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Burden of Disease and Change in Practice in Critically Ill Infants with Bronchiolitis

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Take home message: Thresholds to admit bronchiolitis patients to PICU have changed over the past decade with a major impact on costs and resource utilization.

Authors and Contributions:

Dr. Schlapbach and Dr. Straney had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Schlapbach was responsible for the study design, prepared the first manuscript draft and approved the final version. Drs Straney and Schibler were involved in study design, analyses, preparation of the first manuscript draft and final version.

Dr. Slater led the design and maintenance of the ANZPIC Registry since inception, was involved in study design, and approved the final version.

Dr. Whitty and Mrs Franklin performed healthcare cost related analyses and interpretation. Drs Beca, Wilkins, Erickson, Croston, Gebhard, Ganu, and Mrs Alexander were involved in study design, data collection, and manuscript preparation, and approved the final version.

ABSTRACT

Bronchiolitis represents the most common cause for non-elective admission to pediatric 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 9,628 (27.6%) of 34,829 non-elective ICU admissions. The estimated population-based ICU admission rate due to bronchiolitis increased by 11.76/100,000 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; 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 a considerable variability in practice between units, with six-fold differences in risk-adjusted intubation rates which were not explained by ICU type, size, nor major patient factors. Annual direct hospitalization costs due to severe bronchiolitis increased to over US$30 M in 2014.

In conclusion, we observed increasing health care burden due to severe bronchiolitis, with a major change in practice in the management from invasive to non-invasive support suggesting thresholds to admit bronchiolitis patients to ICU have changed. Future studies should assess strategies for management of bronchiolitis outside ICUs.

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Keywords: infant; ventilation; bronchiolitis; intensive care; high-flow nasal cannulae

Abbreviations:

OR	Odd's ratio
PICU	Paediatric Intensive Care Unit
PIM	Paediatric Index of Mortality
IV	Invasive ventilation
NIV	non-invasive ventilation
CPAP	continuous positive airway pressure
BIPAP	biphasic positive airway pressure
HFNC	high-flow nasal cannulae

Introduction

Bronchiolitis is a common viral lower respiratory tract infection in infants characterized 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 hospitalized with bronchiolitis require admission to Intensive Care Units (ICU) for respiratory support as a result of progressive respiratory distress with respiratory failure and hypoxemia[2, 3]. Despite a general trend towards a reduction in hospital admissions overall, bronchiolitis-related hospitalization costs have recently increased amounting to US$1.73 billion per year in the US[4]. In the past decades, pharmacological interventions have failed to show any benefit, and as a result, consensus guidelines emphasize supportive treatment options[2, 3, 5-8]. While invasive ventilation (IV) was traditionally considered the cornerstone of treatment for severe bronchiolitis in ICU, over recent years, an increasing number of single center studies have reported benefits associated with early use of non-invasive ventilation (NIV) and High-Flow Nasal Cannula (HFNC) therapy to reduce the need for intubation and IV 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 (see as well Online Supplementary Material)

A multicenter, 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, physiologic variables at admission, intensive care support, diagnoses and outcomes of PICU and general ICU admissions in children <16 years of age in Australia and New Zealand[14], and captures 92-94% of all pediatric ICU admissions.

Inclusion and Exclusion Criteria: Infants aged <729 days and admitted with a diagnosis of bronchiolitis[8] and who were admitted to a pediatric ICU (PICU) or a general ICU in Australia or New Zealand between 1st January 2002 and 31st December 2014 were included. Elective admissions were excluded and infants with preexisting tracheostomies were excluded.

Outcomes and definitions: The primary outcome was defined as the proportion of infants requiring intubation and invasive ventilation (IV). Non-invasive ventilation (NIV) was defined as continous 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 IV and/or NIV. Since 2010, the ANZPIC registry has been prospectively recording the use of high-flow nasal cannulae oxygen (HFNC) therapy. HFNC was defined as > 1L/kg/min flow of a gas oxygen mixture through nasal cannula, and was 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 post widespread introduction of HFNC therapy (2010-2014). With the

exception of one PICU, HFNC was not routinely used in the main PICUs and ICUs prior to 2010.

Cost estimates methodology are provided in the Supplementary Material.

Statistics:

Data are presented as percentages and numbers or means with standard deviation. 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 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 non-significant predictors based on $p>0.05$.

All PICUs 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 6 to 19 during the study period. In order to account for potential reporting bias, the following predefined subgroup analyses were performed: i) specialized pediatric ICUs (PICUs); ii) general (mixed adult and pediatric) ICUs; iii) pediatric and general ICUs that had been contributing for the entire length of the study period to the ANZPIC registry.

Further details of risk prediction models are provided in the Supplementary Material.

All analyses were conducted using Stata (version 12.1, Stata Corp, College Station, Texas, USA). P-values 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 9,628 (27.6%) of 34,829 non-elective admissions in infants below two 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 to 2014 (post widespread introduction of HFNC), 5670 infants were admitted with bronchiolitis in comparison to 3634 during 2002 to 2009 (Table 2). In recent years, infants with bronchiolitis admitted to ICU were older, less likely to retrieved, 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 PIM2 decreased significantly, and ICU and hospital LOS decreased accordingly. The crude mortality over the entire study period was 0.38% (35/9304). The re-calibrated PIM2 standardized mortality ratio declined from 1.53 (0.99-2.26) in 2002-2009 down to 0.54 (0.26-0.98) in 2010-2014.

The annual number of infants with bronchiolitis admitted to ICU (including pediatric 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 11.76/100,000 infants <24 months (95%-CI 8.11 to 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 PICUs (annual increase

5.80/100,000; 95%-CI 3.68 to 7.90), and when restricting to ICUs that had contributed to the registry for the entire study duration (6.21/100,000; 95%-CI 3.80 to 8.63). The increase in bronchiolitis admission was higher compared to admissions due to any respiratory infection, and higher compared to all annual PICU 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 1). In view of the concomitant dramatic increase in bronchiolitis-related ICU admission rates, we calculated estimates of population-based intubation rates (Supplementary Table 2). 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 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 1). Over the same period, the length of mechanical ventilation (IV and/or NIV) decreased significantly from a mean duration of 109 hours to 69 hours (average decrease 3.4 hours per mechanically ventilated patient per year; 95%-CI 2.25 to 4.56). Following the introduction of HFNC therapy in most PICUs, the use of HFNC in infants with bronchiolitis increased during 2010-2014 to 72.6%, which was accompanied by a reduction in the use of NIV. The findings observed in the entire cohort were confirmed in subgroup analyses restricted to PICUs only, and to PICUs and ICUs that had contributed to the registry for the entire study duration (Figure 2 and Supplementary Table 1 and 2).

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 (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 PICU (Supplementary Table 3A). 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 3B).

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 which controlled for year and patient risk factors (Table 3) demonstrated a 39.1% reduction in the variance of the random effect. This suggests that 60.9% of the variation in intubation rates were not 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 a child with bronchiolitis being intubated varied from 6.9% to 36.7% across units.

We assessed total direct hospitalization-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 AU$11.4 M in 2002 to $44.3 M in 2014 (Supplementary Table 4 and Figure 5). The total costs

related to bronchiolitis admitted to specialized PICUs increased from $10.7 M to $31.1 M over the same period.

Discussion

This large binational study including over 9,000 critically ill infants with bronchiolitis demonstrates that severe bronchiolitis is responsible for a huge burden of disease, resulting in over US$30 M 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 intensive care unit, hence reducing associated health-care 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 are not requiring 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 PICUs, and restricted to those centers 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, older, and their predicted mortality was lower, suggesting changing thresholds for ICU admission. At the same time, we observed a considerable variability in practice between units, with over six-fold differences in

risk-adjusted intubation rates which was not explained by ICU type, size, nor major patient factors. Our findings support a recent northamerican study on bronchiolitis which observed >3.5-fold variation in the risk of intubation between PICUs, 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 (http://www.chimat.org.uk/variation), ICU resource use have not been investigated. Of note, the study period witnessed the implementation of rapid response teams and early warning tools (EWTs) in the major pediatric hospitals, followed by regional hospitals. While EWTs have been shown to predict the need for ICU admission, and reduce cardiopulmonary arrests in 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, tachypnea, and increased work of breathing, and may relatively rapidly trigger EWTs – with an unknown impact on health outcomes and resource utilization.

Our data shows that this increase in ICU admission rates has been 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 a recent European study, which reported a four times higher cost for children requiring ICU compared to those treated on the ward (EUR €8061 versus €1834)[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 IV dropped, we did not observe a significant reduction in the

absolute number of children requiring IV. Our observation parallels several single center studies reporting 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 randomized 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 4-5cm H_2O CPAP, reduction in inspiratory work of breathing through provision of flows matching or greater than peak inspiratory flows, and washout of nasopharyngeal deadspace have been independently confirmed[27, 28], there is a lack of randomized-controlled trials to support either outcome benefit or cost benefit of HFNC therapy in the pediatric age group. A recent adult single center study has 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 proportion 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. Firstly, 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 optimizing risk stratification to target groups most likely to develop severe respiratory failure. Thirdly, the variation in respiratory support practice suggests a lack of standardized protocols[5, 8]. Fourthly, the dramatic change of practice seen in respiratory support modes warrants a PICU 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 ICU or PICU 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 can not 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 centers 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 hypoxemia. Finally, FiO_2/SpO_2 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 pCO_2 values measured on admission to ICU, however elevated pCO_2 represent a common finding in bronchiolitis and may not indicate necessarily 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 early use of HFNC therapy despite the lack of high-grade evidence for treatment benefit in this age group. Our data suggests 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 utilization 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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Figure legends

Figure 1: Estimated population-based ICU admission rates due to bronchiolitis. ICU admission rates per 100,000 infants < 24 months and year are shown for A) all ICU admissions captured in the Australian and New Zealand Paediatric Intensive Care Registry; B) admissions to Pediatric Intensive Care Units (PICUs); C) admissions to general Intensive Care Units (ICUs); D) admissions to PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014. Red line: age 28days to <90 days; blue line: age neonates <28days; green line: 90 days to <1 year; purple line: 1 year to <2 years.

Figure 2: Changes is respiratory support mode during the study period 2002 to 2014 in infants admitted to ICU with bronchiolitis. Mechanical ventilation (green line) is defined as intubation (purple line: invasive ventilation) and/or non-invasive ventilation (blue line). High-flow nasal cannulae (HFNC) is shown in orange. 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 Pediatric Intensive Care Units (PICUs); C) admissions to general Intensive Care Units (ICUs); D) admissions to PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014.

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 ICU admissions captured in the Australian and New Zealand

Paediatric Intensive Care Registry; B) admissions to Pediatric Intensive Care Units (PICUs); C) admissions to general Intensive Care Units (ICUs); D) admissions to PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014.

Figure 4. Comparison of the probability of an infant with bronchiolitis receiving invasive ventilation between different pediatric and general Intensive Care Units. (Area of bubble indicates relative admission numbers, purple bubbles indicate PICUs, red bubbles indicate general ICUs).

Figure 5: Annual direct hospitalization cost (in AU$ 2014) due to severe bronchiolitis requiring ICU admission in Australia and New Zealand from 2002 to 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 hospital.

Table 1: Baseline and severity characteristics of patients with bronchiolitis 2002-2014.

		Bronchiolitis		
		2002-2009	**2010-2014**	**p**
Total	N	3 634 (100%)	5 670 (100%)	
Age	Median (IQR) [days]	91 (45-201)	139 (57-281)	<0.001
	Neonates <28 days	392 (10.8%)	463 (8.2%)	<0.001
	28d-90d	1 397 (38.4%)	1 680 (29.6%)	
	91d- 1 year	1 558 (42.9%)	2 784 (49.1%)	
	1-2 years	287 (7.9%)	743 (13.1%)	
Sex	% Male	2 128 (58.6%)	3 409 (60.1%)	0.133
Category	Admitted to specialist PICU[a]	2 980 (82.0%)	3 652 (64.4%)	<0.001
	Interhospital transport	1 667 (45.9%)	2 209 (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	1 328 (36.5%)	1 640 (28.9%)	<0.001
Etiology	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 PICU Length of Stay (SD) [days]	3.69 (5.82)	3.18 (4.33)	<0.001
	Mean Hospital Length of Stay (SD)	12.47 (36.21)	9.13 (23.79)	<0.001
	PIM2 (mean probability of death) (SD)	0.96% (1.7%)	0.69% (1.9%)	<0.001
	Median PICU Length of Stay (IQR) [days]	2.29 (1.08-4.46)	2.25 (1.33-3.75)	0.623

	Median Hospital Length of Stay (IQR)	6.93 (4.33-11.47)	5.05 (3.43-8.25)	<0.001
	PIM2 (median probability of death) (IQR)	0.59% (0.21-1.00%)	0.27% (0.18-0.77%)	<0.001
	Death	25 (0.7%)	10 (0.2%)	<0.001

[a]Specialist Pediatric Intensive Care Unit (versus general ICU)

PICU, Pediatric Intensive Care Unit; PIM2, Paediatric Index of Mortality-2.

Table 2: Population-based admission rate of bronchiolitis 2002-2014 (per 100,000 infants <24 months)

	Sites		Total ICU admissions due to respiratory infection		Bronchiolitis admissions rate per 100,000 population <24 months (n)					Proportion of admitted patients	
Year	PICU	General	All	PICU	All	PICU	General	13-year*	General/All (n/n %)	All	PICU
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	1,083	811	106.5 (766)	76.5 (550)	30.0 (216)	78.8 (567)	28.2%	26.7%	23.3%
2011	9	15	1,308	897	123.5 (880)	80.0 (570)	43.5 (310)	85.5 (609)	35.2%	27.8%	23.0%
2012	9	17	1,606	1,098	167.0 (1206)	108.0 (780)	59.0 (426)	114.5 (827)	35.3%	34.4%	29.0%
2013	9	19	1,739	1,189	174.5 (1290)	112.9 (835)	61.5 (455)	120.0 (887)	35.3%	33.6%	28.3%
2014	10**	19	1,969	1,265	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 το 15.45)	5.83 (3.75 το 7.91)	6.01 (4.37 το 7.65)	6.25 (3.86 το 8.63)	0.03 (0.02 το 0.03)	0.02 (0.01 to 0.02)	0.01 (0.01 to 0.01)
		p (for trend)	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	0.0001	<0.0001	<0.0001	<0.0001

- dataset restricted to units that had been contributing data to the registry for the entire study period 2002-2014

** Two PICUs that had contributed data to the registry since 2002 merged at the end of 2014 to one new facility.

Table 3: Multivariate model to prediction of likelihood of requiring intubation and invasive ventilation in critically ill infants with bronchiolitis. Data are based on a saturated mix-effects logistic regression model clustering on site and adjusted for all variables shown in the table.

	Odds Ratio	(95% CI)	β	(95% CI)	p
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	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

Online Supplementary Material:
Burden of Disease and Change in Practice in Critically Ill Infants with Bronchiolitis in Australia and New Zealand 2002 to 2014

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on behalf of the Australian & New Zealand Intensive Care Society (ANZICS) Centre for Outcomes & Resource Evaluation (CORE) and the Australian & New Zealand Intensive Care Society (ANZICS) Paediatric Study Group

Methods

ANZPIC Registry. The ANZPIC Registry was created in 1997 and prospectively records demographics, physiologic variables at admission, intensive care support, diagnoses and outcomes of PICU and general ICU admissions in children <16 years of age in Australia and New Zealand. The registry captures 92-94% of all pediatric ICU admissions. Data are entered by trained ICU data collectors, and funding is provided by state governments in Australia and New Zealand. Data validation and auditing of PICUs and larger general ICUs are performed biennially.
Population-based admission rate estimates: Age-specific population data were accessed through the Australian Bureau of Statistics (http://www.abs.gov.au/AUSSTATS/abs@.nsf/second+level+view?ReadForm&prodno=3101.0&viewtitle=Australian%20Demographic%20Statistics~Jun%202012~Previous~18/12/2012&&tabname=Past%20Future%20Issues&prodno=3101.0&issue=Jun%202012&num=&view=&) and through Statistics New Zealand (http://www.stats.govt.nz/estimates-projections).
The diagnosis of bronchiolitis was based on the prospective diagnostic coding used in each patient in the ANZPIC Registry, including the principal diagnosis, the underlying diagnosis, or any of the associated diagnoses. The coding is based on the ICU discharge diagnosis by the ICU physicians.

Comorbidity definitions: The following comorbidities were defined to characterize patients with underlying disease: prematurity (< 37 weeks gestational age), chronic lung disease, underlying chronic respiratory disease other than prematurity-related chronic lung disease, congenital heart disease, chronic neurologic disease (encephalopathy; chronic central or peripheral nervous system disease), and other comorbidities (including renal disease, immunodeficiency or immunosuppression, haematological or solid organ tumors, status post bone marrow transplantation, and solid organ transplant recipients).

Cost estimates:
The ANZPIC registry data were used to estimate the costs of bronchiolitis in Australia and New Zealand, using 2014 Australian dollar costings. The costing model applied standardised prices from the National Efficient Price Determination (2014/2015) (https://www.ihpa.gov.au/sites/g/files/net636/f/publications/national_efficient_price_determination_2014-15.pdf). This model presents the activity based funding that would be provided by the Commonwealth to hospitals, based on an assumed Australian Refined Diagnosis – Related Group of Bronchiolitis with complications (E70A), weighted for time spent in intensive care, length of hospital stay and/or paediatric service. For the years 2003-2014 if data for hospital LOS were missing, imputation was used based on the median LOS for that corresponding year for general or paediatric ICU settings. As there were limited hospital LOS data available for 2002, the median LOS for 2003 was imputed for 2002.

Statistics and risk prediction models:
To assess change in risk-adjusted mortality, we recalibrated PIM2 among these patients using the linear prediction of the PIM2 model in a logistic regression model. 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 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 non-significant predictors based on $p>0.05$.
For risk prediction models, we ran a saturated mix-effects logistic regression model clustering on site. The variance of the random effect was used as a measure of unit-level variation. To avoid spurious associations between predictors that were correlated with time, we ran the saturated model with the year of admission. The model building process was undertaken using backward elimination of the covariate with the highest p-value. We selected the final model based on the lowest Akaike information criterion (AIC)[1]. The final model excluded year of admission from the model to calculate risk-adjusted change over time. A risk score for each child was calculated using the fixed effects portion of the model and the mean was calculated to estimate the average risk score of intubation. Unit level variability was reported using the predicted probability of intubation in each site for a child with the mean risk score and the site-specific random effect.

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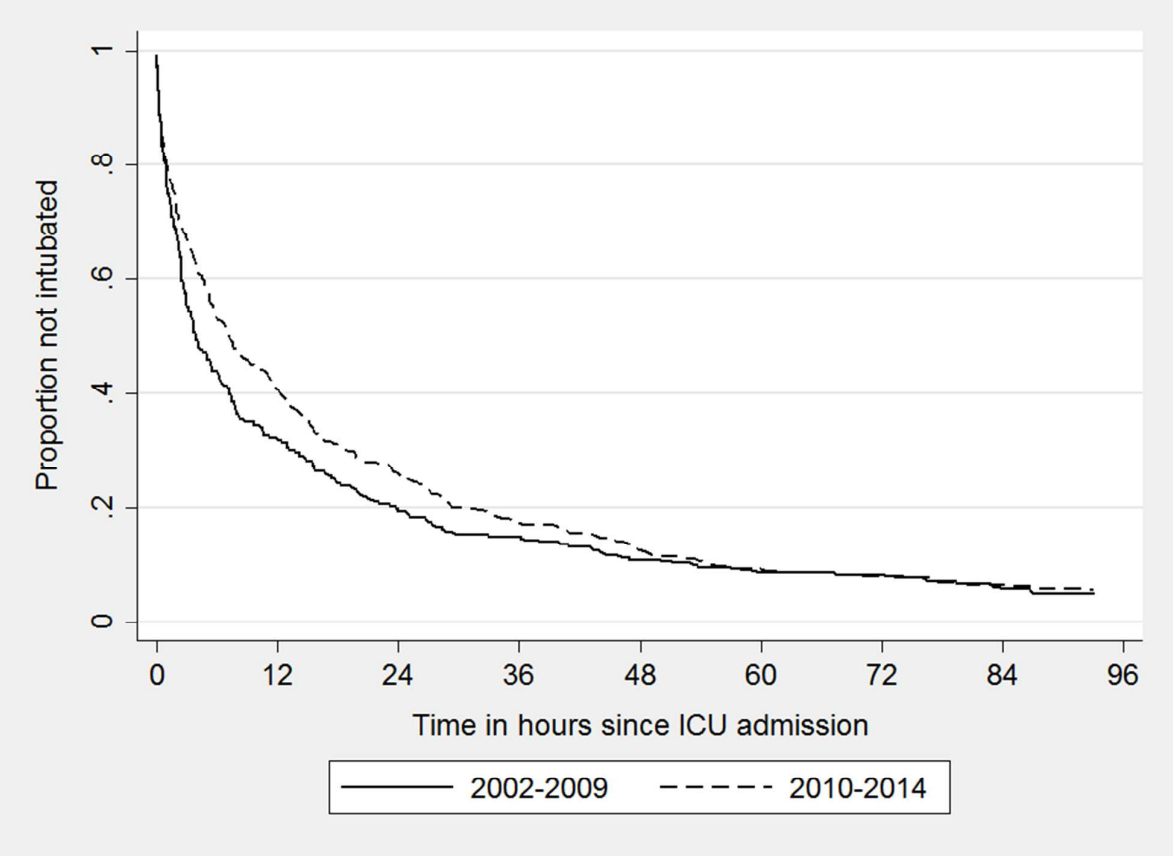
Online Supplement Figure 1: Kaplan-Meyer curves comparing time to intubation (in hours) from PICU admission in infants with bronchiolitis admitted to PICU. Only infants that were not intubated during the first hour of admission were included.



Online Supplement Table 1: Respiratory support mode and duration of respiratory support in infants with bronchiolitis admitted to ICU per year are shown for A) all ICU admissions captured in the Australian and New Zealand Paediatric Intensive Care Registry; B) admissions to Pediatric Intensive Care Units (PICUs); C) admissions to general Intensive Care Units (ICUs); D) admissions to PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014. Mechanical ventilation is defined as intubation and/or non-invasive ventilation. HFNC, High-Flow Nasal Cannulae.

Online Supplement Table 1 A: All ICUs

	Proportion of respiratory support				Mean duration of respiratory support (hours)*				
Year	Mechanical Ventilation**	Invasive ventilation	Non-Invasive Ventilation	HFNC	Mechanical Ventilation**	Invasive ventilation	Non-Invasive Ventilation	HFNC	All respiratory support
2002	57.2%	36.6%	30.5%		108.6	125.5	53.1		62.1
2003	53.9%	30.9%	35.0%		84.1	105.1	36.7		45.4
2004	57.4%	29.2%	42.6%		102.7	147.2	37.2		58.9
2005	56.8%	29.5%	42.4%		93.9	112.4	47.8		53.4
2006	60.5%	26.9%	47.5%		94.1	134.7	43.4		56.9
2007	62.8%	26.5%	49.7%		88.0	126.1	44.0		55.3
2008	53.2%	23.5%	40.9%		87.2	119.9	44.6		46.4
2009	63.4%	25.9%	46.8%		84.7	125.7	45.3		53.7
2010	58.6%	24.5%	42.2%	24.7%	76.7	95.8	50.9	44.3	55.9
2011	62.0%	16.6%	59.3%	35.8%	68.8	109.3	41.4	35.5	55.4
2012	58.1%	20.1%	44.7%	54.7%	70.8	98.7	47.8	37.1	61.5
2013	46.6%	12.6%	38.5%	71.2%	55.6	84.1	39.8	31.6	48.4
2014	44.8%	10.8%	38.2%	72.6%	69.2	122.3	46.6	35.3	56.6
β (95% CI)	-0.01 (-0.01 to 0.00)	-0.02 (-0.02 to -0.01)	0.01 (-0.01 to 0.02)	0.06 (0.04 to 0.09)	-3.40 (-4.56 to -2.25)	-2.23 (-4.77 to 0.30)	0.09 (-0.75 to 0.92)	-2.19 (-5.82 to 1.44)	-0.03 (-0.92 to 0.86)
p (trend)	0.2311	<0.0001	0.2787	0.0001	<0.0001	0.0789	0.8260	0.1503	0.9472

* Among those children receiving this mode of respiratory support
** Defined as intubation and/or non-invasive ventilation
HFNC, High-Flow Nasal Cannulae

Online Supplement Table 1 B: PICU

	Proportion of respiratory support				Mean duration of respiratory support (hours)*				
Year	Mechanical Ventilation**	Invasive ventilation	Non-Invasive Ventilation	HFNC	Mechanical Ventilation**	Invasive ventilation	Non-Invasive Ventilation	HFNC	All respiratory support
2002	56.7%	37.2%	29.6%		109.8	125.2	53.1		62.3
2003	54.1%	32.3%	33.8%		88.0	105.7	39.8		47.6
2004	58.1%	30.4%	42.5%		106.0	148.2	39.0		61.6
2005	65.2%	34.1%	48.5%		94.6	112.4	48.2		61.7
2006	58.1%	31.1%	42.6%		105.0	137.5	42.6		61.0
2007	64.5%	29.3%	51.1%		94.2	129.0	45.0		60.8
2008	56.1%	25.1%	44.8%		90.8	126.6	42.6		50.9
2009	64.9%	27.6%	47.7%		91.2	131.2	48.1		59.2
2010	58.9%	29.6%	38.7%	30.7%	80.4	101.4	44.7	41.4	60.1
2011	58.8%	19.3%	55.4%	48.2%	83.3	120.8	46.3	35.3	66.0
2012	52.4%	21.4%	39.2%	62.1%	80.1	105.2	49.6	40.6	67.2
2013	45.5%	13.7%	37.0%	76.0%	63.9	92.0	44.6	32.1	53.4
2014	46.3%	13.0%	39.4%	74.9%	84.5	135.1	55.0	35.9	66.1
β (95% CI)	-0.01 (-0.02 to 0.00)	-0.02 (-0.02 to -0.01)	0.00 (-0.01 to 0.02)	0.07 (0.04 to 0.10)	-2.54 (-3.83 to -1.24)	-1.24 (-3.90 to 1.42)	0.44 (-0.32 to 1.19)	-1.41 (-5.12 to 2.29)	0.46 (-0.49 to 1.42)
p (trend)	0.0845	0.0000	0.4860	0.0001	0.0012	0.3264	0.2296	0.3119	0.3105

* Among those children receiving this mode of respiratory support
** Defined as intubation and/or non-invasive ventilation
HFNC, High-Flow Nasal Cannulae

Online Supplement Table 1 C: general ICUs

	Proportion of respiratory support				Mean duration of respiratory support (hours)*				
Year	Mechanical Ventilation**	Invasive ventilation	Non-Invasive Ventilation	HFNC	Mechanical Ventilation**	Invasive ventilation	Non-Invasive Ventilation	HFNC	All respiratory support
2002	64.0%	28.0%	44.0%		93.4	130.2	53.0		59.8
2003	52.9%	23.5%	41.2%		63.3	101.5	23.5		33.5
2004	48.1%	14.8%	44.4%		52.8	123.1	16.2		25.4
2005	3.8%	0.0%	3.8%		17.5	0.0	17.5		0.7
2006	70.2%	9.6%	67.3%		57.0	96.5	45.7		40.0
2007	57.1%	17.5%	45.2%		65.9	110.7	40.5		37.6
2008	43.6%	18.0%	27.8%		71.7	88.2	55.2		31.3
2009	58.8%	20.6%	44.1%		63.1	103.3	35.9		37.1
2010	57.9%	11.6%	50.9%	9.3%	67.2	59.4	62.8	68.8	45.2
2011	68.1%	11.6%	66.5%	12.9%	45.7	74.1	33.9	36.9	35.9
2012	68.5%	17.6%	54.7%	41.3%	57.9	84.2	45.5	27.4	51.0
2013	48.6%	10.5%	41.3%	62.4%	41.4	65.4	32.0	30.5	39.2
2014	42.4%	7.5%	36.3%	69.1%	44.0	89.2	32.8	34.2	42.3
β (95% CI)	0.01 (-0.02 to 0.03)	-0.01 (-0.02 to 0.00)	0.01 (-0.02 to 0.04)	0.05 (0.03 to 0.08)	-1.56 (-4.46 to 1.34)	-4.20 (-6.67 to -1.72)	0.65 (-1.75 to 3.04)	-7.55 (-21.18 to 6.07)	0.78 (-1.54 to 3.09)
p (trend)	0.6891	0.1846	0.5180	0.0010	0.2623	0.0036	0.5634	0.1759	0.4756

* Among those children receiving this mode of respiratory support

Online Supplement Table 1 D: PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014.

	Proportion of respiratory support				Mean duration of respiratory support (hours)*				
Year	Mechanical Ventilation**	Invasive ventilation	Non-Invasive Ventilation	HFNC	Mechanical Ventilation**	Invasive ventilation	Non-Invasive Ventilation	HFNC	All respiratory support
2002	57.1%	36.6%	30.5%		109.5	126.3	53.4		62.5
2003	55.8%	32.2%	36.2%		85.4	106.1	37.1		47.6
2004	58.1%	29.9%	43.0%		103.5	147.2	37.5		60.2
2005	59.9%	31.4%	44.6%		93.3	113.4	45.5		55.9
2006	60.0%	29.0%	45.7%		96.9	136.5	40.6		58.1
2007	64.5%	28.1%	51.7%		91.4	129.0	44.1		59.0
2008	53.7%	23.9%	42.4%		84.2	119.2	39.4		45.2
2009	65.9%	28.0%	48.3%		85.6	123.8	45.1		56.4
2010	62.3%	29.8%	42.5%	28.2%	74.4	97.1	40.9	38.8	57.3
2011	59.8%	18.1%	56.7%	42.7%	77.6	119.8	43.7	35.9	61.7
2012	56.0%	21.3%	42.6%	57.1%	73.7	100.2	46.8	39.5	63.8
2013	48.9%	13.4%	40.6%	75.9%	58.6	89.6	41.0	30.3	51.6
2014	49.7%	12.8%	42.5%	75.9%	76.0	129.9	49.7	33.8	63.5
β (95% CI)	0.00 (-0.01 to 0.00)	-0.02 (-0.02 to -0.01)	0.01 (0.00 to 0.02)	0.07 (0.04 to 0.09)	-3.03 (-4.23 to -1.83)	-1.73 (-4.30 to 0.85)	0.17 (-0.63 to 0.97)	-1.55 (-4.87 to 1.77)	0.29 (-0.69 to 1.27)
p (trend)	0.2526	0.0000	0.1868	0.0001	0.0002	0.1682	0.6524	0.2346	0.5223

* Among those children receiving this mode of respiratory support

Online Supplement Table 2: Estimates of population-based intubation rates in infants with bronchiolitis admitted to ICU per year. Analyses are shown for all ICU admissions captured in the Australian and New Zealand Paediatric Intensive Care Registry; admissions to Pediatric Intensive Care Units (PICUs); admissions to general Intensive Care Units (ICUs); and admissions to PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014.

	All PICUs and ICUs		PICU		General ICUs		8 PICUs and 5 ICUs contributing to registry for the entire study duration 2002-2014	
Year	n	Population rate (per 100,000)	n	Population rate (per 100,000)	n	Population rate (per 100,000)	n	Population rate (per 100,000)
2002	140	22.86	133	21.72	7	1.14	139	22.69
2003	98	16.06	86	14.09	12	1.97	97	15.89
2004	107	17.37	103	16.72	4	0.65	107	17.37
2005	112	17.88	112	17.88	0	0.00	111	17.72
2006	143	22.28	133	20.72	10	1.56	134	20.87
2007	140	20.72	118	17.47	22	3.26	118	17.47
2008	136	19.37	112	15.95	24	3.42	108	15.38
2009	142	19.87	114	15.95	28	3.92	124	17.35
2010	188	26.14	163	22.66	25	3.48	169	23.49
2011	146	20.50	110	15.44	36	5.05	110	15.44
2012	242	33.52	167	23.13	75	10.39	176	24.38
2013	162	21.91	114	15.42	48	6.49	119	16.09
2014	165	22.55	119	16.27	46	6.29	130	17.77
β	6.62	0.59	1.99	-0.03	4.63	0.62	2.23	-0.01
(95% CI)	(2.01 to 11.22)	(-0.07 to 1.24)	(-1.62 to 5.60)	(-0.55 to 0.49)	(2.73 to 6.52)	(0.35 to 0.88)	(-1.53 to 5.98)	(-0.55 to 0.52)
p (trend)	0.0091	0.0732	0.2505	0.9020	0.0002	0.0004	0.2185	0.9603

Online Supplementary Table 3: Multivariate model to prediction of likelihood of requiring intubation and invasive ventilation in critically ill infants with bronchiolitis. Data are based on a saturated mix-effects logistic regression model clustering on site and adjusted for all variables shown in the table. Data are restricted to A) Infants that were not intubated within the first hour of ICU admission, and B) to infants treated with HFNC and not intubated during the 1st hour of ICU admission:

A) Multivariate prediction of intubation restricted to infants that were not intubated at time on ICU admission (n=8451)

	Odds Ratio	(95% CI)	β	(95% CI)	p
Age (Days/30)	0.968	(0.953 to 0.984)	-0.032	(-0.048 to -0.016)	<0.001
Interhospital transport	1.621	(1.407 to 1.868)	0.483	(0.342 to 0.625)	<0.001
Chronic Neurological Condition	1.285	(0.815 to 2.024)	0.251	(-0.204 to 0.705)	0.280
Chronic Respiratory Condition	1.531	(1.092 to 2.146)	0.426	(0.088 to 0.764)	0.014
Bronchopulmonary Dysplasia	2.035	(1.546 to 2.679)	0.711	(0.435 to 0.986)	<0.001
Congenital Heart Defect	2.168	(1.737 to 2.707)	0.774	(0.552 to 0.996)	<0.001
Prematurity	1.198	(1.006 to 1.427)	0.180	(0.006 to 0.355)	0.043
RSV	1.609	(1.394 to 1.857)	0.475	(0.332 to 0.619)	<0.001
Influenza/Parainfluenzae	1.978	(1.440 to 2.718)	0.682	(0.364 to 1.000)	<0.001
Systolic blood pressure <=70	2.916	(2.145 to 3.963)	1.070	(0.763 to 1.377)	<0.001
Base Excess	0.974	(0.950 to 0.999)	-0.026	(-0.052 to -0.001)	0.043
(Base Excess)^2	1.007	(1.005 to 1.009)	0.007	(0.005 to 0.009)	<0.001
Constant	0.968	(0.953 to 0.984)	-0.032	(-0.048 to -0.016)	<0.001

Model performance: ROC AUC=0.72 (0.70-0.73)

B) Multivariate prediction of intubation in infants not intubated on arrival and treated with High-Flow Nasal Cannulae (n=3049)

	Odds Ratio	(95% CI)	β	(95% CI)	p
Age (Days/30)	0.935	(0.902 to 0.970)	-0.067	(-0.103 to -0.031)	<0.001
Interhospital transport	0.967	(0.694 to 1.348)	-0.033	(-0.365 to 0.298)	0.845
Chronic Neurological Condition	1.054	(0.357 to 3.118)	0.053	(-1.031 to 1.137)	0.924
Chronic Respiratory Condition	1.673	(0.846 to 3.310)	0.515	(-0.167 to 1.197)	0.139
Bronchopulmonary Dysplasia	2.311	(1.228 to 4.349)	0.838	(0.206 to 1.470)	0.009
Congenital Heart Defect	3.512	(2.273 to 5.425)	1.256	(0.821 to 1.691)	<0.001
Prematurity	1.438	(0.985 to 2.098)	0.363	(-0.015 to 0.741)	0.060
RSV	1.258	(0.909 to 1.742)	0.230	(-0.096 to 0.555)	0.167
Influenza/Parainfluenzae	1.238	(0.569 to 2.692)	0.213	(-0.563 to 0.990)	0.590
Systolic blood pressure <=70	2.730	(1.329 to 5.609)	1.004	(0.284 to 1.724)	0.006
Base Excess	0.914	(0.861 to 0.972)	-0.089	(-0.150 to -0.029)	0.004
(Base Excess)^2	1.006	(1.002 to 1.010)	0.006	(0.002 to 0.010)	0.008
Constant	0.935	(0.902 to 0.970)	-0.067	(-0.103 to -0.031)	<0.001

Model performance: ROC AUC=0.74 (0.70-0.77)

Online Supplementary Table 4: Direct hospitalization costs for infants with bronchiolitis per year. Mean costs per patient, including ICU and ward costs, are shown in AU$, separately for Pediatric Intensive Care Units (PICUs) versus general ICUs. Costs are based on the standardised National Efficient Price estimates.

	Cost per patient				Total cost						Summary		
	General		PICU		General		Pediatric		Total		ICU proportion	General	PICU
Year	Mean	SD	Mean	SD	ICU cost	ward cost	ICU cost	ward cost	ICU cost	ward cost	% total costs	total cost	total cost
2,002	24,571	15,987	29,667	32,428	450,699	177,836	7,301,624	3,370,482	7,752,323	3,548,318	68.6	628,535	10,672,106
2,003	22,613	19,560	32,012	65,878	694,072	459,174	4,773,400	3,741,913	5,467,473	4,201,087	56.5	1,153,247	8,515,313
2,004	19,998	12,780	32,777	39,949	331,252	208,695	6,914,274	4,197,043	7,245,527	4,405,738	62.2	539,947	11,111,318
2,005	18,477	18,041	30,479	26,460	416,145	544,662	6,124,645	3,872,461	6,540,789	4,417,124	59.7	960,807	9,997,106
2,006	26,475	30,715	42,902	133,939	1,492,448	1,260,964	9,179,501	9,139,854	10,671,949	10,400,818	50.6	2,753,411	18,319,356
2,007	23,820	20,253	39,437	61,389	1,698,067	1,303,253	8,114,717	7,778,538	9,812,784	9,081,791	51.9	3,001,320	15,893,255
2,008	29,820	34,239	33,455	52,525	1,805,356	2,160,746	8,513,158	6,407,941	10,318,514	8,568,687	54.6	3,966,102	14,921,098
2,009	23,370	25,861	37,490	85,851	1,960,210	1,218,117	8,838,224	6,645,107	10,798,435	7,863,224	57.9	3,178,327	15,483,332
2,010	19,872	11,628	36,773	56,309	2,480,658	1,811,645	10,091,138	10,133,951	12,571,796	11,945,596	51.3	4,292,303	20,225,089
2,011	20,153	16,027	33,503	38,340	3,636,948	2,610,413	11,129,047	7,967,907	14,765,994	10,578,320	58.3	6,247,360	19,096,954
2,012	24,410	38,743	34,022	62,482	6,128,484	4,270,114	14,533,286	12,003,541	20,661,770	16,273,655	55.9	10,398,598	26,536,827
2,013	22,540	23,417	25,997	30,383	5,851,196	4,404,621	13,388,088	8,319,706	19,239,284	12,724,327	60.2	10,255,817	21,707,795
2,014	21,645	29,875	33,924	81,866	7,983,325	5,241,709	17,126,139	13,982,132	25,109,464	19,223,840	56.6	13,225,034	31,108,271

1. Akaike H. A new look at the statistical model identification. *IEEE Transactions on Automatic Control* 1994; **19**(6): 716-23.

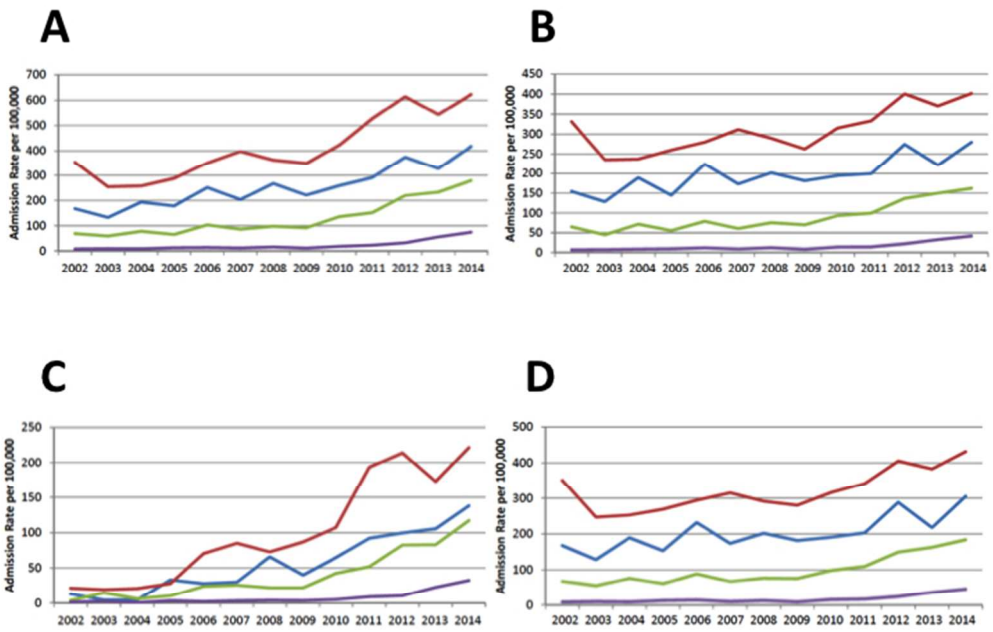


Figure 1: Estimated population-based ICU admission rates due to bronchiolitis. ICU admission rates per 100,000 infants < 24 months and year are shown for A) all ICU admissions captured in the Australian and New Zealand Paediatric Intensive Care Registry; B) admissions to Pediatric Intensive Care Units (PICUs); C) admissions to general Intensive Care Units (ICUs); D) admissions to PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014. Red line: age 28days to <90 days; blue line: age neonates <28days; green line: 90 days to <1 year; purple line: 1 year to <2 years.

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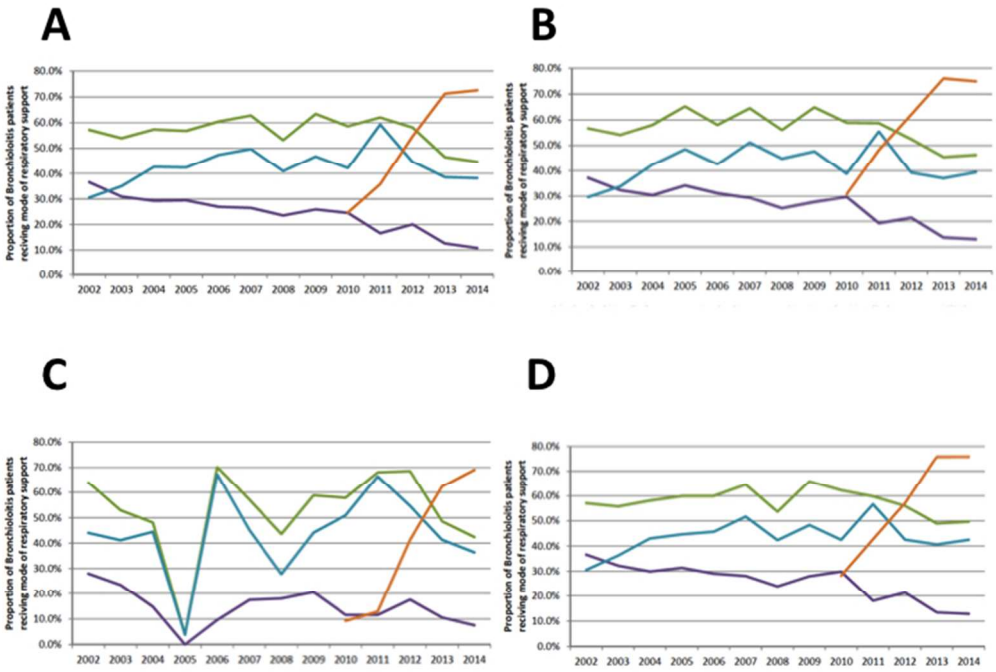

Figure 2: Changes is respiratory support mode during the study period 2002 to 2014 in infants admitted to ICU with bronchiolitis. Mechanical ventilation (green line) is defined as intubation (purple line: invasive ventilation) and/or non-invasive ventilation (blue line). High-flow nasal cannulae (HFNC) is shown in orange. 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 Pediatric Intensive Care Units (PICUs); C) admissions to general Intensive Care Units (ICUs); D) admissions to PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014.

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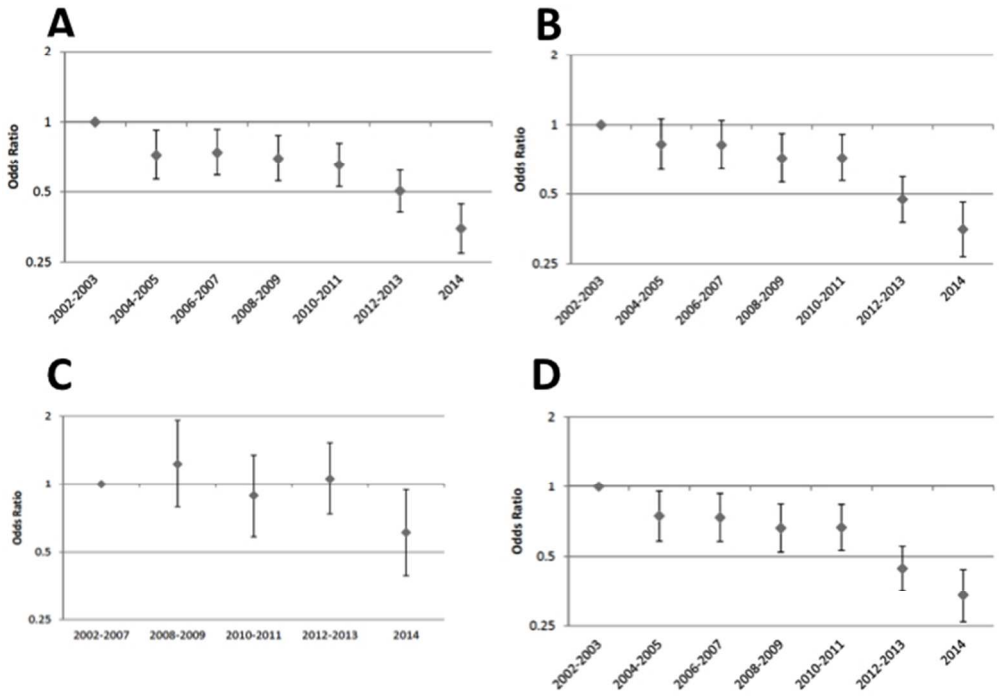

Figure 3: Adjusted risk for intubation/invasive ventilation in infants with bronchiolitis during the study period. Odds ratios are adjusted for age, interhospital transport, chronic respiratory and neurological conditions, prematurity, congenital heart disease, specific respiratory viruses, low systolic blood pressure, and are shown for A) all ICU admissions captured in the Australian and New Zealand Paediatric Intensive Care Registry; B) admissions to Pediatric Intensive Care Units (PICUs); C) admissions to general Intensive Care Units (ICUs); D) admissions to PICUs and ICUs that had contributed to the registry for the entire study duration 2002-2014.

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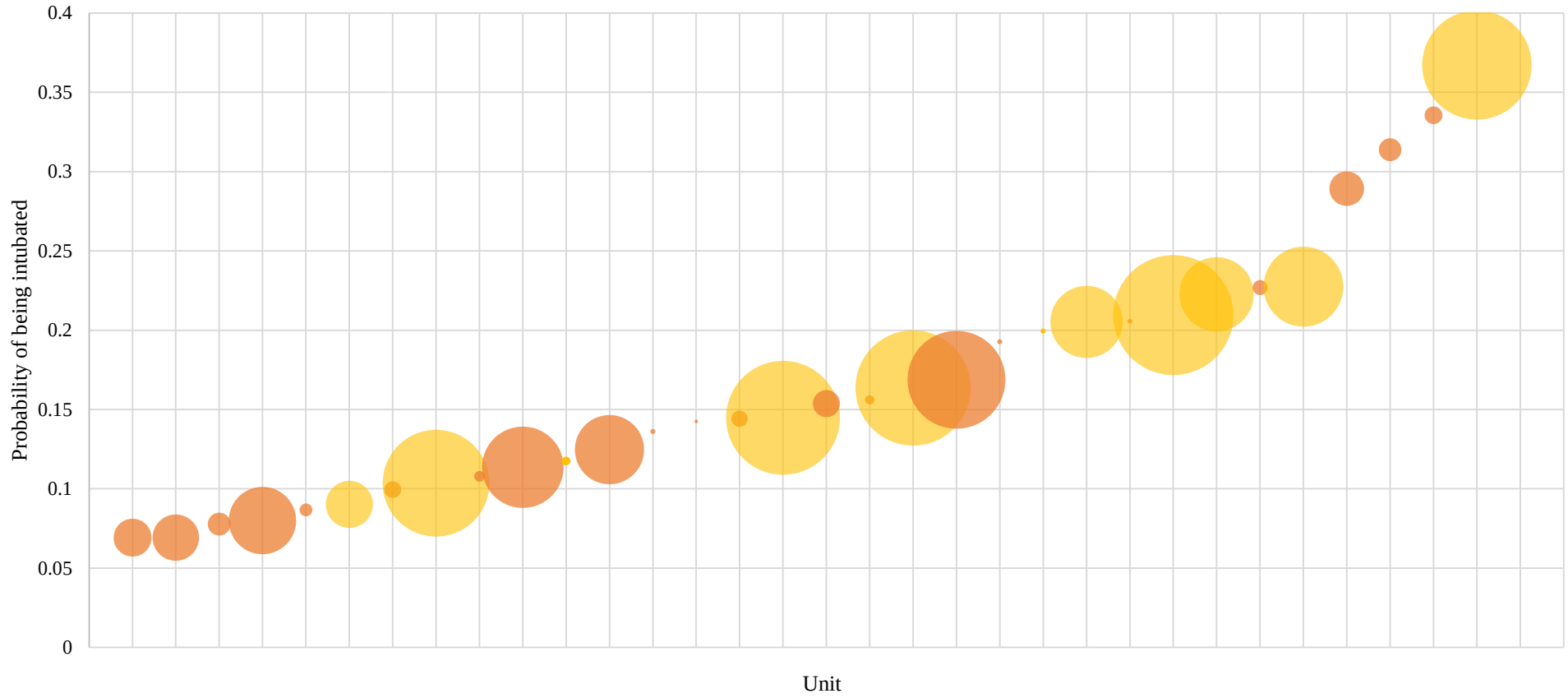
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Probability of being intubated
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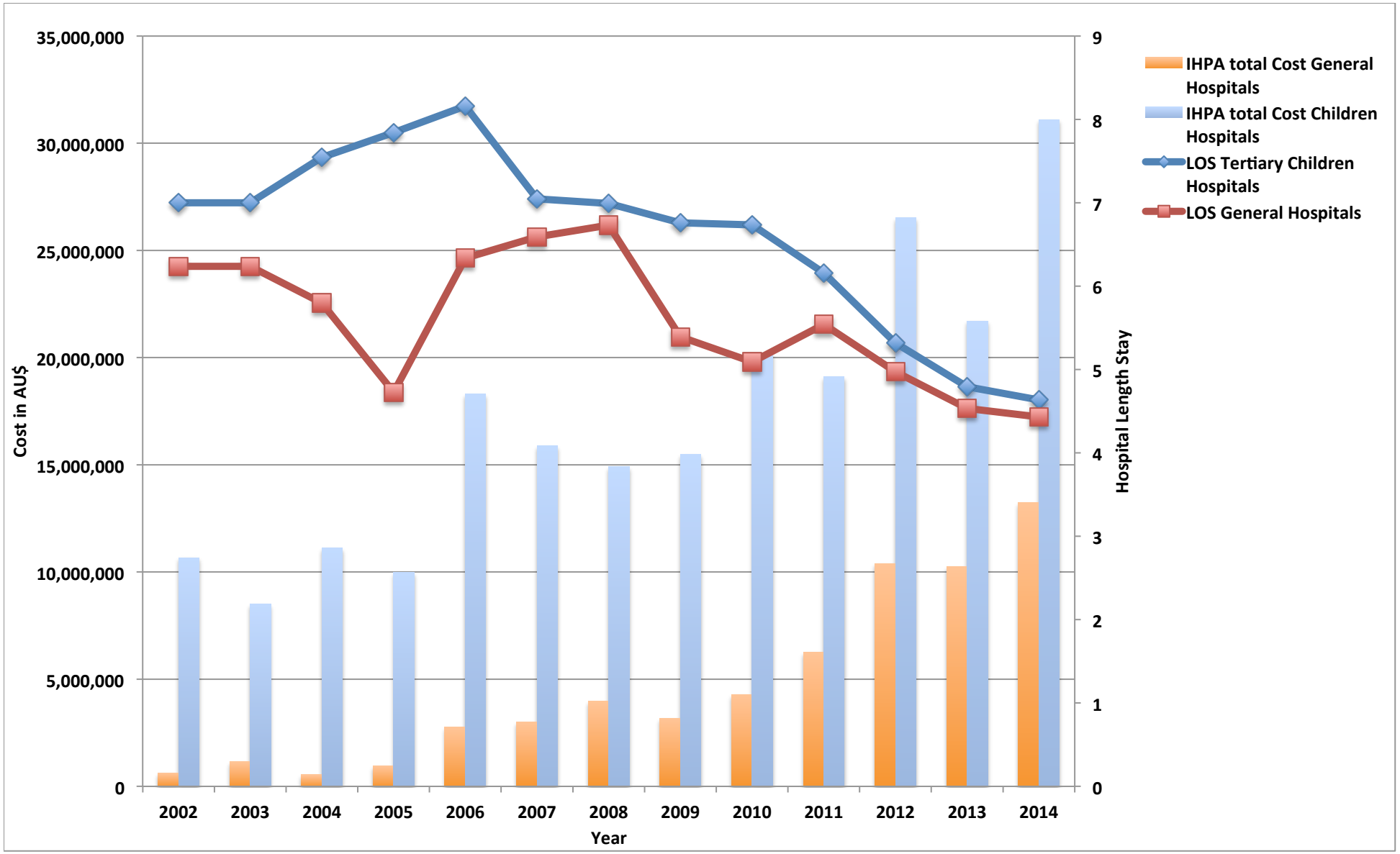
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IHPA total Cost General Hospitals
IHPA total Cost Children Hospitals
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LOS General Hospitals