Journal of Paediatrics and Child Health

doi:10.1111/jpc.15905

ORIGINAL ARTICLE

Characteristics, management and changing incidence of children with empyema in a paediatric intensive care unit

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Aim: Paediatric intensive care unit (PICU) admissions for empyema increased following the 13-valent pneumococcal conjugate vaccine (PCV13). We describe the clinical characteristics, management and outcomes for children with empyema and compare incidence before and after PCV13.

Methods: Retrospective study of patients <18 years admitted to The Royal Children's Hospital Melbourne PICU with empyema between January 2016 and July 2019. We investigated the incidence of empyema during two time periods: 2007–2010 (pre-PCV13) and 2016–2019 (post-PCV13).

Results: Seventy-one children (1.9% of all PICU admissions) were admitted to PICU with empyema between 2016 and 2019. Sixty-one (86%) had unilateral disease, 11 (16%) presented with shock and 44 (62%) were ventilated. Streptococcus pneumoniae and group A Streptococcus were the most commonly identified pathogens. Forty-five (63%) were managed with video-assisted thoracoscopic surgery (VATS).

There was a 31% reduction in empyema hospitalisations as a proportion of all hospitalisations (IRR 0.69, 95% CI 0.59–0.8), but a 2.8-fold increase in empyema PICU admissions as a proportion of all PICU admissions (95% CI 2.2–3.5, P < 0.001). For the PICU cohort, this was accompanied by reduction in PIM2 probability of death (median 1% vs. 1.9%, P = 0.02) and duration of intubation (median 69 h vs. 126.5 h, P = 0.045).

Conclusions: In children with empyema in PICU 62% required ventilation, 16% had features of shock and 63% received VATS. Empyema admissions, as a proportion of all PICU admissions, increased in the era post-PCV13 compared to pre-PCV13 despite no increase in illness severity at admission.

Key words: empyema; paediatric intensive care; parapneumonic effusion; pneumonia.

What is already known on this topic

1 Whilst paediatric community-acquired pneumonia hospitalisations have reduced following the introduction of the 13-valent pneumococcal vaccine, hospitalisations and paediatric intensive care unit (PICU) admissions for empyema have increased over the same period.
2 It is unclear whether this increase in PICU empyema admission rates represents increased disease severity, and the published data on the clinical characteristics of these children are limited.

What this paper adds

1 Children admitted to a PICU with empyema were mostly previously well with unilateral disease, nearly two-thirds received mechanical ventilation and one in six had features of shock.
2 In this single centre study, there was an increase in empyema admission to PICU as a proportion of all PICU admissions in the post-PCV13 era despite no increase in illness severity at PICU admission.

The pneumococcal vaccine has reduced the incidence and changed the aetiology of community-acquired pneumonia (CAP) in children, with a 21% reduction in hospitalisations (95% CI 20–22 reduction) in Australia following the introduction of the 13-valent conjugate vaccine (PCV13) in July 2011.[1,2] There was a concurrent increase in empyema hospitalisations by 25% (95% CI 9–44 increase), and evidence of increased paediatric intensive care unit (PICU) empyema admissions.[1,3] Empyema describes purulent parapneumonic pleural effusion with significant fibrin formation and is associated with prolonged hospitalisation and invasive procedures including intrapleural fibrinolytic therapy and/or surgical management.[4]

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Conflict of interest: None declared.

Accepted for publication 26 January 2022.

It is not yet clear whether the trend of increased empyema admissions to PICU represents increasing CAP disease severity, increasing PICU admissions to facilitate invasive management such as pleural drainage, or shifting PICU admission criteria. Empyema is an important reason for PICU admission because children often have features of severe sepsis, need respiratory support and require pleural drainage. Between 10% and 38% of children admitted to hospital with empyema are admitted to PICU, and these children represent 25% of PICU admissions with CAP.[3,5–7] *Streptococcus pneumoniae*, group A *Streptococcus* (GAS) and *Staphylococcus aureus* are the most commonly isolated pathogens from blood or pleural fluid of children with empyema, and those with GAS have a higher risk of requiring direct PICU admission.[3,8] Compared to all PICU admissions with severe and/or complicated CAP, children with parapneumonic effusion (PPE) or empyema have a low risk of mortality.[9]

Data relating to the clinical characteristics of children with empyema admitted to PICU are limited. Within the existing literature, there is heterogeneity introduced by differences in empyema definitions and management, and lack of a validated CAP severity scoring system to determine criteria for PICU admission.[6,10,11] To further understand this population, we aimed to describe the clinical features, microbiology and management of children admitted to PICU with empyema. We also assess empyema admission rates to our hospital and PICU in time periods before and after the introduction of PCV13.

Methods

We conducted a retrospective study of children with CAP complicated by empyema admitted to the PICU at The Royal Children's Hospital Melbourne (RCH) between January 2016 and July 2019, and investigated the incidence of empyema hospital and PICU admissions between two time periods: pre-PCV13 (2007–2010) and post-PCV13 (2016–2019).

RCH is the largest paediatric hospital in Victoria, with approximately 50 000 admissions per year and 350 beds. The hospital's PICU has separate cardiac and general units, with the general PICU admitting approximately 1000 children annually.

Inclusion and exclusion criteria

Patients less than 18 years old on admission with a diagnosis of CAP complicated by pleural empyema were included. Patients admitted with pleural effusions due to malignancy, following surgery, or from other non-infective cause were excluded.

Empyema was defined as CAP and pleural fluid requiring chest drainage by surgically or percutaneously placed chest drains, with or without video-assisted thoracoscopic surgery (VATS).

Data including age, sex, associated diagnoses, intensive care therapies and outcomes were recorded from the PICU database. Paediatric Index of Mortality (PIM) scores were also recorded. The PIM is a logistic regression model that predicts a child's probability of death in PICU, based on information collected within 1 h of admission to the unit.[12] Shock was considered present if 40 mL/kg IV fluid resuscitation or vasoactive agents were administered. Chest x-ray and ultrasound reports were categorised by the presence of unilateral or bilateral consolidation and effusion. Ultrasound findings of a complex effusion were defined as septation, cavitation, or abscess. Treatment was categorised as chest drain only, chest drain with fibrinolytics, or VATS. Pathogens detected by culture of blood and pleural fluid, and by polymerase chain reaction (PCR) (where available), were recorded.

Intensive care therapies such as the proportion requiring respiratory support, continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) were recorded. Respiratory support included non-invasive ventilation (high-flow nasal cannula [HFNC], continuous positive pressure [CPAP], bi-level positive airway pressure [BiPAP]) and mechanical ventilation. Outcomes included empyema complications (pulmonary and systemic), duration of respiratory support and mechanical ventilation, PICU length of stay and mortality.

Hospital and PICU incidence

General hospital and intensive care databases were used to identify the number of hospital and PICU admissions between January 2007 and December 2019, overall and for empyema. ICD-10 codes for pleural effusion, empyema, lobar or bacterial pneumonia and pneumonia secondary to specific bacterial pathogens were used to identify patients with CAP and empyema. Annual hospital and PICU incidence rates of empyema were calculated relative to total admissions for CAP and total number of admissions to hospital and PICU, respectively. The 7-valent pneumococcal conjugate vaccine (PCV7) introduced in 2005 was replaced by PCV13 in the Australian schedule in July 2011.[2] Between 2007 and 2019, >90% of 1-year-old children in Victoria were fully immunised.[13] We compared incidence of pneumonia and empyema, and markers of disease severity, in a 4-year period pre-PCV13 (2007–2010) and post-PCV13 (2016–2019): the latter period chosen to reflect the most current comparative cohort.

Statistical analysis

Demographic and clinical characteristics were described using frequencies and proportions, with asymmetrically distributed data described by median and interquartile range (IQR). Incidence was described using incidence rate ratios (IRR) and 95% confidence intervals (CI), with a P-value <0.05 deemed statistically significant. We compared paired summary statistics using non-parametric test of significance (Mann–Whitney U-test). Stata 16 was used for all analyses (Statacorp 2019, Texas, USA). The study was approved by the RCH Human Research Ethics Committee (QA/56146/RCHM-2019).

Results

Clinical presentation and managed in PICU

Of 3644 PICU admissions between January 2016 and July 2019, 71 (1.9%) were admitted with empyema (Table 1). The median age was 24 months (IQR 13–48 months). Sixty-seven (94%) children were previously well. Empyema management, intensive care therapy and outcomes are described in Table 2. VATS was performed in 37 (52%) children as initial therapy. In an additional eight children, VATS was rescue therapy for incomplete

Table 1 Presentation and management in intensive care (2016–2019)

Clinical presentation and imaging	$N = 71$
Sex, *n* (%)	
Female	36 (51)
Age (months) median IQR	24 (13–48)
Associated diagnosis, n (%)	
Nil	67 (94)
Developmental – cerebral palsy, Turner syndrome, CHARGE syndrome, infantile spasms	4 (5.7)
Shock at presentation, *n* (%)	11 (16)
Admission source, *n* (%)	
Transfer from other hospital	30 (42)
Operative theatre	16 (23)
Ward	13 (18)
Emergency department	12 (17)
Initial chest drain insertion, n (%)	
Operative theatre	39 (55)
PICU	26 (37)
Pre-arrival	4 (5.6)
Emergency department	2 (2.8)
Chest x-ray changes, *n* (%)	
Unilateral consolidation and effusion	61 (86)
Bilateral consolidation, unilateral effusion	8 (11)
Bilateral effusion	2 (3)
Ultrasound ($n = 62$), *n* (%)	
Simple	24 (39)
Complex – septations, cavitation, abscess formation	38 (61)

CHARGE, Coloboma, Heart defects, Atresia (choanal), Retardation of growth, Genital/urinary defects, Ear anomalies or deafness; IQR, interquartile range.

Table 2 Intensive care and operative management

Management and outcomes		$N = 71$
Initial management, *n* (%)	Drain alone	23 (32)
	Drain plus fibrinolytics	11 (16)
	VATS alone	36 (50)
	VATS plus fibrinolytics	1 (1.5)
Rescue procedure, *n* (%)	None required	63 (89)
	VATS	8 (11)
Duration of intercostal drain placement – median days (IQR)		5 (3–10)
Intensive care therapies		
Respiratory support, *n* (%)	Nil or low flow O_2	12 (17)
	NIV	15 (21)
	Mechanical ventilation	44 (62)
	Prior to VATS	7
	With VATS	27
	No VATS	10
	Duration of intubation (median hours, IQR)	69 (16–182)
CRRT		5 (2 on ECMO)
ECMO		2

CRRT, continuous renal replacement therapy; ECMO, extra-corporeal membrane oxygenation; IQR, interquartile range; NIV, non-invasive ventilation; VATS, video-assisted thoracoscopic surgery.

drainage (maximum time between initial drain and VATS of 9 days): six managed initially with drainage alone, and two with drainage plus fibrinolytics.

Forty-four (62%) children were mechanically ventilated for a median duration of 69 h (IQR 16–182). For 27 (61%) of 44 of these children, intubation facilitated VATS. Fifteen (21%) children received non-invasive ventilation.

Two children, aged 20 months and 6 years, were managed with ECMO for 167 and 142 h respectively, and five required CRRT. Median PICU length of stay was 93 h (IQR 46–173 h). There were no deaths to PICU discharge. There were 30 complications in 28 children (Appendix I). Nine (13%) developed a bronchopleural fistula, but no cases were managed with lung resection.

Diagnostic radiological findings

All patients were imaged with plain chest x-rays, which demonstrated unilateral changes in 61 (86%) of 71. Ultrasound examinations were performed in 62 (87%) of 71, with the majority showing complex effusions (Table 1). Three children had computerised tomography evidence of necrotising pneumonia.

Microbiology

Blood and pleural fluid culture results were available for all children. A pathogen was isolated in 55 (77.5%) cases (Table 3). Sixteen (22.5%) had bacteraemia. The most common organism identified (all methods) was *Streptococcus pneumoniae* (47.9%). One child with tuberculosis was a close contact of a known adult case. Pleural fluid pneumococcal PCR was used routinely through this period for culture-negative cases and identified 25 additional cases of pneumococcal empyema. More selective and sporadic use of an experimental in-house group A *Streptococcus* (GAS) PCR identified five additional cases of GAS disease in otherwise culture negative cases. Respiratory viral PCR panel testing provided evidence of viral co-infection in 27%, including parainfluenza ($n = 5$), HMPV ($n = 4$), RSV ($n = 3$), influenza A ($n = 2$) and multiple viral co-infection ($n = 5$).

Empyema incidence and disease severity between 2007–2010 and 2016–2019

Total hospital and PICU admissions and admissions for pneumonia and empyema were recorded from 2007 to 2019 (Appendix II). Comparing periods before and after PCV13 introduction, as a proportion of all hospital admissions, there was a 32% reduction in CAP hospital admissions (IRR 0.68, 95% CI 0.65–0.71) and a 31% reduction in empyema hospital admissions (IRR 0.69, 95% CI 0.59–0.8). There was no change in the proportion of CAP admissions complicated by empyema (Table 4).

There was a 2.8-fold increase in the incidence of empyema admission to PICU as a proportion of all PICU admissions in the

Table 3 Microbiological aetiology of empyema ($N = 71$ children)

		S. pneumoniae	GAS	MRSA	MSSA
Pleural	Culture	1	5	4	2
	PCR	25	7	-	-
Blood	Culture	8	4	3	1
	PCR	1	0	-	-
Both	Culture	0	2	1	0
	PCR	0	0	-	-
	Pleural PCR + blood culture	1	2	-	
Total		34 (48)	12 (17)	6 (8.5)	3 (4.2)

One child in 2019 (not represented in table) was positive for mycobacterium tuberculosis from pleural fluid. GAS, group A *streptococcus*; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.

period from 2016 to 2019 compared to the period from 2007 to 2010: (IRR 2.8, 95% CI 2.2–3.5, $P < 0.001$). Children admitted in the latter time-period had a lower PIM2 probability of death (median 1% vs. 1.9%, $P = 0.02$), shorter duration of intubation (69 h vs. 126.5 h, $P = 0.045$), and more were managed with VATS (63% vs. 5%, $P < 0.001$) (Table 5). There were no statistically significant differences in age at admission or length of stay.

Discussion

We report on all PICU empyema admissions over a 3.5-year period, and CAP and empyema trends in our institution over 12 years. This study shows a persistent burden of CAP complicated by empyema in our tertiary level PICU, over more than a decade during which the PCV13 was introduced. There has been a significant increase in empyema admissions to our PICU as a proportion of all PICU admissions, despite a reduction in CAP admissions to hospital overall.

Approximately 20% of children admitted to hospital with CAP are admitted to PICU.[6] Predictive scores for severe paediatric CAP – defined as PICU admission, ventilation or death – have included extremes of age, comorbidities, clinical signs (e.g. hypoxaemia, altered mental state) and nature of disease (multi-lobar or bilateral pneumonia).[6,9] In these studies, the presence of parapneumonic effusion or empyema is not independently predictive of poor outcomes, in keeping with low mortality reported in studies of all empyema hospitalisations.[14] Empyema, however, is an important disease in children admitted to intensive care because the combination of sepsis/septic shock, hypoxia and the need for evacuation of pleural fluid requires careful assessment and early therapies such as respiratory support, haemodynamic support and thoracic drainage. Importantly in our cohort, a large proportion also required inter-hospital transport, which adds complexity to management. In our study, most children were admitted to PICU primarily to manage localised disease: 86% had unilateral pneumonia and empyema. However, an important proportion presented with features of shock. While 44 (62%) of 71 children were mechanically ventilated, 27 (61%) of 44 were intubated to facilitate VATS procedure. Australian and New Zealand guidelines, published in 2011, suggest the options of VATS or drainage with instillation of fibrinolytics as the primary treatment for empyema in children, depending on resources and unit preference.[10] In general, in more recent years, VATS has become the preferred treatment option in our

Table 4 Incidence of community-acquired pneumonia (CAP) and empyema before and after the introduction of the 13 valent pneumococcal vaccine

	Pre- pneumococcal 13 valent vaccine PCV13 (2007–2010)	Post-pneumococcal 13 valent vaccine PCV13 (2016–2019)	Incidence rate ratio (95% CI); *P*-value
Hospital incidence			
Total hospital admissions (*n*)	138 117	198 893	-
Hospital CAP admissions (*n*)	1806	1771	-
CAP per 1000 hospital admissions	13.1	8.9	0.68 (0.65–0.71), $P < 0.001$
Hospital Empyema admissions (*n*)	169	167	-
Empyema per 1000 hospital admissions	1.2	0.83	0.69 (0.59–0.8), $P < 0.001$
Empyema per 1000 CAP admissions	93.6	94.3	1 (0.85–1.2), $P = 0.91$
PICU incidence			
Total PICU admissions (*n*)	2691	3644	-
PICU empyema admissions (*n*)	19	71	-
PICU empyema per 1000 PICU admissions	7.1	19.5	2.8 (2.2–3.5), $P < 0.001$
PICU empyema/total empyema (%)	11.2	42.5	$P < 0.001$

Table 5 Patient characteristics, management and outcomes of empyema in PICU before and after the introduction of the 13 valent pneumococcal vaccine

	Pre- pneumococcal 13 valent vaccine PCV13 (2007–2010)	Post- pneumococcal 13 valent vaccine PCV13 (2016–2019)	*P*-value
Age (months)	37 (19–83)	24 (13–48)	0.18
PICU LOS (h)	129.5 (32.3–294)	93 (46–173)	0.40
ICU discharge to hospital discharge (days)	14 (7–23)	10 (6–15)	0.19
PIM 2 probability of death (%)	1.9 (1.1–4)	1 (0.8–1.3)	0.02
Intubation (%)	14/19 (74)	44/71 (62)	0.29
Intubation duration (h)	126.5 (80–212)	69 (16–182)	0.045
CRRT (%)	3 (16)	5 (7)	0.23
VATS (%)	1 (5)	45 (63)	<0.001

All summary statistics are median (interquartile range) or percentages. CRRT, continuous renal replacement therapy; LOS, length of stay; PIM 2, Paediatric Index of Mortality score; VATS, video-assisted thoracoscopic surgery.

institution but early fibrinolysis has a key role in sicker children needing urgent drainage. Consistent with this, half of patients admitted to PICU during 2016–2019 were managed with VATS as initial therapy, and approximately one in six received fibrinolysis.

Between 2007–2010 and 2016–2019, there was a significant increase in both the proportion of hospitalisations for empyema admitted to PICU (11.2% vs. 42.5%, $P < 0.001$) and an increase in the rate of PICU empyema admissions as a proportion of total PICU admissions (7.1 vs. 19.5 per 1000, $P < 0.001$). Previous studies have reported PICU admission in 10–38% of empyema hospitalisations: a lower proportion than in the latter period of our cohort.[3,5–7] A recent Australian study by Haggie *et al.* examined the period 2011–2018, and reported an increase in the proportion of empyema managed in PICU from 18% to a peak of 34%.[3]

In our study, comparing the two time periods before and after PCV13, children admitted to PICU with empyema in 2016–2019 had a small but lower predicted probability of death by PIM2 score, more were managed with VATS and had as shorter duration of intubation. There are limitations in extrapolating these data to compare disease severity. The PIM2 score was developed to predict PICU mortality not disease severity and is an insensitive maker of change for a condition with a low baseline risk of mortality. Similarly, duration of intubation is determined by a number of factors, including indication for mechanical ventilation, and more children were ventilated to facilitated VATS in 2016–2019. Nevertheless, our findings suggest that the increase in PICU empyema admission observed in the study may not be explained by an accompanying increase in disease severity. In 2016, to streamline the management of children with severe CAP, large effusions and empyema and to prevent deterioration on the ward, our PICU admission criteria were more clearly specified to include all children with a 'large effusion or "white out" of a lung field'. These changes in PICU admission guidelines were made in the broader context of other relevant organisational changes focused on early recognition and treatment of the sick child, namely mandatory medical emergency response system (introduced in 2013), and adoption of state-wide observation and response charts in 2014. It is likely that these measures, both specific to empyema (PICU admission guidelines and increasing use of VATS), and general (measures for early detection of deterioration), have contributed to the increasing proportion of children with empyema admitted to PICU.

Microbiological testing of pleural fluid samples changed over the study period, with culture by standard methods supplemented by newer molecular tests. From September 2017, culture-negative samples were routinely tested for pneumococcal PCR (lytA) and, if negative, for broader bacterial PCR testing (16s rRNA PCR). From 2014, selected culture-negative cases with a high suspicion of GAS infection (e.g. with toxin-mediated clinical signs) were tested with GAS PCR (speB), developed for research purposes.[15] These changes have increased the likelihood of isolating pneumococcus and GAS over time. Whilst our methodology does not allow an assessment of whether aetiology in PICU is different to non-PICU empyema hospitalisations, the predominance of *S. pneumoniae* and GAS in our cohort is similar to that reported previously for all hospitalised empyema.[16] The burden of *S. aureus*, isolated in nine of 71 children in our PICU cohort – including six with MRSA 44 was reported by Haggie *et al.*, predominantly affecting children of indigenous background.[3]

Strengths and limitations

With reports of increasing PICU empyema admissions, our study describes the clinical profile of a cohort for which published data are limited. Access to the PICU database and electronic hospital medical records allowed individual case note reviews and extraction of detailed clinical information. We did not use pleural fluid cell count or biochemistry in defining empyema in the PICU cohort, which may have overestimated the incidence of empyema. We relied on a more pragmatic combination of needing intensive care and requiring chest drainage of VATS. Our definition reflects the clinical overlap between different forms of parapneumonic pleural disease, and that in practice, management decisions are based on clinical presentation and progress, radiology, as well as institutional experience, rather than pleural fluid analysis. We standardised case definitions of the larger hospital empyema cohort by using ICD-10 diagnostic codes.

Our single centre, retrospective, study design has inherent limitations. We describe trends in hospitalisations and PICU

admissions for empyema in the pre- and post-PCV13 era, and present data on surrogate markers of disease severity for PICU admissions in the two time periods. But we cannot establish whether these changes are due to PCV13, and cannot control for the changes in management over time such as the increasing use of VATS and fibrinolytics, which may have affected the incidence of intensive care admissions and outcomes. We did not collect data on vaccination status for individual patients, nor on pneumococcal serotypes which may have provided more insight into the effect of PCV vaccination. Subgroup analyses, such as disease severity between the two eras, are limited by small numbers particularly for the earlier time-period.

Conclusions

Children admitted to a PICU with empyema were mostly previously well, nearly two-thirds required mechanical ventilation and 1 in 6 had features of shock. Pneumococcus was identified in 50% of cases. Pulmonary complications were common, and all children survived to PICU discharge. There was a reduction in the hospital incidence of CAP and empyema admission as a proportion of all hospital admissions in the era post-PCV13, but an increase in empyema admission to the PICU as a proportion of all PICU admissions, with no increase in illness severity at admission.

Acknowledgement

Open access publishing facilitated by The University of Melbourne, as part of the Wiley – The University of Melbourne agreement via the Council of Australian University Librarians. [Correction added on May 13, 2022, after first online publication: CAUL funding statement has been added.]

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Appendix I

Complications in 28 children ($n = 71$)

Complication	*n* (%)
Pneumothorax	14 (20)
Bronchopleural fistula	9 (13)
Re-accumulation	3 (4.2)
Other	4 (5.6) – Haemolytic Uraemic Syndrome (2), subcutaneous emphysema (1), pericardial effusion (1)

Appendix II

Annual hospital and intensive care admissions for community acquired pneumonia and empyema 2007–2019

Year	All admissions	Pneumonia admissions	Pneumonia per 1000 hospital admits	Empyema	Empyema per 1000 hospital admissions	PICU admits	PICU empyema	Empyema per 1000 PICU admissions
2007	35 103	392	11.2	43	1.2	712	2	2.8
2008	35 132	412	11.7	38	1.1	646	5	7.7
2009	33 864	462	13.6	41	1.2	673	6	8.9
2010	34 018	540	15.9	47	1.4	660	6	9.1
2011	34 277	506	14.8	49	1.4	766	5	6.5
2012	34 361	399	11.6	39	1.1	769	6	7.8
2013	38 780	491	12.7	50	1.3	963	7	7.3
2014	44 245	519	11.7	36	0.8	1045	12	11.5
2015	44 310	590	13.3	62	1.4	1019	7	6.9
2016	46 400	550	11.9	50	1.1	951	16	16.8
2017	49 005	384	7.8	43	0.9	1028	19	18.5
2018	51 474	418	8.1	48	0.9	1067	23	21.6
2019	52 014	419	8.1	26	0.5	598†	13†	21.7
Total	532 983	6082	11.4	597	1.1	10 897	127	11.7

†Numbers for PICU admissions in 2019 are up to July.