Respiratory syncytial virus-associated hospitalisations in Australia, 2006–2015

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The known: Respiratory syncytial virus (RSV)-associated disease is a major cause of hospitalisation of young children. In Australia, there are no national data on RSV-associated hospitalisations across the age spectrum.

The new: We report data for RSV-coded hospitalisations in Australia during 2006–2015, stratified by age, sex, Indigenous status, jurisdiction, and season. Hospitalisation rates were 6.6 times as high for adults aged 65 or more as for people aged 5–64 years, and 3.3 times as high for Indigenous as for non-Indigenous Australians.

The implications: Our national population-level analysis provides valuable insights into severe RSV-associated disease that will inform future research and prevention strategies.

Abstract

Objective: To estimate rates of respiratory syncytial virus (RSV)-associated hospitalisation across the age spectrum, and to identify groups at particular risk of serious RSV-associated disease.

Design, setting and participants: Retrospective review of National Hospital Morbidity Database data for all RSV-associated hospitalisations in Australia, 2006–2015.

Main outcomes and measures: RSV-coded hospitalisation rates by age, sex, Indigenous status, jurisdiction, and seasonality (month and year); hospital length of stay; in-hospital deaths.

Results: During 2006–2015, there were 63 814 hospitalisations with an RSV-specific principal diagnostic code; 60 551 (94.9%) were of children under 5 years of age. The hospitalisation rate for children under 5 years was 418 per 100 000 population; for children under 6 months of age it was 2224 per 100 000 population; the highest rate was for infants aged 0–2 months (2778 per 100 000 population). RSV-coded hospitalisation rates were higher for adults aged 65 or more than for people aged 5–64 years (incidence rate ratio [IRR], 6.6; 95% CI, 6.2–7.1), and were also higher for Indigenous Australians than other Australians (IRR, 3.3; 95% CI, 3.2–3.5). A total of 138 in-hospital deaths were recorded, including 82 of adults aged 65 years or more (59%).

Conclusions: Prevention strategies targeting infants, such as maternal or early infant vaccination, would probably have the greatest impact in reducing RSV disease rates. Further characterisation of RSV disease epidemiology, particularly in older adults and Indigenous Australians, is needed to inform health care strategies.

Respiratory syncytial virus (RSV) is the leading viral cause of acute lower respiratory infections in young children.[1] Severe RSV disease in older adults is also being reported more frequently, and is associated with substantial morbidity and mortality.[2,3] National data on the RSV disease burden in Australia, needed to inform future research and prevention strategies, is scarce.

The estimated global annual incidence of acute lower respiratory infections caused by RSV is 33.1 million episodes, and 3.2 million children under 5 years of age are admitted to hospital with RSV-associated disease.[1] The incidence of severe RSV disease is higher among children in lower income countries, but in all regions the highest RSV-associated hospitalisation rates are for children less than 6 months old.[1] Young age is an independent risk factor for severe RSV disease; most hospitalised children are otherwise healthy.[4]

Severe RSV disease can also affect adults, particularly older people and those with chronic cardiopulmonary diseases,[2,3] but the burden of disease in adults is less well characterised. In the United Kingdom, more general practitioner visits, hospitalisations, and deaths of younger children and older adults are attributable to RSV infections than to influenza in most years.[2,5]

As RSV infections are not notifiable in Australia[6] and testing practices differ between locations and for different population groups,[7,8] obtaining accurate population-based estimates of incidence is challenging. One Australian study based on published sentinel laboratory data, supplemented with RSV-coded hospitalisation data, estimated national hospitalisation rates,[6] but the information regarding age of patients and their hospitalisations available to the authors was limited. A number of studies have estimated RSV hospitalisation rates for young children in specific Australian regions,[6,7,9–11] and have identified groups at particular risk, including Aboriginal and Torres Strait Islander children[9–11] and children born pre-term or with bronchopulmonary dysplasia.[10] Studies describing RSV-associated hospitalisations of Australian adults have not been reported.

In our study, we analysed national RSV-coded hospitalisation rates during 2006–2015 to estimate the rates of RSV-associated hospitalisation across the age spectrum and to identify groups at particular risk of serious RSV disease.

Methods

Data sources

De-identified national hospitalisation data for the period 1 January 2006 – 31 December 2015 were obtained from the Australian Institute of Health and Welfare National Hospital Morbidity Database. We extracted hospitalisations with International Classification of Diseases, tenth revision, Australian modification (ICD-10-AM) diagnosis codes for RSV pneumonia (J12.1), RSV bronchitis (J20.5), RSV bronchiolitis (J21.0), and RSV as the cause of diseases classified to other chapters (RSV organism) (B97.4). These codes were selected on the basis of earlier studies[6,10,12,13] and expert opinion. Hospitalisations of children

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• doi: 10.5694/mja2.50159 • See Editorial (Moore).

under 24 months of age with a principal diagnosis code of unspecified acute bronchiolitis (J21.9) were also extracted, as this diagnosis is frequently associated with RSV disease.[14,15] Hospitalisation data for Aboriginal and Torres Strait Islander (Indigenous) Australians were also separately analysed from 2011 onwards, when completeness of Indigenous identification was considered adequate in all jurisdictions.[16] Mid-year population estimates for Australia, by state and territory (jurisdiction), sex, and age, were based upon Australian Bureau of Statistics census estimates for 2016 (Australia)[17] or 2011 (Indigenous Australians).[18]

Data analysis and statistical methods

We describe hospitalisations with an RSV code (ICD-10-AM codes J12.1, J20.5, J21.0, B97.4) by diagnostic code, age at admission, sex, jurisdiction of residence, and Indigenous status (principal diagnosis or other diagnosis). We describe hospitalisations with an RSV code by month and year of admission, length of stay (LOS), and in-hospital deaths (principal diagnosis only). Hospitalisation rates were calculated using mid-year population data (Poisson distribution assumed) and are presented as rate per 100 000 total population; subgroup rates were compared as incidence rate ratios (IRRs) with 95% confidence intervals (CIs). Median LOS with interquartile range (IQR) is reported; episodes with LOS exceeding 29 days were excluded (191, 0.3%) as disaggregated data for later years were not available (ie, stays of more than 29 days were reported as "> 29 days").

RSV is the most frequently detected pathogen in people hospitalised with acute bronchiolitis,[7,19] but such patients may be assigned a non-RSV-specific code, such as unspecified acute bronchiolitis (J21.9).[14,15] For this reason, we conducted a separate analysis of hospitalisations of children under 24 months of age with a principal diagnosis code of unspecified acute bronchiolitis (J21.9), comparing rates with those of children under 24 months of age with a principal diagnosis code of RSV bronchiolitis (J21.0). In this analysis, we excluded 585 episodes coded as unspecified acute bronchiolitis with an RSV-specific code listed in an additional diagnosis field.

Statistical analyses were conducted in SPSS 25 (IBM), Excel 16 (Microsoft), and EpiBasic 1.0.

Ethics approval

Ethics approval for this study was granted by the Sydney Children's Hospital Network Human Research Ethics Committee (reference, LNR/17/SCHN/487).

Results

Summary characteristics and seasonality of hospitalisations

During 2006–2015, there were 86 687 hospitalisations with an RSV code in at least one diagnostic field, including 63 814 (73.6%) with an RSV code in the principal diagnostic field (Box 1). For all states and territories apart from the Northern Territory, the clear peak in hospitalisation numbers was during autumn–winter; the magnitude of the peak rate and month varied by year and jurisdiction (Supporting Information, figure 1).

Respiratory syncytial virus-coded hospitalisations

The characteristics of RSV-coded hospitalisations (diagnostic code, age, sex, jurisdiction of residence, and Indigenous status) are summarised in Box 1. RSV bronchiolitis was the most frequent RSV-coded principal diagnosis, and was also the most frequent principal RSV code among children under 24 months of age (Supporting Information, figure 2). The RSV organism code was listed in a diagnostic field (principal or additional) for 18 035 hospitalisations with an RSV code (20.8%); the most frequent principal diagnosis codes for these episodes were unspecified acute upper respiratory infection (3180, 17.7%), unspecified acute lower respiratory infection (2973, 16.5%), unspecified asthma (1786, 9.9%), and chronic obstructive pulmonary disease with acute lower respiratory infection (1531, 8.5%).

RSV-coded hospitalisation rates were higher for boys than girls under 5 years of age (IRR, 1.2; 95% CI, 1.2–1.3) or under 6 months of age (IRR, 1.2; 95% CI, 1.2–1.3). The RSV-coded hospitalisation rate was lower for men than women over 65 years of age (IRR, 0.8; 95% CI, 0.7–0.9).

The hospitalisation rates for young children were fairly constant across the study period. The hospitalisation rate for adults over 65 increased from one per 100 000 population in 2006 to 20 per 100 000 population in 2015. There were smaller rises in older children and other adult age groups (Box 2). The hospitalisation rate was higher for adults aged 65 or more than for people aged 5–64 years (IRR, 6.6; 95% CI, 6.2–7.1).

The numbers of hospitalisations of children under 5 years of age with an RSV code peaked at one month of age, then declined with age (Box 3).

Hospitalisations of Indigenous Australians

Of the 36 024 RSV-coded hospitalisations during 2011–2015, 3395 (9.4%) were of Indigenous Australians, including 3310 (97.5%) under 5 years of age. The hospitalisation rate for Indigenous Australians was 97 per 100 000 population, and age-specific rates for children under 5 years of age and adults 35–54 years of age were significantly higher than for non-Indigenous Australians (Box 4).

Bronchiolitis in children under 24 months of age

A total of 52 916 children under 24 months of age were hospitalised with an RSV bronchiolitis code (J21.0), comprising 93.4% of the 56 639 primary diagnosis RSV-coded hospitalisations in this age group. In addition, 100 098 children under 24 months were hospitalised with an unspecified acute bronchiolitis code (J21.9), with seasonal variation similar to that of RSV bronchiolitis-coded hospitalisations (Box 5).

Hospital length of stay and deaths

RSV-coded hospitalisations required a total of 224 305 bed-days during 2006–2015. The population median LOS was 3 days (IQR, 2–4 days); it was 3 days (IQR, 1–4 days) for children under 5 years, 3 days (IQR, 2–5 days) for children under 6 months, and 6 days (IQR, 4–9 days) for adults aged 65 years or more. For Indigenous Australian children under 5 years of age (2011–2015), median LOS was 3 days (IQR, 2–5 days); for non-Indigenous children during this period it was 2 days (IQR, 1–4 days).

Of the 138 in-hospital deaths of people hospitalised with a RSV code as principal diagnosis (0.2% of admissions), 120 episodes were coded as RSV pneumonia (87%) and 15 as RSV bronchiolitis (11%); 82 deaths (59%) were of adults aged 65 years or more,

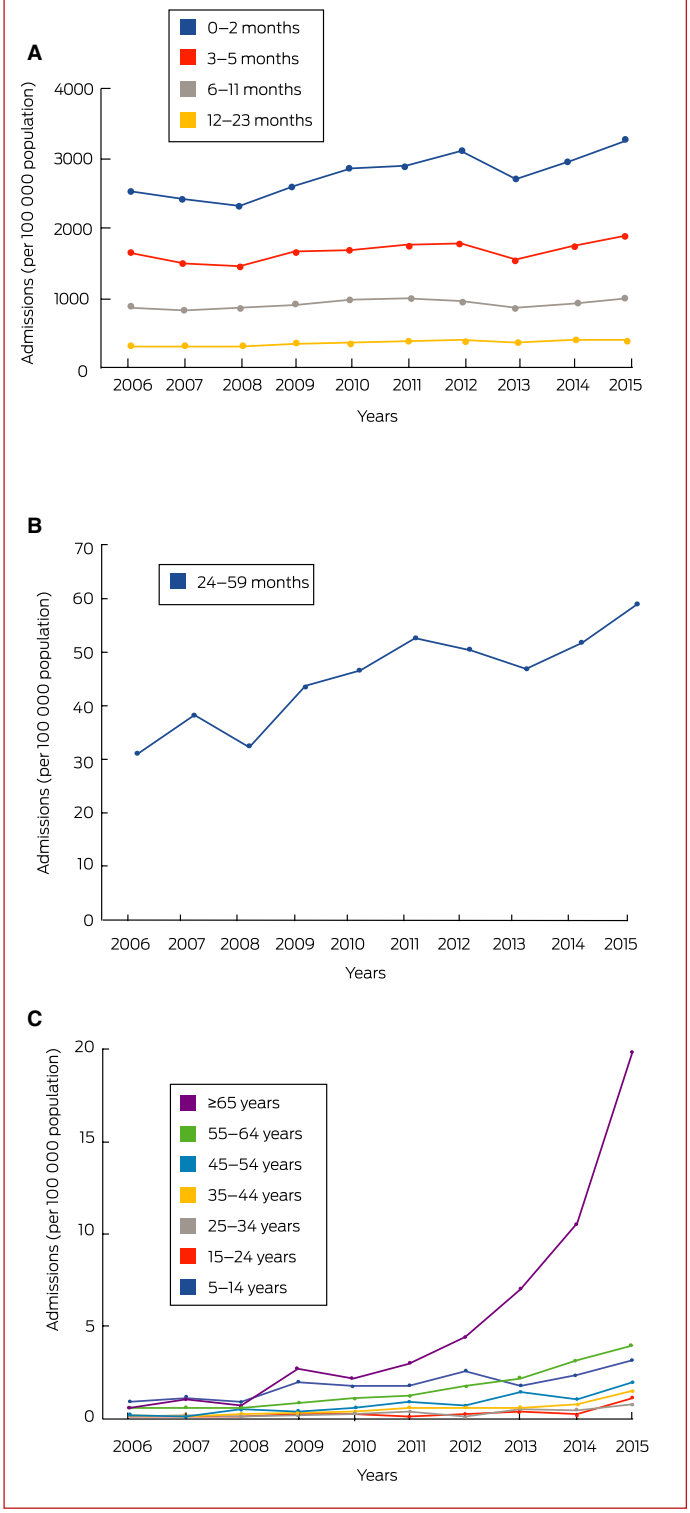
1 Respiratory syncytial virus-coded hospitalisations, Australia, 2006–2015

Characteristics	Hospitalisations with respiratory syncytial virus (RSV) code			
	As principal diagnosis		As principal or other diagnosis	
	Number	Rate* (per 100 000 population)	Number	Rate* (per 100 000 population)
Total number of admissions	63 814		86 687	
Diagnostic code†				
RSV bronchiolitis (J21.0)	54 513 (85.4%)	25	57 205 (66.0%)	26
RSV pneumonia (J12.5)	8571 (13.4%)	4	11 468 (13.2%)	5
RSV bronchitis (J20.5)	666 (1.0%)	< 0.5	862 (1.0%)	< 0.5
RSV organism (B97.4)	64 (0.1%)	< 0.5	18 035 (20.8%)	8
Age‡				
< 6 months	32 855 (51.5%)	2224	36 458 (42.1%)	2468
< 5 years	60 551 (94.9%)	418	74 206 (85.6%)	513
All ages		29		39
0–2 months	20 524 (32.2%)	2778	23 114 (26.7%)	3129
3–5 months	12 331 (19.3%)	1669	13 344 (15.4%)	1806
6–11 months	13 516 (21.2%)	915	15 250 (17.6%)	1032
12–23 months	10 268 (16.1%)	352	14 571 (16.8%)	500
24–59 months	3912 (6.1%)	46	7927 (9.1%)	92
5–14 years	516 (0.8%)	2	1708 (2.0%)	6
15–24 years	89 (0.1%)	< 0.5	411 (0.5%)	1
25–34 years	98 (0.2%)	< 0.5	388 (0.4%)	1
35–44 years	168 (0.3%)	1	658 (0.8%)	2
45–54 years	236 (0.4%)	1	1012 (1.2%)	3
55–64 years	413 (0.6%)	2	1744 (2.0%)	7
≥ 65 years	1742 (2.7%)	6	6558 (7.6%)	21
Sex				
Males	35 757 (56.0%)	32	47 442 (54.7%)	43
Females	28 057 (44.0%)	25	39 245 (45.3%)	35
Jurisdiction§				
Northern Territory	1249 (2.0%)	54	1648 (1.9%)	72
South Australia	7269 (11.4%)	45	11 051 (12.7%)	68
Queensland	15 853 (24.8%)	36	22 409 (25.9%)	51
New South Wales	23 768 (37.2%)	33	30 183 (34.8%)	42
Australian Capital Territory	1051 (1.6%)	29	1375 (1.6%)	38
Western Australia	6464 (10.1%)	28	8590 (9.9%)	37
Tasmania	891 (1.4%)	18	1200 (1.4%)	24
Victoria	6912 (10.8%)	13	9694 (11.2%)	18
Indigenous status (2011–2015)				
Indigenous Australians	3395 (9.4%)	97	4306 (8.3%)	123
Non-Indigenous	32 629 (90.6%)	29	47 296 (91.7%)	42

* Denominator based on Australian Bureau of Statistics census data. † For "principal or other diagnosis" hospitalisations, more than one RSV-associated code could be listed for a single hospitalisation. For all subsequent categories, individual hospitalisation episodes were censored to exclude those with multiple RSV-associated diagnostic codes being counted twice. ‡ Missing data: principal diagnosis, one; any diagnosis, two. § Missing data: principal diagnosis, 357; any diagnosis, 537. ◆

for whom 78 (95%) episodes were coded as RSV pneumonia. Twenty-one children under 5 years of age (15% of deaths) died in hospital; 12 episodes were coded as RSV bronchiolitis and nine as RSV pneumonia. Seven children under 6 months of age died (5% of deaths); four hospitalisations were coded as RSV bronchiolitis and three as RSV pneumonia.

2 Respiratory syncytial virus-coded hospitalisation rates (principal diagnosis only), Australia, 2006–2015, by age group and year: A. children under 2 years of age; B. children from 2 years to under 5 years of age; C. children aged 5 years or more and adults



Discussion

Our population-based study is the first to estimate national RSV-coded hospitalisation rates in Australia by age, sex, Indigenous status, jurisdiction, and season. We found RSV is a frequently recorded cause of hospitalisation of children under 5 years of age. We also found high rates of hospitalisation of adults over 65, and that rates were generally higher for Indigenous than non-Indigenous Australians.

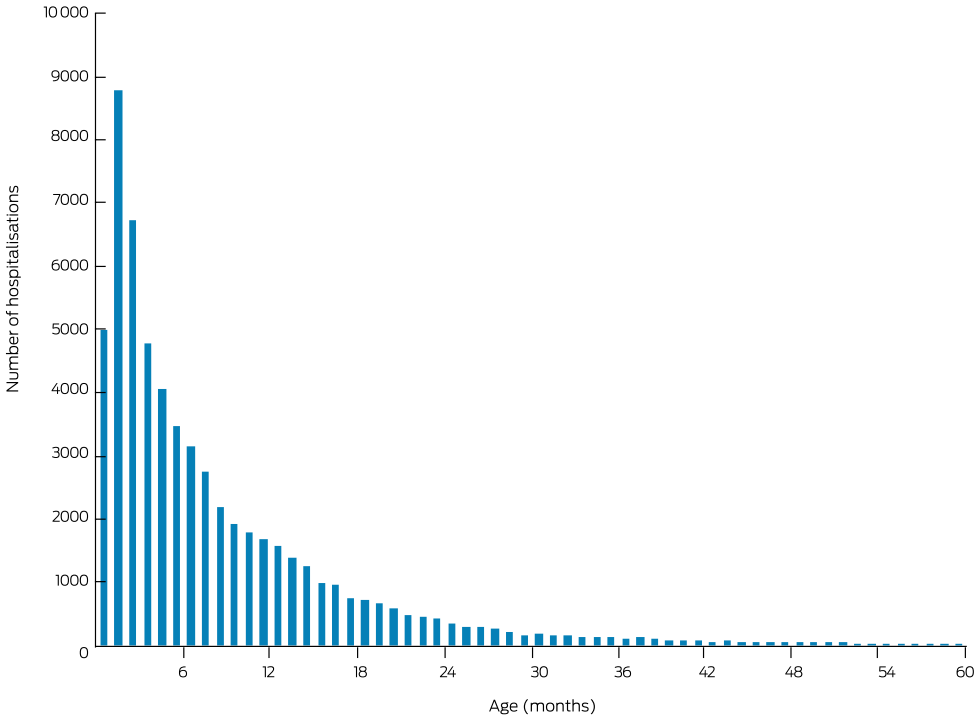
We analysed national hospitalisation data for ten consecutive RSV seasons. The seasonal RSV-coded hospitalisation patterns we found were consistent with those in previous Australian reports.[10,20–22] Differences in rates between jurisdictions may reflect environmental, infrastructural, and population differences, but probably also variations in clinical and coding practices. The greater monthly variation in the NT hospitalisation rate is probably attributable to the tropical climate of the Top End.[23] The estimated national RSV-coded hospitalisation rate of 29 per 100 000 population is consistent with the earlier national estimate based on laboratory surveillance data of 10–30 per 100 000 population for 1990–2000.[6] Our findings for children under 5 years of age (418 per 100 000 population) are similar to those of a NSW birth cohort study based on linked data for 2001–2010 (490 per 100 000 population).[10]

Most RSV-associated hospitalisations are of children under 6 months of age; published rate estimates range from 1700 to 4590 per 100 000 population, depending on the study population and methodology.[1,4,5,10,13] It has been reported that there are more RSV-associated hospitalisations of young Australian children than influenza-associated hospitalisations.[6] Our findings are consistent with this statement: for children under 6 months of age, the estimated national influenza-associated hospitalisation rate, derived from ICD-coded principal and additional diagnoses (2006–2013), was 187 per 100 000 population,[24] and we estimated the RSV-coded hospitalisation rate for this age group to be 2468 per 100 000. Children under 6 months of age are considered a priority group for RSV disease prevention, and proposed strategies include maternal vaccination and passive monoclonal antibody prophylaxis.[25] A recombinant RSV fusion protein nanoparticle vaccine has been found to be safe and immunogenic, protecting healthy women of child-bearing age against RSV infection, and is now undergoing phase 3 clinical trials.[25,26] Such a vaccine could substantially reduce the number of RSV-associated hospitalisations in Australia.

Our study provides important new data on RSV morbidity among Australian adults. In the UK, the estimated hospitalisation rate for adults aged 65 or more was 156 per 100 000 population (1995–2009).[2] Our estimates, based on RSV-specific codes, are lower, but we found a 20-fold increase in RSV-coded hospitalisations in this age group during 2006–2015, probably reflecting increased recognition of and testing for RSV disease in older adults;[2,3,8] RSV-associated hospitalisations in this age group may still be under-recognised. Compared with other age groups, we found that adults over 65 had longer hospital stays, and the proportion of in-hospital deaths was greater. This is consistent with overseas findings of longer hospital stays and high mortality rates for older adults hospitalised with RSV infections.[3] Older people are a recognised target group for preventing RSV disease,[3,25] and further investigation of their disease burden is needed.

We found that the RSV-coded hospitalisation rate was 3.3 times as high for Indigenous Australians as for other Australians. The higher rate of RSV-associated hospitalisations among Indigenous children[9–11] has been attributed to the greater prevalence of socio-economic risk factors for severe RSV disease, including premature birth, low birthweight, and exposure to smoking.[27] We identified that the risk of RSV-associated hospitalisation was also 2.9–4.3 times as high for Indigenous adults aged 35–54 years as for non-Indigenous adults of corresponding age. The risk factors underlying these differences should

3 Respiratory syncytial virus-coded hospitalisations (principal diagnosis only) of children under 5 years of age, Australia, 2006–2015, by age



be investigated to inform targeted prevention strategies.

Limitations

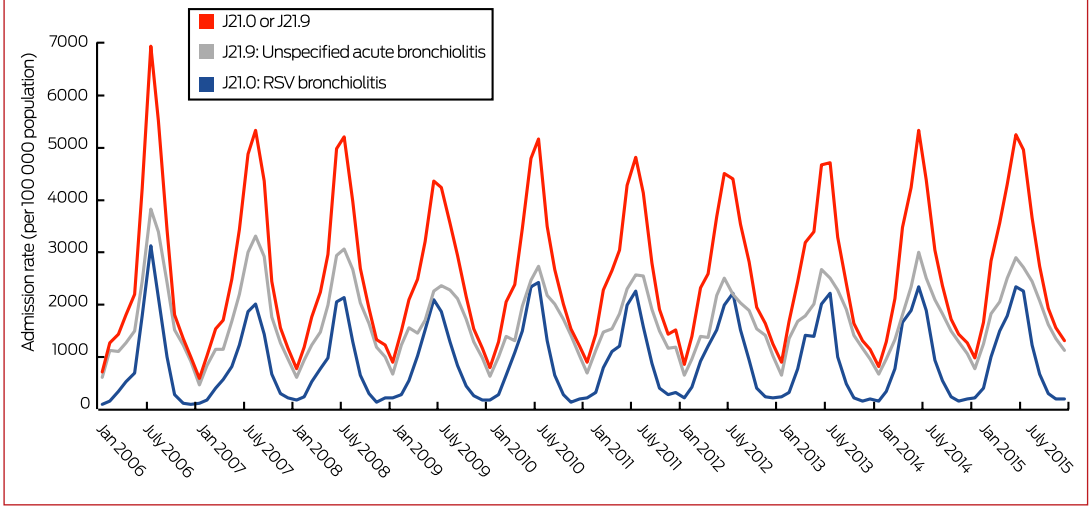
The main limitation of our study was that we estimated RSV-associated hospitalisation rates on the basis of RSV-specific ICD codes, an approach that can underestimate the pathogen-specific disease burden of respiratory infections.[7,13–15,24,28] Diagnostic codes other than RSV-specific codes have also been assigned to RSV-associated hospitalisations.[7,13,15] We found that the seasonal patterns of hospitalisations for conditions coded as unspecified acute bronchiolitis were similar to those of RSV bronchiolitis, which suggests the involvement of RSV as a pathogen in bronchiolitis may be under-ascertained. RSV is detected in 50–70% of young children hospitalised for bronchiolitis, but other pathogens, including parainfluenza viruses, human metapneumovirus and influenza viruses, are also associated with this diagnosis.[7,19] RSV

4 Respiratory syncytial virus-coded hospitalisations (principal diagnosis only) of Indigenous and non-Indigenous Australians, 2011–2015, by age group

	Indigenous Australians		Non-Indigenous Australians		
Age group	Number	Rate* (per 100 000 population)	Number	Rate* (per 100 000 population)	Incidence rate ratio (95% CI)
Total number	3395	97	32 629	29	3.3 (3.2–3.5)
< 6 months	1851 (54.5%)	4310	16 155 (49.5%)	2253	1.9 (1.8–2.0)
< 5 years	3310 (97.5%)	789	30 063 (92.1%)	420	1.8 (1.8–2.0)
0–2 months	1003 (29.5%)	4671	10 364 (31.8%)	2890	1.6 (1.5–1.7)
3–5 months	848 (25.0%)	3949	5791 (17.7%)	1615	2.5 (2.3–2.6)
6–11 months	805 (23.7%)	1875	6386 (19.6%)	891	2.1 (2.0–2.3)
12–23 months	497 (14.6%)	589	5323 (16.3%)	371	1.6 (1.4–1.7)
24–59 months	157 (4.6%)	63	2199 (6.7%)	51	1.2 (1.1–1.5)
5–14 years	22 (0.6%)	3	311 (1.0%)	2	1.2 (0.7–1.8)
15–24 years	7 (0.2%)	1	58 (0.2%)	< 0.5	2.5 (1.0–5.6)
25–34 years	4 (0.1%)	1	70 (0.2%)	< 0.5	1.9 (0.5–5.1)
35–44 years	9 (0.3%)	2	120 (0.4%)	1	2.9 (1.3–5.6)
45–54 years	16 (0.5%)	5	170 (0.5%)	1	4.3 (2.4–7.1)
55–64 years	10 (0.3%)	5	317 (1.0%)	2	2.0 (1.0–3.7)
≥ 65 years	17 (0.5%)	8	1520 (4.7%)	9	0.9 (0.5–1.4)

CI = confidence interval. * Denominator based on Australian Bureau of Statistics census data. ◆

5 Hospitalisation rates for children under 24 months of age with respiratory syncytial virus bronchiolitis (International Classification of Diseases, J21.0) or unspecified acute bronchiolitis (J21.9) codes (principal diagnosis only), 2006–2015, by month and year of hospitalisation



has been implicated in syndromes not specific to RSV infection, including unspecified acute lower respiratory infection, pneumonia, upper respiratory infection, asthma, and exacerbation of chronic obstructive pulmonary disease;[3,4,7,15] further characterisation of the contribution of RSV infections to hospitalisations for these conditions is needed.

Similarly, variations in respiratory virus testing practices[7,8] probably affect diagnostic coding, perhaps contributing to the differences in hospitalisation rates we found. Consistent with other recent reports,[10] we found that the rate of RSV-associated hospitalisations of young children was relatively constant. However, increased respiratory virus testing in recent decades[7,8] may explain the rises in RSV-coded hospitalisation rates for some age groups. A specific limitation of de-identified hospitalisation data is the inability to identify inter-hospital transfers and readmissions for a single episode of illness.

Data linkage studies incorporating clinical and laboratory data and based on birth cohorts can improve the ascertainment and characterisation of RSV-associated hospitalisations.[7,10,13] Such studies, however, have not yet been undertaken in most Australian states and territories, and the analysis of RSV-coded hospitalisations provides an appropriate alternative for assessing the population-level burden of disease in order for informing targeted interventions for groups at particular risk.[6,10,12] Further, validation studies of RSV-associated ICD codes would be valuable for assessing the sensitivity and specificity of our analysis.

Conclusion

Despite its limitations, our study provides comprehensive estimates of RSV-coded hospitalisation rates in Australia. Consistent with previous reports, we found that the highest incidence of RSV-associated hospitalisations was among young children, particularly those less than 6 months old. We also found that adults aged 65 or more are more frequently hospitalised with RSV disease than younger adults, and that Indigenous Australians are hospitalised more than other Australians. Our analysis provides a starting point for designing RSV disease prevention strategies across the age spectrum, and will inform future investigations in this area.

Acknowledgements: This study formed part of Gemma Saravanos' doctoral research at the University of Sydney Children's Hospital at Westmead Clinical School, funded by a University of Sydney Postgraduate Award and supported by the National Centre for Immunisation Research and Surveillance (NCIRS). Nicholas Wood is supported by a National Health and Medical Research Council Career Development Fellowship. We acknowledge the Australian Institute of Health and Welfare for providing the hospitalisation data.

Competing interests: No relevant disclosures.

Received 16 November 2018, accepted 22 February 2019 ■

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Supporting Information

Additional Supporting Information is included with the online version of this article.