

Trends in Bacteremia Over 2 Decades in the Top End of the Northern Territory of Australia

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Background. Information on the local distribution of bloodstream pathogens helps to guide empiric antibiotic selection and can generate hypotheses regarding the effectiveness of infection prevention practices. We assessed trends in bacterial blood culture isolates at Royal Darwin Hospital (RDH) in the Northern Territory of Australia between 1999 and 2019.

Methods. Species identification was extracted for all blood cultures first registered at RDH. Thirteen organisms were selected for focused analysis. Trends were examined graphically and using univariable linear regression.

Results. Between 1999 and 2019, 189 577 blood cultures from 65 276 patients were processed at RDH. Overall, 6.72% (12 747/189 577) of blood cultures contained a bacterial pathogen. *Staphylococcus aureus* was the most common cause of bacteremia during the first decade, with an estimated incidence of 96.6 episodes per 100 000 person-years (py; 95% CI, 72.2–121/100 000 py) in 1999. Since 2009, *S. aureus* bacteremia has declined markedly, whereas there has been an inexorable rise in *Escherichia coli* bacteremia (30.1 to 74.7/100 000 py between 1999 and 2019; $P < .001$), particularly in older adults. Since 2017, *E. coli* has been more common than *S. aureus*. Rates of *Streptococcus pneumoniae* bacteremia have reduced dramatically in children, while *Burkholderia pseudomallei* remained the fourth most common bloodstream isolate overall.

Conclusions. The incidence of *S. aureus* bacteremia, though high by international standards, is declining at RDH, possibly in part due to a sustained focus on both community and hospital infection prevention practices. Gram-negative bacteremia, particularly due to *E. coli*, is becoming more common, and the trend will likely continue given our aging population.

Keywords.: Australia; bacteremia; *Escherichia coli*; Northern Territory; *Staphylococcus aureus*.

Locally relevant information on the distribution of bloodstream pathogens helps to guide appropriate empirical antibiotics for patients with sepsis. It can also generate hypotheses regarding the effectiveness of infection prevention and control practices. Historically, *Staphylococcus aureus* has been the predominant bloodstream pathogen in most regions, with a significant proportion of infections being acquired in health care institutions [1]. With greater emphasis on hand hygiene, vascular access device antisepsis and guideline-directed removal, and surgical antibiotic prophylaxis (among other measures), *S. aureus* bacteremia has declined in some industrialized countries, with gram-negative organisms, such as *Escherichia coli*, taking over as the predominant pathogens [2].

The tropical Top End of the Northern Territory of Australia has a unique demography and bacterial ecology. Some of Australia's most socioeconomically deprived and geographically isolated people live in this region, many of whom identify as First Nations Australians (Indigenous Aboriginal and Torres Strait Islander peoples). Annual monsoonal rains and persistently warm temperatures allow certain tropical environmental pathogens such as *Burkholderia pseudomallei* and *Acinetobacter baumannii* to flourish [3, 4]. High rates of infectious pyoderma, often secondary to scabies infestations, and rheumatic heart disease, as well as burgeoning epidemics of type II diabetes mellitus and end-stage kidney failure necessitating renal replacement therapy, have contributed to very high rates of *S. aureus* and Group A streptococcal bacteremia in this setting [5–9]. Overall, infectious diseases account for a very large proportion of presentations to Royal Darwin Hospital, with ~35%–60% of inpatients on antibiotics at any one time [10]. Appropriate empirical antibiotic choices are therefore critical for the avoidance of infectious morbidity and mortality in this environment.

We aimed to assess trends in the distribution of bacterial bloodstream pathogens in patients of all ages at Royal Darwin Hospital in the 21 years between 1999 and 2019.

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METHODS

Site and Local Population

Royal Darwin Hospital (RDH) is the sole tertiary referral hospital in the Northern Territory of Australia. It has around 350 beds (though it is often over capacity) and provides a full array of specialty medical services, excluding cardiac surgery and acute solid organ and bone marrow transplantation.

Patients at RDH come from a large area of ~500 000 km² encompassing much of the Top End of Australia. The resident population of the Top End is ~160 000, of whom 22% are Indigenous [11]. Aside from concentrated populations in the Darwin and Palmerston urban areas, the remainder of Top End inhabitants live in small, and often very geographically isolated, communities and their 2 regional service towns of Gove and Katherine—both with small hospitals. As the sole tertiary hospital in the Top End of the Northern Territory, a large proportion of bacteremic patients from the remote communities are admitted to Royal Darwin Hospital, including some transferred from Katherine and Gove hospitals.

Data

This study includes results of all blood cultures first registered at Royal Darwin Hospital between January 1, 1999, and December 31, 2019. No distinction could be made between community-acquired and nosocomial bacteremias. Patients of all ages were included.

Throughout the study period, blood cultures were incubated for 5 days as standard using the Bactec (Becton, Dickinson, Wokingham, UK) system before 2011 and the Bact/Alert 3D (Biomérieux, Lyon, France) system from 2011 onwards. Most pediatric patients had a single pediatric blood culture bottle collected, whereas most adult patients had both an aerobic and anaerobic bottle taken. Results, including species identification and antimicrobial susceptibilities, were entered into the TrakCare (InterSystems, Cambridge, MA, USA) laboratory data management system. Some microbial detection techniques have changed over the study period, but most bacterial identification at our lab still relies on classical benchtop methods. Current automated analytical instruments for species identification include the Vitek2 and Vitek MS (MALDI-TOF) systems (Biomérieux, Lyon, France).

Blood culture results were extracted from the TrakCare database by querying the result of the first species identification field for the full study accrual period. Relatively rare polymicrobial bacteremias (~3.8% of all bacterial bloodstream infections in 2019) will therefore have been assigned to the presumed primary pathogen (as assessed by a microbiology scientist or clinical microbiologist according to typical organism virulence and abundance in the specimen). Blood culture results were first categorized as positive or negative. Positive results were then subcategorized into those

containing a bacterial pathogen, those containing a low-pathogenicity bacterial organism (see [Supplementary Table 1](#) for a list of organisms classified as having low pathogenicity), and those containing a fungal organism. Five gram-positive and 8 gram-negative bacterial organisms or groups of organisms of particular interest because of commonness or virulence were selected for more targeted analysis, including *Staphylococcus aureus*, Group A *Streptococcus*, *Streptococcus pneumoniae*, *Enterococcus* species, hemolytic *Streptococci*, *Escherichia coli*, *Klebsiella* species, *Proteus* species (other than *vulgaris*), *Pseudomonas aeruginosa*, nontyphoidal *Salmonella* species, other “ESCAPPM” organisms ([Supplementary Table 2](#)), *Burkholderia pseudomallei*, and *Acinetobacter* species. In this analysis, we did not include antimicrobial susceptibility data, as methodological changes confounded temporal trend analysis.

Statistical Analysis

All analyses and graphing were done in STATA, version 15.1 (StataCorp, College Station, TX, USA). Overall blood culture positivity is presented as absolute numbers and as the percentage of blood cultures positive for a bacterial pathogen by time. For analyses of individual pathogens or groups of pathogens, data were concatenated such that repeat isolations of the same pathogen within a 90-day period were counted as a single “episode” of bacteremia. This comparatively prolonged period was selected due to the high local incidence of *Burkholderia pseudomallei* bacteremia and bloodstream infections associated with diabetic foot infections, both of which frequently recrudescence many weeks after the onset of infection. [Supplementary Table 3](#) provides the distribution of bacteremia episodes using a cutoff of 30 days for comparison. Temporal trends for individual pathogens were presented as number of bacteremia episodes per 100 blood cultures taken (thus allowing for changes in the proportion of patients having blood cultures taken) and as incidence of bacteremia per 100 000 person-years. Population data for all prespecified age groups (<1 year, 1 to <15 years, 15 to <65 years, and ≥65 years) for the entire Northern Territory were obtained for every year from 1999 to 2019 from the Bureau of Statistics. A multiplication factor of 0.651 was used to estimate the population of the Top End specifically serviced directly by Royal Darwin Hospital, based on the proportion of people living in the Greater Darwin and Daly-Tiwi-West Arnhem statistical areas in the 2016 national census [11]. Statistical analysis of temporal trends in incidence was done by means of univariable linear regression models, without splines, for the entire study accrual period. We have presented robust standard errors to allow for within-patient correlation due to repeated episodes of bacteremia. Coefficient estimates were obtained from linear regression models for the years 1999 and 2019 to demonstrate changes in incidence by time, with *P* values referring to the slope of linear

regression trend lines. Throughout, 2-sided *P* values <.05 were regarded as statistically significant. We did not make corrections for multiple comparisons.

Ethical Approval

This study used anonymized, routinely collected data and was not deemed to pose a risk to the individuals included. We did not seek ethics committee approval for this research.

RESULTS

Between January 1, 1999, and December 31, 2019, 189 577 blood cultures from 65 276 patients were registered, and subsequently processed, at Royal Darwin Hospital (Figure 1). There was a linear increase in the number of blood cultures received at the laboratory over the study period, with a minimum of 5524 in 2000 and a maximum of 14 158 blood cultures in 2019 (Figure 2). Overall, the proportion of blood cultures containing a bacterial pathogen was 6.72% (12 747/189 577), and the proportion containing a low-pathogenicity bacterial isolate (likely reflecting blood culture contamination) was 2.64% (5002/189 577). Low-pathogenicity organisms were slightly more frequently isolated in children as compared with adults, whereas bacterial pathogens were more frequently isolated in adults (<1 y = 4.82% [920/19 104], 1 to <15 y = 3.66% [696/18 993], 15 to <65 y = 7.24% [8424/116 363], ≥65 y 7.59% [2631/34 662]). The proportion of blood cultures containing a

pathogen declined for all age groups during the study period, but most noticeably for adults (Figure 2). The overall proportion of blood cultures yielding low-pathogenicity organisms also declined during the 21 years of the study (1999: 3.76%; 95% CI, 3.36%–4.15%; 2019: 1.86%; 95% CI, 1.57%–2.15%; *P* < .001). There was no difference in the proportion of blood cultures containing a pathogen between males and females.

Specific Bloodstream Pathogens

The specific organisms presented in this analysis accounted for 86.8% (11 060/12 747) of all pathogenic blood culture isolates during the study period (Table 1) and caused 7800 discrete episodes of bacteremia. Overall, 53.7% (5941/11 060) of these blood cultures contained a gram-positive organism (associated with 4259 episodes of gram-positive bacteremia [54.6%]), and 46.3% (5119/11 060) contained a gram-negative organism (3541 [45.4%] episodes of bacteremia). *Staphylococcus aureus* was easily the most common gram-positive organism, accounting for 32.5% of all pathogenic blood culture isolates and 35.7% of the episodes of bacteremia. *Streptococcus* Group A and *S. pneumoniae* accounted for 6.46% and 5.42% of the episodes of bacteremia, respectively. Of the gram-negatives, *E. coli* was by far the most common (16.6% of all blood cultures), followed by *B. pseudomallei* and *Klebsiella* species (8.97% and 4.35%, respectively).

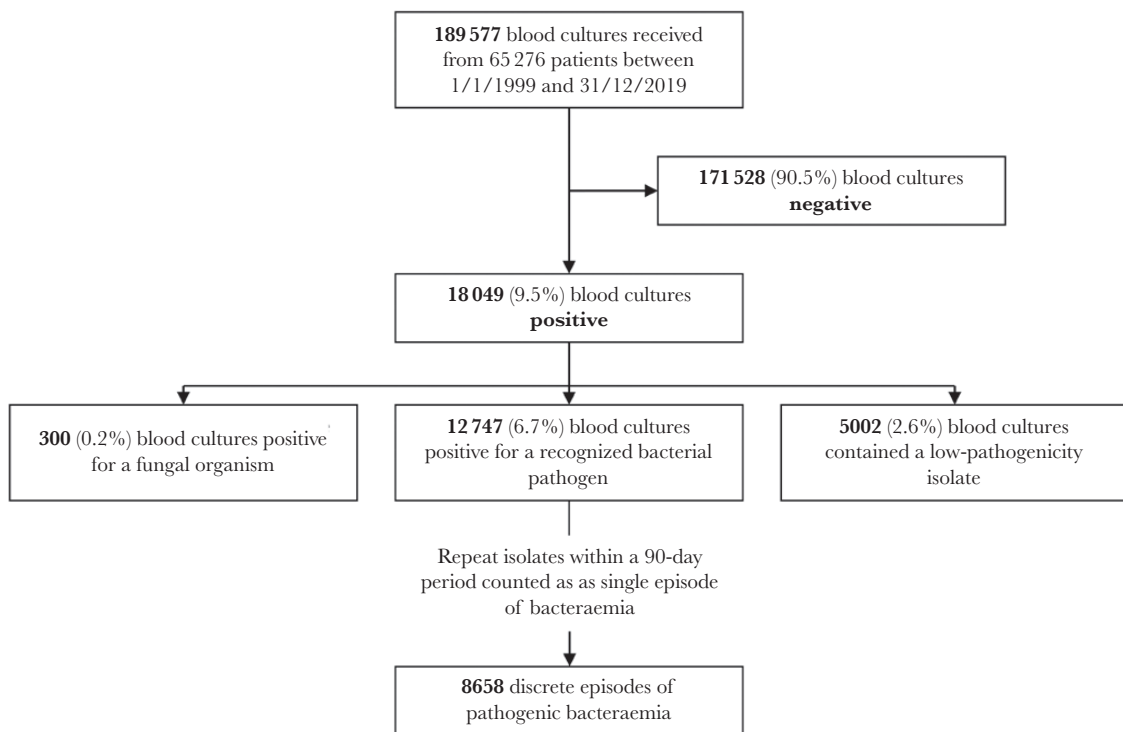


Figure 1. Study profile.

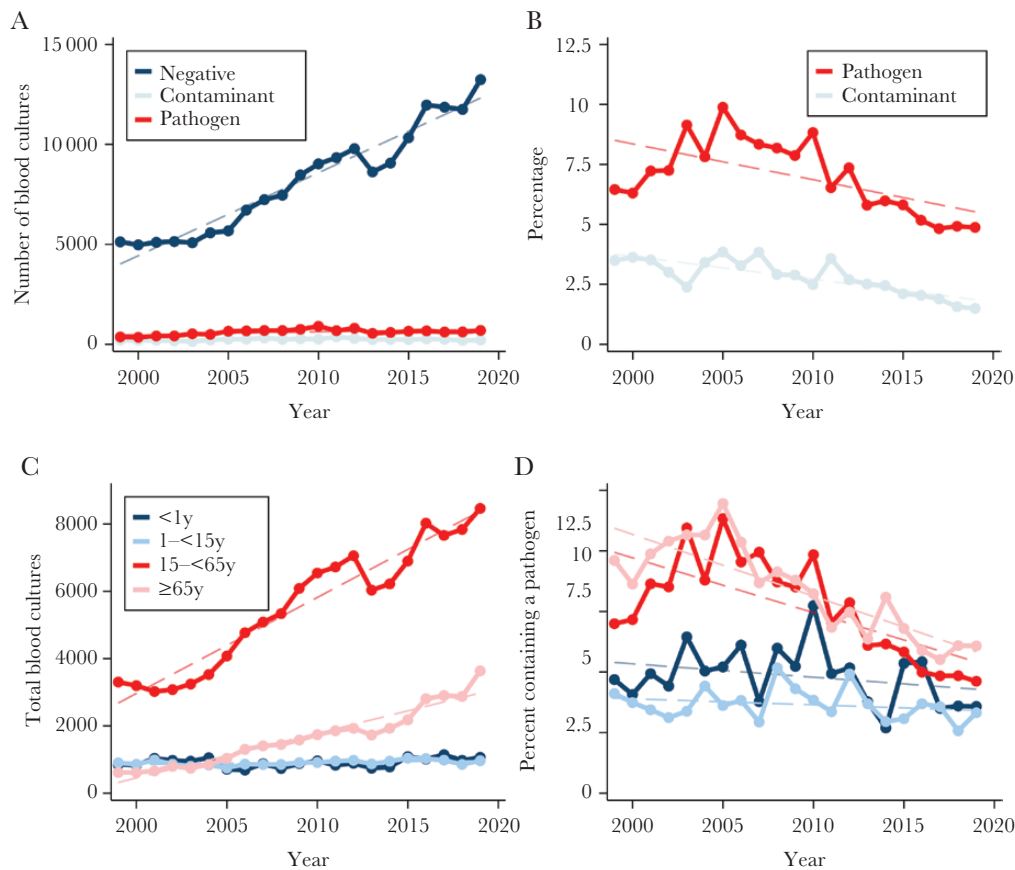


Figure 2. Trends in numbers and positivity of blood cultures received at Royal Darwin Hospital Laboratory between 1999 and 2019. A, Numbers are broken down by positivity. B, Percentage of all blood cultures containing a bacterial pathogen or a low-pathogenicity organism. C, Total blood cultures received by age group. D, Percentage of blood cultures containing a pathogen by age group.

Infants <1 year of age had a disproportionately high burden of *S. aureus* and nontyphoidal *Salmonella* bloodstream infections, while adults older than age 65 years were at particularly high risk of *E. coli* bacteremia. Bacteremia in children aged between 1 and 15 years was rare.

Temporal Trends in Specific Bloodstream Pathogens

Several trends emerged over the 21-year study period. There was an initial increase and then a sharp decline after 2009 in episodes of *S. aureus* bacteremia, resulting in an overall nonsignificant trend to a reduction in estimated incidence from 96.6 episodes per 100 000 person-years (py) in 1999 (95% CI, 72.2–121 per 100 000 py) to 86.4 per 100 000 py (95% CI, 65.3–107 per 100 000 py) in 2019 ($P = .570$) (Table 2, Figures 3 and 4). The trend to an overall reduction in *S. aureus* bacteremia was seen in all age groups except for children between 1 and 15 years of age. Pneumococcal bacteremia, though much less common than *S. aureus* bacteremia, declined substantially in frequency in infants (81.6 per 100 000 py; 95% CI, 32.7–131 per 100 000 py; to 1.59 per 100 000 py;

95% CI, 0–38.0 per 100 000 py; $P = .043$) and children aged 1 to <15 years (23.7 per 100 000 py; 95% CI, 17.9–29.6 per 100 000 py; to 6.68 per 100 000 py; 95% CI, 0.96–8.39 per 100 000 py; $P < .001$).

The opposite trends were seen for several gram-negative pathogens. The estimated incidence of *E. coli* bacteremia increased 2.5-fold from 30.1 episodes per 100 000 py (95% CI, 24.7–35.6 per 100 000 py) to 74.7 episodes per 100 000 py (95% CI, 66.5–82.8 per 100 000 py; $P < .001$), with absolute numbers of episodes exceeding those of *S. aureus* bacteremia for the last 3 years of the study. This increase was only apparent in the 15–<65- and ≥ 65 -year-old age groups. Statistically significant increases in estimated incidence were also seen for *Klebsiella* and nontyphoidal *Salmonella* bacteremias, with the latter occurring across all age groups but being particularly marked in infants (17.7 episodes per 100 000 py; 95% CI, 0–70.1 per 100 000 py; to 210 per 100 000 py; 95% CI, 101–320 per 100 000 py; $P = .017$). There were large peaks in the incidence of *Burkholderia pseudomallei* bloodstream infections in 2010 and 2012 coinciding with 3 particularly wet monsoon seasons.

Table 1. Distribution of Bloodstream Bacterial Isolates by Age Group

Pathogen	<1 Year			1 to <15 Years			15 to <65 Years			≥65 Years			All Ages ^a		
	No. (% of All Pathogenic BC)	No. Episodes (% of Episodes)	No. (% of All Pathogenic BC)	No. Episodes (% of Episodes)	No. (% of All Pathogenic BC)	No. Episodes (% of Episodes)	No. (% of All Pathogenic BC)	No. Episodes (% of Episodes)	No. (% of All Pathogenic BC)	No. Episodes (% of Episodes)	No. (% of All Pathogenic BC)	No. Episodes (% of Episodes)	No. (% of All Pathogenic BC)	No. Episodes (% of Episodes)	
Gram-positive															
<i>S. aureus</i>	483 (52.50)	372 (55.77)	301 (43.25)	224 (50.0)	2656 (31.53)	1684 (34.61)	683 (25.96)	491 (27.41)	4136 (32.45)	2784 (35.69)					
<i>Streptococcus</i> Group A	23 (2.50)	23 (3.45)	29 (4.17)	28 (6.25)	455 (5.40)	352 (7.23)	112 (4.26)	100 (5.58)	620 (4.86)	504 (6.46)					
<i>S. pneumoniae</i>	21 (2.28)	21 (3.15)	97 (13.94)	94 (20.98)	320 (3.80)	264 (5.43)	51 (1.94)	40 (2.23)	494 (3.88)	423 (5.42)					
Hemolytic <i>Streptococcus</i> sp.	41 (4.46)	37 (5.55)	3 (0.43)	3 (0.67)	205 (2.43)	162 (3.33)	116 (4.41)	96 (5.36)	366 (2.87)	299 (3.83)					
<i>Enterococcus</i> sp.	31 (3.37)	27 (4.05)	6 (0.86)	4 (0.89)	195 (2.31)	142 (2.92)	87 (3.31)	70 (3.91)	325 (2.55)	249 (3.19)					
Gram-negative															
<i>E. coli</i>	60 (6.52)	54 (8.10)	18 (2.59)	18 (4.02)	1388 (16.60)	1059 (21.76)	638 (24.25)	501 (27.97)	2114 (16.58)	1632 (20.92)					
<i>B. pseudomallei</i>	3 (0.33)	2 (0.30)	8 (1.15)	3 (0.67)	957 (11.36)	387 (7.95)	173 (6.58)	98 (5.47)	1143 (8.97)	491 (6.29)					
<i>Klebsiella</i> sp.	36 (3.91)	26 (3.90)	11 (1.58)	9 (2.01)	333 (3.95)	240 (4.93)	174 (6.61)	140 (7.82)	555 (4.35)	416 (5.33)					
<i>P. aeruginosa</i>	12 (1.30)	11 (1.65)	12 (1.72)	8 (1.79)	233 (2.77)	152 (3.12)	128 (4.87)	103 (5.75)	385 (3.02)	274 (3.51)					
Other ESCAPPM sp.	25 (2.72)	19 (2.85)	6 (0.86)	5 (1.12)	230 (2.73)	174 (3.58)	106 (4.03)	84 (4.69)	367 (2.88)	282 (3.62)					
Nontyphoidal <i>Salmonella</i> sp.	74 (8.04)	60 (9.00)	53 (7.61)	46 (10.27)	94 (1.12)	67 (1.38)	11 (0.42)	10 (0.56)	232 (1.82)	183 (2.35)					
<i>Acinetobacter</i> sp.	17 (1.85)	15 (2.25)	6 (0.86)	6 (1.34)	183 (2.17)	142 (2.92)	19 (0.72)	17 (0.95)	225 (1.77)	180 (2.31)					
<i>Proteus</i> sp.	0 (0)	0 (0)	0 (0)	0 (0)	49 (0.58)	41 (0.84)	48 (1.82)	41 (2.29)	98 (0.77)	83 (1.06)					
Total	826 (89.78)	667 (100)	550 (79.02)	448 (100)	7308 (86.75)	4866 (100)	2346 (89.17)	1791 (100)	11 060 (86.77)	7800 (100)					

Abbreviations: BC, blood culture; ESCAPPM, organisms with chromosomally mediated, inducible beta-lactamase activity (see [Supplementary Table 2](#) for the list of organisms included in this group).

^aIncludes a small number of patients with unknown age.

Table 2. Modeled Incidence of Bacteremia by Bacterial Organism, Year, and Age Group

	Episodes of Bacteremia per 100000 Person-Years (95% CI), P_{trend}														
	<1 Year			1 to <15 Years			15 to <65 Years			≥65 Years			All Ages ^a		
	1999	2019	P	1999	2019	P	1999	2019	P	1999	2019	P	1999	2019	P
Gram-positive															
<i>S. aureus</i>	841 (637–1045)	607 (343–871)	.223	31.2 (24.2–38.3)	36.1 (26.7–45.5)	.465	86.0 (61.5–110)	70.0 (49.4–90.5)	.379	342 (232–451)	272 (195–349)	.358	96.6 (72.2–121)	86.4 (65.3–107)	.570
<i>Streptococcus</i> Grp A	35.9 (0–72.2)	53.7 (1.78–106)	.638	2.74 (0–5.97)	5.68 (2.95–8.40)	.231	13.4 (8.95–17.9)	18.7 (14.2–23.2)	.158	51.6 (27.7–75.5)	65.8 (50.0–81.6)	.402	12.2 (8.56–15.9)	20.4 (17.4–23.3)	.006
<i>S. pneumoniae</i>	81.6 (32.7–131)	1.59 (0–38.0)	.043	23.7 (17.9–29.6)	6.68 (0.96–8.39)	<.001	13.8 (8.91–18.7)	10.7 (7.72–13.7)	.348	39.8 (13.9–65.6)	13.3 (0–31.5)	.187	18.6 (15.1–22.1)	9.6 (6.80–12.4)	.002
Hemolytic <i>Streptococcus</i> sp.	673 (13.4–121)	78.6 (0–163)	.854	0.09 (0–0.95)	0.80 (0–1.98)	.414	5.36 (3.79–6.94)	9.36 (7.51–11.2)	.004	26.8 (0–54.5)	78.8 (56.8–101)	.019	5.61 (3.95–7.28)	13.6 (11.5–15.7)	<.001
<i>Enterococcus</i> sp.	84.1 (22.2–146)	2.15 (0–55.7)	.155	1.11 (0–2.34)	0.11 (0–0.76)	.201	5.14 (2.28–8.01)	7.83 (5.74–9.92)	.169	37.7 (13.7–61.7)	45.2 (27.7–62.7)	.677	6.48 (4.33–8.62)	9.71 (7.39–12.0)	.087
Gram-negative															
<i>E. coli</i>	116 (38.5–193)	97.1 (34.3–160)	.760	3.09 (0.33–5.85)	2.34 (0.08–4.60)	.709	28.5 (22.1–35.0)	67.1 (59.3–75.0)	<.001	248 (172–325)	338 (293–384)	.097	30.1 (24.7–35.6)	74.7 (66.5–82.8)	<.001
<i>B. pseudomallei</i>	10.4 (0–32.4)	0 (0–3.45)	.340	0.95 (0–2.14)	0 (0–0.51)	.195	15.0 (10.5–19.5)	20.2 (13.0–27.4)	.209	51.3 (31.6–71.0)	64.8 (38.4–91.2)	.442	12.7 (9.04–16.4)	19.0 (12.7–25.4)	.087
<i>Klebsiella</i> sp.	35.0 (0–75.7)	675 (27.6–107)	.322	2.72 (0.60–4.83)	0.02 (0–1.38)	.091	7.70 (4.92–10.5)	14.1 (11.1–17.1)	.018	76.4 (41.9–111)	90.1 (58.7–121)	.616	9.12 (7.08–11.2)	17.7 (15.8–19.6)	<.001
<i>P. aeruginosa</i>	29.4 (1.46–573)	13.4 (0–38.5)	.467	0.20 (0–1.39)	2.20 (0.09–4.32)	.180	8.44 (5.25–11.6)	5.74 (3.75–7.73)	.222	75.0 (35.2–115)	53.7 (29.9–77.5)	.461	9.07 (6.02–12.1)	8.93 (6.42–11.4)	.954
Other ESCAPPM sp.	66.2 (11.9–121)	8.10 (0–48.0)	.171	1.27 (0–2.73)	0.24 (0–1.56)	.398	7.57 (4.89–10.3)	8.46 (4.70–12.2)	.756	53.1 (30.0–76.3)	49.3 (34.1–64.5)	.787	8.65 (6.48–10.8)	9.81 (6.42–13.2)	.633
Non-typhoidal <i>Salmonella</i> sp.	17.7 (0–70.1)	210 (101–320)	.017	3.71 (1.48–5.95)	10.1 (6.33–13.8)	.016	0.92 (0–2.50)	5.00 (2.48–7.52)	.037	2.95 (0–10.4)	8.11 (3.04–13.2)	.284	2.07 (0.11–4.02)	9.51 (5.79–13.2)	.009
<i>Acinetobacter</i> sp.	37.1 (14.0–60.2)	21.2 (0–46.6)	.401	2.09 (0.27–3.91)	0 (0–0.73)	.063	6.42 (2.41–10.4)	6.60 (3.83–9.36)	.953	13.3 (2.87–23.8)	8.19 (0.95–15.4)	.455	6.16 (2.90–9.42)	5.63 (3.57–7.69)	.821
<i>Proteus</i> sp.	0	0	-	0	0	-	1.71 (0.26–3.16)	2.07 (1.07–3.07)	.723	22.7 (6.49–38.9)	26.4 (7.83–44.9)	.800	2.00 (0.68–3.33)	3.38 (2.02–4.75)	.221

Abbreviation: ESCAPPM, organisms with chromosomally mediated, inducible beta-lactamase activity (see [Supplementary Table 2](#) for the list of organisms included in this group).

^aIncludes a small number of patients with unknown age.

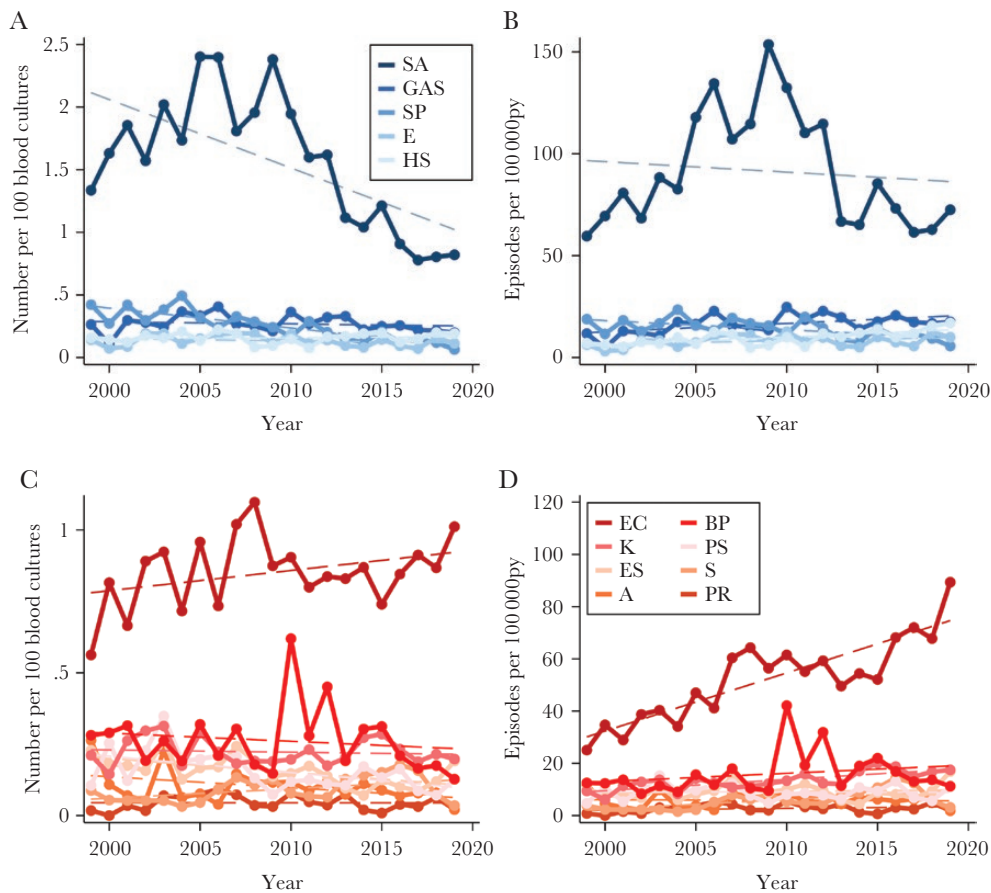


Figure 3. Number of episodes of bacteremia per 100 blood cultures received (A and C) and incidence of bacteremia per 100 000 person-years (B and D) for individual bacterial organisms or groups of organisms. Abbreviations: A, *Acinetobacter* species; BP, *Burkholderia pseudomallei*; E, *Enterococcus* species; EC, *Escherichia coli*; ES, other ESCAPPM organisms; GAS, Group A *Streptococcus*; HS, other hemolytic streptococcal species; K, *Klebsiella* species; PR, *Pseudomonas aeruginosa*; PS, *Proteus* species; py, person-years; S, nontyphoidal *Salmonella* species; SA, *Staphylococcus aureus*; SP, *Streptococcus pneumoniae*.

DISCUSSION

This is the largest and longest reported series of bacteremias from a single site in Australia. Three salient trends emerged over the 21-year period of the study with applicability to clinical care in the Northern Territory but also potentially further afield. These included a predominance of gram-positive pathogens, in particular *S. aureus*, during the first 11 years of the study, with a subsequent marked reduction in incidence from 2009 onwards; a steady increase in the incidence of *E. coli* bacteremias in older age groups, with absolute numbers exceeding those for *S. aureus* for the first time in 2017; and a substantial reduction in pneumococcal bacteremias in children.

Staphylococcus aureus is a leading national and international cause of community-acquired and health care-associated bacteremia. The predominance of this pathogen during the early 2000s is consistent with findings from other Australian studies, including from the Northern Territory [5, 7, 12, 13]. At its peak, in 2009, the incidence of *S. aureus* bacteremia in our population of 154 episodes per 100 000 person-years was among the highest reported in the Western World, likely attributable to a

combination of very high rates of superficial skin diseases such as staphylococcal and streptococcal pyoderma, often complicating severe scabies infestations, socioeconomic conditions facilitating easy community transmission, and very high rates of renal replacement therapy necessitating vascular access devices or frequent percutaneous puncture, particularly among Aboriginal Australians [8]. The subsequent marked reduction in the incidence of *S. aureus* bacteremia since 2009 (Figures 3 and 4) has been seen in other settings [14, 15] though this trend is not universal [16, 17]. The annual incidence of *S. aureus* bacteremia in the industrialized world is now typically between 10 and 50 episodes per 100 000 person-years [1, 17–19]. Over the last 5 years, the incidence rates of *S. aureus* bacteremia in our population have been between 60 and 75 episodes per 100 000 person-years, so although our rates in tropical Australia are declining, they remain high on a global scale. The reduction in the incidence of *S. aureus* bacteremia in Darwin may have multiple potential causes. There has been a prolonged focus on infection control in the hospital, particularly targeting hand hygiene and antisepsis of vascular access devices [20].

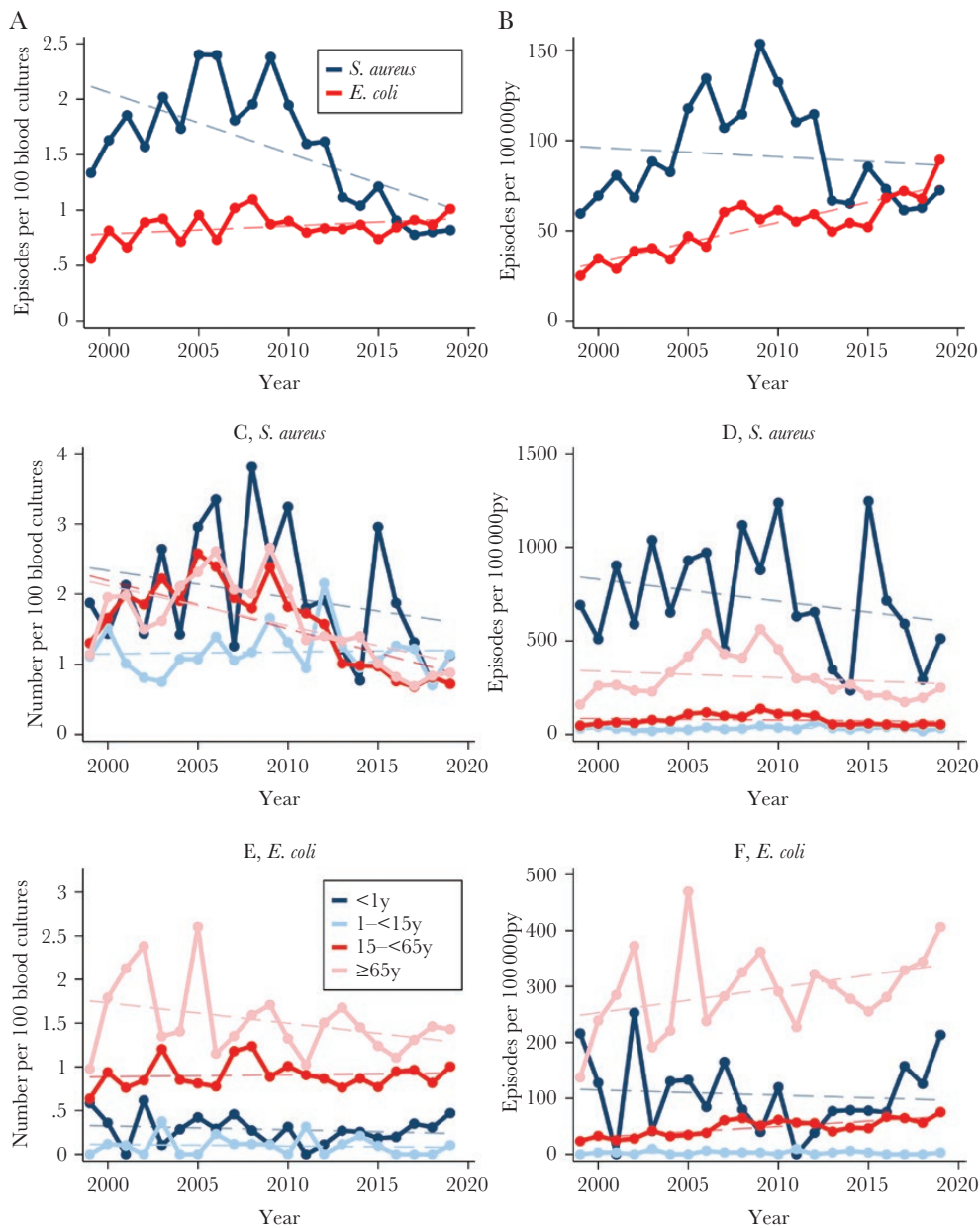


Figure 4. Number of episodes of bacteremia per 100 blood cultures received (A, C, and E) and incidence of bacteremia per 100 000 person-years (B, D, and F). A and B, Patients of all ages. C, D, E, and F, broken down by age group. Abbreviation: py, person-years.

Co-trimoxazole prophylaxis against melioidosis has been introduced in the renal dialysis and immunosuppressed populations and may have had some prophylactic effect against staphylococcal infection [21]. Various public health prevention and treatment programs in remote communities across the NT targeting skin health, trachoma (mass drug administration with azithromycin), and rheumatic heart disease (monthly intramuscular penicillin) may also have had indirect effects on *S. aureus* bacteremia through reduction in the incidence of superficial and invasive skin infections [22, 23]. Previous research has shown that community-acquired non-multidrug-resistant methicillin-resistant *S. aureus* (nmMRSA) increased

as a proportion of all *S. aureus* isolates in the Top End between 1994 and 2012 [24]. In 2012, 26.5% of *Staphylococcus aureus* isolates from any source at RDH were categorized as nmMRSA, compared with 36% in 2019 [25].

Escherichia coli bloodstream infections increased steadily over the 21 years of our study, with the incidence in all age groups combined rising from ~30 episodes per 100 000 py to 75 per 100 000 py ($P_{\text{trend}} < .001$) (Table 2; Figures 3 and 4). *Escherichia coli* is now the most common pathogenic blood culture isolate in our setting and has been since 2017. The vast majority of *E. coli* bacteremias occurred in adults, with the estimated incidence in those >65 years being particularly high

(338 episodes per 100 000 py in 2019). Bonten et al. pooled studies of *E. coli* incidence from around the globe and found that rates typically exceeded 300 per 100 000 py in those aged >75 years [2], while Kennedy and colleagues found a rate of 463 episodes per 100 000 py in males \geq 80 years old in Canberra [26]. Although the Northern Territory population has remained relatively stable over the 21 years of our study, the population aged >65 years has increased almost 3-fold [11]. This change in age structure will have compounded the increase in *E. coli* bacteremia. However, we suspect greater use of blood culture as a diagnostic tool, and increased rates of invasive urological and gastrointestinal surgical procedures may also be partly responsible. Of concern, the estimated proportion of *E. coli* isolates at RDH (any source) possessing an extended-spectrum beta-lactamase has increased from 8.5% in 2012 to 13.5% in 2019 [25]. Given our aging population and the increasing antimicrobial resistance of *E. coli* isolates, more frequent use of broad-spectrum antimicrobials is expected unless overall antibiotic selection pressure can be reduced substantially.

Pneumococcal bacteremia has reduced dramatically since 1999 among children in the Top End (Table 2). Seven-valent conjugant pneumococcal vaccination with a 23-valent polysaccharide vaccine booster at 18 months was introduced for all Aboriginal infants in Australia in 2001 [27]. The 7-valent conjugate vaccine was then rolled out to all Australian infants in 2005 and was subsequently replaced by a 13-valent conjugate vaccine in 2011 [28]. Population-scale studies have shown both reduced oropharyngeal carriage of invasive strains of pneumococcus and reduced incidence of invasive pneumococcal disease contemporaneously with vaccine roll-out, and this certainly seems the most feasible explanation for the reduction in pneumococcal bloodstream infections seen in our study [27, 28].

Blood culture contamination can have major cost implications and can cause unnecessary antibiotic use, contributing to antimicrobial resistance and patient morbidity. We noted a reduction in the proportion of blood cultures yielding a low-pathogenicity organism during the 21 years of this study (Figure 2). We suspect that this primarily relates to disproportionately increased rates of blood culture requests in adult patients, who have a lower risk of blood culture contamination than infants and children. In addition, there has been a focus on improving bedside techniques for taking blood cultures and improved hand antisepsis throughout Australian hospitals over the last decade, and this may also have contributed to the decline.

Our study has some important strengths. Consistent use of the same laboratory data system and data entry procedures allowed valid assessment of temporal trends in bacterial species over a long period. It also led to accrual of a large number of episodes of bacteremia, minimizing the play of chance variation with time. The microbiology scientists at Royal Darwin Hospital are particularly attuned to the identification of tropical

environmental pathogens such as *Burkholderia pseudomallei* and *Acinetobacter baumannii* complex, and therefore ascertainment of these organisms is likely to have been very thorough.

Our study also had some notable limitations. Susceptibility data could not be presented using this database, as testing methodology changed sufficiently during the accrual period to invalidate temporal trend assessments. The 90-day period used in this study to define repeat isolations of the same organism as a single episode of bacteremia is longer than that used in several other studies, hampering direct data comparisons. When numbers of episodes were recalculated using a 30-day cutoff, changes, if any, were negligible (Supplementary Table 3). We were not able to differentiate community-acquired from nosocomial bacteremias. Certain pathogens such as Group A *Streptococcus*, *Streptococcus pneumoniae*, and *Burkholderia pseudomallei* will have been almost exclusively community-acquired, whereas a significant proportion of *S. aureus* infections will likely have been health care-associated [29]. Elucidating this proportion may have provided stronger evidence of a potential causal link between the reduction in *S. aureus* bacteremia and enhanced infection control procedures at the hospital. Our population estimates were based on usual hospital referral patterns. Sometimes, particularly unwell patients bypass or are transferred from the community hospitals in Gove and Katherine and are admitted to Royal Darwin Hospital. This may have artificially inflated the apparent incidence of bloodstream infections in Darwin, particularly those due to the most virulent organisms such as *S. aureus*, Group A *Streptococcus*, and pneumococcus. Due to changes in regional census boundaries (and therefore lack of comparability of regional populations) over the study accrual period, a single multiplication factor obtained from the 2016 Australian census was used to estimate the size and age structure of the Royal Darwin Hospital catchment population from yearly territory-wide figures. If local population changes, including age distributions, were not proportionate to the NT as a whole, our bacteremia incidence figures, but not our absolute numbers, may have been subject to bias. Given that the hospital's catchment population accounts for approximately two-thirds of the NT population, any disproportionality is likely to have been relatively minor.

Our 2-decade-long series of bloodstream infections at Royal Darwin Hospital in the tropical Top End of Australia has revealed a substantial shift in the types of bloodstream pathogens most commonly identified. *Staphylococcus aureus* bacteremia is on the decline, possibly related to enhanced hospital and community-based infection control and prevention interventions, and has now been superseded by *E. coli* bacteremia, particularly in older age groups. Given the aging population in the Northern Territory and the apparent increase in prevalence of extended-spectrum beta-lactamases in local *E. coli* strains, our use of broad-spectrum antibiotics is predicted to increase. Careful prospective studies of antimicrobial susceptibility

patterns in blood culture isolates will be important for guiding empiric antibiotic management of severe sepsis at Royal Darwin Hospital.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. This study used anonymized, routinely collected data and was not deemed to pose a risk to the individuals included. We did not seek individual patient consent or ethics committee approval for this research.

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