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Natasha K Brusco, Annette Alafaci, Jane Tuckerman, Helena Frawley, Jeremy Pratt, Andrew J Daley, Angela K Todd, Yi-Mo Deng, Kanta Subbarao, Ian Barr, Nigel W Crawford

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# The 2018 annual cost burden for children under five years of age hospitalised with respiratory syncytial virus in Australia

Natasha K Brusco, Annette Alafaci, Jane Tuckerman, Helena Frawley, Jeremy Pratt, Andrew J Daley, Angela K Todd, Yi-Mo Deng, Kanta Subbarao, Ian Barr, Nigel W Crawford

## Abstract

Respiratory syncytial virus (RSV) is one of the principal causes of acute bronchiolitis and respiratory tract infections in young children. Routine RSV surveillance in Australian children is limited; vaccines are in late stage development; prophylactic monoclonal antibody (mAb) treatment is available but expensive; and there has been uncertainty around the cost burden. The objective of this study was to determine the annual cost burden for children under five years of age hospitalised with RSV in a single health service in 2018, with national extrapolation based on published Australian prevalence data. The methods utilised individual patient-level cost data prospectively collected for hospitalised children under five years of age in a tertiary Melbourne paediatric hospital. Results were extrapolated to all Australian children under five years of age to determine the national annual health cost burden, from a healthcare sector perspective over a 12 month time horizon. The results included 363 children with a mean age of 9.2 months (standard deviation, SD: 8.5 months). The mean cost per child was \$17,120 (SD: \$37,562), with a combined health service cost of \$6,214,439. The reported Australian hospitalisation rate for RSV in the target age group ranged from 2.2 to 4.5 per 1,000 children under five years of age, resulting in a 2018 extrapolated cost range of \$59,218,844–\$121,129,453 for the estimated 3,459–7,075 children affected (combined index and all-cause six-month readmissions). This study concluded that RSV represents a significant cost burden to Australia's health care system. These data are important for future health economic assessments of preventative therapies, such as new RSV mAb treatments and maternal/childhood RSV vaccines, and provides valuable insights to inform health care planning and health policy.

*Keywords: Respiratory syncytial virus, respiratory infection, cost burden, economic evaluation, paediatrics*

## Introduction

Respiratory syncytial virus (RSV) is one of the principal causes of acute bronchiolitis and respiratory tract infections in young children,<sup>1</sup> with a peak incidence at 2–5 months of age and an almost universal exposure by three years of age.<sup>2–4</sup> The RSV health care utilisation burden is borne by both primary and tertiary health care,<sup>1</sup> with significant social, economic, and health impact on a global scale, including in Australia.<sup>5</sup> Variable prevalence and incidence

rates have been reported, with the reported rates consistently higher in communities with lower socio-economic status, younger age groups and medically vulnerable populations.<sup>1,5,6</sup>

More recently, the public health measures during the coronavirus disease 2019 (COVID-19) pandemic have highlighted behaviours that mitigate viral transmission of other respiratory viruses, such as RSV. An association between the implementation of public health measures and a reduction in the burden of RSV disease in

children reported in New South Wales, Western Australia and Victoria through winter 2020.<sup>7-9</sup> However, following the relaxation of COVID-19-related public health measures, there was a large spring and summer RSV surge reported in New South Wales and Western Australia, beginning in September 2020, and a delayed resurgence in Victoria (until early 2021), likely a result of a prolonged and more intense restrictions in that jurisdiction.<sup>9,10</sup> These outbreaks highlight that RSV can be sustained in countries for many months or years, even without importation of new cases from overseas.

Globally, the proportion of infant RSV cases requiring hospitalisation is estimated to be 0.5–2%,<sup>11,12</sup> with hospitalisations for children aged under 5 years to be an estimated 3.2–3.4 million per annum.<sup>13,14</sup> Australia had also been reliant on international estimates as, at the time of this study, there was no systematic national monitoring of RSV activity,<sup>15</sup> with hospitalisations the main source of disease identification. Ranmuthugala et al. highlighted the age-related risk in Australia, with a fourfold increase in RSV-related incidence in the under-1 year age group (8.7 per 1,000) compared to the under-5 year age group (2.2 per 1,000).<sup>15</sup> There is currently no RSV vaccine commercially available globally.<sup>4</sup> The only preventative option is monoclonal antibody (mAb) treatment, which is prohibitively expensive, requires monthly injections over the RSV season, and is not funded on the Pharmaceutical Benefits Scheme.<sup>16</sup> Some individual Australian hospitals, including Royal Children's Hospital (RCH) Melbourne, only provide RSV mAb to identified high-risk groups (e.g. congenital heart disease in the first year of life). Newer mAb, with a longer duration of action, are in phase 3 clinical trials, but are not yet used clinically in high-risk patients.<sup>17</sup>

Literature on the national cost burden of RSV is scarce, with only one Australian study and a few international studies. In summary, when international costs are converted into \$AUD[2018/2019], the cost of hospitalisation for RSV has been estimated at between \$2,567 and \$15,015 per admission, with national annual

burdens estimated at \$21–44M for Australia, \$965M for the United States of America and \$34M for Canada.<sup>3,6,12,15,18,19</sup> A literature review of the international RSV cost data has been detailed in Appendix A, Table A.1.

In Australia, the lack of routine surveillance for RSV at the time of this study impeded the development of a national public health policy. This study is the first in which the cost burden of RSV for children has been undertaken using individual patient-level data in Australia. This study used whole-of-hospital data for children under five years of age hospitalised with RSV at RCH Melbourne, to determine the 2018 health service costs for this age group, and then extrapolated the national annual cost burden for RSV hospitalisations in children under five years of age Australia-wide, to represent the most affected group.

## Methods

Individual patient-level cost data were prospectively collected for all confirmed RSV admissions meeting the World Health Organization (WHO) severe acute respiratory infection (SARI) definition (requiring hospitalisation; onset within 10 days; clinical signs of cough or shortness of breath; apnoea in children under 6 months) in children under five years of age.<sup>20</sup> These data were then modelled to determine the 2018 RSV national annual cost burden for children under five years of age. This study reported the cost of usual hospital care only. There was no intervention nor comparator group. This study was reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist for economic evaluations.<sup>21</sup> Data were held in a Murdoch Children's Research Institute (MCRI) REDCap database with RCH Ethics approval 37185.

## Population

Children under five years of age admitted to RCH in 2018 with an RSV laboratory confirmed polymerase chain reaction (PCR) positive

infection, who met the SARI criteria, were included in the study. An emergency department (ED) presentation alone did not meet the criterion of “admitted”. There were no exclusion criteria. Subjects were also tested for other respiratory virus co-infections by an in-house multiplex respiratory PCR assay. The following co-infections were on the same panel as RSV during 2018, therefore tested together: Influenza virus A; influenza virus B; parainfluenza virus 1; parainfluenza virus 2; parainfluenza virus 3; and human metapneumovirus. *Bordetella pertussis* was tested on a separate panel alongside the RSV multiplex-panel. The 2018 calendar year was chosen for the time horizon for the index admission, to capture the winter seasonal effect of RSV (particularly March to August). A priori sub-group analysis was planned for children born prematurely (gestation < 37 weeks).

### Setting and location

The location was RCH, Melbourne, Australia, acute health care service setting.

### Study perspective

This study took a health service perspective and was inclusive of the index admission and all cause re-admissions within six months post-discharge. Health care utilisation and costs refers to ambulance, ED, acute ward and intensive care resources for the index admission, as well as all ED, acute ward and intensive care resources for any re-admissions in the 30-days and 1–6-months post-discharge periods, with all cost parameters reported independently. Ambulance costs were not included in the re-admissions as we did not have access to these data. Cost data were collected in the 2017/2018 and 2018/2019 financial years. The 2017/2018 data were inflated by the Consumer Price Index (CPI)<sup>i</sup> to yield a net present value (NPV) in \$AUD[2018/2019].

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i Accessed in February 2020: <https://www.abs.gov.au/ausstats/abs@.nsf/mf/6401.0>.

### Outcomes

Outcome measures included the cost of RSV for hospitalised children under five years of age with a sub-group analysis for prematurity. These data were extrapolated to derive the main outcome measure of this study, a national annual cost estimate for children with RSV under five years of age, the most affected group. This study also reported on the following clinical outcomes: respiratory support and antibiotic administration, additional admissions for a subsequent acute respiratory infection and an asthma diagnosis.

### Resources and costs

Resources and costs were collated from two data sources following identification of relevant cases. The first was through manual medical record audits of cases including demographic data health care utilisation, admission into ED, acute wards and intensive care, ambulance usage, and discharge information, but not cost data. The second data source was an extract of individual patient-level cost and utilisation data from RCH Decision Support Unit for the index admission and all-cause re-admissions. Opportunity costs for the parents (e.g. lost wages, employment productivity), as well as other costs outside of admissions to the health service (e.g., ambulatory health services), were not included in this cost analysis.

### Analysis

Cost analyses were completed for children under five years of age, as well as for children in the under-one-year age group, to represent RSV-related costs for RCH, presented as a mean and standard deviation (SD). The manual medical record audit was used to report ambulance utilisation, which was costed at the 2018/2019 rate at \$930.26 per episode. This was based on 3,537,829 national ambulance episodes in 2016/2017 at a total cost of \$3,163,305,000 (p25 and p75, \$AUD[2016/2017]),<sup>22</sup> resulting in an average cost of \$894.14 per ambulance episode, with the 2016/2017 rate inflated

by CPI to calculate the NPV of \$930.26 in \$AUD[2018/2019]. The sub-group analysis for prematurity status included all children < 37 weeks at birth. The extrapolation used June 2018 Australian Bureau of Statistics data under five years of age,<sup>23</sup> as well as for children under one year of age, who were RSV positive and hospitalised in Australia.<sup>15</sup>

## Results

### Population

Individual-level cost data were collected for 363 children admitted to RCH with confirmed RSV positive SARI in the period January 2018 to December 2018. There were an additional 194 RSV confirmed cases admitted to the RCH during this period who were not eligible to be enrolled as they were not SARI cases, (n = 45 cases under six months of age; n = 27 cases aged 6–11 months; n = 70 cases aged 1–4 years; n = 52 aged 5+ years; Figure 1). Admission and discharge data are presented in Table 1, based on the index admission, as well as any re-admissions in the thirty-days and 1–6-months post-discharge periods.

For the index admission, 164/363 cases (45%) were female and the mean age was 9.2 months (SD 8.5 months; range 9 days to 4.7 years). It is noted that 9% were neonates (aged ≤ 28 days [n = 32]) and 36% (n = 130) were aged 1–3 months. Of the 362 children (> 99%) who were typed, 176 children were RSV type A (49%) and 186 were RSV type B (51%). Additionally, 2% of the children (n = 6) had a previously-confirmed RSV infection and 3% (n = 12) had a co-existing respiratory pathogen detected (complete data available for n = 362).

Admissions displayed a typical seasonal trend, with 60% of admissions occurring during May–July 2018. Overall, 33% of cases (n = 119) reported one or more risk factors. This includes two children (0.5%) with bronchopulmonary dysplasia (data available for n = 361), 20 children (6%) with chronic respiratory disease (data available for n = 361), five children (1%) oxygen

dependent (data available for n = 361), and 51 children (14%) with previous bronchiolitis (data available for n = 362). Only a few co-infections were detected: these included human metapneumovirus (n = 6); human parainfluenza viruses (n = 6); and *B. pertussis* (n = 1); none were detected in children aged ≥ 24 months. Notably, there were no influenza co-infections. Given the small number of co-infections, we were not able to determine reliable estimates on increased costings.

In addition, 76 children (22%) were born with prematurity (data available for n = 352); of these children, the average gestation was 33 weeks (range 23–36 weeks) and the average birth weight was 2010 grams (range 553–3568 grams; birth weight data unknown for n = 22).

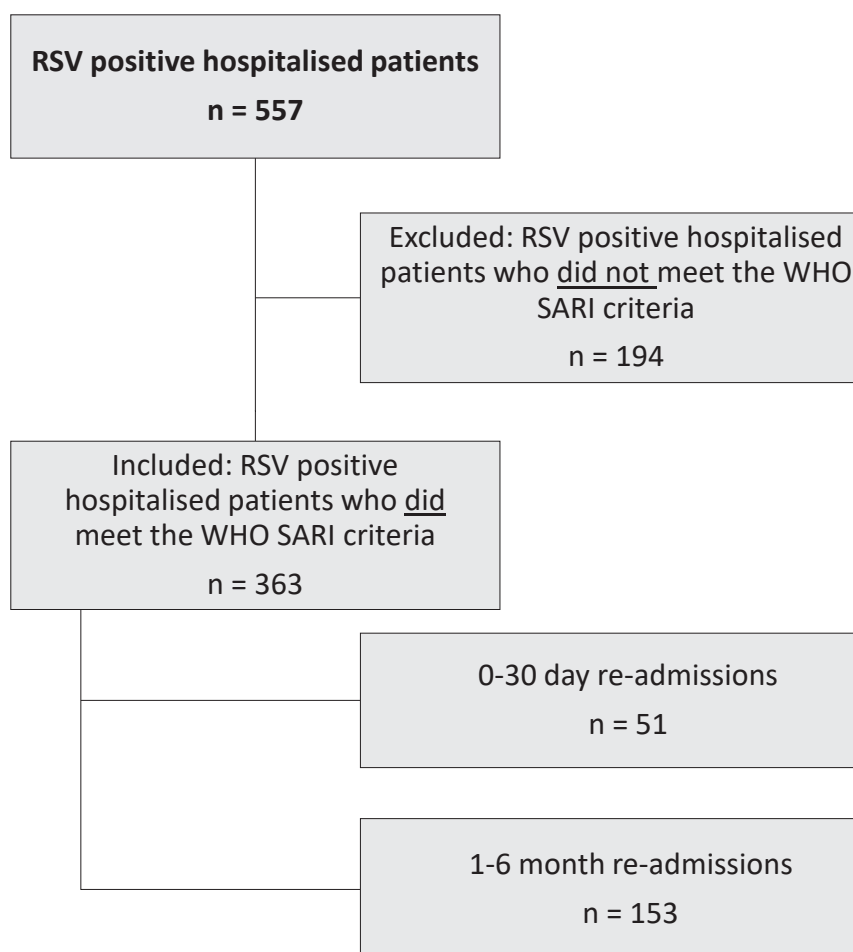
Overall, 88% of children displayed accessory respiratory muscle use at presentation. Specifically, accessory respiratory muscle use at presentation included 33 children (10%) with marked accessory respiratory muscle use, including head bobbing or tracheal tug; 120 children (35%) with mild intercostal recession; 149 children (44%) with moderate accessory respiratory muscle use; and 39 (11%) with none (data available for n = 341).

For the 363 children admitted, 51 (14%) were re-admitted 0–30 days post discharge, and 153 (42%) from 1–6 months post discharge. For the index admission, 58 (16%) children were transferred from another hospital, 18 (5%) utilised an ambulance, 94 (26%) children were admitted to ICU and the majority (n = 318; 88%) presented to ED prior to admission compared to a direct admission to the ward (Table 1).

Australian Refined Diagnosis-Related Groups (AR-DRG) are detailed in Appendix A, Table A.2 for the index admission and re-admissions. The top ten AR-DRGs for the index admission are detailed in Table 2; these make up 296 of the 363 index admission AR-DRGs (82%).

Respiratory support included seven different modes of delivery (Table 3). In the index

Figure 1: Flow of participants through the study



admission, the most common mode was low-flow oxygen (n = 138; 38%), followed by high-flow oxygen (n = 113; 31%) and CPAP/BiPAP (n = 32; 9%). Antibiotics were given to 189 children (52%) in the index admission, 29 (57%) in the 0–30 day readmissions, and 113 (74%) in the 1–6 month readmissions. A new diagnosis of asthma was given to three children (1%) in the index admission, none in the 0-30 day readmissions, and four (3%) in the 1–6 month readmissions.

### Resources and costs

Health service resource utilisation has been reported in Tables 4 and 5, with Table 4 only including children with a re-admission, and Table 5 including all children. Health service cost has been reported in Table 6. For index admissions, ICU hours were skewed due to three children requiring extended ICU care,

specifically 1,050 hours, 936 hours and 560 hours. Total hospital length of stay (LOS) was equal highest for index admissions and 0–30 day readmissions (3.7 days, SD 5.4; and 3.7 days, SD 8.1 respectively), with a shorter LOS in the 1–6 month readmissions (2.3 days, SD 2.9) (Table 2). Index admission (n = 363) cost per child was \$12,643 (SD \$21,644); combined index (n = 363) plus 6-month readmission (n = 204) cost per child was \$17,120 (SD \$37,562), with a combined health service cost for all admissions of \$6,214,439.

### Extrapolation

The cost per child has been extrapolated across the Australian population using published RSV hospitalisation rates for children under five years of age who are RSV positive.<sup>15</sup> According to the Australian Bureau of Statistics, there were 1,572,293 children under five years of age

**Table 1: Admission and discharge data for hospitalised children aged 0–4 years**

under five years of age	Index admission (N = 363)		0–30 day re-admissions (N = 51)		1–6 month re-admissions (N = 153)	
	Number	%	Number	%	Number	%
Transfer from another hospital	58	16.0	5	9.8	24	15.7
Utilisation of an ambulance	18	5.0	2	3.9	12	7.8
Present to ED prior to admission	318	87.6	47	92.2	135	88.2
Patient admission location - Ward	289	79.6	41	80.4	115	75.2
Patient admission location - ICU	74	20.4	10	19.6	38	24.8
Admitted to ICU (NICU or PICU)	94	25.9	15	29.4	57	37.3
Discharge destination: Death	0	0.0	0	0.0	0	0.0
Discharge destination: Home with nil support	293	80.7	30	58.8	82	53.6
Discharge destination: Home with hospital support	54	14.9	19	37.3	67	43.8
Discharge destination: Home with community support / other	17	4.7	2	3.9	7	4.6
Discharge destination: Another hospital	10	2.8	2	3.9	2	1.3

in 2018.<sup>23</sup> With a reported hospitalisation rate of 2.2–4.5 per 1,000 among children under five years of age,<sup>15</sup> it was estimated that between 3,459 and 7,075 children under five years of age would be hospitalised annually in Australia. Accounting for upper and lower hospitalisation estimates, the index admission alone, with an average cost of \$12,643, has an extrapolated annual national cost between \$43,729,242 and \$89,446,176. Similarly, for the combined index and subsequent readmissions within six months, with an average cost of \$17,120, there is an extrapolated annual national cost between \$59,218,844 and \$121,129,453. The same methodology has been repeated for children under one year of age and the results have been reported in Table 7.

### Sub-group analysis

A sub-group analysis was completed for children born with prematurity (< 37 weeks; n = 76) compared to those born at term (n = 276); 11 not reported. The index admission LOS for premature infants was 5.8 days (SD 9.7) compared to LOS for term infants of 3.1 days (SD: 3.2), with a mean difference of 2.7 days (95% confidence interval [CI]: 1.3 to 4.0,  $p < 0.001$ ), with lesser costs favouring the term infants. The index

admission cost for children born prematurely was \$20,811 (SD: \$39,216) and term infants was \$10,409 (SD: \$12,964) with a mean difference of \$10,402 (95% CI: \$4,928 to \$15,876,  $p < 0.000$ ) favouring term infants. When the index costs are combined with readmission costs within six months, for children born prematurely the cost was \$27,353 (SD: \$54,312) and the cost for term infants was \$14,441 (SD: \$31,761) with a mean difference of \$12,913 (95% CI: \$3,296 to \$22,529,  $p = 0.009$ ) favouring term infants.

Based on the previous extrapolation, using the minimum rate of 2.2 children hospitalised annually due to RSV per 1,000 children under five years of age, corresponding to an annual total of 3,459 hospitalised children aged under five years, it is estimated<sup>ii</sup> that 297 hospitalised children (8.6%) would have been born preterm and 3,162 would not have been preterm. At \$27,353 per child born pre-term and \$14,441 per child not born pre-term, the minimum extrapolated cost would be \$53,786,283 ( $297 \times \$27,353 + 3,162 \times \$14,441$ ). Similarly, using instead the maximum rate of 4.5 children hospitalised annually due to RSV per 1,000, corresponding

ii <https://www.aihw.gov.au/reports/mothers-babies/australias-mothers-babies/contents/summary>.



**Table 2: The top ten Australian Refined Diagnosis-Related Groups (AR-DRG) for the index admission**

AR-DRG	Description	Index admission
E70B	Whooping Cough and Acute Bronchiolitis, Minor Complexity	107
E41A	Respiratory System Disorders W Non-Invasive Ventilation, Major Complexity	36
E41B	Respiratory System Disorders W Non-Invasive Ventilation, Minor Complexity	34
E70A	Whooping Cough and Acute Bronchiolitis, Major Complexity	26
E62B	Respiratory Infections and Inflammations, Minor Complexity	24
E62A	Respiratory Infections and Inflammations, Major Complexity	19
D63B	Otitis Media and Upper Respiratory Infections, Minor Complexity	17
E75B	Other Respiratory System Disorders, Minor Complexity	13
P68B	Neonate, AdmWt >=2500g W/O Sig GI/Vent>=96hrs, >=37 Comp Wks Gest, Maj Comp	11
E75A	Other Respiratory System Disorders, Major Complexity	9

to an annual total of 7,075 hospitalised children aged under five years, the maximum extrapolated cost would be \$110,026,381 ( $608 \times \$27,353 + 6,467 \times \$14,441$ ). Both the minimum and maximum extrapolated costs using pre-term categorisation approximate the primary extrapolation.

## Discussion

For RSV, routine surveillance in Australian children is limited and relies mainly on hospitalisation data, with little data available on the cost burden of this disease. Vaccines against RSV are in late stage development and while prophylactic mAb treatment is currently available it is extremely expensive, but newer, longer acting, and cheaper mAb may soon be available for clinical paediatric use. However, a major limiting factor to the introduction of these new counter measures and for the development of future RSV health policy has been the lack of data on the hospital care costs of RSV.

This current study addresses this issue and for the first time utilises individual patient-level data to estimate the cost burden of RSV in children in Australia. Access to this relevant, robust and recent cost burden data will provide

valuable insights to inform health care planning and health policy including future vaccines or antibody treatments. RSV presents a significant cost to the Australian health care system. The findings from the current study add detail to the previous estimates of direct healthcare costs of RSV for hospitalised children. The annual total cost of care in 2018, a typical RSV season, for all children under five years of age who were hospitalised with RSV at RCH, was estimated to be \$6,214,439, or \$17,120 per child. Using these figures, the extrapolated annual national cost for children under five years of age ranged between \$59M and \$121M, when including the index admission and subsequent all-cause readmissions within the following six months. The current study also found that for children under five years of age, there was an average cost of \$12,642 for the index RSV admission. This is compared to previously-published Australian costs from 1991 to 2000 for this same age group with an average cost of \$7,888 per admission,<sup>15</sup> and to previously published international costs per admission for the UK ranging from \$2,567 to \$15,015;<sup>6,12</sup> France \$6,927;<sup>19</sup> Canada \$9,959;<sup>18</sup> and USA \$11,221<sup>3</sup> (all costs converted into \$AUD[2018/2019]).

**Table 3: Respiratory support for children under five years of age<sup>a</sup>**

Respiratory support technique	RSV index admission			Follow-up period (only including children with a re-admission)											
	Index admission (N = 363)			0–30 day re-admissions (N = 51)						1–6 month re-admissions (N = 153)					
	n	%	Hours	n	%	Mean	SD	Range	n	%	Mean	SD	Range		
CPAP/Bi-PAP <sup>b</sup>	32	8.8	5.3	6	11.8	11.5	40.2	0–196	29	19.0	17.9	47.7	0–229		
Mechanical ventilation – conventional	13	3.6	5.9	6	11.8	28.9	146.5	0–1,026	21	13.7	13.4	40.5	0–188		
Mechanical ventilation – HFOV <sup>c</sup>	1	0.3	0.6	1	2.0	4.2	30.0	0–214	8	5.2	11.2	47.8	0–214		
Mechanical ventilation – jet ventilator	1	0.3	0.4	1	2.0	2.6	18.8	0–214	8	5.2	7.0	29.9	0–134		
ECMO <sup>d</sup>	1	0.3	0.01	1	2.0	0.1	0.7	0–5	0	0	0	—	—		
High-flow	113	31.1	13.5	14	27.5	12.2	25.2	0–100	54	35.3	16.8	28.6	0–130		
Low-flow	138	38.0	12.3	15	29.4	8.5	18.2	0–94	78	51.0	17.6	31.0	0–202		

<sup>a</sup> Note: the costs of respiratory support have been incorporated into the general ward and ICU costs for each admission.

<sup>b</sup> CPAP: continuous positive airway pressure. Bi-PAP: bi-level positive airway pressure.

<sup>c</sup> HFOV: high frequency oscillatory ventilation.

<sup>d</sup> ECMO: extracorporeal membrane oxygenation.

**Table 4: Quantity of resource allocation for children under five years of age (only including children with a re-admission in follow-up period calculations)**

Resource allocation unit	RSV index admission (N = 363)		Follow-up period (only including children with a re-admission)			
			0–30 day re-admissions (N = 51)		1–6 month re-admissions (N = 153)	
	n	%	n	%	n	%
Ambulance	18	5.0	2	3.9	12	7.8
ED presentation prior to the acute admission	318	87.6	47	92.2	135	88.3
	<b>Hours/days per child</b>		<b>Hours/days per child</b>		<b>Hours/days per child</b>	
	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>
ICU hours during admission	30.2	92.9	7.3	29.6	3.8	13.9
Total hospital admission length of stay, in days	3.7	5.4	3.7	8.1	2.3	2.9

**Table 5: Quantity of resource allocation for children under five years of age (follow-up period calculations include all children)**

Resource allocation unit	RSV index admission (N = 363)		Follow-up period (across all children)					
			0–30 day re-admissions (N = 363)		1–6 month re-admissions (N = 363)		Total (index admission and re-admissions) (N = 363)	
	n	%	n	%	n	%	n	%
Ambulance	18	5.0	2	0.6	12	3.3	32	8.8
ED presentation prior to the acute admission	318	87.6	47	12.9	135	37.2	500	137.7
	<b>Hours/days per child</b>		<b>Hours/days per child</b>		<b>Hours/days per child</b>		<b>Hours/days per child</b>	
	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>	<b>Mean</b>	<b>SD</b>
ICU hours during admission	30.2	92.9	0.5	5.4	3.1	31.2	33.8	102.4
Total hospital admission length of stay, in days	3.7	5.4	0.5	3.3	1.0	4.4	5.2	10.3

**Table 6: Cost of resource allocation for children under five years of age**

Resource allocation unit	RSV index admission (N = 363)		Follow-up period (across all children)				Total (index admission and re-admissions) (N = 363)	
	Mean	SD	0–30 day re-admissions (N = 363)		1–6 month re-admissions (N = 363)		Mean	SD
			Mean	SD	Mean	SD		
Ambulance	\$54	\$217	\$8	\$84	\$46	\$487	\$108	\$680
ED presentation prior to the acute admission	\$1,147	\$979	\$116	\$431	\$345	\$1,278	\$1,608	\$1,666
ICU admission	\$5,342	\$15,139	\$127	\$1,284	\$752	\$8,078	\$6,221	\$18,713
Hospital admission (excluding ED and ICU costs)	\$6,101	\$9,265	\$995	\$6,834	\$2,088	\$9,959	\$9,183	\$19,990
ALL CHILDREN: hospital admission (including ED and ICU costs, excluding ambulance costs)	\$12,589	\$21,604	\$1,238	\$7,530	\$3,185	\$17,873	\$17,012	\$37,239
ALL CHILDREN: hospital admission (including ED, ICU and ambulance costs)	\$12,643	\$21,644	\$1,246	\$7,582	\$3,231	\$17,978	\$17,120	\$37,562
CHILDREN UNDER 1 YEAR: hospital admission (including ED, ICU and ambulance costs)	\$12,346	\$21,414	\$1,112	\$7,081	\$2,453	\$10,237	\$15,912	\$31,231

**Table 7: Extrapolation based on hospital admission and cost per child (including ED, ICU and ambulance costs)**

Age group	Index hospital admission only		Total hospital costs (index admission and re-admissions)		Prevalence per 1,000 in Australia	Population size in Australia in 2018	Population affected in Australia	Australia-wide extrapolated costs	
	Mean	SD	Mean	SD				Index hospital admission only	Total hospital costs (index admission and re-admissions)
	<b>Under five years of age</b> (extrapolated from N = 363)	\$12,643	\$21,644	\$17,120	\$37,562	2.2 to 4.5	1,572,293	3,459 to 7,075	\$43,729,242 to \$89,446,176
<b>Under one year of age</b> (extrapolated from N = 242)	\$12,346	\$21,414	\$15,912	\$31,231	8.7 to 17.4	303,407	2,640 to 5,279	\$32,593,440 to \$65,174,534	\$42,007,680 to \$83,999,448

The current study estimated that the annual national cost for just the index admission of children under five years of age was between \$44M and \$89M. The previously-published Australian annual cost data for the same age group from 1991 to 2000 was estimated at \$21,472,441 to \$44,216,043,<sup>15</sup> with most of the cost difference attributed to the lower cost per admission reported in the previous study (\$7,888 compared to \$12,643 in the current study, with both figures expressed in \$AUD[2018/2019] units). Internationally, the national annual burden for children hospitalised with RSV was estimated at \$965M in the United States of America<sup>3</sup> and \$34M in Canada<sup>18</sup> (all costs converted into \$AUD[2018/2019] units). The current study has provided a conservative estimate of the true cost of RSV in Australia, as it excludes the RSV positive hospitalised patients who did not meet the WHO SARI criteria, and it excludes also the cost of community-managed RSV which can include ED presentations, GP consultation, pharmaceuticals, as well as lost employment productivity for parents.<sup>24</sup>

The top three AR-DRGs for the index admission have been compared to published data from the Australian National Hospital Cost Data Collection (NHCCD) Round 23 data which reports the national average length of stay and cost for each AR-DRG admission. The most common AR-DRG was E70B “Whooping Cough and Acute Bronchiolitis, Minor Complexity” (n = 107/363; 29%), followed by E41A “Respiratory System Disorders W Non-Invasive Ventilation, Major Complexity” (n = 36/363; 10%) and E41B “Respiratory System Disorders W Non-Invasive Ventilation, Minor Complexity” (n = 34/363; 9%). National data reported the average length of stay and cost to be 1.6 days and \$2,867 for E70B; 12.1 days and \$29,509 for E41A, and 6.2 days and \$13,684 for E41B. This is comparable to the current study data which has reported the average length of stay and cost to be 2.0 days (SD: 1.2) and \$5,648 (\$4,054) for E70B; 6.8 days (SD: 4.2) and \$27,188 (SD \$18,153) for E41A; and 4.4 days (SD: 2.4) and \$15,092 (SD 8,770) for E41B.

In this study, premature infants who tested positive for RSV consumed significantly more healthcare resources per patient than did the full term infants who tested positive. This is consistent with the literature where published data reports that RSV rates and the subsequent health care utilisation are higher in vulnerable populations such as presence of prematurity, congenital heart defects, or immunosuppression.<sup>6,19,25</sup> These premature infants are also more likely to have multiple hospital admissions in the first year of life, so preventative therapies will be very important for this special risk group.

These RSV findings can be compared to the global impact of influenza which was associated with 10% of respiratory infections in children under 18 years of, with an estimated 870,000 hospital admission for children under five years of age.<sup>25</sup> In Australia, reported annual influenza hospitalisations ranged from 1,879 to 9,930 between 2006 and 2013. The highest rate of hospitalisation were in children under six months of age (187 per 100,000); between 6 and 24 months (108 per 100,000), and in adults over 75 years of age (48 per 100,000).<sup>26</sup> The annual cost burden for all age groups of people hospitalised in Australia for influenza was reported at \$50 million (based on 6,973 annual admissions, CPI inflated from \$AUD 2005), with \$6 million attributed to children aged under 5 (based on 1,171 annual admissions).<sup>26,27</sup> These results have influenced policy, with influenza vaccine now on the Australian National Immunisation Program for children aged 6 months to < 5 years. Compared to influenza, the annual cost burden for hospitalised children under five years of age in Australia for RSV was \$44 million (current study conservative estimate for index admission only), seven times as large as the hospitalisation cost burden of influenza. The lack of an affordable preventative therapy for RSV is a major barrier; however, this may alter in the near future with the introduction of cheaper and longer-lasting prophylactic mAb treatments for infants and maternal RSV vaccines designed to protect infants aged zero to six months.<sup>28,29</sup> Hopefully, robust and current RSV cost burden data will provide valuable insights

to inform Australian health care planning and policy to allow accurate cost-benefit assessments of future monoclonal antibody treatments and vaccines.

While access to individual patient-level cost data with a six-month follow-up is a strength of the current study, the main limitation is that only one health service (RCH) was accessed, and that individual age groups did not inform the extrapolation due to limitations with the prevalence data (limited to the age groups of under one year and under five years of age). It is, however, a large paediatric tertiary hospital, with similar centres in each of the major Australian capital cities. It is possible that the costs at the RCH are higher than elsewhere due to the specialised nature of the hospital. An expanded study Australia-wide would provide more accurate cost estimates. The present study also excluded 194 RSV-positive hospitalised patients who did not meet the WHO SARI criteria, indicating this current study was a conservative estimate of the full RSV cost burden for the health service. It is unknown if the inclusion of the 194 RSV-positive admissions who did not meet the SARI criteria would have impacted the cost data on a per-child basis. While a comparison of the SARI and non-SARI admissions might be of interest, further data on these excluded patients was not available.

## Conclusion

RSV presents a significant cost burden to the Australian health care system. Accounting for upper and lower hospitalisation estimates, the extrapolated 2018 annual national cost of RSV for children under five years of age ranged from \$AUD59M to \$AUD121M, inclusive of the index admission and six-month all-cause readmissions. The conservative estimate for index admissions is 7 times as high as the influenza hospitalisation cost burden for children aged less than five years. These data are important for future assessments of preventative therapies such as RSV monoclonal antibody and

maternal/childhood RSV vaccines and will provide valuable insights to inform healthcare planning and health policy.

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## Competing interests / conflict of interest

Competing interests: no relevant disclosures.

## Data sharing statement

Requests for individual participant data that underlie the results reported in this article, after deidentification, will be considered by the corresponding author on a case by case basis, for researchers who provide a methodologically sound proposal. Data sharing will begin three months and end five years following article publication.

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## Appendix A

Table A.1: Review of the international RSV cost of burden literature for children

Study	Country and cohort	Context of the burden of cost	Cost data as presented in the paper	Cost data converted to \$AUD[2018/2019]	Additional comments
15	Australia Children under five years of age	Health service perspective. Data collection between 1991 and 2000. Cost data modelled for the estimated 2,773 to 5,710 influenza or pneumonia hospital admissions per year for children aged 0–4, index admission only.	<b>AUD 2005</b> Per hospitalisation: \$5,245 National annual total direct cost of hospitalisation: \$14,544,000 to \$29,949,000	Per hospitalisation: \$7,888 National annual total direct cost of hospitalisation: \$21,472,441 to \$44,216,043	This study notes that hospital costs account for around 60% of the total direct health care costs of RSV infections in young children; as such, the cost of RSV on the Australian health system is estimated to be between \$35 to \$74 million (AUD 2005 \$24 to \$50 million) annually.
18	Canada Children under five years of age	Health system perspective. Cost of RSV related hospitalisation in 1994 across 9 Canadian hospitals for children aged under five years of age. Based on 5,714 children with combined direct costs (including total hospital expenditures, physician fees and outpatient care), indirect costs and total costs presented.	<b>USD 1993</b> Per hospitalisation: \$3,026 National annual total direct cost of hospitalisation \$10,464,245	Per hospitalisation: \$9,959 National annual total direct cost of hospitalisation \$34,439,331	This study also reported an assumed reinfection rate of 33% for children aged 2–4 years. Total cohort combined direct cost of hospitalisation \$55,983,877 (USD 1993 \$17,010,179) and indirect cost of \$4,955,930 (USD 1993 \$1,505,813) totalling \$60,939,807 (USD 1993 \$18,515,992).
6	United Kingdom Children under two years of age	Health service perspective. Based on 411 preterm infants who had 497 RSV related hospitalisations over three consecutive RSV seasons, 1996–99, 83% had 1 admission, 15% had two admissions and 32% had three admissions. Length of stay was a median of 2 days (range 0–19 days).	<b>GBP 2003</b> Per hospitalisation: £849 Total cohort cost of hospitalisation: £421,938	Per hospitalisation: \$2,567 Total cohort cost of hospitalisation: \$1,275,942	Preterm infants of less than 36 weeks gestation, who were under 6 months of age accounted for 11% of these costs. RSV re-hospitalisations (including ICU admissions) of children under 2 years of age contributed to 8.1% of total RSV related health authority costs.
12	United Kingdom Children under two years of age	Health service perspective. Based on 2000–2007 data from two local hospitals of premature infants (32–35 weeks of gestation) and their RSV related healthcare utilisation during the first 2 years of life. Data was collected on 20 RSV positive infants and this reflected multiple hospitalisations with an average of 2.3 hospital admissions per child, and combined length of stay was a mean of 9.6 days.	<b>GBP 2003</b> Per hospitalisation: £4,755 Cost of 2.3 admissions over two years was £10,936, multiplied by 20 infants totalled £218,720	Per hospitalisation: \$15,015 Cost of 2.3 admissions over two years was \$34,534, multiplied by 20 infants totalled \$690,670	The cost of care for each admission was calculated as the number of days the infant spent at each level of care, that is in a paediatric ward, HDU or ICU multiplied by the cost of care of that level of care.
3	United States of America Children under five years of age	Third party payer perspective. Cost of RSV in 2000 was reported for children under five years of age with data extracted from 3 separate national databases. The annual cost of illness was based on healthcare resource use and direct medical costs in the hospital inpatient, hospital outpatient, emergency room and office visit settings in the US. For inpatient data, billed charges were converted to costs.	<b>USD 2002</b> Per hospitalisation: \$4,581. National annual total direct cost of hospitalisation: \$394 million.	Per hospitalisation: \$11,221 National annual total direct cost of hospitalisation: \$965 million.	National annual total direct cost of hospitalisation was \$965 million (USD 2002 \$394 million) represented 60% of the total direct annual medical costs of \$1,597 million (USD 2002 \$652 million); with the other 40% representing other medical encounters at a cost of \$631 million (USD 2002 \$258 million).
19	France Children in first year of life (up to one year of age)	Health service perspective. Cost of RSV was reported for a cohort of 350 newborns in a university hospital between 2012 and 2016. An episode of hospitalisation was defined as a new admission to one of the conventional paediatric hospital departments with an RSV positive sample at admission.	<b>Euro 2016</b> Per hospitalisation: €3,973. Total cohort cost: €364,269	Per hospitalisation: \$6,927 Total cohort cost: \$635,099	Related direct medical annual cost for the 350 newborns was mostly attributed to children born during the RSV season \$404,418 (Euro 2016 €231,959) and children born premature \$189,470 (Euro 2016 €108,673), based on modelled economic data.

**Table A.2: Australian Refined Diagnosis-Related Groups (AR-DRG)**

AR-DRG	AR-DRG Description	Index admission (N = 363)	0-30 day re-admissions (N = 51)	1-6 month re-admissions (N = 153)	All admissions combined (N = 567)
A06A	Tracheostomy W Ventilation >95 hours W Catastrophic CC	1	0	0	1
A13A	Ventilation >=336hours, Major Complexity	1	0	0	1
A14C	Ventilation >=96hours & <336hours, Minor Complexity	2	0	0	2
B02B	Cranial Interventions, Intermediate Complexity	0	0	1	1
B41B	Telemetric EEG Monitoring, Minor Complexity	0	0	2	2
B42B	Nervous System Disorders W Ventilator Support, Intermediate Complexity	1	0	0	1
B75Z	Febrile Convulsions	2	1	1	4
B76A	Seizures, Major Complexity	1	0	1	2
B76B	Seizures, Minor Complexity	0	0	1	1
B80B	Other Head Injuries, Minor Complexity	0	1	0	1
B81A	Other Disorders of the Nervous System, Major Complexity	0	1	0	1
B81B	Other Disorders of the Nervous System, Minor Complexity	0	0	1	1
D03A	Surgical Repair for Cleft Lip and Palate Disorders, Major Complexity	0	0	1	1
D40Z	Dental Extractions and Restorations	0	0	1	1
D63A	Otitis Media and Upper Respiratory Infections, Major Complexity	2	0	2	4
D63B	Otitis Media and Upper Respiratory Infections, Minor Complexity	17	2	1	20
E01A	Major Chest Interventions, Major Complexity	1	0	0	1
E40A	Respiratory System Disorders W Ventilator Support, Major Complexity	1	0	0	1
E40B	Respiratory System Disorders W Ventilator Support, Minor Complexity	1	0	0	1
E41A	Respiratory System Disorders W Non-Invasive Ventilation, Major Complexity	36	1	6	43
E41B	Respiratory System Disorders W Non-Invasive Ventilation, Minor Complexity	34	2	3	39
E62A	Respiratory Infections and Inflammations, Major Complexity	19	0	1	20

AR-DRG	AR-DRG Description	Index admission (N = 363)	0–30 day re-admissions (N = 51)	1–6 month re-admissions (N = 153)	All admissions combined (N = 567)
E62B	Respiratory Infections and Inflammations, Minor Complexity	24	7	2	33
E63A	Sleep Apnoea, Major Complexity	0	0	1	1
E63B	Sleep Apnoea, Minor Complexity	0	0	1	1
E67A	Respiratory Signs and Symptoms, Major Complexity	4	3	3	10
E67B	Respiratory Signs and Symptoms, Minor Complexity	5	0	16	21
E69B	Bronchitis and Asthma, Minor Complexity	2	1	11	14
E70A	Whooping Cough and Acute Bronchiolitis, Major Complexity	26	1	3	30
E70B	Whooping Cough and Acute Bronchiolitis, Minor Complexity	107	8	23	138
E75A	Other Respiratory System Disorders, Major Complexity	9	1	3	13
E75B	Other Respiratory System Disorders, Minor Complexity	13	3	3	19
F04A	Cardiac Valve Interventions W CPB Pump W/O Invasive Cardiac Invest, Major Comp	0	0	1	1
F69B	Valvular Disorders, Minor Complexity	0	0	1	1
F76A	Arrhythmia, Cardiac Arrest and Conduction Disorders, Major Complexity	1	0	0	1
G03B	Stomach, Oesophageal and Duodenal Interventions, Intermediate Complexity	0	1	0	1
G05B	Minor Small and Large Bowel Interventions, Minor Complexity	0	0	2	2
G10B	Hernia Interventions, Minor Complexity	0	0	4	4
G46A	Complex Endoscopy, Major Complexity	0	0	2	2
G47B	Gastroscopy, Intermediate Complexity	0	0	1	1
G66A	Abdominal Pain and Mesenteric Adenitis, Major Complexity	0	1	1	2
G66B	Abdominal Pain and Mesenteric Adenitis, Minor Complexity	0	1	0	1
G67A	Oesophagitis and Gastroenteritis, Major Complexity	1	0	2	3
G67B	Oesophagitis and Gastroenteritis, Minor Complexity	2	0	4	6
G70B	Other Digestive System Disorders, Intermediate Complexity	0	2	3	5

AR-DRG	AR-DRG Description	Index admission (N = 363)	0–30 day re-admissions (N = 51)	1–6 month re-admissions (N = 153)	All admissions combined (N = 567)
G70C	Other Digestive System Disorders, Minor Complexity	0	0	1	1
I23B	Local Excision & Removal of Internal Fixation Device, Except Hip & Fmr, Min Comp	0	1	0	1
I76B	Other Musculoskeletal Disorders, Minor Complexity	0	1	0	1
J65B	Trauma to Skin, Subcutaneous Tissue and Breast, Minor Complexity	0	0	1	1
J67A	Minor Skin Disorders, Major Complexity	1	0	0	1
J68A	Major Skin Disorders, Major Complexity	0	1	0	1
K62A	Miscellaneous Metabolic Disorders, Major Complexity	1	2	0	3
K62B	Miscellaneous Metabolic Disorders, Intermediate Complexity	1	0	1	2
K62C	Miscellaneous Metabolic Disorders, Minor Complexity	1	1	2	4
L09C	Other Interventions for Kidney and Urinary Tract Disorders, Minor Complexity	0	0	1	1
L63A	Kidney and Urinary Tract Infections, Major Complexity	0	0	1	1
M03B	Penis Interventions, Minor Complexity	0	0	2	2
M04Z	Testes Interventions	0	0	1	1
P05A	Neonate, AdmWt 2000–2499g W Significant GI/Vent>=96hrs, Major Complexity	1	0	0	1
P05B	Neonate, AdmWt 2000–2499g W Significant GI/Vent>=96hrs, Minor Complexity	1	0	0	1
P06A	Neonate, AdmWt >=2500g W Significant GI/Vent>=96hrs, Major Complexity	4	0	0	4
P06B	Neonate, AdmWt >=2500g W Significant GI/Vent>=96hrs, Minor Complexity	2	0	0	2
P60B	Neonate W/O Sig GI/Vent>=96hrs, Died/Transfer Acute Facility <5 Days, Min Comp	3	0	0	3
P66A	Neonate, AdmWt 2000–2499g W/O Significant GI/Vent>=96hrs, Extreme Comp	1	0	0	1
P66B	Neonate, AdmWt 2000–2499g W/O Significant GI/Vent>=96hrs, Major Complexity	1	0	0	1
P68A	Neonate, AdmWt >=2500g W/O Sig GI/Vent>=96hrs, >=37 Comp Wks Gest, Ext Comp	7	0	0	7
P68B	Neonate, AdmWt >=2500g W/O Sig GI/Vent>=96hrs, >=37 Comp Wks Gest, Maj Comp	11	0	0	11
P68C	Neonate, AdmWt >=2500g W/O Sig GI/Vent>=96hrs, >=37 Comp Wks Gest, Int Comp	3	0	0	3

AR-DRG	AR-DRG Description	Index admission (N = 363)	0–30 day re-admissions (N = 51)	1–6 month re-admissions (N = 153)	All admissions combined (N = 567)
P68D	Neonate, AdmWt >=2500g W/O Sig GI/Vent>=96hrs, >=37 Comp Wks Gest, Min Comp	1	0	0	1
Q60B	Reticuloendothelial and Immunity Disorders, Minor Complexity	0	0	1	1
Q62B	Coagulation Disorders, Minor Complexity	0	0	1	1
R04A	Other Neoplastic Disorders W Other GIs, Major Complexity	1	0	0	1
R62A	Other Neoplastic Disorders, Major Complexity	0	0	1	1
R62B	Other Neoplastic Disorders, Intermediate Complexity	0	0	4	4
R63Z	Chemotherapy	0	4	9	13
T60B	Septicaemia, Intermediate Complexity	1	0	0	1
T60C	Septicaemia, Minor Complexity	1	0	0	1
T62A	Fever of Unknown Origin, Major Complexity	2	0	0	2
T62B	Fever of Unknown Origin, Minor Complexity	2	0	4	6
T63B	Viral Illnesses, Minor Complexity	4	1	7	12
U66B	Eating and Obsessive-Compulsive Disorders, Minor Complexity	0	2	0	2
X61B	Allergic Reactions, Minor Complexity	0	0	2	2
X63A	Sequelae of Treatment, Major Complexity	0	0	1	1
X63B	Sequelae of Treatment, Minor Complexity	0	0	2	2
Z61B	Signs and Symptoms, Minor Complexity	0	1	1	2
Z64B	Other Factors Influencing Health Status, Minor Complexity	0	0	1	1