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ORIGINAL ARTICLE

Evolving insights into the epidemiology of *Moraxella* species bloodstream infection from two decades of surveillance in Queensland, Australia

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Abstract

The epidemiology of *Moraxella* species bloodstream infection (BSI) is poorly defined due to their rarity. We sought to determine the incidence, risk factors, and outcomes of *Moraxella* species BSI in a large Australian population. All *Moraxella* species BSIs in patients admitted to Queensland (population estimate 5 million) public health facilities between 2000 and 2019 and submitted to Queensland pathology laboratory-based surveillance were included. Clinical and hospitalisation data were matched with laboratory-based surveillance data. Incidence rate ratios (IRR) with 95% confidence intervals (CI) were calculated. In total, 375 incident *Moraxella* species BSI occurred during 86 million person-years of surveillance, with an annualised age and sex standardised incidence of 4.3 per million residents. Isolates were most commonly identified as *M. catarrhalis* ($n = 128$; 34%) and community-associated ($n = 225$; 60%). Incidence was highest in infants, with increasing age associated with lower incidence rate. Males were at higher risk (incidence 2.9 vs. 2.0 per million, IRR1.4; 95% CI, 1.2–1.8), this was most pronounced at age extremes. Two-thirds of adults and 43% of children with *Moraxella* BSI had at least one comorbid illness. When compared to infections in adults, children were more likely to have community-associated disease, and a head and neck source focus of infection. The all-cause 30-day case-fatality rate was 4% (15/375) and this was significantly higher among adults (14/191; 7% vs 1/183; 1%; $p < 0.001$). Our findings demonstrate the low burden of *Moraxella* species BSI in a state-wide cohort, for which young children have the highest risk.

Keywords Bloodstream infection · Epidemiology · Moraxella species · Infection prevention · Surveillance

Introduction

Moraxella species infections are infrequent causes of bloodstream infections (BSI) and most commonly recognised to cause otitis media in children and exacerbations of chronic lung disease in adults [1]. They are large, extracellular, Gram-negative cocci. Although most human infections are due to *M. catarrhalis*, reports of other species including *M. osloensis*, *M. nonliquefaciens*, *M. atlantae*, and *M. lacunata* have been reported in both children and adults, particularly

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in those with significant co-morbidities [2, 3]. While most infections are upper or lower respiratory tract related, BSI associated with infections at other body sites including bone and joint, central nervous system, and endovascular infections have been reported [4–7].

The present understanding of the clinical characteristics and outcome associated with *Moraxella* species BSI is based on anecdotal case reports and a few small case series [8–10]. The largest case series reported to date included 17 patients from a single centre, with cumulative global reports describing numbers in the low hundred(s) [9–11]. Bacterial BSIs are a leading cause of mortality and morbidity in healthcare. As such it is important to gain a greater understanding of the epidemiology of *Moraxella* species infections which remain poorly defined due to low burden and isolated case reports. Therefore, the objective of this study was to define the incidence, risk factors, and outcome of *Moraxella* species BSI in a large, all-age Australian population.

Methods

Design, participants, and setting

A retrospective cohort study of prospectively collected BSI data, from January 2000 to December 2019, was undertaken in Queensland, Australia. Queensland has a population of ~ 5 million persons (2019; ~ 1.5% growth rate per annum) dispersed over a total area of 1,730,648 square kilometres. Queensland residents, of any age, with an identified BSI due to *Moraxella* species, in the public healthcare system, were included in the analysis. The state's public health system spans 16 hospitals and health services. Residents outside of Queensland were excluded. Ethical approval was obtained from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (LNR/2020/QRBW/62494). Our study is reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [12].

Study procedures

Blood culture testing was performed by Pathology Queensland. Susceptibility testing was performed using the disc diffusion method, on Mueller Hinton 5% Horse Blood Agar (MH-F) with 20 mg/L NAD (nicotinamide adenine dinucleotide) at 35 ± 1 °C in 4–6% CO2 for 18–20 h, with beta—lactamase testing using nitrocephin (M. catarrhalis are intrinsically beta-lactamase positive), and zone diameters interpretated using EUCAST (ref: EUCAST Breakpoint Tables for Interpretation of MICs and Zone Diameters, version 11.0, or earlier versions current at the time of testing). If requested, MIC testing was performed by E-test (bioMérieux). All other laboratory processes were as per standard practise as previously reported [13]. *Moraxella* species BSI were retrospectively identified by the Clinical Information System Support Unit (CISSU), Queensland Health. In Australia, hospital-level reporting of these infections is recommended nationally and supported by state surveillance programmes [14]. We defined an incident episode of bacteraemia by the first isolation of a *Moraxella* species per patient, with subsequent isolations of the same species within 30 days of the index episode classified as a recurrent bacteraemic episode. Polymicrobial infection was defined as an episode where a *Moraxella* species was co-isolated with one or more other significant pathogens within a 48 h period [15].

BSIs were classified as hospital-onset if the index blood culture was drawn 2 calendar days after admission or within 2 calendar days of hospital discharge [16]. Community-onset BSIs were diagnosed in the community or within the first 2 calendar days of hospital admission.

Healthcare-associated BSIs were those that occurred at a healthcare institution (including nursing home residents) and/or admission to hospital for more than 2 days within the 90 days prior to index blood culture [16]. Community-onset BSI that did not fulfil criteria for healthcare-associated infections were classified as community-associated. Co-morbidities were defined using the Paediatric complex chronic conditions classification system [17] for children and the Charlson Comorbidity Index [18, 19] for adults. A clinical focus was assigned based on the review of diagnosis-related group and primary diagnosis hospital discharge codes.

Patient demographic, clinical, and outcome data were obtained through state-wide database linkage including hospital admission and discharge dates, discharge survival status, as well as all diagnostic codes (ICD-10AM). Linkage with the Queensland Hospital Admitted Patient Data Collection (QHAPDC) was undertaken to obtain private and public health institution separations within the preceding 2 years and 1 year following index blood culture. For the purpose of this and the determination of the length of stay, multiple admission episodes occurring within a continuous time period (e.g., inter-hospital transfers) were deemed to represent a single hospital admission. Patient mortality was confirmed through a query to the Registry of General Deaths as of December 31, 2020.

Statistical analyses

Descriptive statistics were produced for clinical, demographic, and laboratory data. Where data was not normally distributed, median and interquartile range (IQR) were used to summarise continuous variables and percentages and counts for categorical variables.

Incident BSI episodes were the primary unit of analysis and reported as age- and sex-standardised (to 2019 Queensland population) annual rates per million population. Denominator data was stratified by age and sex using data from the Australian Bureau of Statistics [20]. Incidence rate ratios were (IRR) with exact 95% confidence intervals (CI) were calculated and tabulated for group comparison, with or missing data described in tables. An alpha value of < 0.05 was considered statistically significant. Data were analysed using Stata 16.1 (StataCorp, College Station, USA).

Results

Incidence

During 86 million person-years of surveillance, 375 incident *Moraxella* species BSI occurred, resulting in an annualised age and sex-standardised incidence of 4.3 per million residents. No individual had repeat incident infections during surveillance. Isolates were identified as *M. catarrhalis in* 128 (34%), *M. osloensis* in 61 (16%), *M. nonliquefasciens* in 8 (2%), *M. lacunata* in 3 (1%), and *M. phenylpyruvica* in 3 (1%), *M. atlantae* in 2 (< 1%), and were not further speciated in 170 (45%). Among the 375 incident cases (acquired), 46 (12%) were classified as hospital-onset, 104 (28%) as healthcare-associated, and 225 (60%) as community-associated BSIs. Despite year-to-year variability, with peak incidence in 2016, no distinct temporal trend in the overall age- and sex-standardised incidence of *Moraxella* species BSI was observed as shown in Fig. 1.

Demographic factors

Median age was 18.9 years (interquartile range [IQR], 2.0–61.3) with 155 (41%) incident episodes in females. Across the spectrum of ages, males were at significantly higher risk for developing *Moraxella* species BSI (2.9 vs. 2.0 per million, IRR 1.4; 95% CI, 1.2–1.8). Infants (< 1 year of age) were at the highest risk for *Moraxella* species BSI, with the risk decreasing during childhood to adolescence as shown in Fig. 2. Among the 56 incident infections in infants, 11 occurred within the first 2 days of birth; four in infants aged 3–29 days; five in infants aged 30–89 days and 20 in infants aged 90 to 364 days. The rate of infant *Moraxella* species BSI was 4.8 per 100,000 live births. Among adults, rates were low during middle age with subsequent increased risk in the oldest individuals (Fig. 2).

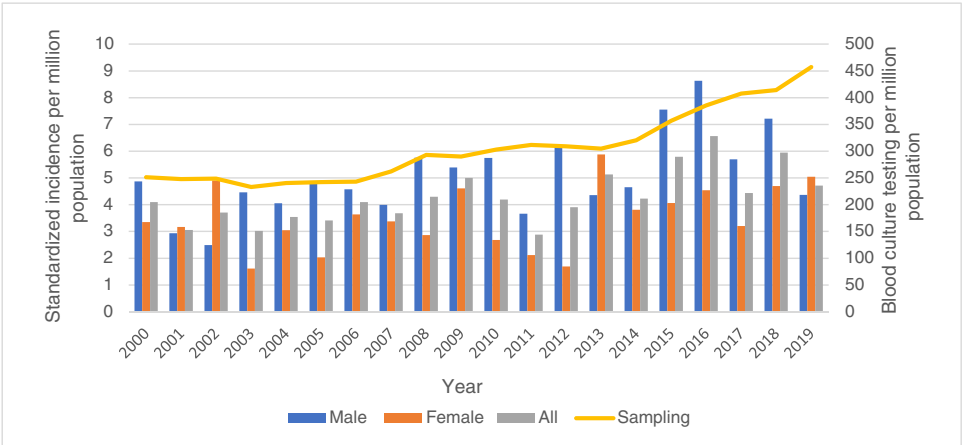

Fig. 1 Incidence of *Moraxella* species BSI

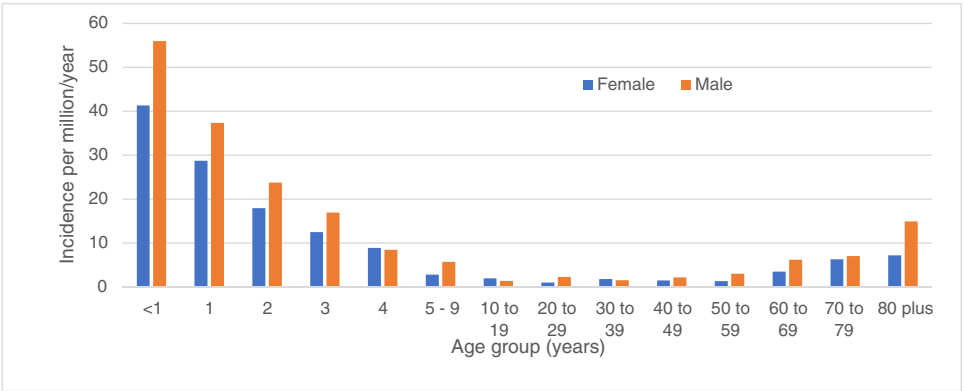

Fig. 2 Incidence of *Moraxella* species BSI per age group

Clinical characteristics and antimicrobial resistance patterns

Univariate analysis comparing clinical characteristics of adults and children with *Moraxella* species BSI is presented in Table 1. There were significant differences between adult and paediatric *Moraxella* species BSI cases. There was a small but significant difference in the onset classification related to a higher proportion in children of community- as compared to healthcare-associated BSI among community-onset infections. The distribution of organisms was also significantly different although the proportion of those not identified at the species level was much higher in the adult cohort. Paediatric cases, relative to adult cases, were more likely to have a focus of infection identified and four times more likely for this to be of a head and neck source. Among isolates reported (Table 2), 60% (128/212) were resistant to ampicillin (noting the potential of intrinsic Ampicillin resistance), with 86/112 paediatric and 42/100 adult cases ($p < 0.001$).

Role of comorbidities

Within the 189 adult cases (99%) for which detailed information was available, the median Charlson Co-morbidity Index was 2 (interquartile range, 0–3), and 63 (33%), 30 (16%), 38 (20%), and 58 (31%) had scores of zero, 1, 2, and ≥ 3, respectively. The most common individual co-morbid illnesses were malignancy, diabetes mellitus, and chronic lung disease. The presence of comorbidity was not associated with an increased mortality risk. Twenty-three percent of paediatric cases had a comorbidity compared with 67% of adults; 11% of adults had two or more comorbidities with haematologic/immunologic comorbidities most common.

Hospital admission and outcome

All but five cases were hospitalised, with a median length of stay of 5 (IQR 2–10) days. Geographical distribution of infections is presented in Table 3, with greater incidence rates identified in northern, tropical locations. The 30-day all-cause case-fatality was 4% (15/375) which was significantly higher for adults (7%; 14/191) than for children (1%; 1/184; $p = 0.001$). Among the 17 adults who died, 12 had comorbidities (86%) however this was not associated with an increased risk of mortality (risk ratio 3.24; 95% CI 0.74–14.05).

Discussion

This paper reports unique population-based data describing the incidence of *Moraxella* species BSI. To our knowledge, this is the largest population-based study to report *Moraxella* species BSI incidence, with previous case series and reports documenting cumulative cases in the low hundred(s) [9–11]. Furthermore, we report incidents for all patients allowing comparison across the age groups. Despite year-to-year variability, we did not identify a distinct trend in the overall age- and sex-standardised incidence of *Moraxella* species BSI and identified no recurrent infections. *Moraxella* species BSI were more common in men; however, this was not statistically significant. These findings add weight to the observed male dominance seen in BSIs and highlight the importance of addressing modifiable BSI risk factors that reduce the burden of BSI on the patient, family, and health care system [21].

Infants (< 1 year of age) had the highest risk of *Moraxella* species BSI, and were more likely to have community-onset infection, with incidence at age < 1 year being 30 times that of individuals aged 20 to 29 (lowest incidence age group). Adults were most commonly infected with *M. oslonensis* while > 50% of children were colonised with *M. catarrhalis*. Current evidence demonstrates children, in particular, aged less than 2 years tend to acquire a number of different *Moraxella* species strains [22] with high carriage rates in schools, playgroups, and nurrseries [23]. *M. catarrhalis* is the third most common pathogen of the respiratory tract in children, following *S. pneumoniae* and *H. influenzae* [23, 24]. Importantly in the immunocompromised child (10% of the paediatric cohort) the bacterium can cause severe infection including pneumonia, and in very rare cases meningitis [25]. Previous population-based studies of *Moraxella* species have shown by age of 1 year, two-thirds of infants have become colonised with *M. catarrhalis* species [22]. This high rate of colonisation is associated with an increased risk of otitis media. Our data support these findings with 51% of species identified as *M. catarrhalis* however most cases had an unverified focus of infection, followed by a lower respiratory or head and neck focus. Advancing age reduced the risk of infection during teenage years.

Across our cohort, *Moraxella* species BSIs in North Queensland made up a higher proportion of infection when compared to urban regions (incidence rate 20.9 versus 3.9 on the Gold Coast; heavily populated costal city). Our findings align with existing evidence which suggest individuals may experience poorer health with increasing remoteness, lower socio-economic status, and poorer access to healthcare [26, 27]. Poor accessibility to health facilities is a particularly important aspect of surveillance and disease control, as it delays or limits case detection through existing surveillance systems [28]. Furthermore, North Queensland has climates ranging from tropical to temperate and climate parameters which positively influence the development of primary BSIs [29, 30]. It would therefore be reasonable to work towards improving

Table 1 Clinical characteristics of bloodstream infections due to *Moraxella* species among individuals with and without underlying co-morbid medical illnesses, Queensland, 2000–2019

Variable	Age 18 years and older ($n=191$)	Age less than 18 years ($n=184$)	p-value
Sex, Male	114 (60%)	106 (58%)	0.8
Immunologic or haematological co-morbidity	44 (23%)	17 (10%)	< 0.001
Onset classification			0.037
Hospital onset	21 (11%)	25 (14%)	
Healthcare-associated	64 (34%)	40 (22%)	
Community-associated	106 (56%)	119 (65%)	
Focus of infection			0.004
No focus	91 (48%)	72 (40%)	
Soft tissue	10 (5%)	11 (6%)	
Bone and joint	7 (4%)	5 (3%)	
Head and neck	8 (4%)	30 (17%)	
Lower respiratory	38 (20%)	41 (23%)	
Endovascular	4 (2%)	1 (1%)	
Central nervous system	2 (1%)	1 (1%)	
Abdominal	18 (10%)	16 (9%)	
Urinary/pelvic	11 (6%)	4 (2%)	
Species			< 0.001
M. atlantae	2 (1%)	0	
M. catarrhalis	35 (18%)	93 (51%)	
M. lacunata	3 (2%)	0	
M. nonliquefasciens	5 (3%)	3 (2%)	
M. osloensis	37 (19%)	24 (13%)	
M. phenylpyruvica	2 (1%)	1 (1%)	
Moraxella species	107 (56%)	63 (34%)	
Polymicrobial infection	22 (12%)	17 (9%)	0.5
Charlson co-morbidity	189[+]		
Malignancy	44 (23%)		
Diabetes mellitus	40 (21%)		
Chronic pulmonary	29 (15%)		
Renal disease	23 (12%)		
Congestive heart failure	21 (11%)		
Liver disease	16 (8%)		
Peripheral vascular disease	13 (7%)		
Myocardial infarction	12 (6%)		
Cerebrovascular disease	10 (5%)		
Dementia	10 (5%)		
Plegia	9 (5%)		
Rheumatic	4 (2%)		
Peptic ulcer disease	1 (1%)		
HIV	1 (1%)		
Paediatric CCC		184[$]	
Haematologic or immunologic		17 (10%)	
Metabolic		13 (8%)	
Neurologic and Neuromuscular		12 (7%)	
Malignancy		8 (5%)	
Respiratory		6 (4%)	
Cardiovascular		4 (2%)	
Renal and Urologic		3 (2%)	
Gastrointestinal		4 (2%)	
Other Congenital or Genetic Defect		4 (2%)	

Table 1 (continued)

Variable	Age 18 years and older ($n=191$)	Age less than 18 years ($n=184$)	p-value
Premature and Neonatal		2 (1%)	
Other		6 (4%)	
None		142 (77%)	

+, 2 missing data; $, 17 missing data

Table 2 Species antimicrobial resistance

Moraxella species	Age 18 years and older ($n=100$)*	Age less than 18 years ($n=112$)*
M. atlantae		
Resistance		
Ampicillin	1 (0.1%)	0
Amoxicillin-clavulanate	0	0
Co-trimoxazole	0	0
M. catarrhalis		
Resistance		
Ampicillin	28 (28%)	84 (75%)
Amoxicillin-clavulanate	0	1 (1%)
Co-trimoxazole	2 (2%)	1[a] (1%)
M. lacunata		
Resistance		
Ampicillin	0	0
Amoxicillin-clavulanate	0	0
Co-trimoxazole	0	0
M. nonliquefasciens		
Resistance		
Ampicillin	2 (2%)	1 (1%)
Amoxicillin-clavulanate	0	0
Co-trimoxazole	0	0
M. osloensis		
Resistance		
Ampicillin	2 (2%)	0
Amoxicillin-clavulanate	0	0
Co-trimoxazole	2 (2%)	2 (2%)
M. phenylpyruvica		
Resistance		
Ampicillin	1 (1%)	0
Amoxicillin-clavulanate	0	0
Co-trimoxazole	0	0
Moraxella species		
Resistance		
Ampicillin	8 (8%)	1 (1%)
Amoxicillin-clavulanate	0	0
Co-trimoxazole	3[b] (3%)	1 (1%)

*212 tested out of 375; 140 resistant, 3 intermediate, 69 susceptible; [a]2 intermediate; [b]1 intermediate

Table 3 Geographical representation of *Moraxella* BSI

Hospital and health service	Cases ($n=375$)	Incidence rate (%)
Cairns and Hinterland	35	7.6
Central Queensland	20	4.9
Central West	0	0.0
Darling Downs	10	1.9
Gold Coast	40	3.9
Mackay	9	2.8
Metro North	67	3.9
Metro South	75	3.8
North West	8	13.4
South West	3	5.9
Sunshine Coast	35	4.9
Torres and Cape	10	20.9
Townsville	20	4.6
West Moreton	22	4.7
Wide Bay	21	5.4

primary care infrastructure and human resources for health in these regions to support improved accessibility and equity of access across geographical locations.

Our study is a unique, population-based analysis of a large state dataset with linked microbiological and clinical data. We studied all patients in the Queensland population across many settings including community, inpatient, and outpatient thus rates are reflected across these populations making our results generalisable to the Queensland population. However, our study has some limitations. Firstly, this study was retrospective and limited to existing variables collected in electronic medical records, limiting our ability to undertake targeted data collection (e.g., indigenous status). Secondly, we only included cultures performed within the public healthcare system and did not include patients presenting to private hospitals however the large sample size suggest that our reports represent a true estimate of the number of cases occurring in Queensland. Finally, it is likely that some of the isolates could represent contaminants, but due to the retrospective nature of the data, it was not possible to further validate this.

Implications for future practise, policy, and research

Future research could examine how sex differences (shape of immune response attributed to genetic, hormonal, and environmental factors) could be addressed to reduce BSI risk. Additional research could focus on how health behaviours, cardiovascular risk factors, comorbidities, and geography play a role in the *Moraxella* species BSI. Knowledge of factors impacting infection risk together with recognition of geographical determinants of health is important for public health leaders, researchers, and clinicians to inform preventive programs and identify individuals at high risk. Finally, investigation into antimicrobial therapy treatment including timing of empirical treatment, dosage regimes, and duration of therapy to extend our understanding of *Moraxella* species BSI, particularly in at-risk patient groups such as infants, and provide important information to progress treatment recommendations.

Conclusion

This study provides a comprehensive analysis of the incidence of *Moraxella* species BSIs and identifies patients at increased risk of these infections. To our knowledge, it is the largest population-based study to report incidents, and quantify associated mortality and hospitalisation rates, providing important new data for targeted prevention activities.

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Author contribution FE, KL conceived the study, gained ethics and governance approvals and designed the statistical analysis plan.

JS, FE, KC, KL completed the data analysis, drafted the first manuscript and reviewed and approved the final manuscript.

Data availability Please contact the corresponding author for data requests.

Code availability Please contact the corresponding author for data requests.

Declarations

Ethics approval Royal Brisbane and Women's Hospital Human Research Ethics Committee (LNR/2020/QRBW/62494).

Consent to participate Not applicable, deidentified data, ethics and governance approvals obtained.

Conflict of interest The authors declare no competing interests.

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