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Research paper

Molecular epidemiology of methicillin-resistant *Staphylococcus aureus* isolates in New South Wales, Australia, 2012—2017

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Abstract *Background:* To better understand the molecular epidemiology of MRSA and to assess the utility of 19-target binary typing we undertook large-scale epidemiological surveillance of MRSA from invasive and non-invasive clinical specimens, and screening swabs.
Methods: Binary typing was performed on clinical MRSA isolates collected in New South Wales (NSW), Australia between 01/01/2012 - 31/12/2017. Binary type (BT) predicted multilocus sequence type (ST) and spa types based on results from isolates which had been characterised by both methods.
Results: 7624 MRSA isolates were analysed of which 3581 (47%) were wounds or skin & softtissue isolates (W/SSTI), 2436 (32%) screening swabs, 469 (6%) blood cultures (BC), 780 (10%) others, and 358 (5%) unknown. We identified 731 BTs, 54 spa types, and 31 STs. ST239 was the commonest MRSA clone in 2012 (30%), but it decreased to 7% in 2017 ($p < 0.001$). In contrast, <0.5% of MRSA were ST45 in 2012 compared to 14% in 2017 ($p < 0.001$). An emergence of PVL-positive ST22 was also noted. Of all isolates, 28% (2122/7624) were lukS/PVL positive; the proportion, among prospectively collected isolates increased from 24% (1406/5858) to 33% (1933/5858) between 2012 and 2017 ($p < 0.0001$). 43% (1534/3581) W/SSTI, 20% (95/469) BC and 10% (239/2436) screening swabs were PVL-positive.
Conclusions: A major change in the epidemiology of MRSA was noted with a decline of ST239, an emergence of ST45 and PVL-positive ST22, and a significant increase in PVL-positive isolates. Binary typing can be a useful routine laboratory test for prospective molecular surveillance of MRSA colonisation and infection.

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Highlights

- Analysis of more than 7500 MRSA isolates collected over a period six years.
- Includes analysis of MRSA from screening swabs and non-invasive clinical specimens.
- Major changes in the molecular epidemiology of MRSA in NSW is described.
- A significant increase in PVL-positive MRSA isolates in NSW was noted.
- Supports the utility of binary typing as a routine laboratory tool.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common pathogen, which can cause asymptomatic colonisation or infections ranging from trivial to life-threatening [1]. It was first recognised in 1961 in the United Kingdom (UK) [2], and first isolated in Australia in 1966, in Sydney, from an overseas patient already known to be infected with MRSA [3]. However, it was not until the mid-1970s that MRSA became endemic in hospitals in the eastern States of Australia [4—6]. Western Australia noted its first case only in 1982 [7]. By 1987, MRSA accounted for 14.4% of *S. aureus* (SA) isolates from Australian teaching hospitals overall, but with notable variation between States [8].

In New South Wales (NSW) — the most populous State in Australia - MRSA accounted for 37% of nosocomial SA isolates in 2011 [9], 25% of all community SA isolates in 2012 [10], and 23% of SA blood culture isolates in 2015 compared to 18% of blood culture isolates nationally [11]. These rates are remarkably high compared to some European countries, where MRSA prevalence remains less than five percent [12] as a result of enhanced surveillance and control methods.

In this report, we describe large-scale epidemiological surveillance of MRSA isolates collected in NSW during the six-year period 2012—2017. Our aims were a) to analyse changing trends in the prevalence of MRSA multilocus sequence types (STs), through prospective surveillance of isolates collected from sterile and non-sterile sites, and b) to describe the micro-epidemiology of major MRSA STs, using binary typing.

Methods

MRSA isolates from clinical specimens and screening swabs were collected, prospectively, between 1st January 2012 and 31st December 2017 from patients whose specimens were referred to the Centre for Infectious Diseases and Microbiology (CIDM), Institute for Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, in Sydney. NSW has a population of 7.9 million (December 2017), and is divided into 15 local health districts (LHDs), each of which contains multiple hospitals. The majority of isolates were from Westmead and other hospitals in the Western Sydney LHD (WSLHD), which were routinely strain-typed. We also included isolates referred, ad hoc, from 13 of the 14 other LHDs in NSW, and analysed separately.

Molecular typing, using a multiplex PCR and reverse line blot hybridisation (mPCR/RLB) assay, was performed at the CIDM. The method has been described in detail previously [13,14]. Briefly, strain types were determined by the presence or absence of 19 gene targets (oligonucleotide primers) - including toxin genes, phage derived open reading frames and SCC*mec* elements - expressed as a 19-digit binary number (0 = absent; 1 = present) converted to a decimal number e.g. binary number 0000011001110000000 translates to binary type (BT) BT13184. The BT predicted multilocus sequence type (MLST) and *spa* type [13], based on results from isolates previously characterised by all three methods e.g. BT13184 corresponded to ST22 and *spa* type *t032*. MLST and *spa* typing (based on conventional typing or whole genome sequencing "WGS") were performed on representative isolates of the common BTs (BTs with >10 isolates) and any isolates that were nontypeable by mPCR/RLB (Supplementary table A).

At Westmead Hospital, routine screening for MRSA was performed, as per the hospital's screening policy, on admission and at least weekly using nasal and perianal/perineal swabs, in high risk settings, namely adult and neonatal intensive care, haematology/bone marrow transplant, renal transplant/haemodialysis units. The screening policy in Westmead has remained constant during the study period.

Patients' age, specimen type, date of collection and body site were recorded. Clinical isolates (defined as isolates from all specimens other than screening swabs) collected more than 48 h after an admission to hospital were defined as healthcare onset (HO). Community onset, and healthcare-associated community onset information could not be distinguished. Repeat isolates from individual patients were only typed after an interval of at least six months, unless they were sterile site isolates, all of which were typed. If there were two or more isolates with the same BT from an individual patient within six months, the most clinically relevant was included for analysis (blood culture > other sterile site > non-sterile site > screening swabs). In a patient with multiple isolates from the same specimen type (e.g. multiple positive blood cultures), only the first isolate collected was recorded for analysis. Differences between categorical variables were analysed by

Table 1 Yearly distribution of 7624 MRSA isolates collected in New South Wales, Australia and included in this report.

LHDs	Total	2012	2013	2014	2015	2016	2017
WSLHD[a] (N, % of 5-year total)	5858	1081 (18)	1034 (18)	1019 (17)	827 (14)	910 (16)	987 (17)
ST239[b] (N, % of WSLHD for year)	968 (17)	319 (30)	256 (25)	148 (15)	95 (11)	81 (9)	69 (7)
ST45[b](N, % of WSLHD for year)	456 (8)	4 (0.4)	25 (2)	87 (9)	103 (12)	105 (12)	132 (13)
Other LHDs[c](N, % of 5-year total)	1766	291 (16)	257 (15)	672 (38)	123 (7)	385 (22)	38 (2)

Abbreviations - LHD: Local Health District; N: number of isolates.
[a] Western Sydney LHD (WSLHD) is represented by two large acute hospitals — Westmead and Blacktown Hospitals. WSLHD isolates were prospectively collected. Only ST239 and ST45 shown.
[b] Percentage for ST239 and ST45 indicates % of WSLHD isolates for the corresponding year.
[c] Other LHDs (selectively referred): Nepean Blue Mountains LHD (NBMLDH: 424 isolates); Illawarra Shoalhaven LHD (ISLHD: 404 isolates); Sydney LHD (SLHD: 281 isolates); Hunter New England LHD (HNELHD: 233 isolates); Central Coast LHD (CCLHD: 190 isolates); Murrumbidgee LHD (MLHD: 119 isolates); Western NSW LHD (WNSWLHD: 40 isolates); South East Sydney LHD (SESLHD: 31 isolates); Northern Sydney LHD (NSLHD: 24 isolates); Southern NSW LHD (SNSWLHD: 9 isolates); South Western Sydney LHD (SWSLHD: 6 isolates); Northern NSW LHD (NNNSWLHD: 3 isolates) and Far West LHD (FWLHD: 2 isolates)]. No isolates were from available from Mid North Coast LHD (MNCLHD), which is a relatively small LHD with 3% of the state population (December 2017).

Table 2 Specimen type from which MRSA isolates were collected in NSW between 2012 and 2017.

Specimens	WSLHD[a] N (%)[c,a]	other LHDs[b] N (%)[c,b]	Total N (%)[c]	PVL-positive N (%)[d]
SSTI/wounds	2817 (48)	764 (43)	3581 (47)	1534 (43)
Screening swabs	2094 (36)	342 (20)	2436 (32)	239 (10)
Blood culture	303 (5)	166 (10)	469 (6)	95 (20)
Sputum	320 (5)	59 (3)	379 (5)	29 (8)
other invasive[e]	233 (4)	39 (2)	272 (3)	72 (26)
Urine	91 (2)	38 (2)	129 (2)	3 (2)
Unknown	—	358 (20)	358 (5)	150 (42)
TOTAL	5858	1766	7624	2122 (28)

Abbreviations - N: number of isolates; PVL: Panton-Valentine leukocidin; SSTI: skin and soft tissue infections; LHD: Local Health District; WSLHD: Western Sydney LHD; NSW: New South Wales.
[a] Prospectively collected isolates (Total = 5858 isolates).
[b] Selectively referred isolates (Total = 1766 isolates).
[c] Percentage of the column total shown.
[d] Percentage of the total for each specimen type.
[e] Other invasive includes tissue, aspirate, broncho-alveolar lavage, bone, line tip and drain samples.

Fisher's exact test or chi-squared tests as appropriate. P values of <0.05 were considered significant.

Results

We performed binary typing on 7624 MRSA isolates (Table 1). Of these, 5858 (77%) were from 5474 WSLHD patients, of whom 52% were aged >60 years and 6% were <15 years old. Eight hundred and twelve (22%) of the 3764 clinical isolates from WSLHD were HO (26% in 2012; 16% in 2017). There were 1766 (23%) referred isolates; patient ages were available for only 576 (33%) and, of these, 67% were from individuals aged >60 years. The majority of all isolates were from wounds or skin and soft tissue infections (W/SSTI) or screening swabs (Table 2).

Binary types (BTs)

731 BTs (623 from WSLHD and 308 from other LHDs) were identified amongst 7624 MRSA isolates. Twenty-six isolates (0.3%) had no target detected on mPCR/RLB (BT 0). The top 10 BTs accounted for 50% and 58% of isolates in WSLHD and in other LHDs respectively.

Predicted multilocus sequence types (STs)

Thirty-one STs were inferred from 6324 (83%) isolates. The remaining isolates (1300, 17%) belonged to 582 uncommon BTs for which a predicted ST was not available. ST22, ST93, ST239, ST45, ST30, ST1 and ST5 were the seven most common STs in both WSLHD and other LHDs, accounting for 75% of the isolates in WSLHD and 78% in other LHDs. Changes in major STs during the survey period (2012—2017) are shown in Fig. 1. ST distribution between different specimen types is shown in Table 3, and by age groups in Supplementary Table B.

Predicted *spa* types

Fifty-four *spa* types were identified from 6375 (84%) isolates. *Spa* type could not be inferred from BT for the remaining 1249 isolates, which belonged to 582 uncommon BTs for which *spa* typing had not been performed. Of the

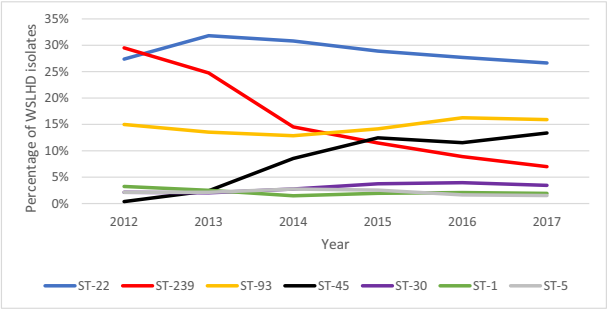

Figure 1 Changes in proportions of common MRSA multilocus sequence types (STs) between 2012 and 2017 at Western Sydney Local Health District. *Analysis of prospectively collected 5858 MRSA isolates (includes isolates from all body sites). The isolates from the other LHDs are not included as yearly trend would be unreliable given these are selectively referred. Note: Decrease in ST239 MRSA (red line), and emergence of ST45 MRSA (black line) (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.).

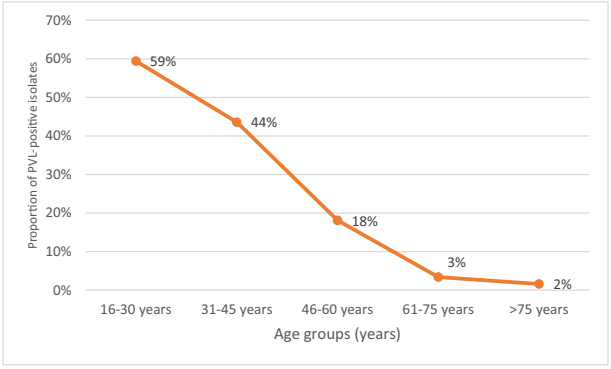

Figure 2 Distribution of *luk*S/PVL-positive MRSA isolates in adults, by age-group, among 6434 isolates collected in NSW between 2012 and 2017. *Age 15 or under excluded as it was not a true representative sample (43/48 isolates were from those aged <1 year). Age not available for 1190 isolates, 30% were PVL-positive. Abbreviations - PVL: Panton-Valentine leukocidin.

identified *spa* types, t032, t037, t202, t1081 and t515 were the five most common in both WSLHD and other LHDs, accounting for 62% of the isolates. The number of different BTs within each of these five commonest *spa* types ranged from 3 to 22. Distribution of the common BTs within these *spa* types, among WSLHD and other LHD isolates, were similar.

Panton-Valentine leukocidin (PVL)

*luk*S is one of two genes encoding PVL and one of the 19 targets used to determine a BT (other toxin targets were staphylococcal enterotoxins A [*sea*], C [*sec*] and D [*sed*]) [13]. Of the 7624 MRSA isolates, 2122 (28%) were *luk*S/PVL positive; the proportion, among prospectively collected WSLHD isolates, increased from 24% to 33% between 2012 and 2017 ($p < 0.001$). Proportions of PVL-positive isolates differed between isolates from different age groups (Fig. 2) and in specimen types (Table 2). PVL-positive isolates were unevenly distributed between STs (Supplementary Table C — also includes results for *sea*, *sec* and *sed*).

Micro-epidemiological analysis of major STs in WSLHD

i. **PVL-positive ST22:** Of 274 (of 2156; 13%) PVL-positive ST22 isolates, 223 (81%) were from WSLHD patients. In 2012, BT37248 (17; 52%) and BT45441 (13; 48%) were identified with similar frequency among 33 PVL-positive ST22 isolates in WSLHD. Since then BT37248 has become the predominant PVL-positive ST22 MRSA strain: 45 of 49

Table 3 Distribution of MRSA multilocus sequence type (ST) between 7266 isolates[a] from different specimen types (all LHDs).

ST	Wounds/SSTI (N = 3581)	Screening swab (N = 2436)	Blood culture[b] (N = 469)	Sputum (N = 379)	other invasive[c] (N = 272)	Urine (N = 129)
N (%) for each column						
ST22	887 **(25)**	839 **(34)**	123 **(26)**	121 **(32)**	71 **(26)**	35 (27)
ST93	863 (24)	80 (3)	53 (11)	17 (4)	43 (16)	1 (1)
ST239	346 (10)	473 (19)	88 (19)	121 **(32)**	60 (22)	22 (17)
ST45	372 (10)	237 (10)	40 (9)	37 (10)	18 (7)	39 **(30)**
ST30	169 (5)	18 (1)	7 (1)	2 (1)	4 (1)	—
ST1	67 (2)	67 (3)	18 (4)	5 (1)	6 (2)	3 (2)
ST5	59 (2)	58 (2)	11 (2)	6 (2)	4 (1)	3 (2)
others	231 (6)	197 (8)	48 (10)	17 (4)	25 (9)	7 (5)
NA	587 (16)	467 (19)	81 (17)	53 (14)	41 (15)	19 (15)

Abbreviations - ST: multilocus sequence type; others: other STs; NA: ST undetermined; LHD: Local Health District; WSLHD: Western Sydney LHD.

[a] Specimen type was not known in 358 isolates.

[b] 65% (303) blood culture isolates were from WSLHD, of which 22% (68/303) were ST239. An annual decrease in the rate of healthcare onset MRSA bacteraemia was primarily due to a decrease in ST239 bacteraemia: 2012 (13/20); 2013 (14/18); 2014 (8/11); 2015 (7/11); 2016 (2/3); 2017 (2/5).

[c] 'other invasive' includes tissues, aspirate, broncho-alveolar lavage, bone, line tip and drain samples.

(92%) isolates in 2017 vs three (6%) of BT45441. The majority of PVL-positive ST22 MRSA isolates were not HO (177/223; 79%).

Patients' ages were not available for 38 (14%) of 274 PVL-positive ST22 isolates. Of the remaining 236 isolates, 36 (15%) were from neonates (35 from screening swabs; one from a W/SSTI swab); 161 (68%) from patients aged 16–60 years and 27 (12%) from patients aged >60 years. Overall, 174 (64%) were from W/SSTI, 65 (24%) from screening swabs, nine (3%) from blood cultures and nine (3%) from other specimens. Specimen type was not available for 17 (6%) isolates.

A similar, but a less marked, change in proportions of PVL-negative ST22 strains was noted in WSLHD; of the two most common BTs, BT13184 increased from 45% (117/263) in 2012 to 58% (124/214) in 2017, while BT78720 fell from 16% (43/263) to 3% (6/214) in the same period.

ii. **Decline in ST239:** A total of 968 ST239 isolates were collected from WSLHD patients, in decreasing numbers, between 2012 and 2017 (Table 1) across all age groups. This was most notable in the predominant BT280845 which fell from 42% (134/319) in 2012 to 16% (11/69) in 2017 ($p < 0.001$). During the same period, the overall number of different BTs fell from 16 to seven. ST239 was isolated in similar proportions from screening swabs (437/968; 45%) and clinical isolates (W/SSTI 292; 30%; blood cultures 68; 7%). Overall, 46% (244/531) of ST239 clinical isolates were HO, but the proportion significantly decreased between 2012 and 2017 (80/160; 50% and 14/45; 31% p 0.024) (Table 3).

iii. **Rise of ST45:** A total of 456 ST45 isolates were collected in WSLHD during the study period. In contrast to ST239, the numbers increased progressively (Table 1). ST45 included nine BTs, of which three (including BT1296 – see below) represented 86% of ST45 isolates. It was isolated particularly from patients >60 years (369/456; 81%) and from both screening swabs (170/456; 37%) and clinical isolates (W/SSTI 200; 44%; blood cultures 27; 6%). Overall, 25% (71/286) of ST45 clinical isolates were HO.

ST45 in Illawarra Shoalhaven (IS)LHD. Among 402 consecutive MRSA isolates referred from ISLHD over 17 months (November 2013 to March 2015), 225 (56%) were ST45. Of these, 92% (206) were BT1296; 24% (55) were from screening swabs, 60% (136) from W/SSTI and 16% other specimens including only 1% [3] from blood cultures.

Discussion

Among over 7000 MRSA isolates collected in NSW in 2012–2017, there was a significant decline in ST239 MRSA, an emergence of ST45 and PVL-positive ST22 MRSA isolates, and an increase in the overall proportion of PVL-positive isolates. The findings indicate a major change in the molecular epidemiology of MRSA in our region, with a shift to non-nosocomial acquisitions. A decline of ST239 MRSA, a typical nosocomial strain, was not associated with a decline of another typical nosocomial MRSA (mainly PVL negative ST22; also known as EMRSA 15) (Fig. 1).

We included MRSA isolates from screening swabs and both invasive and non-invasive clinical specimens. Although the majority of isolates were from a single LHD, 14 of the 15 NSW LHDs were represented (Table 1) and covered the full range of age groups. We believe that such a large geographically diverse sample provides a comprehensive molecular epidemiological picture of MRSA in NSW, although proportions within various categories are reliable only for the prospectively collected isolates from WSLHD. The findings are consistent with other epidemiological studies in NSW [11,15], which have also shown a decrease in ST239 MRSA isolates overall, and frequent isolation of community strains from younger individuals. Furthermore, a prospective study like ours, with a consecutive and a comprehensive collection of MRSA isolates from all body sites, and a timely availability of results, augments findings of selective MRSA surveys such as those conducted by the Australian Group on Antimicrobial Resistance (AGAR) [11,16].

The high discriminatory power of this typing system [13], results in a large number of BTs. Moreover, binary typing can reliably identify MRSA clones, STs and *spa* types for most isolates [13,14], which allows comparison with other studies. Half of all isolates belonged to 10 BTs and two-thirds to four STs. MLST, *spa* typing, pulsed field gel electrophoresis (PFGE) and WGS are more commonly used methods to define MRSA clones. However, costs, availability and the time to results remain a limiting factor for these methods [17,18]. Binary typing is rapid, high-throughput and inexpensive (AU $2.5 per isolate); its discriminatory power is similar to that of PFGE and much greater than MLST or *spa* typing [13]. Binary typing results are available within an actionable timeframe (usually less than a week). We have used it routinely at WSLHD since 2012 to identify MRSA transmission events, facilitate outbreak investigations and monitor the effectiveness of infection control interventions [13,19,20].

Our report of a decrease in ST239 MRSA corresponds to trends elsewhere [21,22]. Replacement of the common MRSA clones is well recognised [17,23,24], but the reasons remain unclear and is likely multifactorial including the natural MRSA cycles possibly due to selection pressure in healthcare environments [17,23], enhanced hospital infection control programs [21]), differential ability to persist in the environment as reservoirs or in humans as colonisers [25], or due to climate/environmental factors as noted by geographical differences in MRSA clones [22,25].

PVL-positive isolates increased in number and proportion between 2012 and 2017 due to both the decline in ST239, which is generally PVL-negative, and the emergence of PVL-positive ST22 MRSA.

PVL-positive ST22 MRSA is believed to have arisen, independently of PVL-negative ST22, from a PVL-positive ST22 MSSA precursor [17,26]. It is an uncommon pathogen outside India [27], but has caused nosocomial outbreaks in other countries [25,28]. WSLHD has a large population of residents born in India. In 2016, 6% of WSLHD residents were born in India compared to 2% in all of NSW [29]; 39% (55,706/143,459) lived in WSLHD. Thirteen percent of our ST22 isolates were PVL-positive - 9% in 2012 compared to

19% in 2017. In WSLHD, they were first noted in the neonatal intensive unit, in 2011, where two fatal cases of sepsis were followed by a prolonged outbreak of nosocomial transmission, due to a predominant BT (BT37248) [19]. Since then PVL-positive ST22 belonging to several BTs have been detected in 11 of the 14 LHDs.

Our study is not without limitations. 77% of isolates were from a single LHD and a significant proportion was from screening swabs from patients in high acuity wards where screening is done routinely. However, the screening policy in WSLHD was consistent during the study period and all clinical and screening isolates were collected prospectively and typed routinely. Only a few isolates were available from children aged over 1 month. There were also few isolates from private laboratories, and only six LHDs referred >100 isolates, which represented varied proportions of the total. Therefore, the distributions of STs and BTs in different categories may not be representative geographic areas outside Western Sydney and those results must be interpreted as such.

Despite these limitations, these comprehensive data from WSLHD - as one of the most populous LHDs in NSW - offers a representative epidemiological picture, and addition of isolates from other LHDs allowed us to compare results, which were broadly consistent, for a more complete view of the molecular epidemiology of MRSA in NSW. However, further research is necessary to explore the differential ability of the two nosocomial MRSA strains (ST239 and PVL-negative ST22) to persist in a hospital environment. We speculate that ST239 is more susceptible to infection control activities such as alcohol-based cleaning and hand-hygiene, and a loss of fitness has resulted in its decline. Long term care facilities remain a major reservoir of PVL-negative ST22 [8]. Also, an increase in non-nosocomial acquisitions of MRSA and an increase in PVL-positive isolates in younger individuals suggests a need to increase community awareness on MRSA.

In conclusion, we have described the large-scale molecular epidemiology of MRSA isolates in Western Sydney and throughout NSW between 2012 and 2017. The key identified trends were a decrease of ST239, and the emergence of ST45 and PVL-positive ST22 as clinically important strains. Binary typing can be a useful routine laboratory test for prospective molecular surveillance and detection and investigation of outbreaks of MRSA colonisation and infection.

Ethics

Ethics approval and a waiver for individual patient informed consent was obtained from the Western Sydney Local Health District Human Research Ethics Committee.

Authorship statement

R.D. analysed the data and prepared the manuscript. M.V.N.O'. and G.L.G. provided the data, and together with J.S.D. (Ph.D. supervisors for R.D.), guided data analysis and manuscript preparation. P.J.N. helped with data analysis and critically reviewed the manuscript.

Conflict of interest

Nil.

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Provenance and peer review

Not commissioned; externally peer reviewed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idh.2019.04.002.

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