

# RESPIRATORY SYNCYTIAL VIRUS – THE UNRECOGNISED CAUSE OF HEALTH AND ECONOMIC BURDEN AMONG YOUNG CHILDREN IN AUSTRALIA

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## Abstract

Respiratory syncytial virus (RSV) presents very similar to influenza and is the principle cause of bronchiolitis in infants and young children worldwide. Yet, there is no systematic monitoring of RSV activity in Australia. This study uses existing published data sources to estimate incidence, hospitalisation rates, and associated costs of RSV among young children in Australia. Published reports from the Laboratory Virology and Serology Reporting Scheme, a passive voluntary surveillance system, and the National Hospital Morbidity Dataset were used to estimate RSV-related age-specific hospitalisation rates in New South Wales and Australia. These estimates and national USA estimates of RSV-related hospitalisation rates were applied to Australian population data to estimate RSV incidence in Australia. Direct economic burden was estimated by applying cost estimates used to derive economic cost associated with the influenza virus. The estimated RSV-related hospitalisation rates ranged from 2.2–4.5 per 1,000 among children less than 5 years of age to 8.7–17.4 per 1,000 among infants. Incidence ranged from 110.0–226.5 per 1,000 among the under five age group to 435.0–869.0 per 1,000 among infants. The total annual direct healthcare cost was estimated to be between \$24 million and \$50 million. Comparison with the health burdens attributed to the influenza virus and rotavirus suggests that the disease burden caused by RSV is potentially much higher. The limitations associated with using a passive surveillance system to estimate disease burden, and the need to explore further assessments and to monitor RSV activity are discussed. *Commun Dis Intell* 2011;35(2):177–184.

Keywords: respiratory syncytial virus, respiratory tract infections, burden of disease, Australia

## Introduction

The Influenza A H1N1 pandemic of 2009 served as a reminder of the importance of monitoring in the detection and management of infectious disease outbreaks. In Australia, laboratory confirmed influenza is by law, a notifiable disease that needs to be reported to the National Notifiable Diseases Surveillance System and is thereby reported routinely. There is however little recognition of the role that the respiratory syncytial virus (RSV) plays in the

burden of disease that is attributed to the influenza virus the world over.

With a disease spectrum ranging from rhinitis and otitis media to bronchiolitis and pneumonia, RSV infection presents very similar to influenza and contributes to the influenza-like illness that occurs in the community.<sup>1-2</sup> It is the principal cause of bronchiolitis in infants and young children worldwide, with incidence peaking between 2 and 5 months of age and almost all children being exposed to RSV by the time they reach 3 years of age.<sup>3</sup>

Overseas studies suggest a high disease burden in industrial nations. In the United Kingdom, it is estimated that among the under 5 years age group, general practitioner consultation rates due to RSV are similar to that of influenza, while RSV accounts for more hospital admissions than does influenza (35,540 and 9,967 respectively), particularly among pre-school aged children.<sup>4</sup> In the year 2000 in the United States of America (USA), RSV-related hospital admissions accounted for 17% of all hospitalisation of infants aged 3–12 months.<sup>5</sup> In Japan, it is estimated that a quarter (26.2%) of children aged less than 3 years of age are treated annually for RSV and 13.6% are hospitalised.<sup>6</sup> The medical cost associated with RSV in children less than 5 years of age in the USA in 2000 was estimated to be \$US652 million; 60% of this cost attributed to hospitalisations.<sup>5</sup>

In Australia, while a small number of studies have examined viral cultures taken in hospital to help create a picture of RSV burden, there is no systematic collection of data on RSV to estimate the health and economic burden specific to Australia. This study draws on published data to derive an estimate of RSV occurrence in Australia and compares the disease burden with that caused by other highly prevalent viruses.

## Methods

RSV is not a notifiable disease in Australia and there is no single data source that accurately measures RSV activity across Australia. The primary data source for this study is the Laboratory Virology and Serology Reporting Scheme (LabVISE), a passive surveillance system involving a network of 17–20 laboratories across Australia voluntarily sub-

mitting monthly reports on the laboratory identification of viruses and other organisms.<sup>7</sup> Specifically, two studies that have examined RSV reporting in LabVISE have been used to estimate the number of cases of RSV-related hospitalisations and hospitalisation rates that occur in Australia.<sup>8-9</sup>

The first of the two LabVISE based studies was published in 2000 and presents the number of RSV cases in New South Wales reported to LabVISE during the period January 1993 and December 1997.<sup>8</sup> The authors, in presenting the number of RSV cases reported to LabVISE, identify that these numbers are 'likely to represent hospitalised cases (and that the data) reflect a pattern of hospitalisation rather than RSV infection in the community.'<sup>8</sup> Given the absence of more comprehensive data sources, and recognising the limitations of using a passive surveillance system to estimate the occurrence of disease, the number reported to LabVISE is used in this study as a surrogate indicator of the number of RSV hospitalisations in New South Wales.

The second study published in 2002 reviewed Australia-wide reporting of RSV as part of viral and non-viral pathogen identifications reported to LabVISE during the 10 year period 1991–2000.<sup>9</sup> As with the RSV reporting for New South Wales, the number of RSV cases reported across Australia is used in this study as a surrogate indicator for RSV hospitalisations in Australia. This study does not provide an age breakdown of RSV occurrence in Australia. Being uncertain about how the New South Wales age distribution of RSV compares with that of Australia, and in view of the fact that the age distribution of the Australian and the USA populations and the New South Wales and the Australian populations are similar,<sup>10</sup> the age distribution of RSV from a national estimate for the USA<sup>5</sup> was applied to the number of RSV cases reported in Australia to estimate RSV hospitalisation rates in Australia (Table 1).

The number of RSV hospitalised cases obtained from the two studies (Table 1) were then applied to the New South Wales and Australian population distributions of 1996 and 2000 to derive RSV hospitalisation rates for New South Wales and Australia (Table 1).

A second data source used in this study to inform the number of RSV-related hospitalisations in Australia is the National Hospital Morbidity Database (NHMD) as reported by the Australian Institute of Health and Welfare (AIHW).<sup>11</sup> The number of hospital separations registered from all states and territories in Australia in the NHMD with a discharge diagnosis of ICD-10-AM codes B97.4 (RSV), J12.1 (RSV pneumonia), J20.5 (acute RSV bronchitis), or J21.0 (acute RSV bronchiolitis) for the year 1999–2000 was obtained via the data cubes

published on the AIHW website.<sup>12</sup> Table 2 presents and compares the NHMD derived estimates of hospitalisation rates with those presented in Table 1 and with national USA estimates.

To estimate the incidence of RSV in Australia, the proportion of RSV cases expected to be hospitalised was applied to the hospitalisation rates presented in Table 2. Given the absence of a definite estimate of the proportion of RSV cases that require hospitalisation, the upper end of the published statistics that 0.5%– 2% of all cases with RSV in the infant age group require hospitalisation<sup>3</sup> was used as the proportion. The upper end was used as this would provide a lower estimate of incidence, thereby reducing the likelihood of over-estimating RSV occurrence. Since RSV hospitalisation rates derived from NHMD were higher than the LabVISE estimates (Table 2) and given the fact that NHMD is an actual count of the number of RSV-related hospital separations as opposed to an estimation based on a passive surveillance system, the NHMD derived hospitalisation rates have been used separately to estimate RSV incidence in Australia. The LabVISE estimated hospitalisation rates and the USA national estimate have been combined as a range.

The estimated incidence and hospitalisation rates are used to calculate an economic burden of RSV in Australia. In the absence of data to inform the economic costing, the cost estimation is limited to the direct health care costs associated with hospitalisation. The average cost of a RSV-related hospital admission was taken to be \$5,245, which is the Australian Refined Diagnosis Related Groups based average cost of a hospital admission for influenza or pneumonia over the period 1998–2005 (in 2005 dollar value) used to estimate the economic cost of influenza to the Australian health system.<sup>13</sup> Applying the value used to estimate the cost of influenza is justifiable on the basis that influenza and RSV are very similar in terms of clinical presentation and have comparable lengths of stay in hospital (median of 2–4 days for RSV<sup>5,14</sup> and 2 days for influenza<sup>15</sup>). In estimating the total direct healthcare costs associated with RSV infections, it is assumed, based on existing literature,<sup>5</sup> that 60% of direct costs are incurred in hospital.

To place these estimates in perspective, the RSV-related burden of disease estimated in this study was compared against published hospitalisation rates for influenza in Sydney, New South Wales, for the period 1994–2001.<sup>16</sup> Given that the influenza vaccine was introduced in Australia as part of the mass immunisation program in 1999, the period 1994–2001 mostly represents pre-vaccination period for influenza virus and is therefore comparable to the current RSV situation of no vaccination. Also used as a comparator was the number of reports of influenza to LabVISE from 1991–2000.<sup>9</sup> Once again,

**Table 1: Estimated respiratory syncytial virus-related hospitalisation rates for New South Wales and Australia, based on reporting to LabVISE**

Study	Study years	Study population	Age group (per 1,000 population)	Cases per year	Population	Hospitalisation rate*
Lister <sup>†</sup>	1993–1997	NSW	All ages	770–1,131	6,038,696 (1996 Census)	0.1–0.2 (all ages)
			<3 months	276 <sup>‡</sup> (29% of all cases) <sup>‡</sup>	85,302 (live births, 1996) <sup>  </sup>	3.2 per 1,000 live births
			<6 months	504 <sup>‡</sup> (53% of all cases) <sup>‡</sup>	85,302 (live births, 1996) <sup>  </sup>	5.9 per 1,000 live births
			<1 year	742 <sup>‡</sup> (78% of all cases) <sup>‡</sup>	85,302 (live births, 1996) <sup>  </sup>	8.7 per 1,000 live births
			<5 years	937 <sup>‡</sup> (98.5% of all cases) <sup>‡</sup>	427,696 (1996 Census)	2.2 per 1,000 pop <5 years
Roche <sup>§</sup>	1991–2000	Australia	All ages	2,555 to 4,641	17,892,423 (1996 Census)	0.1–0.3 (all ages)
			<3 months	1,259 <sup>‡</sup> (35% of all cases) <sup>§</sup>	255,445 (live births, 2000) <sup>  </sup>	4.9 per 1,000 live births
			<6 months	1,979 <sup>‡</sup> (55% of all cases) <sup>§</sup>	255,445 (live births, 2000) <sup>  </sup>	7.7 per 1,000 live births
			<1 year	2,699 <sup>‡</sup> (75% of all cases) <sup>§</sup>	255,445 (live births, 2000) <sup>  </sup>	10.6 per 1,000 live births
			<5 years	3,598 <sup>‡</sup> (98% of all cases) <sup>§</sup>	1,273,589 (2000 projections)	2.8 per 1,000 pop <5 years

\* Estimating hospitalisation rate is based on using the number of cases reported to the Laboratory Virology and Serology Reporting Scheme (LabVISE) as a surrogate indicator of the number of respiratory syncytial virus hospitalisations.

† Based on an average of the annual number of cases reported in the paper, assuming a normal distribution in the number of cases reported every year. The average for the Lister study was 951 cases per year (for New South Wales)<sup>§</sup> and the Roche study was 3,598 cases per year (for Australia).<sup>§</sup>

‡ Proportion of cases by age group as reported in Lister et al, 2000.<sup>§</sup>

§ Proportions of cases reported in Paramore et al. 2004<sup>§</sup>

|| NSW Department of Health. *NSW Mothers and Babies 1996*. N S W Public Health Bull 1998;Suppl. (State Health Publication No (ESB) 970146).

¶ Australian Institute of Health and Welfare. Australia's mothers and babies. Canberra: Australian Institute of Health and Welfare; 2000.

this largely constitutes the pre-immunisation period for influenza and is therefore a suitable comparison.

Just as RSV is now recognised to be a major contributor to lower respiratory tract infections in infants and young children, rotavirus is the major cause of gastroenteritis among infants and young children in Australia. In common with RSV, rotavirus transmission in temperate climates is seasonal, occurring predominantly during the winter season. Estimated RSV-related hospitalisation rates are compared with published reports on rotavirus-related hospitalisation rates and disease burden for the period 1991–2002.<sup>11,17</sup> Rotavirus immunisation was not added to the Australian National Immunisation Program until 2007.

## Results

In New South Wales a total of 4,665 cases of RSV was reported to LabVISE between January 1993 and December 1997, with the number of cases per year ranging from 770–1,131.<sup>8</sup> Across Australia, RSV was the single most common virus reported to LabVISE during the 10 year period 1991–2000 with a total of 36,346 cases reported, and the annual number of cases ranging from 2,555 to 4,641.<sup>9</sup> Consistent with published literature and similar to influenza,<sup>18–19</sup> annual epidemics occurred in winter and the majority of cases of RSV reporting was for children less than 5 years of age.<sup>9</sup>

The hospitalisation rates estimated based on the number of cases reported to LabVISE, suggest that while the rates for New South Wales were marginally lower than rates based on the 10-year review of Australia-wide reporting of RSV, the estimates for New South Wales and Australia were not dissimilar (Table 1). The difference, if at all, was more among the young infant age group.

Table 2 compares the estimates from the two LabVISE studies with hospitalisation rates derived from the NHMD and the national USA estimates. The NHMD rates are higher than rates estimated from the LabVISE-based studies and are more in keeping with the USA national estimate reported by Paramore et al<sup>5</sup> (Table 2). As a result, the NHMD derived hospitalisation rates were used separately for estimating the RSV incidence for Australia.

Applying the hospitalisation rates derived in Table 2 to the 2006 Australian Census population estimates that up to 5,710 RSV-related hospital episodes may occur every year among children less than 5 years of age in Australia (Table 3). Assuming the upper limit from the published literature that up to 2% of RSV cases are hospitalised,<sup>3</sup> this converts to up to 285,481 cases of RSV occurring in Australia among children aged less than 5 years; with the majority of these cases occurring among the less than 1 year age group (Table 3). There wasn't sufficient data to examine in detail the distribution within the less than 1 year age group as would have been ideal given that the literature suggest a high disease burden observed in the less than 3 month age group.

Applying the average cost of \$5,245 per hospital admission, the 2,773 to 5,710 hospital episodes estimated per year for the < 5 year age group (Table 3) will cost the Australian health system between \$14.544 m and \$29.949 m per year in hospital costs (Table 4). If, as suggested by USA and Canadian literature, hospital costs account for around 60% of the total direct health care costs of RSV infections in young children, the cost of RSV on the Australian health system is estimated to be between \$24 and \$50 million annually (in 2005 value). No information is available to estimate non-health care or indirect costs attributable to RSV.

**Table 2: Age-specific respiratory syncytial virus (RSV) related-hospitalisation rates per 1,000 population for Australia and the United States of America (USA) as estimated by various sources**

	LabVISE* (1993–1997) NSW	LabVISE (1991–2000) Australia	NHMD† (1999/2000) Australia	Paramore (2001) USA (national estimate)
RSV hospitalisations (n)	770–1,131 per year‡	2,555–4,640 per year§	5,244	87,105 annually
<b>Hospitalisation rate by age group (per 1,000 population)</b>				
All ages	0.1–0.2	0.1–0.3	–	–
<1 year	8.7	10.6	16.8	17.4
<5 years	2.2	2.8	3.9	4.5

\* Laboratory Virology and Serology Reporting Scheme.

† National Hospital Morbidity Dataset.

‡ Number of cases in New South Wales as reported in Lister et al, 2000.<sup>8</sup>

§ Number of cases across Australia as reported in Roche et al, 2002.<sup>9</sup>

|| From Table 1.

Comparing the estimated RSV-related disease burden with those attributed to the influenza virus and rotavirus suggest that in Australia amongst children, RSV is responsible for a much higher disease burden than the routinely monitored influenza virus and rotavirus (Figure). A Sydney-based study reports influenza-related hospitalisation rates varying from 0.95–6.94 per 1,000 population among children aged less than 1 year (the group with the highest rate of hospitalisation),<sup>16</sup> whereas this study's estimates of RSV-related hospitalisation rates for the less than 1 year age group were almost 10 times higher (8.7 and 16.8 per 1,000 age-specific population) (Tables 1 and 2). The annual number of cases reported to LabVISE is also lower for influenza with approximately 200–1,000 cases per month of influenza A and 10–300 cases per month of influenza B reported during peak influenza season.<sup>9</sup> This is in contrast to about 1,000 cases of RSV reported per month as the usual number, with up to about 1,600 cases a month reported in one year.<sup>9</sup> A total of 13,191 cases of influenza A and 3,614 cases of influenza B cases was reported to LabVISE over the 10-year period (from 1991 to 2000), whereas a total of 36,346 cases of RSV was reported to LabVISE during the same

10 year period.<sup>9</sup> Hospitalisation rates in Australia for rotavirus among children less than 5 years of age have been estimated previously to be between 3.0 per 1,000 (for 1–4 year age group) and 4.1 per 1,000 (for the less than 1 year age group),<sup>11</sup> which once again is less than the 2.2–4.5 per 1,000 that was estimated for this same age group for RSV (Table 2).

## Discussion

Our analysis based, on limited available data on RSV in Australia, suggests that RSV potentially causes a higher disease burden compared with viruses such as influenza or rotavirus that are monitored through surveillance programs and are vaccinated against as part of the national immunisation program in Australia. The lack of systematic monitoring systems in Australia for RSV meant that this study was limited to using data from published sources. This meant that the data are not the most recent and are subject to systematic errors when used to estimate the burden of disease for Australia.

The limitations of using a passive surveillance system as the primary source of data are recognised, and it

**Table 3: Estimated incidence of respiratory syncytial virus infections, Australia, based on hospitalisation rates**

Age group	Hospitalisation rate per 1,000 population (A)	Age-specific Population <sup>†</sup> (B)	Expected number of hospitalisations (C) = (A)x(B)	Number of RSV cases /year <sup>‡</sup> (D)=(C) x 50	Incidence per 1,000 population <sup>§</sup> [(D) / (B)] x 1,000
<1 year	16.8 (Table 2 NHMD)*	260,101	4,362	218,095	838.5
<1 year	8.7–17.4 (Table 2 range)	260,101	2,263–4,521	113,144–226,028	435.0–869.0
<5 years	3.9 (Table 2 NHMD)*	1,260,403	4,916	245,779	195.0
<5 years	2.2–4.5 (Table 2)	1,260,403	2,773–5,710	138,644–285,481	110.0–226.5

\* National Hospital Morbidity Dataset (NHMD) derived hospitalisation rates have been applied separately as these rates were higher than the Laboratory Virology and Serology Reporting Scheme–derived rate estimates for Australia (Table 2).

† Australian Bureau of Statistics Census 2006 accessed via the Australian Bureau of Statistics web site, Census data, 2006 Census (Australia, quick statistics).

‡ Assumes that hospitalisation = 2% of incidence.<sup>3</sup>

§ Per 1,000 age-specific population (Australia).

**Table 4: Estimated cost of hospitalisation and direct health care cost for respiratory syncytial virus infections, Australia, (2005 value)**

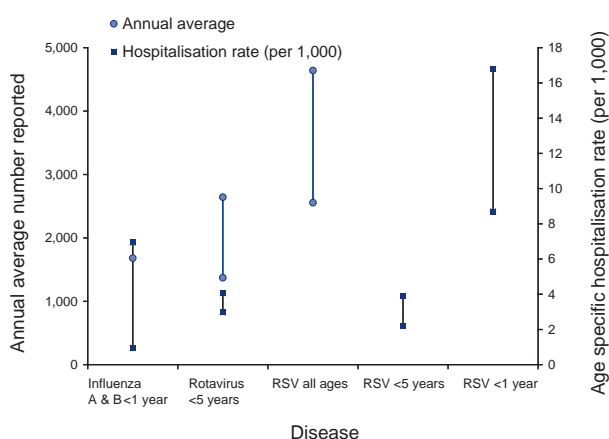
Age group	<1 year	<5 years
Estimated number of RSV hospitalisations (annual)	2,263–4,521*	2,773–5,710*
Direct cost of hospitalisation per year (\$ million) <sup>†</sup>	\$11.869–\$23.713	\$14.544–\$29.949
Total direct health care cost per year (\$ million) <sup>‡</sup>	\$19.782–\$39.521	\$24.241–\$49.915

\* From Table 3.

† Unit cost = average cost of influenza/pneumonia as estimated by Newall et al = \$5,245.<sup>13</sup>

‡ Total healthcare costs estimated based on reports that hospitalisation costs in respiratory syncytial virus (RSV) account for 60% of all direct health care costs associated with RSV.<sup>5</sup>

**Figure: Disease burden caused by influenza A and B, rotavirus, and respiratory syncytial virus in Australia**



Reference period for annual average and hospitalisation rates, respectively:

Influenza A & B:	2001 and 1994-2001.
Rotavirus:	1991-2002 and 1999-2000.
RSV all ages:	1991-2000.
RSV <5 years:	1993-2000.
RSV <1 year:	1993-2000.

is acknowledged that such surveillance systems only provide a means of examining overall trends.<sup>9</sup> The implication of LabVISE being a passive surveillance system on this study is that the derived estimates underestimate the true disease burden. This fact is supported to some extent by the finding that the LabVISE estimated RSV hospitalisation rates were less than the NHMD derived rates (Table 2). The use of LabVISE to estimate hospitalisation has been considered previously by Roche and colleagues who state that the ‘number of LabVISE reports of RSV was of the same order as total admissions for bronchiolitis.’<sup>20</sup> They go on to say that ‘It is likely (that) LabVISE captures the majority of hospitalised cases of RSV through its networks or tertiary hospital laboratories in major Australian cities.’<sup>20</sup> For the purpose of this study, it is believed that LabVISE and the use of NHMD jointly provide information to demonstrate the high disease burden caused by RSV, particularly in relation to the influenza viruses and rotavirus.

Another limitation is the absence of a recent and definite estimate of the proportion of RSV cases that require hospitalisation, and the consequent use of statistics from a text book quoted in a journal paper. The implication of using the 2% upper end of the quoted range is that the incidence would be lower than had the 0.5% lower end of the range been used. The 0.5%–2% hospitalisation rate also relates to infants, and since infancy is a significant risk factor for hospitalisation,<sup>21</sup> it is reasonable to assume that

the hospitalisation rates across all ages would be lower. The decreasing hospitalisation rate with age was also demonstrated in a conference paper presented by the Centre for Disease Control personnel in 2010 presenting national estimates of RSV-related hospitalisations for the period 1997 to 2006 for the USA. The estimates presented for the less than 1 age group were 2.63% in 1997–1999 and 2.34% in 2004–2006. The rates reduced with age, from 1.19% in the 1 to less than 2 year age group, to 0.19% in the 2 to less than 5 year age group.<sup>22</sup>

Counter arguments may also exist to explain higher rates of RSV being reported when in fact RSV infection rates are no more than the occurrence of influenza or rotavirus. For example, it may be possible that the diagnosis of influenza or rotavirus is often made based on clinical judgement not requiring serological assay, while testing for RSV may be undertaken more frequently. This may result in a higher number of RSV reportings that do not necessarily reflect the true disease burden.

Notwithstanding these limitations and possible explanations, the finding in this study that RSV is possibly contributing to a significant disease burden in Australia, especially when compared with influenza and rotavirus that are considered sufficiently significant to warrant monitoring and vaccination, needs further investigation. If RSV is a significant contributor to influenza-like illness and the associated economic burden, there is a need to accurately assess and understand the burden and to identify goals and strategies to protect and reduce morbidity, especially among high-risk groups.

The benefits of preventing RSV extend beyond reducing morbidity and mortality directly related to RSV among the high-risk groups. In common with other respiratory tract viral pathogens, RSV is associated with exacerbation of asthma.<sup>23</sup> While the majority of infants and young children infected with RSV experience a full recovery, there is evidence to suggest an association between RSV infection in early childhood and the likelihood of wheezing, or developing asthma.<sup>3,24–27</sup> This association is of particular relevance for Australia given that the prevalence of asthma in Australia is among the highest in the world, affecting 14%–16% children and 10%–12% adults.<sup>28</sup>

To date, no vaccine has been proved to be safe and effective in the control of RSV, and treatment is largely symptomatic. Prophylactic monoclonal antibody therapy has been shown to be effective in reducing the morbidity associated with RSV, however given the significant cost of the intervention, the current recommendation by the National Health and Medical Research Council is to limit its use to high risk groups.<sup>29</sup>

Given that this study suggests a disease burden higher than those attributed to the influenza viruses or rotavirus prior to the introduction of vaccines, there is a need to further assess the disease burden and explore the value of monitoring RSV activity in Australia, primarily to establish a baseline level of activity, but also to assist in prioritising, implementing, and assessing control measures that may be required.

## Ethical consideration

This study utilised aggregated data available in the public domain and did not require approval from an ethics committee.

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