**How do the epidemiology of paediatric methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *Staphylococcus aureus*** **bacteraemia differ?**

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**Abstract**

**Purpose:** To examine whether the epidemiology of bacteraemia caused by MSSA and MRSA differed in children aged <1 year and in comparison to older age groups.

**Methodology:** English mandatory MRSA and MSSA surveillance data from 2006 and 2011, respectively, were collected. Epidemiological information was descriptively analysed in relation to methicillin susceptibility and patient age. Ninety-five percent confidence intervals (CIs) are reported.

**Results/key findings:** The average incidence rate of MSSA and MRSA bacteraemia in <1 year olds was 60.2 and 4.8 episodes per 100,000 population per year, respectively. Of the cases of MSSA bacteraemia in children aged <1 year, 47.5% (95% CI: 45.1-50.0; n=760/1,599) were in neonates. With increasing age up to one year, more MSSA bacteraemias were detected ≥ seven days after admission, ranging from 0% (95% CI: 0-2.5%) in 0-2 day olds to 68.4% (95% CI: 64.0-72.5%; 333/487) in 8-28 day olds and 50.5% (95% CI: 47.1-54.0%; 423/837) in 29 day-1 year olds, a higher proportion than in older children but similar to MRSA bacteraemia. Amongst <1 year olds with MSSA bacteraemia, the underlying source was most commonly recorded as intravascular devices (34.4% [95% CI: 30.5-38.6%]; n=190/552) whilst in older age groups this declined. A similar trend was observed for MRSA bacteraemia.

**Conclusions:** Our analysis indicates that *S. aureus* bacteraemia in <1 year olds is primarily healthcare-associated, unlike MSSA bacteraemia in older age groups. Paediatric-specific interventions targeted at the healthcare setting, such as neonatal unit-specific care bundles and paediatric device-specific strategies, are required.

**INTRODUCTION**

The paediatric population represents a vulnerable infection-prone patient group. In 2013, based on comparison of English voluntary surveillance data, the incidence of methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteraemia in children <1 year of age (~ 40 cases per 100,000 population) was around 10 times higher than that due to methicillin-resistant *S. aureus* (MRSA) (~3 cases per 100,000 population) [1]. A study of paediatric MRSA bacteraemia undertaken in the UK and Ireland reported that the main burden of disease was in children aged <1 year, particularly in those with a history of invasive procedures [2]. However, no similar studies have been undertaken on paediatric bacteraemia due to MSSA. Moreover, more recently, the overall epidemiology of MRSA bacteraemia has changed from a predominantly healthcare-associated to a community-associated infection. However, analysis has not been specifically undertaken on paediatric patients to ascertain whether they follow the same trend. Several population-based [3, 4, 5, 6] and single centre [7, 8] studies reported that approximately half of identified *S. aureus* bacteraemias (which were predominantly MSSA) were healthcare-associated. Gray & O’Donoghue [8] highlighted that even amongst children with a community-associated infection, many had an intravascular device in situ, suggestive of co-morbidities and healthcare contact. Available comparative data on the underlying source of bacteraemia were conflicting, with two single centre studies [8, 9] reporting catheter and intravascular related infections as the main focus, whilst Frederiksen *et al*. [3] reported that the underlying focus was often unknown, although this could potentially reflect data quality. This paucity of robust information limits the potential for developing targeted interventions to reduce rates of *S. aureus* bacteraemia in children.

 In England, reporting of MRSA bacteraemia was made mandatory in 2001, with patient-level reporting implemented in 2005. This mandatory surveillance programme was expanded by inclusion of MSSA bacteraemia in 2011 [10, 11]. Historically most attention has been paid to MRSA bacteraemia as this infection became the key indicator for healthcare-associated infections from 2001 onwards. A range of hospital-based interventions targeted to reduce incidence were developed including intravascular device care bundles, the “cleanyourhands” campaign, and MRSA screening and decolonisation; concomitantly a decline of over 50% in MRSA bacteraemia incidence occurred [11]. Mandatory MSSA bacteraemia surveillance was introduced because declines in MSSA bacteraemia incidence observed from voluntary surveillance were extremely small [10]: 12.7% reduction from 7,915 (2004) to 6,909 reports (2013) compared to MRSA bacteraemia (the equivalent decline was 82.9% from 5,217 to 892) [1]. One could hypothesise that the epidemiology differs given how declines of MSSA have not reflected those of MRSA bacteraemia. This study aimed to examine whether the epidemiology of bacteraemia caused by MSSA and MRSA differed in children aged <1 year and in comparison to older age groups using a national mandatory surveillance dataset.

**METHODS**

**Data collection**

Mandatory surveillance data on cases of *S. aureus* bacteraemia are reported to Public Health England (PHE) by all (n= 158 at the end of April 2014) English National Health Service (NHS) acute hospital trusts (groups of hospitals run by a single management board). Twenty-eight of these hospital trusts were classified as “teaching”, 19 as specialist, three as multi-service (providing acute and community provision) and the remainder as general acute trusts [12]. Patient-level mandatory reporting of MRSA bacteraemia, including risk factor data, has been in place from late 2005 and MSSA bacteraemia from January 2011. Thus data were extracted for 2006-2014 (MRSA bacteraemia) and 2011-2014 (MSSA bacteraemia). Data from 2006 were included for MRSA bacteraemia to increase the sample size; as the incidence of this infection has dramatically declined recently including data from only 2011 would make comparisons by age group difficult to meaningfully interpret.

**Case definition**

The case definition used here is that of the surveillance programme [13] as this defines how blood cultures are reported. All blood cultures testing positive for *S. aureus* are reported regardless of whether infection is present at a different site at the time of identification in blood; MRSA is defined as a blood culture positive for *S. aureus* that is resistant to one or more of methicillin, oxacillin, cefoxitin or flucloxacillin, whilst MSSA is defined as a blood culture positive for *S. aureus* that is susceptible to the previously listed antibiotics. All reported episodes of *S. aureus* bacteraemia were eligible for inclusion in the study. Within-episode (where an episode is 14 days) duplicate entries for the same patient were identified using their NHS number (unique identifier) or where this was not completed, using date of birth and hospital number; such duplicates were removed from analysis with data on the earliest specimen retained.

**Analysis**

Epidemiological data relating to the patients, their admission, and the specimen were analysed with regard to patient age at the time of specimen collection. Patient age was categorised as: <1 year; 1-14 years; 15-44 years; 45-64 years; 65-74 years; 75years and over. Age groups in <1 year olds (yos) were further categorised as: 0-2 days (a proxy for early-onset sepsis [EOS] as other diagnostic information was not available); 3-7 days (a proxy for late-onset sepsis [LOS] as other diagnostic information was not available); 8-28 days; and 29 days to < 1 year. Records where date of birth was missing were omitted from analysis. Adults are included in the analysis to allow detailed comparison with paediatric data as the epidemiology, thus interventions, may differ. Onset of bacteraemia in relation to hospital admission was calculated as the difference (in days) between admission and specimen collection and grouped as follows: specimen collected on admission or the day after (0-1 day after admission; a proxy for community-onset infection); 2-6 days after admission; 7 days or more after admission. The latter two categories were considered proxies for healthcare-onset infection; where the onset was 2-6 days after admission the bacteraemia may be associated with healthcare contact other than the admitting hospital, whilst those with onset 7 or more days after admission are more likely to be associated with the admitting hospital. Data on source of bacteraemia is either selected from a list or entered as free text; free text entries were coded to existing categories or new categories, as appropriate, for analysis. The following represented a small proportion of reported sources and were aggregated into “other”: endocarditis; osteomyelitis; prosthetic joint infection; septic arthritis; urinary tract infection; ventilator associated pneumonia; other.

Incidence rates were calculated using the most appropriate Office for National Statistics mid-year resident population estimates [14] as the denominator. The numerator was averaged over the number of years of data used. Descriptive analyses of the data are presented. Ninety-five percent confidence intervals (CIs) are provided and differences in proportions assessed statistically using the z test statistic. All data management and analysis was undertaken using Stata 13.1 [15].

**RESULTS**

**Incidence**

After removal of within episode duplicates (n =423 [MSSA] and 84 [MRSA]) and reports with missing date of birth (n=19 [MRSA only]), there were 35,958 reports of MSSA bacteraemia from 2011 to 2014, and 22,363 reports of MRSA bacteraemia from 2006 to 2014. There were 1,599 MSSA reports and 288 MRSA bacteraemia reports in <1yos, an average rate of 60.2 (MSSA) and 4.8 (MRSA) episodes per 100,000 population per year, respectively. From 2011 to 2014, MSSA bacteraemia reports increased by 10.7% (n=8,680 to 9,608), however amongst <1 yos a decrease of 19.3% (n=466 to 376) was observed. MRSA bacteraemia reports decreased by 79.6% (n=6,743 to 780) from 2006 to 2014, with a similar percentage decrease in <1 yos (75.9%; n=37 to 8). Overall, MSSA bacteraemia incidence increased over time by 8.2% (16.3 to 17.7 per 100,000 population) but with a reduction in incidence in <1 yos of 17.5% (68.6 to 56.6 per 100,000 population).

By age, incidence showed U-shaped and J-shaped patterns for MSSA and MRSA bacteraemia, respectively, Figure 1. Amongst <1 yos the distribution of episodes by age for MSSA and MRSA bacteraemia was similar, with approximately half the cases comprising neonates (i.e. age <=28 days) (47.5% [95% CI: 45.1-50.0] n=760/1,599 and 49.0% [95% CI: 43.1-54.9%] and n=141/288, respectively) (Table 1). Amongst neonates, proportionately twice as many MSSA as MRSA bacteraemia episodes were EOS: 19.6% (95% CI: 16.8-22.6%; n=149) versus 10.6% (95% CI: 6.1-16.9%; n=15), respectively (p=0.01).

Gender was reported as “unknown” for 891 MSSA bacteraemia episodes and 343 MRSA bacteraemia episodes and was missing for 127 MRSA bacteraemia episodes. By pathogen and age group, the percentage of infections among males was higher than amongst females. Where reported, for patients with MSSA bacteraemia, the percentage of infections amongst males ranged from 66.2% (95% CI: 65.2-67.2%; n=5,718) amongst 45-64 year olds to 57.1% (54.6-60.0%; n=887) amongst 0-<1 yos (p<0.001). For patients with MRSA bacteraemia the percentage of males ranged from 67.6% (95% CI: 66.2-69.0%; n=2,922) amongst 65-74 year olds to 52.5% (46.5-58.4%; n=148) amongst 0-1 year olds (p<0.001).

**Time of bacteraemia onset**

Bacteraemia onset could not be calculated for 84 MSSA and 842 MRSA bacteraemia reports due to missing admission details. Amongst MSSA bacteraemia episodes, time of onset varied by age. Among <1 yos, 37.9% (95% CI: 35.5-40.3%; 605/1,597) had their infection detected ≤1 day after admission whilst for those over 1 year this represented 63.2% (95% CI: 62.3-64.1%; 7,574/11,502 [75 years and over]) to78.1% (95% CI: 76.1-79.9%; 1,466/1,878 [1-14 years]) of reports. Infants aged ≤2 days were primarily (85.2% [95% CI: 78.5-90.5%]; 127/149) diagnosed on admission i.e. the day they were born. Of the 22 patients aged ≤2days with specimens not collected on admission, 19 were admitted at birth with specimens collected 2 days after birth/admission; 3 were not admitted at birth but had specimens collected ≤2 days after birth. With increasing age up to one year, a greater proportion of infections were detected seven or more days after admission, ranging from 0% (95% CI: 0-2.5%) in 0-2 day olds to 68.4% (95% CI: 64.0-72.5%; 333/487) in 8-28 day olds and 50.5% (95% CI: 47.1-54.0%; 423/837) in 29 day-1 year olds. For patients with MRSA bacteraemia there was less variation in time of onset of bacteraemia for patients aged 15 years and over with 45.2% (95% CI: 42.9-47.4% [872/1,930]; 15-44 year olds) to 49.1% (95% CI: 47.6-50.6% [2,127/4,333]; 65-74 year olds) of episodes detected 7 or more days after admission. In the paediatric population there was more variability; 64.3% (95% CI: 58.5-69.9%; 184/286) of infections in <1 yos were detected 7 or more days after admission but only 34.4% (95% CI: 28.0-41.3%; 72/209) in those aged 1-14 years. In <1 yos this was primarily driven by infants aged 8-28 days (95% CI: 82.5% [73.4-89.4%]; 80/97) and 29 days to 1 year (95% CI: 68.2% [60.1-75.6%]; 101/148). Infants aged 0-2 days were predominantly diagnosed 0-1 day after admission (i.e. when they were born): 73.3% (95% CI: 44.9-92.2%; 11/15).

**Source of bacteraemia**

Source of bacteraemia was available for 12,791 MRSA and 8,938 MSSA bacteraemia episodes. Amongst <1 yos with MSSA bacteraemia, an intravascular device source accounted for 34.4% (95% CI: 30.5-38.6%; 190/552), skin and soft tissue infection (SSTI) for 18.5% (95% CI: 15.3-22.0%; n=102), mother to child transmission for 1.6% (95% CI: 0.75-3.1%; n=9) with the source reported as Not Known for 28.1% (95% CI: 24.4-32.0%; n=155) Figure 2(a). Of intravascular device-related infections 86.8% (95% CI: 81.2-91.3%; n=165) were detected two or more days after admission with the remainder detected ≤1 day after admission. Pneumonia accounted for only a small percentage of reported MSSA bacteraemia sources in this age group (2.5%; 1.4-4.2%; n=14). Amongst infants with EOS MSSA bacteraemia, the source was reported as Not Known in 42.5% of cases (95% CI: 27.0-59.1%; 17/40); whilst in other <1yo infants, intravascular devices comprised at least half of reported sources. In those aged over 1 year, intravascular devices comprised 8.5% (95% CI: 7.7-9.4%; 426/4,195 [75 year olds and over]) to 22.0% (95% CI: 18.8-25.5%; 135/613 [1-14 year olds]) of reported sources and SSTI for 20.2% (95% CI: 18.6-21.9%; 467/2,315 [65-74 year olds]) to 31.0% (95% CI: 28.9-33.1%; 615/1,986 [15-44 year olds]). Overall, the predominant underlying sources for episodes of MRSA bacteraemia were intravascular devices, with SSTIs less commonly reported Figure2(b). Amongst <1 yos with MRSA bacteraemia, the number of episodes was relatively small (n=118) thus further breakdown by source of bacteraemia and age in days yielded low numbers. Intravascular device was the single commonest named source of bacteraemia overall in this age group and ranged from 33.3% (9.9-65.1%; 4/12 [3-7 day olds]) to 50% (95% CI: 11.8-88.1%; 3/6 [0-2 day olds]). SSTIs were only reported in infants aged 8 days and older, comprising 14.0% (95% CI: 5.3-27.9%; 6/43 [8-28 days]) and 12.3% (95% CI: 5.1-23.7%; 7/57 [29 days to <1 year]).

**DISCUSSION**

This national study shows that the epidemiology of MSSA bacteraemia in children aged <1 yos in England differs from that in older patients with evidence that it is a healthcare rather than community associated infection, similar to the epidemiology of MRSA bacteraemias in children aged ≤1 y, reported here and historically [2]. Whilst particular attention should be paid to reducing paediatric MSSA bacteraemia, given its high burden compared to MRSA bacteraemia, their similar epidemiology means that interventions may be effective in reducing both paediatric MSSA and MRSA bacteraemia incidence rates. Both the timing of infection onset (predominantly after hospital admission/birth), and source of bacteraemia in <1 yos (mainly intravascular devices) highlight the importance of the healthcare setting, which is consistent with the literature [3, 4, 5, 6, 7, 8, 9]. In contrast, in older age groups with MSSA bacteraemia up to 80% of reports were diagnosed on admission, with a large percentage of SSTI-associated infections, suggestive of community associated infection.

The main burden of *S. aureus* bacteraemia in <1 yos is in neonates. Whilst we did not collect gestational age and comorbidities, we can hypothesise that a large proportion of these infants may have had significant comorbidities, invasive devices in situ, and may have been premature [2, 16], all of which increase infection risk. These infants are amongst the most vulnerable to infection in terms of the immaturity of their immune systems. Thus interventions to reduce *S. aureus* bacteraemia in <1 yos should primarily focus on the healthcare setting. Intravascular device-related interventions are needed to reduce infection developing from paediatric-specific invasive devices, such as tunnelled or umbilical catheters.

An important subset (10-20%) of neonates had EOS suggesting perinatal mother to child transmission, for example from maternal vaginal or skin colonisation. Carriage rates of MSSA, associated with increased risk of subsequent infection, are reportedly high in neonates; Achermann *et al.* [16] and Johnson *et al*. [2] identified that half of children with MRSA bacteraemia had a sample other than blood positive for MRSA a week prior to the bacteraemia. Additionally, a recent study indicated that healthcare workers and parents play an important role in MSSA transmission in neonatal intensive care units primarily through poor hand hygiene. This may facilitate MSSA outbreaks within neonatal units [16], although one may expect a similar impact on MRSA bacteraemia. Although further work is required to estimate colonisation rates of SA in infants and pregnant women in England, screening and decolonisation of these populations has the potential to reduce SA bacteraemia incidence and may be cost effective [17]. Further care bundles targeted at NICUs may be required to improve hand hygiene compliance in this setting.

We noted a decrease in MSSA bacteraemias in <1 yos of around 20% over time against an overall increase of around 11%, however incidence in <1 yos is still extremely high, and attempts should still be made to reduce burden. The reduction we observed may be the result of the hospital-based interventions targeting MRSA bacteraemia but further interventions may be required to reduce incidence more. Furthermore as the number of preterm deliveries is increasing [18] the population at particular risk of MSSA bacteraemia, and other infections is expanding. Unless interventions are implemented it will be unsurprising if disease incidence does not rise.

There are several limitations to our study. We did not have information on gestational age, co-morbidities, or colonisation (infant or maternal) history, all of which may influence the risk of infection as well as identify particular groups of <1 yos at increased risk. For example, if most of these infants were pre-term deliveries interventions could be targeted here. The sizeable percentage of episodes without source information completed also limited the records available for analysis; patients with this information may or may not be representative. Due to the small number of MRSA bacteraemias reported in recent years we have included MRSA data from 2006, whilst MSSA data starts from 2011 to allow for a larger sample size when comparing data by age group and other factors, thus reducing limitations in interpreting small sample sizes. This may however introduce some bias as we know overall the epidemiology of MRSA has changed over time. However the study benefits from being based on a large national mandatory dataset thus limiting the biases associated with smaller studies.

This study has highlighted the importance of healthcare contact and intravascular device-related MRSA and MSSA bacteraemia in patients in their first year of life and specifically in the neonatal period. Age-specific interventions are relevant as the epidemiology of MSSA bacteraemia described here suggests a greater importance of the community setting in the older paediatric population. Paediatric-focussed interventions are needed which take into account potentially higher risk devices used in paediatric medicine, such as tunnelled and umbilical catheters. Additionally screening for MSSA carriage, appropriate decolonisation and aseptic technique and improved hand hygiene amongst healthcare workers and parents may also reduce incidence. Further research is still required to identify specific reasons why MSSA bacteraemia incidence in <1yos is so much higher than MRSA given that their epidemiology in the current study appears very similar.

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Competing interests:

None

Ethical approval:

The data analysed for this work was collected by Public Health England as part of routine mandatory infectious disease surveillance.

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Figure Legends:

Figure 1. Average annual rate per 100,000 population of *Staphylococcus aureus* bacteraemia cases by methicillin sensitivity and age group

Figure 2. Source of *Staphylococcus aureus* bacteraemia by age group for patients with a) MSSA bacteraemia and b) MRSA bacteraemia

Figure 2.a MSSA bacteraemia (2011-2014)

Figure 2.b MRSA bacteraemia (2006-2014)