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Progress towards a coordinated, national paediatric antimicrobial resistance surveillance programme: *Staphylococcus aureus*, enterococcal and Gram-negative bacteraemia in Australia

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Background: There is increasing knowledge of antimicrobial usage in children yet limited availability of nationally representative paediatric-specific data on antimicrobial resistance.

Objectives: Paediatric data from this national surveillance programme are presented to explore differences between childhood and adult bloodstream infections and antimicrobial resistance surveillance.

Methods: Using information collected from a prospective coordinated antimicrobial resistance surveillance programme, children ≤18 years and adults >18 years with a positive blood culture for *Staphylococcus aureus*, *Enterococcus* spp. or Gram-negative spp. presenting to one of 34 Australian hospitals during 2013–16 were evaluated. Consistent methodologies for key sepsis pathogens were employed and a comparative analysis between children and adults was conducted.

Results: There are stark contrasts between children and adults in this national antimicrobial resistance (AMR) data set. Notable differences include lower rates of AMR, different clinical and molecular phenotypes and lower mortality amongst children. The burden of Gram-negative resistance is disproportionately experienced in children, with higher odds of death with an ESBL versus non-ESBL bacteraemia in comparison with adults.

Conclusions: These data support that children are not just 'little adults' in the AMR era, and analyses by age group are important to detect differences in antibiotic susceptibility, clinical phenotype and genetic virulence factors. Antimicrobial surveillance incorporated into routine laboratory practice is vital to inform an array of wider applications including antimicrobial guidelines, stewardship and direction for prioritization of novel antimicrobial development.

Introduction

Antimicrobial resistance (AMR) is an established global threat and carries an increased risk of infection-associated death in children infected with an MDR organism (MDRO).[1] This issue is compounded by restricted treatment options for children with MDROs and a limited development pipeline for new antimicrobials.[1] AMR is a dynamic landscape requiring coordinated microbiological laboratory surveillance, ideally embedded in existing laboratory systems. The Australian Group on Antimicrobial Resistance (AGAR), founded in 1986, has grown over time to achieve targeted surveillance for *Staphylococcus aureus*, *Enterococcus* species and Gram-negative bacteraemia across all Australian states and territories.[2] We present paediatric-specific data from this national surveillance programme to explore differences between childhood and adult bloodstream infections and AMR, highlighting the need for targeted paediatric-specific inclusion and analysis in surveillance programmes.

Materials and methods

Children ≤18 years and adults >18 years with a positive blood culture for *S. aureus*, *Enterococcus* spp. or Gram-negative spp. presenting to one of 34

Australian hospitals (31 public hospitals including 22 containing secondary paediatric services and 3 private hospitals) serviced by 26 laboratories across all Australian states and territories were included prospectively (2013–16). Twenty-five out of 30 principal referral centres (PRCs) in Australia were captured through this mechanism, including two out of six PRCs for children and 50% (11/22) of all level three neonatal ICUs (NICUs) nationally.[3–5] A new bacteraemia episode was recorded if >14 days had elapsed from the index sample. Hospital- and community-onset bacteraemia were those collected >48 h or ≤48 h after admission. Standard bacterial identification (MALDI-TOF; Bruker Daltonics, Bremen, Germany) and semi-automated susceptibility platforms (Vitek 2, bioMérieux, France; and Phoenix and BD, USA) were employed. MIC breakpoints from CLSI M100 were used: non-susceptibility included both resistant and intermediate susceptibility.[2] Each laboratory entered key demographic, clinical and microbiological data. A limit of up to 200 Gram-negative isolates were captured per laboratory. Annual cumulative population incidence rates were calculated using Australian Bureau of Statistics census population estimates for ≤18 and >18 years, taking into account the proportion of paediatric and adult PRCs captured through AGAR, along with the number of bacteraemia presentations captured for key pathogens over the 4 year period.[6] Selected isolates were transferred to national reference laboratories for typing, molecular detection of resistance mechanisms and WGS. A more detailed description of laboratory techniques can be found at http://agargroup.org.au/agar-surveys. Statistical analysis was performed using STATA v15 (StataCorp LLC, College Station, TX, USA). Ethics approval was obtained from each laboratory hospital site.

Results

Paediatric isolates from 2013–16 comprised 5% (2025/40 034) of all isolates submitted to the AGAR surveillance programme. The proportion of *S. aureus* bacteraemia (SAB) isolates from children was 8%, *Enterococcus* spp. 5% and Gram-negative spp. 4% (Table 1).

S. aureus bacteraemia

There were 751 paediatric (8.56 per 100 000/year) and 8508 adult (14.11 per 100 000/year) SAB isolates captured through national surveillance.[6] The median age of children and adults was 5.6 years (IQR 0.45–12) and 64 years (IQR 49–78), respectively. Indigenous Australians were over-represented: 14% of paediatric SAB isolates were from Indigenous children (6% of the population ≤18 years old) and 5% from Indigenous adults (3% of the population >18 years old).[7] Compared with adults, paediatric SAB was twice as likely to have a skeletal focus, whilst endocarditis was four times more frequent amongst adults (Table 1).

The predominant phenotype in children was community onset, methicillin-susceptible SAB, with a lower proportion of MRSA identified in children versus adults (Table 1). The proportion of MRSA bacteraemia episodes was more than double in Indigenous compared with non-Indigenous populations (Table 1). There was a non-significant increase over time in the proportion of all paediatric (5%, $P = 0.14$) and adult (1%, $P = 0.41$) SAB episodes caused by MRSA. This increase was only statistically significant amongst Indigenous children (37%; $P = 0.01$), with the proportion of MRSA remaining static among Indigenous adults. Clindamycin resistance was low overall (4.5%, 382/8488), but disproportionately observed in adults with MRSA infection (Table 1). No vancomycin-resistant SAB isolates were identified. The most common paediatric MLST MRSA clones were ST93-IV, ST5-IV and ST1-IV: with 15 unique clones identified in children and 55 in adults. Of these, only ST93-IV featured in the top three most frequent types in both cohorts (Table 1). The genes associated with the cytotoxin Panton–Valentine leucocidin were more frequently detected in paediatric (61%) compared with adult MRSA isolates (23%).

In comparison with adults, children with SAB had a shorter length of stay (LOS), less frequent ICU admission and a 30 day all-cause mortality that was five times lower. The point estimate of the odds of death with MRSA versus MSSA bacteraemia was increased in adults and children, although this was only statistically significant in adults [OR in children 1.95 (95% CI 0.61–6.22); OR in adults 1.56 (95% CI 1.35–1.81)].

Enterococcal spp.

A total of 199 paediatric (2.27 per 100 000/year) and 3669 (6.09 per 100 000/year) adult enterococcal bacteraemia isolates were identified.[6] The median age of children and adults was 0.2 years (IQR 0.1–2.8) and 68 years (IQR 56–78), respectively. Enterococcal bacteraemia with a biliary or urinary tract focus predominated in adults, whereas device-related infection, no focus (inclusive of febrile neutropenia) or intra-abdominal focus was a more frequent presentation amongst children (Table 1).

Antimicrobial-resistant enterococci were less commonly identified amongst paediatric isolates in comparison with adult isolates. Ampicillin resistance was identified in almost half of *Enterococcus faecium* bacteraemia in children (56% versus 91% in adults). Vancomycin-resistant *E. faecium* (VREfm) were similarly less prevalent in children compared with adults (31% versus 47%). The *vanA* and *vanB* operons were detected in 29% (204/697) and 71% (494/697) of VREfm isolates, respectively. Of the *E. faecium* isolates, the most common MLST types in both cohorts included ST 796 (Table 1), with 17 different clones identified in the paediatric cohort and 55 in the adult cohort.

Although children had a longer median LOS, adults with enterococcal bacteraemia were more frequently admitted to the ICU and had a 2-fold higher 30 day all-cause mortality. There was no significant impact of VREfm detected on paediatric mortality, with the small cohort captured (OR 6.20; 95% CI 0.22–171), which differed from that in adults (OR 1.33; 95% CI 1.04–1.69).

Gram-negative spp.

Over the 4 year period, 1055 (12.02 per 100 000/year) paediatric and 23 906 (39.65 per 100 000/year) adult Gram-negative bacteraemia isolates were identified, most frequently *Escherichia coli* and *Klebsiella pneumoniae*. By proportion, *Enterobacter* spp. and *Salmonella* spp. were over-represented in children and *Pseudomonas aeruginosa* in adults (Table 1). The median age at presentation in children was 0.7 years (IQR 0.12–5.3) and in adults was 68 years (IQR 54–80). Gram-negative hospital-onset bacteraemia was more frequent in children [33% (346/1059)] versus adults [24% (5671/23 578; $P < 0.0001$)]. Intra-abdominal, no focus or device-related infection predominated in paediatric Gram-negative bacteraemia, compared with adults where urinary and biliary tract foci prevailed.

ESBLs were detected in 9% of paediatric and 11% of adult *E. coli* and *K. pneumoniae* isolates. The proportion of ESBL Gram-negative

Table 1. Paediatric and adult AMR surveillance programme results for *Staphylococcus aureus*, *Enterococcus* spp and Gram-negative bacteraemia

Characteristic	Children	Adults	*P* value
S. aureus bacteraemia (*n* = 9259) cumulative incidence rate[6]	8.56 per 100 000/year	14.11 per 100 000/year	
Demographics			
median age, years (IQR)	6 (0.45–12)	64 (49–78)	
male, % (*n*/*N*)	64% (481/751)	60% (5111/8508)	0.5
Indigenous Australians, % (*n*/*N*)[a]	14% (51/377)[a]	5% (291/5786)[a]	<0.0001
Principal focus, % (*n*/*N*)			
skeletal	38% (203/535)	17% (1304/7705)	<0.0001
device related	18% (94/535)	20% (1570/7705)	0.09
no focus	14% (73/535)	8% (587/7705)	<0.0001
SSTI	13% (69/535)	20% (1523/7705)	<0.0001
endocarditis	2% (10/535)	9% (665/7705)	<0.0001
Susceptibility, % (*n*/*N*)			
PSSA	13% (101/750)	15% (1285/8495)	0.14
MSSA	86% (650/750)	81% (6870/8495)	0.007
MRSA	15% (110/750)	19% (1625/8495)	0.007
MRSA Indigenous Australians	41% (21/51)	36% (105/291)	0.49
clindamycin-resistant MRSA	14% (15/110)	41% (668/1625)	<0.0001
VRSA	0% (0/751)	0% (0/8495)	1
Place of onset, % (*n*/*N*)			
community-onset MRSA	79% (87/110)	68% (1103/1619)	0.0161
hospital-onset MRSA	21% (23/110)	32% (516/1619)	0.0161
Common MLST (MRSA), % (*n*/*N*)			
ST93-IV	38% (40/104)	17% (261/1562)	<0.0001
ST5-IV	16% (17/104)	8% (129/1562)	0.0046
ST1-IV	12% (12104)	10% (155/1562)	0.5128
ST22-IV	7% (7/104)	26% (404/1562)	<0.0001
ST45-V	2% (2/104)	6% (89/1562)	0.0899
PVL positive	61% (63/104)	20% (316/1562)	<0.0001
Outcomes			
median LOS, days (IQR)	15 (7–29)	19 (11–34)	
ICU admission, % (*n*/*N*)[a]	13% (48/364)[a]	17% (929/5629)[a]	0.047
30 day all-cause mortality, % (*n*/*N*)	3% (15/488)	17% (1214/7234)	<0.0001
Enterococcal spp. bacteraemia (*n*=3868) cumulative incidence rate[6]	2.27 per 100 000/year	6.09 per 100 000/year	
E. faecalis, % (*n*/*N*)	81% (162/199)	54% (1996/3669)	<0.0001
E. faecium, % (*n*/*N*)	16% (32/199)	41% (1486/3669)	<0.0001
other Enterococcus spp., % (*n*/*N*)	3% (5/199)	5% (187/3669)	0.20
Demographics			
median age, years (IQR)	0.2 (0.1–3)	68 (56–78)	
male, % (*n*/*N*)	58% (115/199)	66% (2430/3669)	0.0207
Principal focus, % (*n*/*N*)			
no focus	26% (39/150)	16% (552/3493)	0.0012
device related	21% (31/150)	11% (373/3493)	0.0002
intra-abdominal	20% (30/150)	14% (481/3493)	0.039
biliary tract	0.7% (1/150)	17% (598/3493)	<0.0001
urinary tract	7% (10/150)	18% (613/3493)	0.0005
Susceptibility (*E. faecium*), % (*n*/*N*)			
VRE	31% (10/32)	47% (694/1485)	0.07
ARE	56% (18/32)	91% (1342/1481)	<0.0001
Place of onset, % (*n*/*N*)			
hospital-onset VRE	80% (8/10)	80% (554/692)	1
community-onset VRE	20% (2/10)	20% (138/692)	1

Continued

Table 1. *Continued*

Characteristic	Children	Adults	*P* value
Common MLST (*E. faecium*), % (*n*/*N*)			
ST796	33% (5/15)	17% (219/1269)	0.41
ST203	7% (1/15)	17% (214/1269)	0.47
ST555	7% (1/15)	14% (172/1269	0.31
ST17	13% (2/15)	11% (138/1269)	0.45
ST1421	7% (1/15)	9% (116/1269)	0.58
Outcomes			
median LOS, days (IQR)	27 (7–66)	21 (IQR 10–40)	
ICU admission, % (*n*/*N*)[a]	11% (12/107)[a]	16% (418/2540)[a]	0.16
30 day mortality, % (*n*/*N*)	8% (11/139)	20% (641/3256)	0.0005
Gram-negative bacteraemia (*n*=25 422)	12.02 per 100 000/year	39.65 per 100 000/year	
cumulative incidence rate[6]			
E. coli, % (*n*/*N*)	49% (522/1055)	58% (13 748/23 906)	<0.0001
K. pneumoniae, % (*n*/*N*)	11% (118/1055)	14% (3351/23 906)	0.0058
Enterobacter spp, % (*n*/*N*)	12% (125/1055)	7% (1791/23 906)	<0.0001
P. aeruginosa, % (*n*/*N*)[b]	8% (46/586)[b]	10% (1381/13 767)[b]	0.11
Salmonella spp, % (*n*/*N*)	11% (120/1055)	2% (376/23 906)	<0.0001
Demographics			
median age, years (IQR)	0.7 (0.1–5.3)	68 (54–80)	
male, % (*n*/*N*)	57% (613/1074)	53% (12 653/24 058)	0.0102
Principal focus, % (*n*/*N*)			
urinary tract	29% (181/628)	43% (8195/18 880)	<0.0001
intra-abdominal	18% (112/627)	10% (1978/18 880)	<0.0001
biliary	2% (15/628)	16% (2979/18 880)	<0.0001
no focus	23% (142/628)	15% (2749/18 880)	<0.0001
device related	11% (71/628)	6% (1053/18 880)	<0.0001
Susceptibility, % (*n*/*N*)			
ESBL (*E. coli*)			
<18 years old	8% (43/521)	12% (1632/13 676)	
<1 year old	6% (20/338)		
neonates	9% (14/150)		
ESBL (*K. pneumoniae)*	14% (17/118)	9% (298/3335)	
<18 years old	10% (5/50)		
<1 year old	6% (1/17)		
neonates			
ESBL CTX-M positive[c]	72% (36/50)	72% (1201/1658)	1
Carbapenemases	0.3% (3/1053)	0.3% (64/23 901)	1
Place of onset, % (*n*/*N*)			
community-onset ESBL[c]	60% (36/60)	76% (1449/1915)	0.0045
hospital- onset ESBL[c]	40% (24/60)	24% (466/1915)	0.0045
Outcomes			
median LOS, days (IQR)	7 (4-13)	7 (4-21)	1
30 day all-cause mortality, % (*n*/*N*)	9% (48/538)	12% (1997/16 352)[b]	0.0345

SSTI, skin and soft tissue infection; PSSA, penicillin-susceptible *S. aureus*; PVL, Panton–Valentine leucocidin; LOS, length of stay; ARE, ampicillin-resistant enterococci.
[a]Data collected for 2013–15.
[b]Only 2 years of data available 2015–16.
[c]For species *K. pneumoniae* and *E. coli*.

bacteraemia remained static over time (including community-onset ESBL) in both children (3%; $P=0.91$) and adults (2%; $P=0.86$). The majority of ESBLs were of the CTX-M genotype (72% children and adults). Carbapenemases were rare amongst Gram-negative isolates, being detected in only 0.3%.

For Gram-negative bacteraemia, paediatric median LOS was equivalent to that in adults and 30 day mortality was closely aligned (9% versus 12% in adults). In both cohorts there was a significantly greater risk of death when ESBL activity was detected [children OR 2.7 (95% CI 1.0–7.1); adults OR 1.2 (95% CI 1.0–1.5)].

Discussion

To our knowledge, this is the first description of a national AMR surveillance programme comparing children with adults, using consistent methodologies. Whilst there is increasing information regarding antimicrobial usage in children,[8] published data from routine paediatric AMR surveillance embedded in existing laboratory systems remain limited.[9] The recent declaration of the World Society for Paediatric Infectious Diseases (WSPID) on combating AMR advocated that all surveillance programmes present neonatal- and paediatric-specific data to assist with strengthening knowledge.[10]

There are stark contrasts between children and adults in this national AMR dataset. Notable differences include lower rates of AMR, different clinical and molecular phenotypes and lower mortality amongst children. In addition, community-onset *S. aureus* resistance continues to rise dramatically amongst Indigenous children and a likely key contributing factor is lower socioeconomic status.[11] The burden of Gram-negative resistance is disproportionately experienced in children, with higher odds of death with an ESBL versus non-ESBL bacteraemia in comparison with adults.

When compared with international AMR surveillance data from Europe, similar rates of MRSA amongst both adults (21.2%) and children (16.4%) are reported.[9] As demonstrated in this Australian cohort, Antibiotic Resistance and Prescribing in European Children (ARPEC) data demonstrated no significant difference amongst third-generation cephalosporin resistance for the under 1 year versus over 1 year age group.[9] In contrast, incredibly high rates of VRE are reported in Australia in comparison with European surveillance data (31%–47% versus 8%–9%) and, conversely, significantly lower rates of third-generation cephalosporin (9%–14% versus 29.9%–37.1%) and carbapenem (0.3% versus 6.5%–13.5%) resistance amongst *K. pneumoniae* bacteraemia isolates are reported.[9]

Limitations of this study include incomplete inclusion of Australian paediatric PRC hospitals. This has since been rectified, with all six major paediatric PRC hospitals now involved in 2019. Given that not all hospitals in Australia contribute bacteraemia isolates to AGAR and Gram-negative isolates are limited to 200 per laboratory, this may have led to an underestimation of population incidence rates. Similarly, the data captured for children were not targeted to risk factors known to be important for childhood AMR (e.g. prematurity or malignancy).[12] Some data were only available across a portion of the timeframe and not all data fields were captured through routine surveillance, including sequence typing of some isolates. Despite these limitations, more than 2000 paediatric and 40 000 adult isolates were included, as a robust reflection of AMR nationally in Australia. These data support that children are not just 'little adults' in the AMR era, and analyses by age group are important to detect differences in antibiotic susceptibility, clinical phenotype and genetic virulence factors.

Antimicrobial surveillance incorporated into routine laboratory practice is vital to inform an array of wider applications including antimicrobial guidelines, stewardship and infection control policy. These data also assist in providing direction for future research including prioritization of novel antimicrobial development. The value of paediatric-specific analysis of AMR surveillance is demonstrated and the linking of paediatric-specific antimicrobial resistance to antibiotic prescriptions, to allow analysis of the impact of antimicrobial stewardship initiatives, will be paramount in the future.

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Transparency declarations

None to declare.

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