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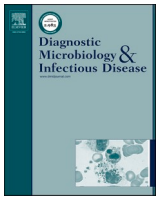

Original Article

Differentiation of *Providencia* species bloodstream infections: A population-based analysis

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ABSTRACT

Background: Although *Providencia* species are recognised as important causes of bloodstream infections (BSI), their epidemiology is not well defined due to their infrequent occurrence. Our objective was to determine the overall incidence, determinants, and outcomes of *Providencia* species BSI, and compare the epidemiology of *P. stuartii* and *P. rettgeri* in a large population.

Methods: All patients within Queensland, Australia with *Providencia* species BSI between 2000-2019 were included with clinical and outcome data collected from state-wide datasets.

Results: Among 268 residents, there was 273 incident episodes of *Providencia* species BSI; with 118 cases (43.2%) due to *P. rettgeri*, 150 cases (55.0%) due to *P. stuartii*, for age and sex adjusted incidence rates of 1.5, and 2.1 per million respectively. Five cases (<2.0%) were due to other *Providencia* species. The median age was 73.9 years, 80% were male, and most episodes were of community onset. As compared to *P. rettgeri*, patients with *P. stuartii* BSI were more likely to have dementia, peptic ulcer disease, and hemiplegia but less likely to have comorbid liver disease. The overall distribution of infection foci were different with *P. stuartii* more commonly associated with lower respiratory tract source and *P. rettgeri* with urinary source. All cause 30-day case fatality was significantly higher for *P. rettgeri* versus *P. stuartii* (35; 29.7% vs. 24; 16%; p=0.007).

Conclusions: Providencia species are important causes of community onset BSI especially in older males. Although they share similar incidence, *P. stuartii* and *P. rettgeri* BSI differ on many clinical aspects.

1. Introduction

Providencia species, most notably *Providencia stuartii* and *Providencia rettgeri*, are Enterobacterales typically found in water, soil, and animal watering tanks[1,2]. Recognised primarily to occasionally cause infections of the urinary tract, *Providencia* species bloodstream infections (BSI) were previously thought to be uncommon. However, there is growing recognition that *Providencia* species BSI can act as an opportunistic pathogen that can cause severe infections, particularly in elderly, institutionalised patients with comorbidities[1,3–5]. Adding further complexity is that management of *Providencia* species BSI presents a challenging and burdensome task due to increasing antimicrobial resistance. Additionally, several studies have reported high associated case fatality rate 20, 24, 29 and 33%[1,2,6,7].

Although *Providencia* species are clinically recognised as important causes of BSI, as a result of their rarity their epidemiology is poorly defined. Prior investigations of *Providencia* species BSI have been typically limited by small sample size, studied in hospital based or single centre settings, and none have been conducted in large, unselected populations[6]. In addition, studies have been underpowered to investigate different clinical determinants and outcomes among species within the genus. Therefore, the aim of this study was to determine the

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overall incidence, determinants, and outcomes of *Providencia* species BSI, and compare the epidemiology of *P. stuartii* and *P. rettgeri* in a large Australian population.

2. Methods

2.1. Study design

A retrospective, population-based, laboratory surveillance cohort design was used.

2.2. Study population

The study included all episodes of incident BSI amongst QLD residents of any age in Queensland Australia, diagnosed with BSI caused by *Providencia* species within the publicly funded healthcare system between January 1, 2000, and December 31st, 2019. Non-residents of QLD and repeat episodes occurring within 30 days were considered to represent the same infection and were excluded from the analysis. Data linkage was conducted by Queensland Health using patient identifiers with deidentified and anonymised data provided to the study investigators for analysis. Ethical approval was obtained from the human research ethics committee at Royal Brisbane and Women's Hospital with a waiver of individual consent in accordance with LNR/2020/QRBW/62494.

2.3. Laboratory procedures

All blood cultures during the surveillance period were processed by Pathology Queensland. The BACT/ALERT® 3D system (bioMérieux, Durham, NC) was used throughout the study period with the exception that as of 2018 the BACT/ALERT® VIRTUO®system (bioMérieux, Durham, NC) was used at the main central laboratory that manages culture submissions from the Greater Brisbane area and several rural Queensland sites. Blood cultures are routinely incubated for 5 days before being discarded for no growth. BacT/ALERT FA plus (aerobic), FN plus (anaerobic), and PF plus (paediatric) media bottles were used for culture. Species identification methods included VITEK® GN ID, API 20E and MALDI-TOF MS. Antibiotic susceptibility testing was performed using both an automated method (i.e. VITEK® AST card) and disc diffusion according to recognised standards (CLSI or EUCAST) at the time of testing.

2.4. Surveillance

Following the identification of positive blood cultures, linkages were performed with state-wide hospital admissions and death registries to obtain clinical and outcome information. Episodes of BSI were classified using previously validated definitions and algorithms[8,9]. Incident episodes were defined by the first isolation of *Providencia* species per patient; repeat isolates within 30 days were deemed to represent the same incident episode. In cases where one or more organisms were co-isolated within a 48 hour period, the BSI was classified as polymicrobial[10].

Admissions to any private or public institutions within the state were identified and discharge diagnostic codes (ICD-10AM) were obtained. The index hospitalisation included all encounters associated with the management of the BSI inclusive of inter-hospital transfers within the state. The Registry of General Deaths was queried as of December 31, 2020, to confirm deaths in any setting within Queensland. Co-morbid medical illnesses were classified using the Charlson Comorbidity Index definitions and an original weighted index using validated algorithms [11,12]. A focus of infection was assigned based on major diagnostic group and primary discharge ICD-10AM codes.

Hospital-onset BSI were defined as those where the index blood culture was drawn more than two calendar days from admission or within two calendar days of hospital discharge[13]. Community-onset BSIs were those where the index culture was drawn in the community or within the first two calendar days of discharge. Healthcare-associated BSI were those community-onset BSIs that occurred among nursing home residents, or those who had encounters at a healthcare institution within 30 days and/or admission to hospital for more than two days within the 90 days prior to index blood culture[14]. Community-associated BSIs were community-onset BSI that were not healthcare-associated.

2.5. Analysis

The statistical software package Stata 17.0 (StataCorp, College Station, USA) was used to analyse the data. The primary unit of analysis was incident BSI episodes and results were presented as age- and sex-standardised (to 2019 Queensland population) annual rates per million population. Denominator data was obtained from Queensland Health and stratified by age, sex, and hospital and health service area, using data available from the Australian Bureau of Statistics[15]. The total number of sets of blood cultures performed by Pathology Queensland per year was also obtained[16]. Skewed continuous variables were described using medians with interquartile ranges (IQR). Categorical data was compared using Fisher's exact test. All statistical tests were two sided, and p-values of <0.05 was considered statistically significant.

3. Results

3.1. Incidence

From 2000-2019, there were 273 incident episodes of *Providencia* BSI among 268 residents, with 5 patients experiencing a subsequent episode. Over 98% of the incident infections were caused by either *P. stuartii* (150/273; 55.0%), or *P. rettgeri* (118/273; 43.2%) whilst *P. alcalifaciens* and *P. rustigianii* accounted for less than 2.0% (4/273 and 1/273 respectively). Consequently, the subsequent analysis compared *P. stuartii* and *P. rettgeri* BSI only.

The age and sex adjusted annual incidence was 3.5 cases per million population. There were 213 cases in males and 55 cases in females for an incidence rate ratio (IRR) of 3.61 (95% CI; 2.59-5.12 $p<0.0001$). As shown in Fig. 1, incidence increased with age and varied by sex. When comparing species, *P. rettgeri* had an age and adjusted annual incidence of 1.5 cases per million, with 98 cases in males and 20 cases in females (IRR 4.93; 95% CI 3.03-8.43; $p<0.0001$) whilst *P. stuartii* had an age and sex adjusted annual incidence of 2.1 per million with 115 cases in males and 35 cases in females (IRR 3.31; 95% CI 2.25-4.98; $p<0.0001$).

There was no evident trend for changing incidence over the two decades of surveillance. Most incidents were reported within regional or metropolitan areas of Queensland accounting for 133/273 (49.8%) and 123/273 (46.1%), respectively. Over one third of cases (102/273; 37.4%) were polymicrobial with the most frequent co-isolates being *Proteus mirabilis, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Enterococcus faecalis*.

3.2. Clinical Features

Hospital onset infections accounted for less than 20% of episodes, with none reported during 2012 and 2013. As shown in Table 1, approximately half of episodes were community associated, and this was consistent between species. Almost all cases (except three) were admitted to hospital, with *P. rettgeri* infections admitted for median 7 days (Interquartile Range (IQR); 5-13) whilst *P. stuartii* infections were admitted for median 10 days (IQR; 6-18).

Several co-morbid medical illnesses, notably diabetes mellitus, renal disease and congestive heart failure were associated with increased risk for developing *Providencia* species BSI. Distinct species-specific

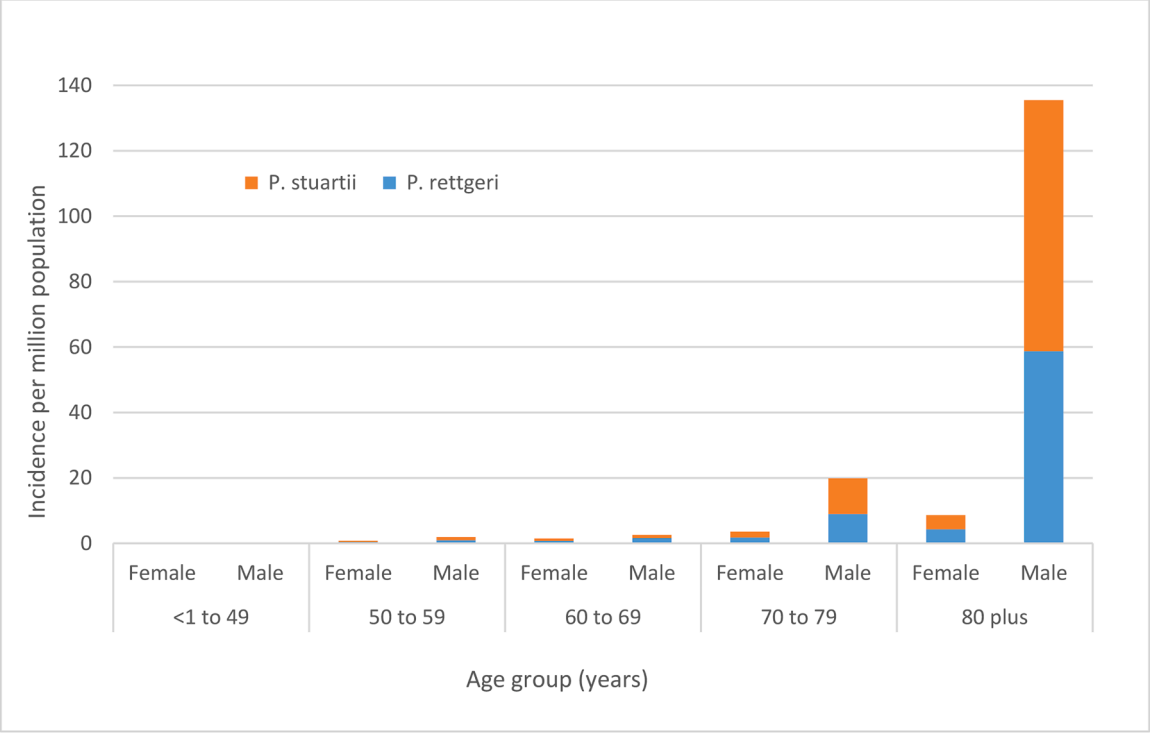

Fig. 1. Age-specific and sex-specific incidence of *Providencia* species bloodstream infection,Queensland Australia.

comorbid differences revealed liver disease was more common for *P. rettgeri* (16; 13.6% vs. 8; 5.3%; p=0.019) whilst plegia (27; 18.0% vs. 10; 8.5%; p=0.025) and dementia (31; 20.7% vs. 11; 9.3%; p=0.011) were more frequent for *P. stuartii*. As shown in Table 1, foci of infections differed between *P. stuartii* and *P. rettgeri* with one-third of *P. stuartii* cases originating from urinary pelvic area which was considerably higher than *P. rettgeri* (50; 33.3% vs. 19; 16.1%; p=0.009).

3.3. Outcome

The overall 30-day all cause case-fatality rate was 22.0% (59/268) and this was 29.7% (35/118) and 16.0% (24/150) for *P. rettgeri* and *P. stuartii*, respectively (p=0.007). Several factors were found to be associated with 30-day case-fatality and are shown in Table 2. Ninety five percent of deaths occurred during hospitalisation (56/59; 95.0%). Further, patients with *P. stuartii* and dementia had an increased the risk of 30-day all-cause mortality (6; 25.0% vs. 2; 2.7%; p=0.053). As shown in table 2, *P. stuartii* resistance appeared to have a much higher impact on 30-day case fatality with significant differences to *P. rettgeri* for Gentamicin (11/24; 45.8% vs. 6/35; 17.4%; p-value=0.022), Tobramycin (13/23; 56.6% vs. 5/32; 15.6%; p-value=0.003) and Ciprofloxacin (4/24; 16.7% vs. 0/33; 0%; p-value 0.027).

4. Discussion

In this study, we report the incidence, determinants and outcomes of species-specific *Providencia* species BSI in a large Australian population. Overall we found that advanced age, male sex, and the presence of comorbidities are considerable risk factors for developing *Providencia* species BSI; with the urinary/pelvic sources the most common. The adjusted incidence rate of *Providencia* species BSI was determined to be 3.5 per million population which highlights the rarity of these infections. These findings are useful given the increasing prevalence of chronic illness and an aging population in many high-income countries such as Australia, which may lead to an increase in the burden of *Providencia* species BSI in the future.

There is a paucity of studies that have specifically compared *P. rettgeri* to *P. stuartii* infections[5,17–21]. In 1973, Washington *et al* reported on 11 cases of *P. rettgeri* and 15 cases of *P. stuartii.* Although they report high rates of plegia and chronic indwelling urinary catheters, no species specific data was analysed[18]. Similarly, Kim and colleagues reported on three cases of *P. rettgeri* and five cases of *P. stuartii* and Choi *et al* reported on a case series of seven *P. rettgeri* and five *P. stuartii* infections but in both studies, the sample size was too small to allow species specific comparisons[5,6]. Other studies have reported on *Providencia* species BSI collectively without specifying the species [19–22]. Given the lack of comparison between *Providencia* species to date, this study represents an important review of the similarities and differences observed in a large patient cohort.

Several studies have reported exclusively on *P. stuartii* as an opportunistic pathogen and noted that this organism predominately affects the elderly with severe underlying conditions[2,7,23,24]. McHale and colleagues and found two-thirds of their isolates (n=77) were from urinary tract infections with the majority of patients being older age males who were catheterised and/or who had urological disorders[24]. Likewise, Woods *et al* reported 49 cases of predominantly older males with all but two having long-term indwelling catheters[7]. Other studies fitting this demographic report on additional comorbidities such as plegia and/or neurological disease being risk factors for infection[6,18,23]. Although our study reports similar trends in age, sex and foci of infection, significantly more *P. stuartii* cases had dementia or plegia as co-morbidities, whilst *P. rettgeri* had a higher proportion of liver disease. Given the lack of studies in *P. rettgeri* to date, further species-specific research is warranted.

Studies dating back to 1968 have reported that *Providencia* species infections were primarily acquired in the hospital settings[6,18–20,22, 24–26]. However, a more recent study by Woods *et al* found no nosocomial infections and reported 96% (47/49) of cases were from nursing homes and two from the community. In our study, we found over 80% of *Providencia* species BSI cases were either healthcare associated or community onset, and all but three cases were admitted to hospital. While it is possible that the epidemiology is changing with time, small sample

Table 1
Clinical determinants of patients with *Providencia rettgeri* and *Providencia stuartii* bloodstream infections.

Factor	*Total (n=268)*	*P. rettgeri (n=118)*	*P. stuartii (n=150)*	*p*-value
Median years of age (IQR)	73.9 (58.9-84.2)	74.1 (60.8-85.2)	73.7 (58.6-83.6)	0.420
Male sex (%)	213 (79.5)	98 (83.1)	115 (79.7)	0.199
Onset class (%)				0.527
Hospital onset	51 (19.03)	20 (17.0)	31 (20.7)	
Healthcare-associated	93 (34.7)	39 (33.1)	54 (36.0)	
Community-associated	124 (46.3)	59 (50.0)	65 (43.3)	
Median Charlson (IQR)	2[1–2]	2.5[1–4]	2[1–4]	0.531
Polymicrobial (%)	100 (37.3)	38 (32.2)	62 (41.3)	0.129
Comorbidities (%)				
Myocardial infarction	23 (8.6)	12 (10.2)	11 (7.3)	0.411
Congestive heart failure	53 (19.8)	22 (18.6)	31 (20.7)	0.680
Peripheral vascular disease	20 (7.5)	11 (9.3)	9 (6.0)	0.304
Cerebrovascular disease	39 (14.6)	13 (11.0)	26 (17.3)	0.145
Dementia	42 (15.7)	11 (9.3)	31 (20.7)	0.011
Chronic pulmonary	33 (12.3)	18 (15.3)	15 (10.0)	0.194
Rheumatic	4 (1.5)	3 (2.5)	1 (<1.0)	0.209
Peptic ulcer disease	9 (3.4)	1 (<1.0)	8 (5.3)	0.043
Liver disease	24 (9.0)	16 (13.6)	8 (5.3)	0.019
Diabetes mellitus	68 (25.4)	29 (24.6)	39 (26.0)	0.790
Plegia	37 (13.8)	10 (8.5)	27 (18.0)	0.025
Renal disease	60 (22.4)	26 (22.0)	34 (22.7)	0.902
Malignancy	42 (15.7)	22(18.6)	20 (13.3)	0.235
Focus of infection (%)				0.009
No focus/primary	133 (49.6)	60 (50.9)	73 (48.7)	
Soft tissue	31 (11.8)	16 (13.6)	15 (10.0)	
Bone and joint	4 (1.5)	3 (2.5)	1 (<1)	
Head and neck	0	0	0	
Lower respiratory	18 (6.7)	11 (9.3)	7 (4.7)	
Endovascular	0	0	0	
Central nervous	0	0	0	
Abdominal	13 (4.9)	9 (7.6)	4 (2.7)	
Urinary/pelvic	69 (25.8)	19 (16.1)	50 (33.3)	
Antimicrobial resistance (%)				
Cefepime	2/198 (1.0)	1/91 (1.1)	1/107 (<1.0)	1
Cefotaxime	14/54 (25.9)	5/22 (22.7)	9/32 (28.1)	0.758
Cefoxitin	5/191 (2.6)	2/89 (2.3)	3 (2.9)	1
Ceftazidime	11/238 (4.6)	6/110 (5.5)	5/128 (3.9)	0.759
Ceftriaxone	6/225 (2.7)	1/100 (1.0)	5/125 (4.0)	0.230
Ciprofloxacin	7/263 (2.7)	0/116 (0)	7/147 (4.8)	0.019
Imipenem	0/50 (0.0)	0/21 (0.0)	0/29 (0.0)	1
Meropenem	0/236 (0.0)	0/109 (0.0)	0/127 (0.0)	1
Pipercillin-Tazobactam	3/190 (1.6)	3/84 (3.6)	0/106 (0)	0.085
Ticarcillin-Clavulanate	10/253 (4.0)	2/111 (1.8)	8/142 (5.6)	0.193

Table 2
Factors associated with 30-day all cause case-fatality due to *Providencia rettgeri and Providencia stuartii* BSI.

Factor	*Total (n=59/268)*	*P. rettgeri (n=35)*	*P. stuartii (n=24)*	*p*-value
Median age (IQR)	74.3 (61.4-84.2)	71.1 (60.9-82.9)	78.8 (65.8-84.6)	0.420
Male sex (%)	42 (71.2)	24 (68.6)	18 (75.0)	0.592
Infection onset (%)				0.673
Hospital	16 (27.1)	8 (22.9)	8 (33.3)	
Healthcare associated	19 (32.2)	12 (34.3)	7 (29.2)	
Community associated	24 (40.7)	15 (42.9)	9 (37.5)	
Median Charlson (IQR)	3[2–6]	4[2–6]	3[1–4]	0.495
Polymicrobial (%)	26 (44.1)	11 (31.4)	15 (62.5)	0.032
Myocardial infarction (%)	6 (10.2)	5 (14.3)	1 (4.2)	0.385
Congestive heart failure (%)	17 (28.8)	12 (34.3)	5 (20.8)	0.382
Peripheral vascular disease (%)	7 (11.9)	6 (17.1)	1 (4.2)	0.223
Cerebrovascular disease (%)	7 (11.9)	3 (8.6)	4 (16.7)	0.427
Dementia (%)	8 (13.6)	2 (5.7)	6 (25.0)	0.053
Chronic pulmonary disease (%)	6 (10.2)	4 (11.4)	2 (8.3)	1
Rheumatic disease (%)	1 (1.7)	0	1 (4.2)	0.407
Peptic ulcer disease (%)	3 (5.1)	0	3 (12.5)	0.062
Liver disease (%)	10 (17.0)	8 (22.9)	2 (8.3)	0.177
Diabetes mellitus (%)	14 (23.7)	8 (22.9)	6 (25.0)	1
Plegia (%)	3 (5.1)	0	3 (12.5)	0.062
Renal disease (%)	16 (27.1)	9 (25.7)	7 (29.2)	0.775
Malignancy (%)	14 (23.7)	9 (25.7)	5 (20.8)	0.762
Focus of infection (%)				0.484
No focus	43 (72.9)	24 (68.6)	19 (79.2)	
Soft tissue	3 (5.1)	2 (5.7)	1 (4.2)	
Lower respiratory	3 (5.1)	3 (8.6)	0	
Abdominal	5 (8.5)	4 (11.4)	1 (4.2)	
Urinary/pelvic	5 (8.5)	2 (5.7)	3 (12.5)	
Antimicrobial resistance (%)				
Cefepime (FEP)	2/45 (4.0)	1/26 (3.9)	1/19 (5.3)	1
Cefotaxime (CTX)	2/14 (14.3)	2/10 (20.0)	0/4 (0.0)	1
Cefoxitin (FOX)	3/44 (6.8)	1/26 (3.9)	2/18 (11.1)	0.558
Ceftazidime (CAZ)	1/52 (1.9)	0/31 (0.0)	1/21 (4.8)	0.404
Ceftriaxone (CRO)	1/49 (2.0)	0/28 (0.0)	1/21 (4.8)	0.429
Ciprofloxacin (CIP)	4/57 (7.0)	0/33 (0.0)	4/24 (16.7)	0.027
Pipercillin-Tazobactam (TAZ)	2/44 (4.6)	2/25 (8.0)	0/19 (0.0)	0.498
Ticarcillin-Clavulanate (TIM)	2/56 (3.6)	1/33 (3.0)	1/23 (4.4)	1

sizes and selection bias with hospital-based designs may partially explain the conflicting results observed in our large population-based study. These findings provide impetus for further research to better understand the epidemiology and outcomes of *Providencia* species infections in other populations.

The current study has several notable strengths and limitations that should be acknowledged. The inclusion of all cases identified within the publicly funded state-wide laboratories including specimens sent from hospital and community collection sites was a notable strength, as this approach minimised the bias (including referral bias) associated with studying selected hospitals or settings. However, since the study only included cases identified within the public system, BSIs diagnosed in private institutions were not identified, which represents a limitation. Although the proportion of cases excluded from the analysis was likely small and estimated as less than 10-20%, the reported incidence rates should be viewed as conservative estimates of the true number of *Providencia* species BSI that occurred during the surveillance period. Another limitation was the retrospective study design. The available data in state-wide databases did not include details regarding procedures to which patients might have been exposed, such as urinary tract instrumentation, which could be a risk factor for both acquisition and adverse outcomes. Furthermore, the absence of specific protocols directing physicians to order blood cultures meant that the possibility exists that bias could have been introduced in the study if decisions to order blood cultures varied among districts, physicians or over time (e.g., among elderly patients with comorbid disease). These limitations should be considered when interpreting the findings of the study.

5. Conclusion

In summary, this study offers an examination of the incidence, determinants and outcome of *Providencia* species BSI in a large Australian population and contributes significantly to the limited body of literature. Although we observed a similar incidence, we observed a number of clinical differences and case-fatality outcome between the two main species. Further studies are warranted to gain a better understanding of their incidence and associated risk factors in other populations.

Ethics approval and consent to participate

The human research ethics committee at Royal Brisbane and Women's Hospital approved this study and granted a waiver of individual consent (LNR/2020/QRBW/62494).

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Data availability

Data cannot be shared publicly due to institutional ethics, privacy, and confidentiality regulations. Data release for the purposes of research under Section 280 of the Public Health Act 2005 requires application to the Director General (PHA@health.qld.gov.au).

CRediT authorship contribution statement

Felicity Edwards: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Kristin H. Edwards:** Writing – review & editing. **Alexis Tabah:** Writing – review & editing. **Patrick N. A. Harris:** Writing – review & editing, Data curation, Conceptualization. **Kevin B. Laupland:** Writing – review & editing, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Patrick Harris reports a relationship with OpGen Inc that includes: consulting or advisory. Patrick Harris reports a relationship with Merck Sharp & Dohme UK Ltd that includes: consulting or advisory. Patrick Harris reports a relationship with Sandoz Inc that includes: consulting or advisory. Patrick Harris reports a relationship with Pfizer that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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