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ORIGINAL RESEARCH

# The point prevalence of respiratory syncytial virus in hospital and community-based studies in children from Northern Australia: studies in a 'high-risk' population

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## ABSTRACT:

**Introduction:** Respiratory syncytial virus (RSV) is the leading viral cause of acute lower respiratory infections globally, accounting for high morbidity and mortality burden among children aged less than 5 years. As candidate RSV vaccine trials in pregnant women and infants are underway a greater understanding of RSV epidemiology is now needed, especially in paediatric populations with high rates of acute and chronic respiratory disease. The objective was to identify RSV prevalence in children living in northern Australia, a region with a high respiratory disease burden.

**Methods:** Data were sourced from 11 prospective studies (four hospital and seven community-based) of infants and children with acute and chronic respiratory illnesses, as well as otitis media, conducted between 1996 and 2017 inclusive. The data from northern Australian children in these trials were extracted and, where available and consented, their nasopharyngeal swabs (biobanked at –80ºC) were tested by polymerase chain reaction assays for RSV-A and B, 16 other viruses and atypical respiratory bacterial pathogens.

**Results:** Overall, 1127 children were included. Their median age was 1.8 years (interquartile range 0.5–4.9); 58% were male and 90% Indigenous, with 81% from remote communities. After human rhinoviruses (HRV), RSV was the second most prevalent virus (15%, 95% confidence interval (CI) 13–18). RSV prevalence was greatest amongst children aged less than 2 years hospitalised with bronchiolitis (47%, 95%CI 41.4–52.4), with more than two-thirds with RSV aged less than 6 months. In contrast, the prevalence of RSV was only 1–3.5% in other age groups and settings. In one-third of RSV cases, another respiratory virus was also detected. Individual viruses other than RSV and HRV were uncommon (0–9%).

**Conclusion:** Combined data from 11 hospital and community-based studies of children aged less than 18 years who lived in communities with a high burden of acute and chronic respiratory illness showed that RSV was second only to HRV as the most prevalent virus detected across all settings. RSV was the most frequently detected virus in infants hospitalised with bronchiolitis, including those aged less than 6 months. In contrast, RSV was uncommonly detected in children in community settings. In northern Australia, effective maternal and infant RSV vaccines could substantially reduce RSV bronchiolitis-related hospitalisations, including admissions of Indigenous infants from remote communities.



Keywords:

Australia, children, hospitalisation, morbidity, respiratory, respiratory syncytial virus.


## FULL ARTICLE:

### Introduction

Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory infections (ALRIs) in infants and young children (aged <5 years) and in older people, accounting for a high burden of morbidity and mortality[1]. In infants and young children, RSV-related ALRIs in young children are primarily bronchiolitis and pneumonia[2,3]. Globally, the impact of RSV is large, accounting for 33 million ALRI episodes, 3.2 million hospitalisations and 59 600 in-hospital deaths in those aged less than 5 years[4]. Nevertheless, these data likely underestimate the true disease burden as they do not account for RSV ALRIs in older children[5], diagnostic misclassification from hospital-based coding practices[6], and out-of-hospital RSV-attributable deaths in low- and middle-income countries[4,7]. To reduce RSV disease in young children, several candidate vaccines are currently undergoing development and clinical trials[8,9]. In preparation for introducing RSV vaccines, better epidemiological data on RSV are needed, including clinic attendance for ALRIs and data relevant to high-risk populations, such as Indigenous children[3,9].

In Australia, Indigenous children have a high ALRI burden[10,11], with hospitalisation rates as high as 427 per 1000 in Indigenous infants from the Northern Territory (NT)[12]. Indigenous children, especially from remote communities, are seven times more likely to be hospitalised with pneumonia than non-Indigenous children[13]. Moreover, hospitalised and recurrent ALRIs in the first few years of life are associated with an increased risk of future impaired lung health[10], reduced lung function[14,15] and bronchiectasis[16-18]. Indeed, the authors' previous work among young children aged less than 24 months hospitalised with bronchiolitis showed that Indigenous children have more severe disease (eg longer duration of hospitalisation and supplemental oxygen requirement)[19,20] and poorer clinical outcomes post-hospitalisation (re-hospitalisation for respiratory illnesses within 6 months) than non-Indigenous children[19,20]. Moreover, Indigenous children with prolonged cough 3–4 weeks after hospitalisation for bronchiolitis were at increased risk of future bronchiectasis (odds ratio (OR) 3.0, 95% confidence interval (CI) 1.1–7.0, $p$=0.03)[21].

RSV is the commonest cause of hospitalised ALRIs in Australian children[22]. National as well as population-based data-linkage studies from the states of Western Australia and New South Wales found RSV hospitalisation incidence rates approximately two-to-four times higher in Indigenous than non-Indigenous children[6,13,23]. Similar disparities in RSV-related ALRIs between Indigenous and non-Indigenous children are reported in hospital-based studies from central Australia[24] and the top end of the NT[25]. However, while community-based studies of RSV–ALRI are needed to capture the full spectrum of severity and for cost-effective analyses of future vaccines, few exist in Australia[26-28].

In addition to the limited community-based data on RSV prevalence among Indigenous children in the northern Australian setting, data relating to co-detection of other viruses with RSV in this population are also scarce. Nevertheless, the clinical relevance of single versus multiple virus detections in ALRIs remains unclear, especially as 23–55% of virus detection in community-based surveillance studies are unaccompanied by any symptoms[26,29-31].

To begin addressing this knowledge gap, the authors of this study determined the point prevalence of RSV in northern Australian children by conducting a secondary analysis of 11 hospital and community-based studies of children with ALRIs (principally bronchiolitis), otitis media and chronic pulmonary disorders, which included investigations during periods without acute respiratory illness and involved mainly Indigenous participants[17,20,32-36]. The secondary aim was to describe the prevalence of RSV co-detections with other respiratory viruses.

## Methods

### *Study design and settings*

Data were sourced from 11 prospective studies (Table 1). Eight involved children with either acute or chronic respiratory illnesses[17,20,32-35], one involved children who acted as case-controls in study 4 and the remaining two focused on otitis media[36]. These were conducted in the NT, central Australia, and in the northern Queensland city of Townsville between 1996 and 2017 inclusive. One of the studies is ongoing, and the main results (reporting of primary aims) of seven studies and a substudy have been published already[17,20,32-37].

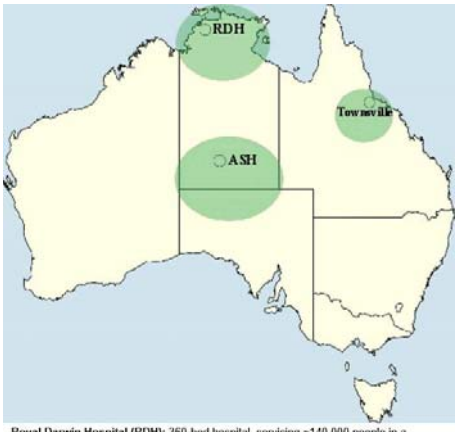
Hospital-based studies included the Royal Darwin Hospital and Alice Springs Hospital in the NT, and the Townsville Hospital in Queensland. The Royal Darwin[38], Alice Springs[39] and Townsville hospitals[40] are 360-, 186- and 580-bed teaching hospitals respectively with each containing the sole specialist paediatric services for their regions (Fig1). Community-based studies were undertaken across the NT, including central Australia, and in Queensland (communities vary according to the original studies, Table 1).

For each study, data custodians provided written approval for data to be accessed. Each original study received ethics approval with informed consent obtained for all nasopharyngeal swabs (NPSs) opting in to approve future analyses.

**Table 1: Description of studies, clinical state and setting**

| Study | Type (reference) | Years | Setting/ clinical state | Region | Number of NPS† | Age group | Brief description |
|---|---|---|---|---|---|---|---|
| 1 | RCT (20) | 2008–11 | Hospital (acute) | NT and Townsville | 96 | <18 months | Infants hospitalised with bronchiolitis were randomised to receive a single 30 mg/kg dose of azithromycin or placebo to improve clinical outcomes (*n*=97). NPS were collected on admission into hospital. |
| 2 | RCT (32) | 2010–13 | Hospital (acute) | NT and Townsville | 184 | ≤24 months | Indigenous infants hospitalised with bronchiolitis were randomised to receive 3 × 30 mg/kg weekly doses of azithromycin or placebo to improve clinical outcomes (*n*=219). NPS were collected on admission into hospital. |
| 3 | Cohort (33) | 2010–11 | Hospital (acute) | NT | 53 | ≤24 months | Infants hospitalised with bronchiolitis were assessed for a severity scoring tool study (*n*=115). NPS were collected on admission to hospital or in the emergency department. Infants in this study could have participated in studies 1 or 2. Inclusion criteria for this analysis were data from children unique to study 3. |
| 4 | Cohort and RCT (17,34) | 2004–10 | Community (acute) | NT and central Australia | 52 | 6 months – 9 years | In the cohort study (ref 15), Indigenous children were reviewed 3-monthly for up to 5 years (*n*=180) to determine the natural history of chronic suppurative lung disease and bronchiectasis. In the RCT (ref 34), children were randomised to receive either weekly azithromycin (30 mg/kg; maximum dose 1 g) or placebo for 12–24 months (*n*=97). Inclusion criteria for this analysis were data from NPS collected at first documented acute exacerbation. |
| 5 | RCT (35) | 2012–17 | Community (acute) | NT | 25 | <18 years | Children with bronchiectasis were randomised to receive either azithromycin (5 mg/kg/day) or amoxicillin-clavulanic acid (45 mg/kg/day) for 21 days for non-severe respiratory exacerbations (Darwin site, *n*=30). Inclusion criteria for this analysis were data from NPS collected at the commencement of an acute exacerbation. |
| 6¶ | Cohort | 2015–17 | Community (non-acute) | NT and central Australia | 92 | <18 years | Indigenous children from studies 1–4 and 8 were reviewed annually for up to 3 years for long-term clinical outcomes (*n*=92), approximately 8 years after completion of the original studies. NPS were collected at their annual clinical review. Inclusion criteria for this analysis were data from NPS collected in year 1. |
| 7¶ | Case-control | 2017 | Community (non-acute) | NT | 156 | <18 years | Indigenous children were from the same community and aged-matched controls for cases from studies 1 and 2 who had not been hospitalised with a respiratory illness (*n*=175). Inclusion criteria for this analysis were data from NPS collected at the single clinical review. |
| 8 | Cohort and RCT (17,34) | 2004–10 | Community (non-acute) | NT and central Australia | 79 | 6 months – 9 years | Indigenous children were clinically reviewed every 3 months for up to 5 years to determine the natural history of chronic suppurative lung disease and bronchiectasis (*n*=180) (ref 17) and/or randomised to receive weekly azithromycin or placebo for 12–24 months (*n*=97) (ref 34). NPS were collected every 3 months at clinical reviews. Inclusion criteria for this analysis were data from NPS collected at the first surveillance. |
| 9¶ | Cohort | 2007 (ongoing) | Hospital (non-acute) | NT | 288 | 3 months – 10 years | Children undergoing flexible bronchoscopy and chest computed tomography scans for suspected bronchiectasis. Children were not acutely unwell at the time of the procedures. There is no sample size for this study, as this is an ongoing opportunistic study. The analysis was censored at 31 December 2017. For children without viral data, aliquots of skim milk tryptone glucose glycerol broth were transported to the Queensland Paediatric Infectious Diseases laboratory in Brisbane for viral polymerase chain reaction assays. Inclusion criteria for this analysis were data from NPS collected at the time of bronchoscopy. |
| 10 | RCT (36) | 1996–2001 | Community (non-acute) | NT | 62 | <24 months | Examining the effect of long-term amoxicillin v placebo for 24 weeks (50 mg/kg/day twice daily) at preventing AOM with perforation in 103 Indigenous infants following their first diagnosed AOM. NPS were collected monthly until 24 months of age. Virus testing was not originally included. As part of a substudy, virus testing was included for NPS collected from children who developed breakthrough episodes of AOM without chronic suppurative otitis media while taking the study medication (ref 37). Inclusion criteria for this analysis were data from NPS with virus testing. |
| 11¶ | Cohort | 2001–04 | Community (non-acute) | NT | 40 | <24 months | Indigenous infants enrolled from birth to determine the impact of the 7-valent pneumococcal conjugate vaccine on any form of otitis media and pneumococcal carriage (*n*=97). Swabs were taken monthly until 24 months of age. Virus testing was not originally included. As part of a substudy, virus testing was undertaken in NPS collected within 21 day priors to an ALRI (ref 37). Inclusion criteria for this analysis were data from NPS with virus testing. |

ALRI, acute lower respiratory infection. AOM, acute otitis media. NPS, nasopharyngeal swab. NT, Northern Territory. RCT, randomised controlled trial.
† Where NPS were available and consent provided; the viruses examined in the specimens are described in the methods section.
¶ Unpublished study.




**Royal Darwin Hospital (RDH):** 360-bed hospital, servicing ~140 000 people in a geographical area of ~400 000 km² (ref 38).
**Alice Springs Hospital (ASH):** 186-bed hospital, servicing ~60 000 people in a geographical area of ~1.6 million km² (ref 39).
**Townsville Hospital:** 580-bed hospital, servicing ~240 000 people in a geographical area of 750 000 km² (ref 40).

**Figure 1: Hospital catchment areas.**

***Geographical region and climate***

The NT consists of two main regions: the tropical north and central Australia. The tropical north has two distinct seasons: the dry (May to October) and wet (November to April) seasons. Central Australia (including the Anangu Pitjantjatjara Yankunytjatjara Lands, of northern South Australia) is a semi-desert region that has a typical four-season pattern. Townsville is a coastal city situated in north-eastern Queensland, with a tropical climate similar to the NT tropical north.

***Study population***

Children aged less than 18 years with recorded NPS virus results, or stored NPS specimens available, and consented for future testing, were eligible for inclusion. No other inclusion criteria were used, as eligibility criteria varied between each of the original studies (Supplementary table 1).

**Supplementary table 1: Summary of included studies**

***Clinical data***

A hierarchical approach was used to identify data from the original studies. For acute hospital or community-based studies[17,20,32-35] where more than one clinical visit was recorded and children were either hospitalised or treated at the local health centre, ALRIs were defined according to previous clinical trials[17,20,32-35]. This was age-adjusted tachypnoea with wheeze or crackles in otherwise previously well infants and young children with bronchiolitis[20,32,33], and any combination of increased cough, dyspnoea, increased sputum volume or purulence, haemoptysis, or new chest examination or radiographic findings in children with known chronic suppurative lung disease or bronchiectasis[17,34,35]. For non-acute studies[17,34], the authors selected the first available healthy visit (ie no acute respiratory illness) with available virus testing data. For the otitis media-related studies[36], the authors selected the first clinical visit where virus testing results were available.

Data custodians extracted de-identified data using a pre-specified list of variables (as available), including age, ethnicity, birth history, breastfeeding, family history, exposure to tobacco (during pregnancy and in the household), chronic pulmonary disorders, other co-existing illnesses (eg pyoderma, otitis media, rheumatic heart disease, faltering growth), setting (hospital/community), viruses, season (dry/wet season in the tropics of the NT and Queensland) and region (urban/remote). As per the authors' previous studies, remoteness was defined as more than 100 km from a tertiary hospital[20,32,33,41]. Before merging data sets, variables were recoded to ensure identical coding between studies.

***Virus data***

In all studies, an NPS was collected and placed into skim milk tryptone glucose glycerol broth (STGGB), and stored at –80°C using standardised procedures at the Menzies School of Health Research[42]. Where virus result data were not already available, an aliquot of the stored STGGB was submitted by courier to the Queensland Paediatric Infectious Diseases laboratory in Brisbane, which had acted as the reference laboratory for all studies. The polymerase chain reaction assays used have been reported previously[20,32,35] and included testing for RSV (A and B), HRV, human adenovirus, parainfluenza (1, 2, 3), influenza virus (A and B), human metapneumovirus, human enterovirus, human coronaviruses (NL63, OC43, 229E, HKU1), human bocavirus and human polyomaviruses (KI, WU).

***Statistical analysis***

Descriptive analyses were conducted using Stata v14 (StataCorp; http://stata.com). As data were not normally distributed, non-parametric measures were used. Patient characteristics are presented as numbers and percentages, median and interquartile ranges (IQR: 25th – 75th percentile). As this was an opportunistic study of available data, sample size calculation was not undertaken.

***Ethics approval***

The Human Research Ethics Committee of the NT Department of

Health and Menzies School of Health Research approved the current study (HREC-17-3025).

## Results

The demographic and clinical data for the 1127 children included in this study are summarised in Table 2. More children were from hospital studies (*n*=621) than community-based studies (*n*=506). The median age of children was 1.8 years (IQR 0.5–4.9); 58% were males, 90% were Indigenous, of whom 81% were from remote communities, and 57% had at least one co-existing illness. Exposure to tobacco smoke varied between studies and settings; however overall, it was very high during pregnancy (54%) and at home (73%). Overall, 77% of NPS collected from children during 'well child' (ie non-acute respiratory) visits and otitis media studies were conducted during the dry season, due to lack of accessibility to remote communities at other times of the year.

**Table 2: Baseline characteristics by setting and condition**

| Characteristic† | Hospital-based studies (*n*=621) | | Community-based studies (*n*=506) | | | All studies |
|---|---|---|---|---|---|---|
| | Bronchiolitis (*n*=333) (% or median (IQR)) | Non-acute respiratory (*n*=288) (% or median (IQR)) | Acute respiratory (*n*=77) (% or median (IQR)) | Non-acute respiratory (*n*=327) (% or median (IQR)) | Otitis media (*n*=102) (% or median (IQR)) | Total (*n*=1127) (% or median (IQR)) |
| Age (years) | 0.4 (0.2–0.8) | 2.4 (1.7–3.9) | 3.4 (1.9–5.4) | 5.8 (4.0–8.2) | 0.3 (0.3–0.5) | 1.8 (0.5–4.9) |
| Age group (months) | | | | | | |
| <6 | 217/333 (65) | 3/288 (1) | 0/77 (0) | 0/327 (0) | 84/102 (82) | 304/1127 (27) |
| 6–12 | 61/333 (18) | 12/288 (4) | 1/77 (1) | 0/327 (0) | 11/102 (11) | 85/1127 (8) |
| 12–24 | 55/333 (17) | 88/288 (31) | 18/77 (23) | 27/327 (8) | 7/102 (7) | 195/1127 (17) |
| >24 | 0/333 (0) | 185/288 (64) | 58/77 (75) | 300/327 (92) | 0/102 (0) | 543/1127 (48) |
| Male | 208 (63) | 158 (55) | 45 (58) | 185 (57) | 56 (55) | 652 (58) |
| Indigenous | 272 (82) | 250 (87) | 63 (82) | 327 (100) | 102 (100) | 1014 (90) |
| Gestational age (weeks) | 38 (36–40) | 38 (35–39) | 38 (34–39) | 38 (36–39) | N/A | 38 (36-39) |
| Pre-term (<37 weeks) | 83/314 (26) | 88/257 (34) | 31/71 (44) | 90/301 (29) | N/A | 292/943 (31) |
| Birth weight (kg) | 3.0 (2.5–3.4) | 2.8 (2.1–3.2) | 2.7 (2.2–3.4) | 2.9 (2.5–3.3) | 2.9 (2.6–3.3) | 2.9 (2.4–3.3) |
| Low birth weight (<2.5 kg) | 77 (23) | 96/252 (38) | 31/72 (43) | 86/316 (27) | 23 (23) | 313/1075 (29) |
| Exclusively breastfed (≤6 months) | 236/327 (72) | N/A | 60/64 (94) | 277/307 (90) | 7/101 (7) | 580/799 (73) |
| Mother smoked during pregnancy | 164/327 (50) | N/A | 31/71 (44) | 167/275 (61) | 15/26 (58) | 377/699 (54) |
| Smoke exposure (household) | 187/330 (57) | 150/190 (79) | 45/71 (63) | 275/309 (89) | 12/19 (63) | 699/919 (73) |
| Region (remote) | 216 (65) | 237 (82) | 47 (61) | 310 (95) | 102 (100) | 912 (81) |
| Wet season visit | 217 (65) | 168 (58) | 45 (58) | 60 (18) | 38 (37) | 528 (47) |
| Dry season visit | 116 (35) | 120 (42) | 32 (42) | 267 (82) | 64 (63) | 599 (53) |
| Family history | | | | | | |
| Gestational diabetes (mother)¶ | 38/330 (12) | N/A | N/A | 46/236 (19) | N/A | 84/566 (15) |
| Atopy (asthma or eczema)¶ | 173/332 (52) | N/A | N/A | 92/246 (37) | N/A | 265/578 (46) |
| Respiratory disease¶ | 58/331 (18) | N/A | N/A | 32/246 (13) | N/A | 90/577 (16) |
| Cardiac disease¶ | 129/329 (39) | N/A | N/A | 121/246 (49) | N/A | 250/575 (43) |
| Co-morbidity | | | | | | |
| Acute otitis media | 66 (20) | N/A | 9 (12) | 15 (5) | 34 (33) | 124/839 (15) |
| Any suppurative otitis media§ | 0 (0) | N/A | 1/25 (4) | 23/171 (13) | 7 (7) | 31/298 (10) |
| Skin infection present | 79 (24) | N/A | N/A | 266 (81) | 32/52 (62) | 377/712 (53) |
| Rheumatic heart disease | 0 (0) | N/A | N/A | 5/5 (100) | N/A | 5/5 (100) |
| Faltering growth | 0 (0) | N/A | N/A | 0 (0) | 1/51 (2) | 1/51 (2) |
| Any co-morbidity | 130 (39) | N/A | 3/25 (12) | 212/248 (85) | 61/102 (60) | 406/708 (57) |

† Missing data: **Gestational age:** not asked, *n*=121; missing, *n*=63. **Pre-term:** missing, *n*=102. **Birth weight:** missing, *n*=52. **Low birth weight:** missing, *n*=52. **Exclusively breastfed (≤6 months):** not asked, *n*=288; missing, *n*=40. **Mother smoked during pregnancy:** not asked, *n*=288; missing, *n*=6. **Smoke exposure (household):** not asked, *n*=15; missing, *n*=193. **Family history** including gestational diabetes, atopy, respiratory disease and cardiac disease: not asked, *n*=546. **Gestational diabetes (mother):** not sure, *n*=5. **Atopy:** not sure, *n*=2. **Respiratory disease:** not sure, *n*=2. **Any otitis media:** not asked, *n*=288. **Any suppurative otitis media:** not asked, *n*=621. **Skin infection present:** not asked, *n*=50; missing, *n*=365. **Rheumatic heart disease:** not asked, *n*=621. **Faltering growth:** not asked, *n*=1025; missing, *n*=51.
¶ Questions only asked in studies 1–3 and 6, 7.
§ Includes acute and chronic suppurative condition with active discharge.
IQR, interquartile range. N/A, not available.

### *Prevalence of respiratory syncytial virus by setting, study type and condition*

The overall point prevalence of RSV was 173/1127 or 15% (95%CI 13–18). RSV grouped by setting and condition are summarised in Table 3. The point prevalence of RSV was highest in hospital-based studies of bronchiolitis in children aged less than 24 months (156/333; 47%, 95%CI 41–52) and of these 107/156 (69%) were infants aged less than 6 months (95%CI 61–76). In contrast, RSV was detected in only 2.1% (17/794, 95%CI 1.3–3.4) of children across other clinical settings. This included children who were clinically stable and undergoing an elective bronchoscopy for chronic respiratory symptoms (study 9). In community-based studies of otitis media (studies 10 and 11), those undergoing a 'well child' outpatient review after hospitalisation for bronchiolitis or who were part of the case-control study (studies 6 and 7), and children with non-severe (non-hospitalised), acute pulmonary exacerbations of chronic suppurative lung disease or bronchiectasis (studies 4, 5 and 8), the prevalence of RSV was 1.4% (7/506, 95%CI 0.6–2.8).

**Table 3: Prevalence of respiratory syncytial virus by setting and condition**

| Setting | Studies† included | Total number of children | Number of children with RSV | Point prevalence (% ((95%CI)) |
|---|---|---|---|---|
| Hospital-based study focus | | | | |
| Bronchiolitis | 1–3 | 333 | 156 | 47 (41.4–52.4) |
| Non-acute respiratory¶ | 9 | 288 | 10 | 3.5 (1.7–6.3) |
| Community-based study focus | | | | |
| Acute respiratory§ | 4, 5 | 77 | 2 | 2.6 (0.3–9.1) |
| Non-acute respiratory‡ | 6–8 | 327 | 3 | 1 (0.2–2.7) |
| Acute otitis media | 10, 11 | 102 | 2 | 2 (0.2–6.9) |

† Study numbers from Table 1.
¶ Chronic respiratory illness without acute respiratory symptoms.
§ Acute exacerbation in those with chronic respiratory illness.
‡ Children with and without chronic respiratory illness, and who did not have acute respiratory symptoms.
CI, confidence interval. RSV, respiratory syncytial virus.

***Other viruses, including RSV co-detections***

Detection of other respiratory viruses in NPS samples varied according to setting and type of illness (Table 4). HRV was the virus detected most commonly in community-based studies, with highest detections in otitis media (prevalence 57%, 95%CI 47–67). The prevalence range for other viruses was 0–9%. At least one virus was detected in 706 (63%, 95%CI 59–68) children with 227 (20%, 95%CI 18–23) having two or more viruses present. Of the 173 RSV detections, 56 (33%, 95%CI 26–40) involved co-detection with other viruses and where HRV co-detection was the most common (27/173, 16%).

**Table 4: Distribution of respiratory viruses and atypical bacterial pathogens by setting and condition**

| Virus (detected alone or in combination)† | Hospital (*n*=621) | | Community (*n*=506) | | | Total (*n*=1127) ((*n* (%)) |
|---|---|---|---|---|---|---|
| | Bronchiolitis (*n*=333) (*n*(%)) | Non-acute respiratory (*n*=288) (*n* (%)) | Acute respiratory (*n*=77) (*n* (%)) | Non-acute respiratory (*n*=327) (*n* (%)) | Otitis media (*n*=102) ((*n* (%)) | |
| HRV | 82 (25) | 90 (31) | 35 (45) | 93 (28) | 58 (57) | 358 (32) |
| RSV | 156 (47) | 10 (3.5) | 2 (3) | 3 (0.9) | 2 (2) | 173 (15) |
| WUPyV | 21 (6) | 24/287 (8) | 9 (12) | 26 (8) | 18 (18) | 98/1126 (9) |
| HAdV | 21 (6) | 27 (9) | 10 (13) | 24 (7) | 6 (6) | 88 (8) |
| HCoV | 9 (3) | 18 (6) | 5 (6) | 27 (8) | 4 (4) | 63 (6) |
| HEV | 5 (2) | 16/176 (9) | 3 (4) | 11 (3) | 6 (6) | 41/1015 (4) |
| Parafflu | 10 (3) | 6 (2) | 8 (10) | 13 (4) | 4 (4) | 41 (4) |
| HBoV-1 | 10 (3) | 13/287 (4.5) | 1 (1.3) | 8 (2.5) | 10 (10) | 42/1126 (4) |
| KIPyV | 7 (2) | 12/287 (4) | 2 (3) | 6 (2) | 3 (3) | 30/1126 (3) |
| Influenza | 13 (4) | 4 (1.4) | 3 (4) | 2 (0.6) | 2 (2) | 24 (2) |
| hMPV | 8 (2.4) | 2 (0.7) | 2 (3) | 3 (0.9) | 1 (1) | 16 (1.4) |
| No virus | 75 (23) | 138 (48) | 19 (25) | 159 (49) | 27 (26) | 418 (37) |
| Any virus | 257 (77) | 148 (51) | 58 (75) | 168 (51) | 75 (74) | 706 (63) |
| ≥2 viruses | 79 (24) | 55 (19) | 20 (26) | 40 (12) | 33 (32) | 227 (20) |
| RSV with other viruses | | | | | | |
| RSV+HRV | 24 (7) | 2 (0.7) | 0 (0) | 1 (0.3) | 0 (0) | 27 (2.3) |
| RSV+WU | 9 (3) | 1 (0.4) | 0 (0) | 2 (0.6) | 0 (0) | 12 (1) |
| RSV+HAdV | 7 (2) | 0 (0) | 1 (1.3) | 0 (0) | 0 (0) | 8 (0.7) |
| RSV+HCoV | 3 (0.9) | 1 (0.4) | 0 (0) | 0 (0) | 0 (0) | 4 (0.4) |
| RSV+any virus¶ | 48 (14) | 4 (1.4) | 2 (2.6) | 2 (0.6) | 0 (0) | 56 (5) |

† Missing data: WUPyV: *n*=1. HEV: *n*=112. HBoV-1: *n*=1. KIPyV: *n*=1.
¶ Respiratory syncytial virus in combination with all possible other viruses.
HAdV, human adenovirus. HBoV, human bocavirus. HCoV, human coronaviruses (NL63, OC43, 229E, HKU1). HEV, human enterovirus. hMPV, human metapneumovirus. HRV, human rhinovirus. Influenza, influenza (A and B). KIPV, KI human polyomavirus. Paraflu, parainfluenza virus (1,2,3). RSV, respiratory syncytial virus. WUPyV, WU human polyomavirus.

## Discussion

This study provides RSV prevalence data for northern Australia derived from 11 prospective hospital- and community-based studies involving 1127 subjects in a setting where children are at high risk of acute and chronic respiratory illnesses[2,10,11]. While limited, it begins to address recommendations made by WHO to gather more information on local RSV epidemiology and disease burden in disadvantaged populations while awaiting future licensed RSV vaccines[43]. It was found that RSV was second only to HRV with an overall prevalence of 15% in the study region. RSV point prevalence of 47% was highest in children aged less than 24 months hospitalised with bronchiolitis, whereas prevalence in community-based studies was only 1.4% in children with either otitis media or in older children aged up to 18 years with or without ALRI respiratory symptoms. In contrast, HRV was common across all clinical settings and ages, including having a point prevalence of 30% in clinically stable children without either ALRI symptoms or otitis media. Finding HRV in asymptomatic children is not surprising as reported in several other studies, such as that described by Advani et al, where HRV was detected in near-equal numbers in hospitalised children with respiratory symptoms (41/148, 27.7%) and those without (34/158, 21.5%)[29]. Viruses other than RSV and HRV were uncommon, with point prevalence rates less than 10%. Co-detection of RSV with other respiratory viruses was 33% across all clinical settings.

The present study data are consistent with other hospital-based ALRI studies that also include Indigenous infants with bronchiolitis, where RSV was detected in 41–83% of patients[4,44,45]. In the present study, 31% of children hospitalised with RSV-related bronchiolitis were aged 6–24 months, when maternal RSV vaccination may no longer be protective,[46], emphasising the importance of also developing active immunisation programs for young infants. In contrast to hospital-based studies, detection of RSV was low in the seven community-based studies (1.4% of children overall; 2.2% in those with and 0.9% without an acute respiratory illness).

It was not possible to calculate the population-based incidence of RSV-ALRI in our studies. In the Australian state of New South Wales, a data-linkage study determined RSV-hospitalisation incidence at 4.9 (11.0 in Indigenous children) per 1000 child years

in those aged less than 5 years (peak incidence at age 0–3 months was 25.6 per 100 child years (58.0 in Indigenous children)[23]. Differences in the incidence of RSV is likely multi-factorial, and influenced by age, disease states, timing (season) and duration of surveillance[4]. Without active surveillance in the study region, the true incidence and disease burden of RSV are unknown, although a higher incidence of RSV-related ALRI in community studies is expected, due to the high burden of respiratory disease among Indigenous people compared to non-Indigenous people[10,11]. The most likely reasons for lower-than-expected rates of RSV detection in community studies include sampling from comparatively older children, and lack of acute respiratory symptoms[26,27]. Most of these children were seen in the dry season (May to October), rather than during the peak respiratory period in the wet season (November to April)[25,47], and this is also likely be a contributing factor to differences in RSV detection.

Co-detection of other viruses with RSV was relatively common, occurring in one-third of cases. The most common co-detected virus was HRV, followed by the DNA viruses, human polyomavirus WU and adenovirus. The clinical relevance of virus co-detections in children with an ALRI remains uncertain[31]. In a recent community-based birth cohort study of young Australian children, single infections with RSV and human metapneumovirus were found to be most strongly associated with symptomatic ALRI; this study observed that new virus co-detections were also associated with a significantly increased attributed risk of symptoms[26].

The present study has several limitations. No prospective longitudinal studies of RSV in at-risk Indigenous children have been reported in the study region. An Australian urban community-based study of healthy infants followed prospectively from birth to age 2 years[28] observed RSV infections were uncommon until after age 6 months, following which there was a steady increase in RSV detections. By age 2 years, 58% of the cohort had at least one documented RSV infection. Similar findings were reported in a birth cohort from semi-rural villages in Vietnam[48] and in Kenya[49]. Nevertheless, these studies may not represent children in the study region who are at high risk of severe ALRIs. This was an opportunistic secondary analysis of data from studies not designed specifically for determining RSV epidemiology. The data had limited seasonal coverage, thus not fully capturing annual outbreaks of RSV. Ninety percent of children were Indigenous, 81% of whom were from remote communities. A prospective, community-based study of non-Indigenous children in the region would be informative. A more comprehensive study is indicated to more accurately identify risk factors for RSV infection and priority target groups for future RSV vaccination. Lastly, the authors were unable to report mortality as these data were not collected.

### Conclusion

This study combines hospital- and community-based studies of children aged less than 18 years who live in settings with a high burden of acute and chronic respiratory illness. The authors found RSV was second only to HRV as the most prevalent virus detected across all settings. RSV was the most frequently detected virus in infants hospitalised with bronchiolitis, including those aged less than 6 months. In contrast, RSV was uncommonly detected in children in community settings. While other respiratory viruses were often co-detected with RSV, their contribution to the child's clinical state is uncertain. Ongoing surveillance of RSV[50] in hospital and community settings is needed to further understand its epidemiology, particularly in at-risk populations (ie Indigenous) within Australia to guide prevention strategies and future RSV vaccine schedules. The young age of most RSV-positive hospitalised cases suggests a potential benefit from future maternal RSV vaccine programs.

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