Burden of disease and change in practice in critically ill infants with bronchiolitis

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Changing thresholds to admit bronchiolitis patients to PICU have had a major impact on cost and resource utilisation http://ow.ly/AVA630a08rx

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ABSTRACT Bronchiolitis represents the most common cause of non-elective admission to paediatric intensive care units (ICUs).

We assessed changes in admission rate, respiratory support, and outcomes of infants <24 months with bronchiolitis admitted to ICU between 2002 and 2014 in Australia and New Zealand.

During the study period, bronchiolitis was responsible for 9628 (27.6%) of 34 829 non-elective ICU admissions. The estimated population-based ICU admission rate due to bronchiolitis increased by 11.76 per 100 000 each year (95% CI 8.11–15.41). The proportion of bronchiolitis patients requiring intubation decreased from 36.8% in 2002, to 10.8% in 2014 (adjusted OR 0.35, 95% CI 0.27–0.46), whilst a dramatic increase in high-flow nasal cannula therapy use to 72.6% was observed (p<0.001). We observed considerable variability in practice between units, with six-fold differences in risk-adjusted intubation rates that were not explained by ICU type, size, or major patient factors. Annual direct hospitalisation costs due to severe bronchiolitis increased to over USD30 million in 2014.

We observed an increasing healthcare burden due to severe bronchiolitis, with a major change in practice in the management from invasive to non-invasive support that suggests thresholds to admittance of bronchiolitis patients to ICU have changed. Future studies should assess strategies for management of bronchiolitis outside ICUs.

Introduction

Bronchiolitis is a common viral lower respiratory tract infection in infants characterised by acute small airway inflammation, and represents the leading cause for hospital admission during the first year of life [1]. In high-income countries, approximately one out of eight infants hospitalised with bronchiolitis requires admission to intensive care units (ICUs) for respiratory support as a result of progressive respiratory distress with respiratory failure and hypoxaemia [2, 3]. Despite a general trend towards a reduction in hospital admissions overall, bronchiolitis-related hospitalisation costs have recently increased, amounting to USD1.73 billion per year in the USA [4]. In the past decades, pharmacological interventions have failed to show any benefit and, as a result, consensus guidelines emphasise supportive treatment options [2, 3, 5–8]. While invasive ventilation was traditionally considered to be the cornerstone of treatment for severe bronchiolitis in ICU, over recent years, an increasing number of single-centre studies have reported benefits associated with early use of noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC) therapy to reduce the need for intubation and invasive ventilation in bronchiolitis [9–13].

The aims of this study were to describe the population-based admission rate and severity of bronchiolitis in infants in Australia and New Zealand admitted to intensive care, to determine risk factors for invasive ventilation, and to assess trends in admission rate, management, outcome and associated direct health-care costs over a 13 year period from 2002–2014.

Methods

Further information regarding the study methods can be found in the supplementary material. A multicentre, binational, retrospective study of all patients reported to the Australian and New Zealand Paediatric Intensive Care (ANZPIC) Registry [14]. The study was approved by the Human Research and Ethics Committee (Mater Health Services HREC, Brisbane, Australia) including waiver of informed consent. The ANZPIC Registry prospectively records demographics, physiological variables at admission, intensive care support, diagnoses and outcomes of paediatric ICU and general ICU admissions in children <16 years of age in Australia and New Zealand [14], and captures 92–94% of all paediatric ICU admissions.

Inclusion and exclusion criteria

Infants aged <729 days who were admitted with a diagnosis of bronchiolitis [8] and admitted to a paediatric ICU (PICU) or a general ICU in Australia or New Zealand between January 1, 2002 and December 31, 2014 were included. Elective admissions and infants with pre-existing tracheostomies were excluded.

Outcomes and definitions

The primary outcome was defined as the proportion of infants requiring intubation and invasive ventilation. NIV was defined as continuous positive airway pressure (CPAP) with or without pressure support delivered through a nasal mask, full-face mask, or a nasopharyngeal tube. Mechanical ventilation was defined as either invasive ventilation and/or NIV. Since 2010, the ANZPIC registry has been prospectively recording the use of HFNC oxygen therapy. HFNC was defined as >1 $L \cdot kg^{-1} \cdot min^{-1}$ flow of a gas oxygen mixture through nasal cannula, and coded separately from mechanical ventilation support [12, 13]. Data analyses were therefore separated into two periods: a period before widespread use of HFNC therapy (2002–2009) and a period after widespread introduction of HFNC therapy (2010–2014). With the exception of one paediatric ICU, HFNC was not routinely used in the main paediatric ICUs and ICUs prior to 2010.

Cost estimate methodology is provided in the supplementary material.

Statistics

Data are presented as percentages and numbers or means with standard deviations. t tests were used to compare subgroups. Population-based admission rate estimates were calculated. We assessed linear trends in respiratory support over the 13-year period. In addition, trends during the 13-year study period were assessed by comparing risk-adjusted need for invasive ventilation. We constructed a multivariate

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prediction model for the need for invasive ventilation. For multivariable models, all significant predictors from the univariable analyses were used. We used a backward stepwise elimination procedure to eliminate nonsignificant predictors based on p>0.05.

All paediatric ICUs in Australia and New Zealand contributed to the ANZPIC registry for the entire duration of the study period. The number of general ICUs contributing to the registry increased from six to 19 during the study period. In order to account for potential reporting bias, the following predefined subgroup analyses were performed: 1) specialised paediatric ICUs; 2) general (mixed adult and paediatric) ICUs; and 3) paediatric and general ICUs that had contributed to the ANZPIC registry for the entire length of the study period.

Further details of risk prediction models are provided in the supplementary material.

All analyses were conducted by using Stata (version 12.1, Stata Corp, College Station, Texas, USA). p-values of less than 0.05 were considered significant.

Results

During the study period, bronchiolitis was the most common cause of ICU admission, and was responsible for 9628 (27.6%) of 34 829 non-elective admissions in infants below 2 years of age. 324 infants with tracheostomies *in situ* at time of admission were excluded. Prematurity (20%), chronic respiratory conditions (10%) and congenital cardiac disease (7%) were the most common underlying conditions (table 1). During 2010–2014 (after widespread introduction of HFNC), 5670 infants were admitted with bronchiolitis in comparison to 3634 during 2002–2009 (table 2). In recent years, infants with bronchiolitis admitted to

TABLE 1 Baseline and severity characteristics of patients with bronchiolitis 2002–2014

	Bronchiolitis		p-value
	2002–2009	2010–2014	
Total n	3634 (100%)	5670 (100%)	
Age days	91 (45–201)	139 (57–281)	<0.001
Neonates <28 days	392 (10.8%)	463 (8.2%)	<0.001
28–90 days	1397 (38.4%)	1680 (29.6%)	
91 days to 1 years	1558 (42.9%)	2784 (49.1%)	
1–2 years	287 (7.9%)	743 (13.1%)	
Males	2128 (58.6%)	3409 (60.1%)	0.133
Category			
Admitted to specialist paediatric ICU[#]	2980 (82.0%)	3652 (64.4%)	<0.001
Interhospital transport	1667 (45.9%)	2209 (39.0%)	<0.001
Risk category			
Prematurity	747 (20.6%)	950 (16.8%)	<0.001
Chronic lung disease	229 (6.3%)	224 (4.0%)	<0.001
Other chronic respiratory disease	117 (3.2%)	200 (3.5%)	0.425
Congenital heart disease	281 (7.7%)	330 (5.8%)	<0.001
Chronic neurological disease	77 (2.1%)	107 (1.9%)	0.433
Any comorbidity	1328 (36.5%)	1640 (28.9%)	<0.001
Aetiology			
RSV	1624 (44.7%)	2039 (36.0%)	<0.001
Influenza	61 (1.7%)	84 (1.5%)	0.454
Human metapneumovirus	0 (0.0%)	120 (2.1%)	<0.001
Parainfluenzavirus	67 (1.8%)	115 (2.0%)	0.531
Adenovirus	41 (1.1%)	192 (3.4%)	<0.001
Severity			
Mean paediatric ICU length of stay days	3.69±5.82	3.18±4.33	<0.001
Mean hospital length of stay days	12.47±36.21	9.13±23.79	<0.001
PIM2 (mean probability of death)	0.96±1.7%	0.69±1.9%	<0.001
Median paediatric ICU length of stay days	2.29 (1.08–4.46)	2.25 (1.33–3.75)	0.623
Median hospital length of stay days	6.93 (4.33–11.47)	5.05 (3.43–8.25)	<0.001
PIM2 (median probability of death)	0.59% (0.21–1.00%)	0.27% (0.18–0.77%)	<0.001
Death	25 (0.7%)	10 (0.2%)	<0.001

Data are presented as median (interquartile range) or mean±SD, unless otherwise stated. ICU: intensive care unit; RSV: respiratory syncytial virus; PIM2: Paediatric Index of Mortality-2. [#]: specialist paediatric ICU *versus* general ICU.

TABLE 2 Population-based admission rate of bronchiolitis 2002–2014 (per 100 000 infants <24 months)

Year	Sites		Total ICU admissions due to respiratory infection		Bronchiolitis admissions rate per 100 000 population <24 months					Proportion of admitted patients	
	Paediatric ICU	General	All	Paediatric ICU	All	Paediatric ICU	General	13-year[#]	General/all (n/n %)	All	Paediatric
2002	9	6	589	549	62.5 (383)	58.5 (358)	4.1 (25)	62.0 (380)	6.5%	19.8%	19.5%
2003	9	7	575	508	51.9 (317)	43.6 (266)	8.4 (51)	49.3 (301)	16.1%	16.7%	15.3%
2004	9	7	629	583	59.4 (366)	55.0 (339)	4.4 (27)	58.1 (358)	7.4%	17.2%	17.0%
2005	9	7	640	568	60.7 (380)	52.4 (328)	8.3 (52)	56.5 (354)	13.7%	19.4%	18.1%
2006	9	8	780	637	82.7 (531)	66.5 (427)	16.2 (104)	72.0 (462)	19.6%	24.3%	22.2%
2007	9	12	824	641	78.3 (529)	59.7 (403)	18.7 (126)	62.2 (420)	23.8%	22.3%	19.9%
2008	9	13	921	747	82.5 (579)	63.5 (446)	18.9 (133)	64.2 (451)	23.0%	23.3%	21.1%
2009	9	15	891	712	76.8 (549)	57.8 (413)	19.0 (136)	62.0 (443)	24.8%	22.9%	20.0%
2010	9	15	1083	811	106.5 (766)	76.5 (550)	30.0 (216)	78.8 (567)	28.2%	26.7%	23.3%
2011	9	15	1308	897	123.5 (880)	80.0 (570)	43.5 (310)	85.5 (609)	35.2%	27.8%	23.0%
2012	9	17	1606	1098	167.0 (1206)	108.0 (780)	59.0 (426)	114.5 (827)	35.3%	34.4%	29.0%
2013	9	19	1739	1189	174.5 (1290)	112.9 (835)	61.5 (455)	120.0 (887)	35.3%	33.6%	28.3%
2014	10[¶]	19	1969	1265	208.9 (1528)	125.3 (917)	83.5 (611)	138.3 (1012)	40.0%	37.1%	30.7%
β (95% CI)			113.65 (86.99–140.32)	61.36 (46.65–76.1)	11.84 (8.24–15.45)	5.83 (3.75–7.91)	6.01 (4.37–7.65)	6.25 (3.86–8.63)	0.03 (0.02–0.03)	0.02 (0.01–0.02)	0.01 (0.01–0.01)
p-value (for trend)			<0.0001	<0.0001	<0.0001	0.0001	<0.0001	0.0001	<0.0001	<0.0001	<0.0001

ICU: intensive care unit. [#]: dataset restricted to units that contributed data to the registry for the entire study period 2002–2014; [¶]: two paediatric ICUs that had contributed data to the registry since 2002 merged at the end of 2014 to one new facility.

ICU were older, less likely to require interhospital transfer, more likely to be admitted to a general ICU, and less likely to have underlying diseases (p<0.001). The average severity of disease as measured by mean probability of death (PIM2) decreased significantly, and ICU and hospital length of stay (LOS) decreased accordingly. The crude mortality over the entire study period was 0.38% (35/9304). The re-calibrated PIM2 standardised mortality ratio declined from 1.53 (0.99–2.26) in 2002–2009 to 0.54 (0.26–0.98) in 2010–2014.

The annual number of infants with bronchiolitis admitted to ICU (including paediatric and general ICUs) increased from 383 cases in 2002 to 1528 cases in 2014 (table 2, figure 1). The total number of all non-elective ICU admissions per year during this time increased from 1933 to 4115. The estimated population-based age-standardised admission rate of bronchiolitis increased during the study period with an average annual increase of 11.76 per 100 000 infants <24 months (95% CI 8.11–15.41). The change in admission rate was most pronounced in general ICUs, which took 40% of all bronchiolitis admissions requiring intensive care in 2014 (p<0.0001). The increase in admission was less marked when restricting analyses to paediatric ICUs (annual increase 5.80 per 100 000, 95% CI 3.68–7.90), and to ICUs that had contributed to the registry for the entire study duration (6.21 per 100 000, 95% CI 3.80–8.63). The increase in bronchiolitis admission was higher compared to admissions due to any other respiratory infection, and higher compared to all annual paediatric ICU admissions, which increased from 1933 to 4115 (table 2).

In 2002, 37% of patients with bronchiolitis were intubated/invasively ventilated, in comparison to only 11% in 2014 (p<0.001, figure 2 and supplementary table S1). In view of the concomitant dramatic increase in bronchiolitis-related ICU admission rates, we calculated estimates of population-based intubation rates (supplementary table S2). Absolute intubation numbers and population-based intubation rates in infants with bronchiolitis did not decrease significantly during the study period (p>0.05). We observed a decrease in the proportion of intubations performed in ICU after the first hour of admission from 66.2% (674/1018) in 2002–2009 to 43.6% (394/903) in 2010–2014. The time to intubation in infants that were not intubated within the first hour of admission did not change during the study period (p=0.840; supplementary figure S1). Over the same period, the length of mechanical ventilation (invasive ventilation and/or NIV) decreased significantly from a mean duration of 109 h to 69 h (average decrease 3.4 h per mechanically ventilated patient per year; 95% CI 2.25–4.56). Following the introduction of HFNC therapy in most paediatric ICUs, the use of HFNC in infants with bronchiolitis increased over 2010–2014 to

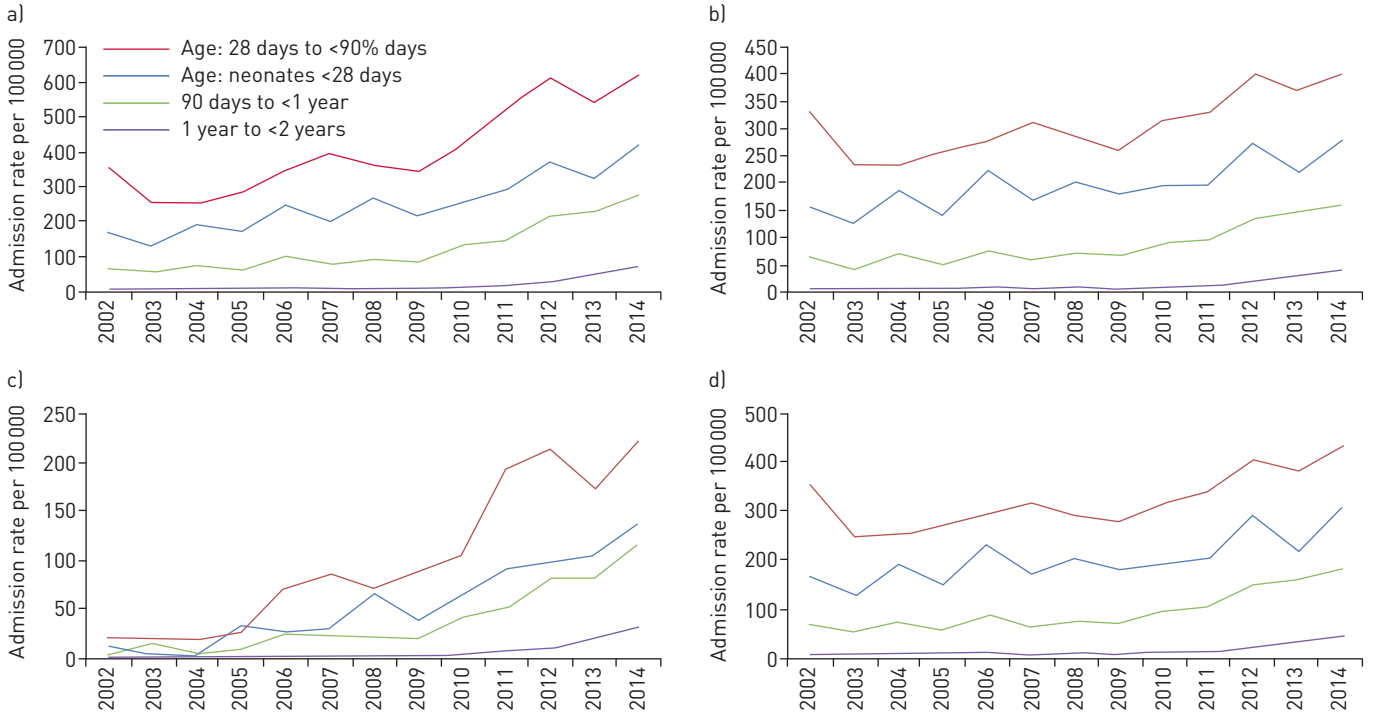

FIGURE 1 Estimated population-based intensive care unit (ICU) admission rates due to bronchiolitis. ICU admission rates per 100 000 infants <24 months of age and year are shown for a) all ICU admissions captured in the Australian and New Zealand Paediatric Intensive Care Registry; b) admissions to paediatric PICUs; c) admissions to general Intensive Care Units (ICUs); and d) admissions to paediatric ICUs and ICUs that contributed to the registry for the entire study duration 2002–2014.

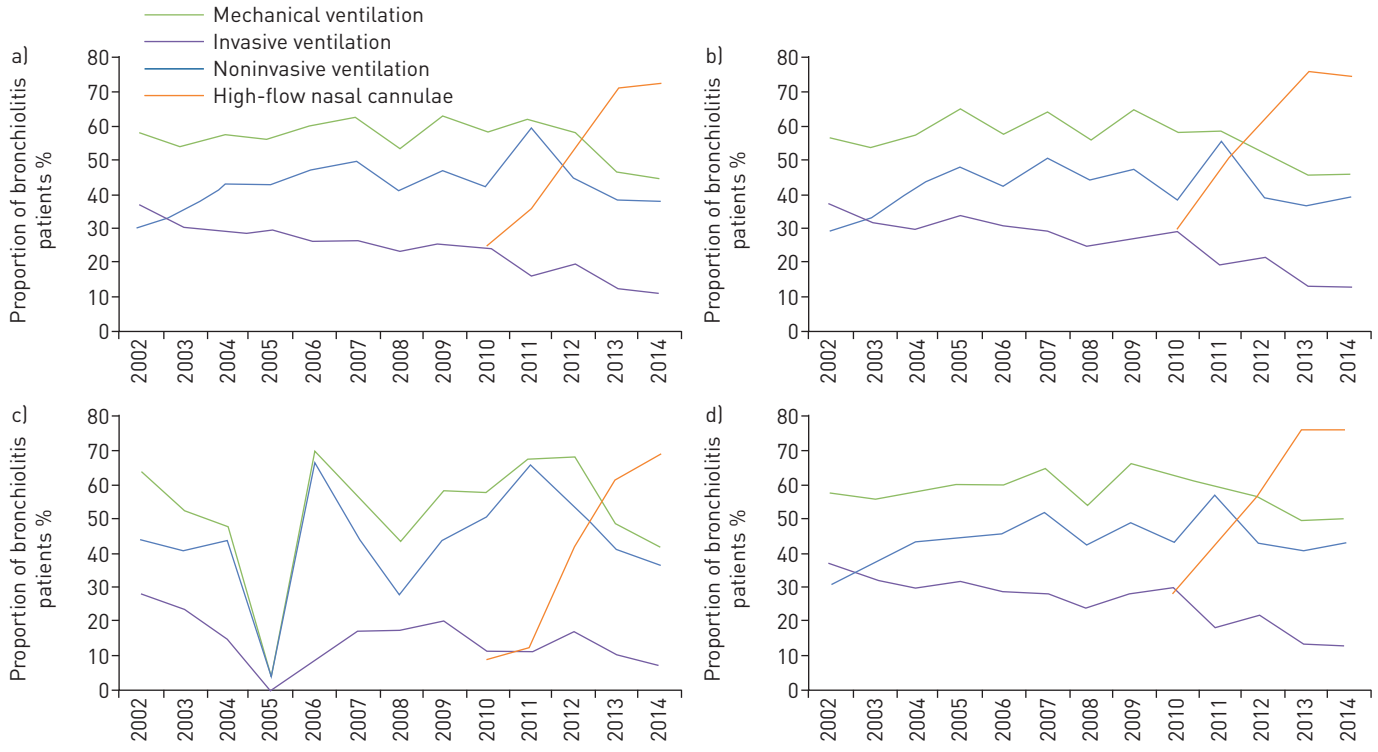

FIGURE 2 Changes in respiratory support mode during the study period 2002–2014 in infants admitted to intensive care unit (ICU) with bronchiolitis. Mechanical ventilation is defined as intubation and/or noninvasive ventilation. Proportions of respiratory support mode used per patient (more than one modality allowed) are shown for a) all ICU admissions captured in the Australian and New Zealand Paediatric Intensive Care Registry; b) admissions to paediatric ICUs; c) admissions to general ICUs; and d) admissions to paediatric ICUs and ICUs that contributed to the registry for the entire study duration 2002–2014.

72.6%; this was accompanied by a reduction in the use of NIV. The findings observed in the entire cohort were confirmed in subgroup analyses restricted to paediatric ICUs only, and to paediatric ICUs and ICUs that had contributed to the registry for the entire study duration (figure 2 and supplementary tables S1 and S2).

In multivariate analyses, age, interhospital transport, major chronic conditions, prematurity, and severity indicators such as low systolic blood pressure were identified as significant predictors for intubation (table 3; AUC 0.76, 0.75–0.77). Each year was associated with a 0.9% decline in the risk of intubation

TABLE 3 Multivariate model to prediction of likelihood of requiring intubation and invasive ventilation in critically ill infants with bronchiolitis

	Odds ratio	95% CI	β	95% CI	p-value
Age (days/30)	0.970	0.957 to 0.983	−0.013	−0.044 to −0.017	<0.001
Interhospital transport	2.718	2.415 to 3.058	0.434	0.882 to 1.118	<0.001
Chronic neurological condition	1.723	1.187 to 2.502	0.236	0.171 to 0.917	0.004
Chronic respiratory condition	1.585	1.182 to 2.124	0.200	0.167 to 0.753	0.002
Bronchopulmonary dysplasia	1.686	1.324 to 2.148	0.227	0.280 to 0.765	<0.001
Congenital heart defect	1.875	1.536 to 2.289	0.273	0.429 to 0.828	<0.001
Prematurity	1.320	1.147 to 1.520	0.121	0.137 to 0.419	<0.001
RSV	1.561	1.387 to 1.757	0.193	0.327 to 0.564	<0.001
Influenza/parainfluenzae	2.001	1.523 to 2.629	0.301	0.421 to 0.967	<0.001
Systolic blood pressure ⩽70 mmHg	4.034	3.160 to 5.151	0.606	1.151 to 1.639	<0.001
Base excess	0.947	0.929 to 0.967	−0.023	−0.074 to −0.034	<0.001
(Base excess)^2	1.010	1.008 to 1.013	0.004	0.008 to 0.012	<0.001
Constant	0.087	0.063 to 0.121	−1.060	−2.768 to −2.113	<0.001

Data are based on a saturated mix-effects logistic regression model clustering on site and adjusted for all variables shown in the table. RSV: respiratory syncytial virus.

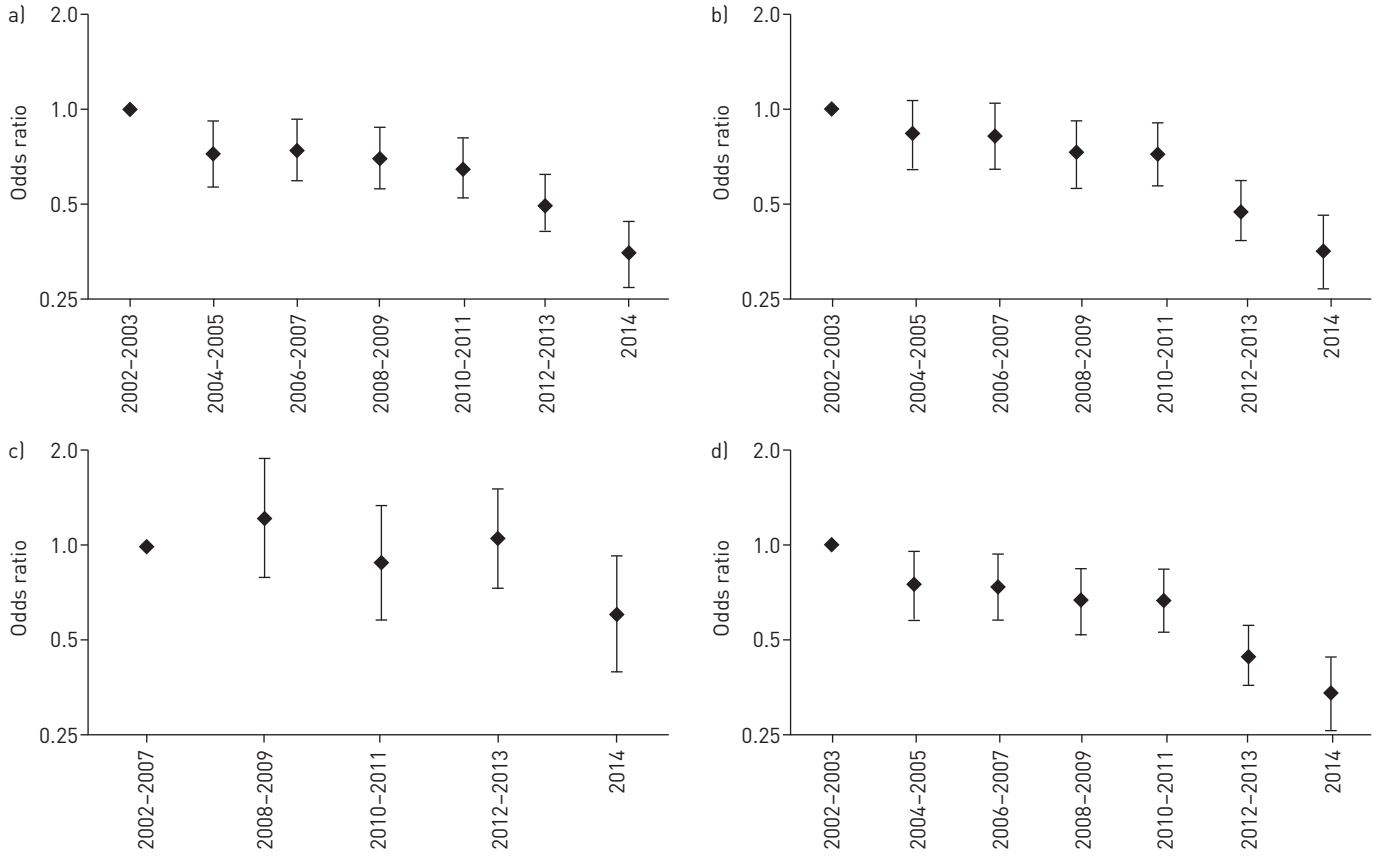

FIGURE 3 Adjusted risk for intubation/invasive ventilation in infants with bronchiolitis during the study period. Odds ratios are adjusted for age, interhospital transport, chronic respiratory and neurological conditions, prematurity, congenital heart disease, specific respiratory viruses, low systolic blood pressure, and are shown for a) all intensive care unit (ICU) admissions captured in the Australian and New Zealand Paediatric Intensive Care Registry; b) admissions to paediatric ICUs; c) admissions to general ICUs; and d) admissions to paediatric ICUs and ICUs that contributed to the registry for the entire study duration 2002–2014.

(95% CI 0.81–1.00%). The overall adjusted odds for intubation decreased significantly from 2002/2003 to 2014 (OR 0.35, 95% CI 0.27–0.44; p<0.001) (figure 3). The model performed comparably when restricted to infants that were not intubated on arrival to paediatric ICU (supplementary table S3A). For children treated with HFNC, younger age, bronchopulmonary dysplasia, congenital heart defects, low blood pressure, and increased negative base excess were the main predictors of intubation (p<0.01) (supplementary table S3B).

When comparing the risk-adjusted rate of an infant with bronchiolitis receiving invasive ventilation, important differences between units were noted (figure 4). When compared to an intercept-only mixed effects model, a model that controlled for year and patient risk factors (table 3) demonstrated a 39.1% reduction in the variance of the random effect. This difference suggests that 60.9% of the variation in

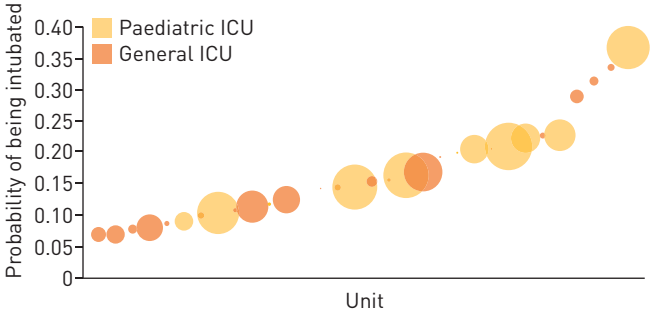

FIGURE 4 Comparison of the probability of an infant with bronchiolitis receiving invasive ventilation between different paediatric and general intensive care units (ICUs). Area of bubble indicates relative admission numbers.

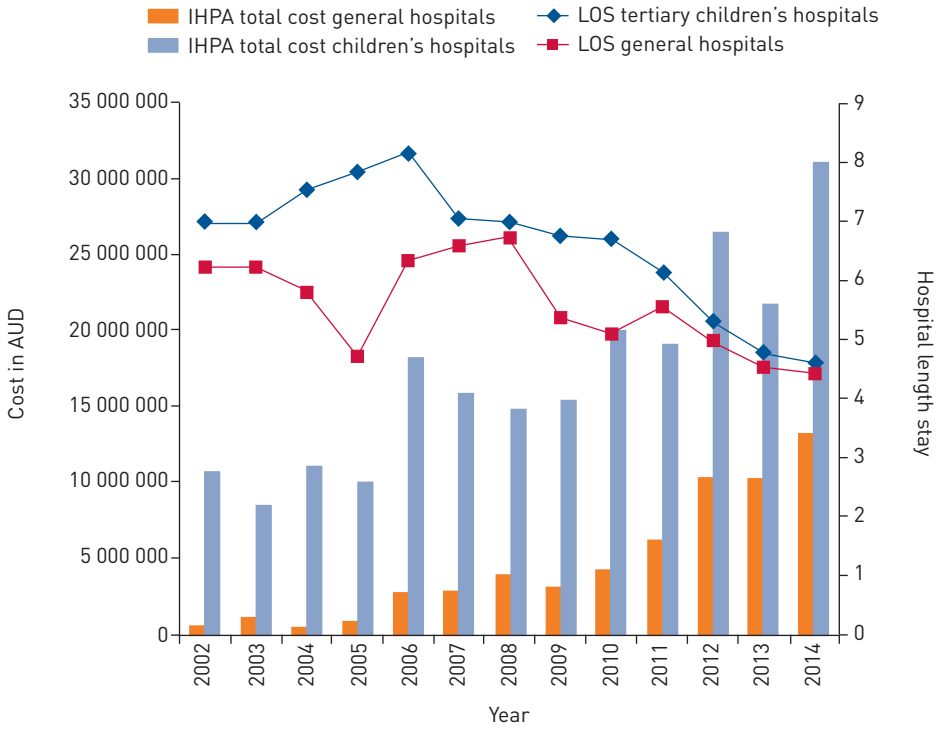

FIGURE 5 Annual direct hospitalisation cost (in AUD 2014) due to severe bronchiolitis requiring intensive care unit admission in Australia and New Zealand, 2002–2014. Length of stay (LOS), and associated costs estimated by Independent Hospital Pricing Authority (IHPE) Efficient Price Determination are shown for children`s hospitals and general hospitals.

intubation rates were neither explained by the case mix nor by time trends, and likely reflect underlying differences in unit-to-unit practice. Using the average risk profile for intubation, the probability of a child with bronchiolitis being intubated varied from 6.9% to 36.7% across units.

We assessed total direct hospitalisation-related costs in infants requiring ICU admission, including ICU and ward costs. Although a reduction in LOS over the period of 2002–2014 occurred, the total annual costs increased from AUD11.4 million in 2002 to $44.3 million in 2014 (supplementary table S4 and figure 5). The total costs related to bronchiolitis admitted to specialised paediatric ICUs increased from $10.7 million to $31.1 million over the same period.

Discussion

This large binational study, including over 9000 critically ill infants with bronchiolitis, demonstrates that severe bronchiolitis is responsible for a huge burden of disease, resulting in over USD30 million direct costs each year in Australia and New Zealand. Bronchiolitis has a major impact on ICU resource consumption, accounting for >25% of non-elective PICU admissions in infants. In the absence of high-grade evidence for treatment of bronchiolitis in ICU, we observed a dramatic increase in the number of children admitted to intensive care in Australia and New Zealand with bronchiolitis, concomitant with the increased use of HFNC therapy. In view of close to zero mortality in infants with severe bronchiolitis, these findings indicate an urgent need for future studies investigating whether a proportion of these patients may be safely managed outside the ICU, hence reducing associated healthcare costs.

By estimating population-based ICU admission rates, we were able to document a major change in practice over the past decade, with a dramatic increase in ICU admissions in infants with bronchiolitis that do not require invasive ventilation. The increase observed in general ICUs may have been enhanced by reporting bias, as more general ICUs have contributed data to the study database over recent years. However, the findings were reproduced in subgroup analyses restricted to paediatric ICUs, and restricted to those centres that had provided data for the entire study duration. Infants with bronchiolitis admitted in recent years to ICU were less likely to have underlying comorbidities, were older, and their predicted mortality was lower, which suggests changing thresholds for ICU admission. At the same time, we observed a considerable variability in practice between units, with over six-fold difference in risk-adjusted intubation rates that was not explained by ICU type, size, nor major patient factors. Our findings support

a recent North American study on bronchiolitis that observed >3.5-fold variation in the risk of intubation between paediatric ICUs, and a high variability in the proportion of patients exposed to other non-evidence-based interventions [15]. While bronchiolitis hospital admission rates and length of stay have been proposed as benchmarks in the NHS Atlas of Variation in Healthcare (www.chimat.org.uk/variation), ICU resource use has not been investigated. Notably, the study period witnessed the implementation of rapid response teams and early warning tools (EWTs) in the major paediatric hospitals, followed by regional hospitals. While EWTs have been shown to predict the need for ICU admission, and reduce cardiopulmonary arrests in the ward setting [16], to the best of our knowledge they have not been validated specifically for bronchiolitis. Indeed, infants with severe bronchiolitis commonly manifest tachycardia, tachypnoea, and increased work of breathing, and may trigger EWTs relatively rapidly, with an unknown impact on health outcomes and resource utilisation.

Our data show that this increase in ICU admission rates was associated with a rapid expansion in costs, despite a reduction in LOS in intensive care and a shorter duration of ventilation. Our costs are comparable to those in a recent European study, which reported a four times higher cost for children requiring ICU compared to those treated on the ward (EUR8061 *versus* EUR1834) [17].

Our study demonstrates that, despite lack of larger trials on HFNC use in infants, HFNC therapy has become the most common support mode for critically ill infants with bronchiolitis in Australia and New Zealand recently, with over 70% of admissions in 2014 supported with HFNC. At the same time, while the proportion of admissions requiring intubation and invasive ventilation dropped, we did not observe a significant reduction in the absolute number of children requiring invasive ventilation. Our observation parallels those of several single-centre studies that reported a drop in intubation rates in patients with severe bronchiolitis following the increased use of NIV and HFNC [10, 12, 13, 18–22], and suggests that these have led to a major change of practice in the absence of higher grade evidence. Recent large randomised trials in adults have demonstrated efficacy of HFNC therapy for acute hypoxemic respiratory failure [23, 24]. In the neonatal population, HFNC therapy was shown to be non-inferior to nasal CPAP [25, 26]. While the physiological effects of HFNC therapy, including provision of 4–5 cmH_2O CPAP, reduction in inspiratory work of breathing through provision of flows matching or greater than peak inspiratory flows, and washout of nasopharyngeal dead space have been independently confirmed [27, 28], there is a lack of randomised controlled trials to support either outcome benefit or cost benefit of HFNC therapy in the paediatric age group. A recent adult single-centre study reported higher mortality in patients treated with HFNC that required delayed emergency intubation [29]. In our cohort, the increasing use of HFNC was not associated with a delay in intubations, and in fact the proportions of late intubations, mortality, length of mechanical ventilation, and length of ICU stay decreased.

Advantages of HFNC therapy include an excellent safety profile, low equipment costs, easy application, and increased patient comfort compared to other forms of respiratory support. As a result, the application of HFNC therapy outside ICU settings has been increasingly tested, and single-centre studies suggest safety, feasibility, and efficiency of such an approach [18], although the translation of this approach into better outcomes remains to be proven. Bronchiolitis is a relatively uniform disease with close to zero mortality, patients mostly demonstrate gradual rather than precipitous deterioration, and predictors can be used to stratify severity [30]. As a result, this disease may in fact be optimally suited to design interventional trials aiming to reduce the number of intensive care admissions [31].

We believe the results of this study have several implications for the design of further research on bronchiolitis. First, they highlight an urgent need to validate early warning tools for bronchiolitis, as these may have a direct impact on intensive care admission rates. Secondly, improved markers of severity, including viral genomic load [32], may assist in optimising risk stratification to the target groups most likely to develop severe respiratory failure. Thirdly, the variation in respiratory support practice suggests a lack of standardised protocols [5, 8]. Fourthly, the dramatic change of practice seen in respiratory support modes warrants a paediatric ICU trial of HFNC therapy *versus* NIV *versus* low-flow oxygen for infants and children with respiratory failure [24]. Finally, our data suggest that it is likely that a considerable proportion of intensive care patients may be good candidates to be considered for treatment outside ICU; whether HFNC therapy provides a cost benefit in such a setting has to be tested by large trials [31]. Importantly, trials on optimal respiratory support outside ICU may inform on the development and implementation of cost-effective interventions relevant at a global scale, with the potential to translate into mortality benefits in resource-poor countries [33].

Several limitations of this study need to be considered. While we were not able to assess overall hospital admissions due to bronchiolitis, we captured every patient admitted to a general or paediatric ICU in Australia and New Zealand providing data to the registry. Although bronchiolitis is well-defined as a clinical entity [8], overlap with reactive airway diseases may lead to diagnostic challenges, potentially

resulting in overdiagnosis of the disease. The use of HFNC was not prospectively captured prior to 2010, and we therefore cannot comment on how frequently HFNC was used as a respiratory support mode prior to 2010. Furthermore, we did not have access to detailed microbiological data, and extended nasopharyngeal virus polymerase chain reaction tests were not consistently performed in centres throughout the study. Because the large majority of infants with bronchiolitis admitted to ICU did not receive intra-arterial monitoring on admission, we were unable to stratify by the degree of hypoxaemia. Finally, inspired oxygen fraction (FIO_2) to arterial oxygen saturation measured by pulse oximetry ratios could not be used as the true FIO_2 is unknown in HFNC or low flow oxygen therapy. In addition, we did not have access to carbon dioxide tension values measured on admission to ICU; however, elevated carbon dioxide tension values represent a common finding in bronchiolitis and may not necessarily indicate a need for intubation [34].

In conclusion, severe bronchiolitis remains responsible for a huge burden of disease. We observed a major change in practice in the management of severe bronchiolitis with dramatically increased use of HFNC therapy despite the lack of high-grade evidence for treatment benefit in this age group. Our data suggest that thresholds to admit bronchiolitis patients to intensive care have reduced over the past decade, with a major impact on healthcare-related costs and resource utilisation in ICUs in Australia and New Zealand. International trials addressing the risk stratification and safe management of bronchiolitis outside intensive care settings are urgently warranted.

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