c]	1 (IQR 1-3)	1.22 (1.12-1.34)	<0.0001	1.21 (1.01-1.45)	0.042*
Osteoarticular focus	273/552(49)	0.42 (0.29-0.59)	<0.0001	0.51 (0.23-1.09)	0.083
Multifocal SAB	87/552 (16)	3.44 (2.15-5.58)	<0.0001	2.08 (0.75-5.66)	0.153
Immune compromise	83/547 (15)	1.65 (1.03-2.65)	0.036	0.54 (0.18-1.54)	0.258
Device removal	88/123 (71)	3.27 (2.00-5.41)	<0.0001	1.68 (0.67-4.24)	0.267
Infective endocarditis focus	31/552 (6)	7.57 (3.25-20.67)	<0.0001	2.46 (0.52-13.69)	0.275
Empiric antibiotics inclusive of a beta-lactam	511/536(95)	0.28 (0.11-0.63)	0.003	0.79 (0.19-3.33)	0.748
Location: Australia	422/552(76)	0.86 (0.58-1.29)	0.464	1.23 (0.58-2.63)	0.594
MRSA	87/552 (16)	1.56 (0.98-2.48)	0.058	1.04 (0.45-2.34)	0.926
Sex: male	342/552(62)	1.10 (0.77-1.57)	0.602	1.01 (0.55-1.84)	0.987
Aboriginal and Torres Strait Islander ethnicity (Australia) [d]	51/356 (14)	2.35 (1.29-4.32)	0.006	2.06 (0.61-7.04)	0.245
Rural residence (Australia) [d]	113/417(27)	1.81 (1.17-2.81)	0.008	1.21 (0.46-3.07)	0.695
Empirical number of antibiotics [e]	2 (IQR 1-3)	2.10 (1.74-2.56)	<0.0001	-	-
≥ 2 comorbidities [e]	49/552 (9)	4.21 (2.27-8.16)	<0.0001	-	-
Age < 28 days [e]	49/552 (9)	4.21 (2.27-8.16)	<0.0001		
Empiric antibiotics inclusive of 3rd generation cephalosporins [e]	134/536 (25)	2.63 (1.77-3.93)	<0.0001	-	-
Device focus [e]	123/552(22)	2.73 (1.81-4.12)	<0.0001		
Days febrile [e]	4 (IQR 2-7)	1.05 (1.02-1.09)	0.003	-	-
Targeted antibiotics inclusive of vancomycin [e]	85/539 (16)	1.99 (1.25-3.18)	0.004	-	-
Vancomycin trough <15mg/L [e]	138/179 (8)	0.39 (0.18-0.81)	0.014	-	-
Empiric antibiotics inclusive of flucloxacillin [e]	362/536 (7)	0.67 (0.47-0.97)	0.035	-	-
Māori ethnicity (NZ) [f]	33/129 (26)	0.54 (0.22-1.22)	0.148	-	-
Pacific ethnicity (NZ) [f]	43/129 (33)	1.21 (0.57-2.54)	0.613	-	-

*** p < 0.001; ** p < 0.01; * p < 0.05

Abbreviations: SAB, *S. aureus* bacteremia; MRSA, methicillin resistant *S. aureus*; CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; aOR, adjusted odds ratio; IQR, interquartile range

[a] Multivariable logistical regression model adjusted for by age, sex, location (by country), source control (number of surgeries performed for SAB management and device removal and methicillin susceptibility

[b] C-statistic: 0.887; Hosmer-Lemeshow Goodness-of-Fit Test: Chi-squared: 6.015, df: 8, p-value: 0.646

[c] Continuous variable, refence is the lowest value

[d] Australian data only included for examining the variables: Aboriginal and Torres Strait Islander (ATSI) ethnicity and rural residence (with location by country removed) in the multivariable logistical regression model

[e] Variables contributing to collinearity in the model, excluded from the model

[f] *p* value on univariate analysis ≥ 0.1, excluded from the model

FIGURE LEGENDS

Figure 1: Study participant flowchart

Abbreviations: SAB, *Staphylococcus aureus* bacteremia; MRSA, methicillin resistant *S. aureus*; MSSA, methicillin susceptible *S. aureus*

[a] Relapse defined as any hospital representation, or *S. aureus* sterile site culture identified > 14-and ≤ 90 days from index blood culture that was deemed by the Infectious Diseases clinical site investigator to be related to the initial SAB episode.

[b] Hospital- and community-onset *Staphylococcus aureus* bacteremia were those collected > 48 hours or ≤ 48 hours after hospital presentation, respectively

Figure 2a: Site and onset of *Staphylococcus aureus* bacteremia infection in neonates and children

[a] Independent variables associated with mortality in children on multivariable logistical regression modelling

[b] Independent variables associated with the composite of: 90-day all-cause mortality, 90-day relapse, Intensive Care Unit (ICU) admission or length of stay > 30 days in children on multivariable logistical regression modelling

Figure 2b: Site and onset of *Staphylococcus aureus* bacteremia infection in neonates and children

[a] Independent variables associated with mortality on multivariable logistical regression modelling

[b] Independent variables associated with the composite of: 90-day all-cause mortality, 90-day relapse, Intensive Care Unit (ICU) admission or length of stay > 30 days on multivariable logistical regression modelling

Figure 1: Study participant flowchart

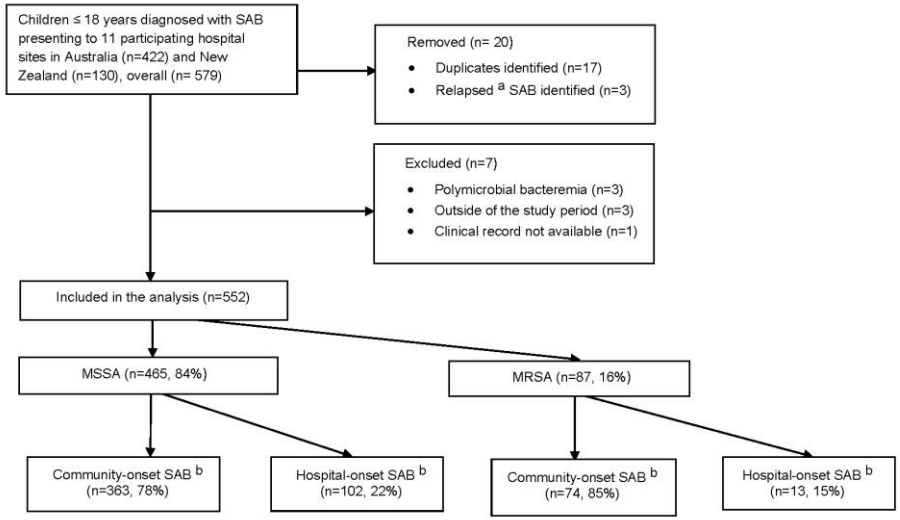

Figure 2: Site and onset of *Staphylococcus aureus* bacteraemia (SAB) infection in neonates (< 28 days, *n*=49) and children and adolescents (>1-18 years, *n*= 416)

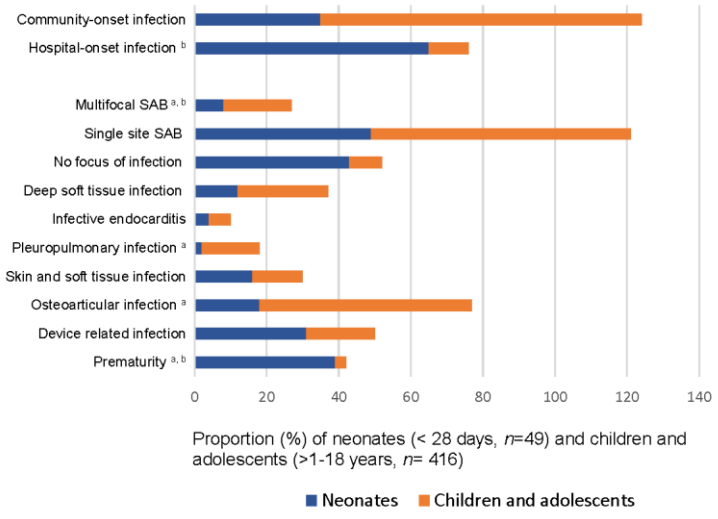

Figure 2: Site and onset of *Staphylococcus aureus* bacteremia infection in neonates and children

Neonates (<28 days, n =49)		Children (>1-18years, n=416)
(65%)[b]	**Hospital-onset infection**	(11%)[b]
(35%)	**Community-onset infection**	(89%)
(43%)	No focus of infection	(9%)
(31%)	Device related infection	(19%)
(18%)[a]	Osteoarticular infection	(59%)[a]
(16%)	Skin and soft tissue infection	(14%)
(2%)[a]	Pleuropulmonary infection	(16%)[a]
(49%)	Infective endocarditis	(6%)
(12%)	Deep soft tissue infection	(25%)
(39%)[a,b]	Prematurity	(3%)[a,b]
(8%)[a,b]	**Multi-focal *S. aureus* bloodstream infection**	(19%)[a,b]
(49%)	**Single site *S. aureus* bloodstream infection**	(72%)