Interactive effects of age and respiratory virus on severe lower respiratory infection

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Abstract

We investigated risk factors for severe acute lower respiratory infections (ALRI) among hospitalised children <2 years, with a focus on the interactions between virus and age. Statistical interactions between age and respiratory syncytial virus (RSV), influenza, adenovirus (ADV) and rhinovirus on the risk of ALRI outcomes were investigated. Of 1780 hospitalisations, 228 (12.8%) were admitted to the intensive care unit (ICU). The median (range) length of stay (LOS) in hospital was 3 (1–27) days. An increase of 1 month of age was associated with a decreased risk of ICU admission (rate ratio (RR) 0.94; 95% confidence intervals (CI) 0.91–0.98) and with a decrease in LOS (RR 0.96; 95% CI 0.95–0.97). Associations between RSV, influenza, ADV positivity and ICU admission and LOS were significantly modified by age. Children <5 months old were at the highest risk from RSV-associated severe outcomes, while children >8 months were at greater risk from influenza-associated ICU admissions and long hospital stay. Children with ADV had increased LOS across all ages. In the first 2 years of life, the effects of different viruses on ALRI severity varies with age. Our findings help to identify specific ages that would most benefit from virus-specific interventions such as vaccines and antivirals.

Introduction

Acute lower respiratory infections (ALRI) are major causes of morbidity and mortality among children worldwide [1]. The most frequently identified pathogen among young hospitalised children with ALRI is respiratory syncytial virus (RSV) [2, 3]; however, adenovirus (ADV), rhinovirus and influenza are also common aetiological agents [4, 5]. The greatest burden of ALRI exists in low-and middle-income countries; but ALRIs are also a significant health issue in high-income countries [1, 6]. Of children hospitalised with ALRI in high-income countries, 5–20% develop very severe disease necessitating intensive care unit admission (ICU) or a prolonged hospital length of stay (LOS) [5, 7–9].

The determinants of severe ALRI among children are complex. Studies show that a combination of host and viral factors influence disease severity, yet the relative impact of each and the role of specific virus types in determining severity remains unclear [10–12]. The majority of studies investigating risk factors for severe ALRI have focused on the 'individual or main effects' of a host factor or of a particular virus. Young age at infection has been frequently found to be the most significant risk factor for severe ALRI [3, 7, 8, 13–15], as it is associated with both host and viral features. For example, young age affects airway size and also defines the naivety of a child's immune system. However, by simply classifying young age as a risk factor for severity and not investigating the interactions between age and virus infection, the impact of specific virus types remains unclear. Such knowledge is necessary for clinical and public health interventions, such as antiviral agents and vaccines, which are virus specific.

In the current study, we aimed to identify risk factors of severe ALRI as defined by the risk of ICU admission and hospital LOS among hospitalised children <2 years. Our intention was to enable a better understanding of the relationship between age and specific respiratory viruses on the risk of severe ALRI outcomes among children.

Methods

Settings and study design

This study was undertaken as part of the Southern Hemisphere Influenza Vaccine Effectiveness Research and Surveillance (SHIVERS) project, which tracked hospitalisations

for acute respiratory illness at the two public hospitals serving the central, eastern and southern Auckland region in New Zealand from 2012 to 2015. In New Zealand, all acute paediatric inpatient care is provided by public hospitals. The regions are predominantly urban and include approximately 53 658 children aged <2 years, of which 25% are Pacific, 27% Asian, 15% Māori (New Zealand's indigenous population) and 33% are of European or other ethnicities [16]. Further information on the SHIVERS surveillance platform, including study setting, patient enrolment and data collection is described elsewhere [17, 18].

The SHIVERS study enrolled all patients who met the World Health Organization (WHO) severe acute respiratory infection (SARI) case definition – reported fever and cough with onset in preceding 7 days (in 2012) or preceding 10 days (2013–2015). From 2013 to 2015, SHIVERS enrolment was extended to include a systematic random sample of children hospitalised with an acute respiratory complaint that did not meet the SARI case definition (i.e. cough and/or fever but not both with 10 days). Study nurses completed detailed case report forms on all enrolled patients and collected nasopharyngeal swab/aspirates. Clinician-ordered laboratory investigations were added to the study dataset after validation of the respiratory virus PCR assay used at each hospital. Only results from assays with a sensitivity >80% and a specificity >95% were included in the study dataset. SHIVERS study data were collected and managed using REDCap electronic data capture tools [19]. Ethical approval for the SHIVERS study was obtained from the New Zealand Health and Disabilities Ethics Committee (NTX/11/11/102).

Laboratory methods

Specimens were tested for respiratory viruses (influenza, RSV, parainfluenza virus 1–3, human metapneumovirus, rhinovirus and ADV) using the United States Centers for Disease Control and Prevention real-time RT-PCR protocol [20, 21] or the AusDiagnostic PCR protocol and real-time PCR assay at hospital laboratories [22]. A sample of viral-positive specimens were further sub-typed. Further information on laboratory methods and sensitivity and specificity of assays are provided in the Supplementary material (Text S1, Table S1).

Study population

The current analysis was limited to consented children <2 years old meeting SARI and non-SARI respiratory case definitions, who had an overnight admission with a primary or secondary discharge diagnosis of an ALRI (ICD-10 codes J09–J22, Supplementary Text S2) during winter seasons (April through October) between 2012 and 2015. Non-SARI respiratory children who had cough and/or fever onset >10 days before admission were excluded to ensure only children with acute symptoms were investigated. For children with a repeat hospitalisation within 14 days, only the first hospitalisation event was included. Respiratory viruses of interest were influenza, RSV, ADV and rhinovirus. We excluded children who were not tested for all four viruses. Comparisons of tested and non-tested children are provided in the Supplementary material (Table S2). No significant differences in demographics and outcome measures were found between the two groups.

Measurements and covariates

Patient demographics and clinical histories collected via SHIVERS surveillance were validated and supplemented with data from the NZ Ministry of Health National Data Collections [23]. Our two measures of disease severity were ICU admission and hospital LOS in days. The primary exposures were age in months and type of respiratory virus identified (influenza, RSV, rhinovirus and ADV). Other exposures that were considered relevant, due to being associated with disease severity and/or with age or virus positivity included patient sex, ethnicity, socio-economic status (SES), influenza vaccination status, viral co-infection, SARI case definition and the presence of other underlying health conditions. SES was quantified using a small area-level measure of household deprivation derived from the national census (NZDep2013) [24]. Underlying health conditions were grouped into three broad categories: preterm birth and/or low birth weight (<37 weeks of gestational age and/or birth weight <2500 g), pre-existing respiratory conditions (asthma, other lung conditions and/or a prior respiratory hospitalisation before the preceding 14 days) or other underlying conditions (congenital heart conditions, immunodeficiency, renal or hepatic disease). Further details on sourcing and defining exposures are available in the Supplementary material (Table S3).

Statistical methods

ICU admission was modelled as a function of exposure variables using logistic regression with risk ratios (RR) derived by applying a substitution method [25, 26]. Hospital LOS was modelled as a continuous outcome using negative binomial regression. Statistical interactions between child age in months and each respiratory virus were assessed on the multiplicative scale by including main effects and interaction terms in regression models. It is recommended to measure biological interactions on both additive and multiplicative scales for dichotomous outcomes [27, 28]. Hence, for ICU admission, we tested for statistically significant interactions on an additive scale by calculating the relative excess risk due to interaction with standard errors [29].

Crude associations were estimated for all exposure variables, in addition to interactions between each virus and age in months. Demographics, influenza vaccination status and underlying conditions were examined as potential confounders of age and virus associations with the outcomes. Multivariable models included exposures and age–virus interaction terms that were statistically significant at $P < 0.05$ in crude models.

Influenza vaccination was excluded from multivariable models due to the very low number of children with a current vaccination ($n = 76/1780$; 4.3%) and the high number of children with missing vaccination status ($n = 155/1780$; 8.7%). Sensitivity analyses for influenza vaccination demonstrated no effect on age or viral associations (Supplementary Table S4) regardless of approach. All analyses were conducted in Stata 14.0 statistical software (Stata Corporation, College Station, TX, USA).

Results

During four winter respiratory seasons, there were 4360 ALRI hospitalisations among children aged <2 years, of which 1780 met study inclusion criteria (Fig. 1). Among the 1780 ALRI hospitalisations, 228 (12.8%) were admitted to ICU (Table 1). The proportion of children admitted to ICU ranged from 8% to
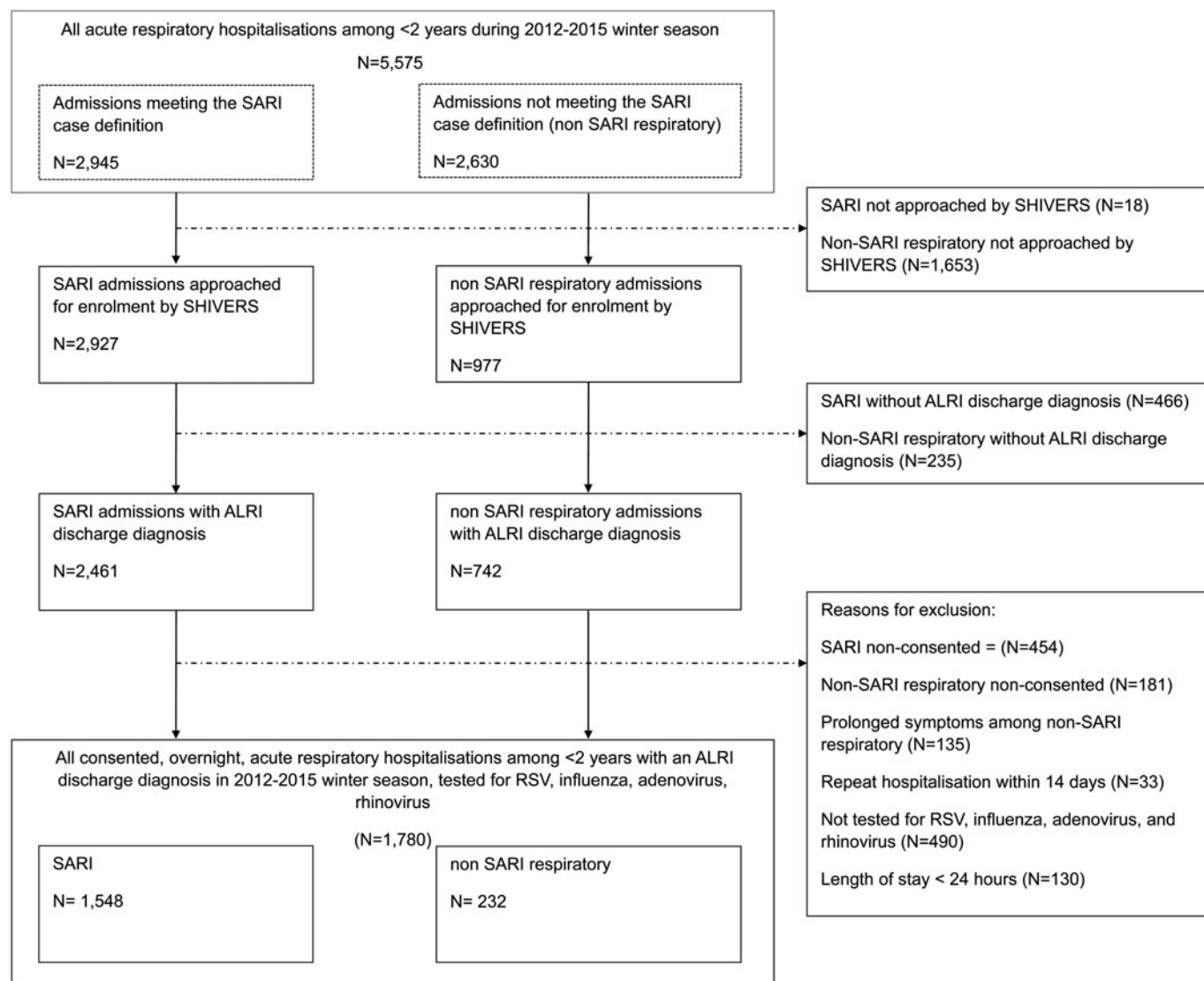
Fig. 1. Study population selection among hospitalisations in children aged <2 years with an acute lower respiratory tract infection (ALRI), 2012–2015 winter seasons, Auckland, New Zealand.

15% per year over the 4-year study period. The median days in hospital was 3 (range: 1–27), with 393 (22.1%) hospitalisations in the upper quartile of 4 or more days LOS (Supplementary Fig. S1). Demographics, clinical characteristics and viral results among all hospitalised cases, ICU admissions and those with ≥4 days in hospital are presented in Table 1.

Children admitted to ICU were younger (median age: ICU = 4 months *vs.* general ward = 7 months, $P < 0.0001$) and more likely to have an underlying condition (ICU = 93% *vs.* general ward 62%, $P < 0.0001$) than those on the general ward. Children admitted to ICU were also less likely to be of Pacific ethnicity (ICU = 42% *vs.* general ward 50%, $P < 0.0001$) or from the lowest SES (ICU = 52% *vs.* general ward 64%, $P < 0.0001$).

Children with ≥4 days LOS were younger (median age: 6 months for LOS ≥4 *vs.* 7 months for LOS <4, $P < 0.0001$) and more likely to have any underlying condition (LOS ≥4 = 84% *vs.* LOS <4 = 62%, $P < 0.0001$) than those with shorter LOS. There was no significant difference in LOS by ethnicity or SES.

Of the 1780 ALRI hospitalisations, 1479 (83.1%) were positive for at least one respiratory virus, of which 855 (48.0%) were RSV; 332 (18.7%) hospitalisations were positive for more than one respiratory virus. Crude associations for all exposures including age and viral interactions are included in the Supplementary material (Table S5).

ICU admissions: main and interactive effects of age and virus

Age had a significant main effect, with decreased ICU admission risk for every month increase in age (RR 0.95; 95% confidence interval (CI) 0.92–0.99) (Table 2) after adjusting for ethnicity, SES, single and co-infection with virus and underlying conditions. The risk of ICU admission was higher for children born prematurely and/or with a low birth weight (RR 1.78; 95% CI 1.36–2.33), those with a pre-existing respiratory conditions (RR 1.80; 95% CI 1.40–2.33) and/or those with cardiovascular, immune, renal or hepatic conditions (RR 2.05; 95% CI 1.36–3.09)

Table 1. Demographic and clinical characteristics of children aged <2 years hospitalised with acute lower respiratory infections in the two main public hospitals within Auckland, New Zealand 2012–2015

	All ALRI hospitalisations		ICU admission		Hospital LOS ≥4	
	n	(Column %)	*n*	(Column %)	*n*	(Column %)
Total	1780	(100.0)	228	(100.0)	393	(100.0)
Age						
0–2 months	352	(19.8)	81	(35.5)	115	(29.3)
3–5 months	368	(20.7)	44	(19.3)	76	(19.3)
6–11 months	601	(33.8)	53	(23.2)	122	(31.0)
12–23 months	459	(25.8)	50	(21.9)	80	(20.4)
Ethnicity						
Maori	513	(28.8)	81	(35.5)	124	(31.6)
Pacific	896	(50.3)	95	(41.7)	185	(47.1)
European, Asian and other	371	(20.8)	52	(22.8)	84	(21.4)
Sex						
Male	1082	(60.8)	146	(64.0)	249	(63.4)
Household deprivation[a]						
NZ dep 1–6 (least deprived)	359	(20.2)	60	(26.3)	87	(22.1)
NZ dep 7–8	282	(15.8)	49	(21.5)	62	(15.8)
NZ dep 9–10 (most deprived)	1139	(63.9)	119	(52.2)	243	(61.8)
Discharge diagnosis						
Bronchiolitis	928	(52.1)	130	(57.0)	196	(49.9)
Pneumonia	770	(43.3)	88	(38.6)	182	(46.3)
Other ALRI[b]	82	(4.6)	10	(4.4)	15	(3.8)
Influenza vaccine						
Influenza vaccine within 12 months	76	(4.3)	12	(5.3)	21	(5.3)
No influenza vaccine	1549	(87.0)	198	(86.8)	341	(86.8)
Unknown vaccination status	155	(8.7)	18	(7.9)	31	(7.9)
Treatment						
Influenza antiviral medication	0	(0.0)	0	(0.0)	0	(0.0)
Underlying conditions						
Respiratory (asthma, other lung disease and/or prior respiratory hospitalisation)	670	(37.6)	115	(50.4)	186	(47.3)
Other underlying conditions (congenital cardiovascular, immune, renal, hepatic)	96	(5.4)	26	(11.4)	42	(10.7)
Premature birth and/or low birth weight[c]	341	(19.2)	71	(31.1)	101	(25.7)
Viral Infection						
Influenza	230	(12.9)	19	(8.3)	46	(11.7)
Influenza A(H1N1)pdm09	68	(3.8)	7	(3.1)	15	(3.8)
Influenza A(H3N2)	97	(5.4)	7	(3.1)	18	(4.6)
Influenza B	65	(3.7)	5	(2.2)	13	(3.3)
RSV	855	(48.0)	102	(44.7)	210	(53.4)
RSV-A	316	(17.8)	24	(10.5)	65	(16.5)
RSV-B	264	(14.8)	21	(9.2)	53	(13.5)
Non-subtyped	275	(15.4)	57	(25.0)	92	(23.4)
Rhinovirus	463	(26.0)	60	(26.3)	85	(21.6)

(*Continued*)

Table 1. (Continued.)

	All ALRI hospitalisations		ICU admission		Hospital LOS ≥4	
	n	(Column %)	n	(Column %)	n	(Column %)
Adenovirus	301	(16.9)	47	(20.6)	83	(21.1)
Adenovirus-1	15	(0.8)	3	(1.3)	3	(0.8)
Adenovirus-7	17	(1.0)	5	(2.2)	12	(3.1)
Adenovirus other	17	(1.0)	3	(1.3)	5	(1.3)
Non-subtyped	252	(14.2)	36	(15.8)	63	(16.0)
Multiple viruses	332	(18.7)	41	(18.0)	88	(22.4)

ICU, intensive care unit; LOS, hospital length of stay; ALRI, acute lower respiratory infection.
[a]Small area-level measure of household deprivation derived from variables collected at the 2013 national census (NZDep2013 Index of Deprivation).
[b]Other ALRI includes unspecified acute lower respiratory infection (ICD-10 J22).
[c]Preterm birth defined as <37 weeks of gestational age. Low birth weight defined as birth weight <2500 g.

Table 2. Association of intensive care unit admission and longer hospital stay with age and virus type among children aged <2 years hospitalised with acute lower respiratory infection in Auckland, New Zealand 2012–2015

Adjusted Models	ICU admission			Prolonged hospital stay		
	RR	(95% CI)	P-value	RR	(95% CI)	P-value
Main effects						
Demographics						
Age in months	0.95	(0.92–0.99)	0.016	0.97	(0.96–0.97)	0.000
European/ Asian/ Other	1.00	(ref)		1.00	(ref)	
Maori	1.34	(0.95–1.89)	0.095	1.04	(0.94–1.16)	0.467
Pacific	1.01	(0.70–1.45)	0.957	0.99	(0.89–1.10)	0.857
NZDep2013 1–6[a] (Least deprived)	0.85	(0.59–1.22)	0.388	1.04	(0.92–1.17)	0.539
NZDep2013 7–8	1.00	(ref)		1.00	(ref)	
NZDep2013 9–10 (Most deprived)	0.53	(0.38–0.72)	0.000	0.95	(0.86–1.05)	0.307
Underlying conditions						
Respiratory (asthma, other lung disease, and/or prior respiratory hospitalisation)	1.80	(1.40–2.33)	0.000	1.20	(1.11–1.30)	0.000
Other underlying conditions (Congenital cardiovascular, immune, renal, hepatic)	2.05	(1.36–3.09)	0.001	1.68	(1.39–2.04)	0.000
Premature birth and/or low birth weight[b]	1.78	(1.36–2.33)	0.000	1.15	(1.05–1.27)	0.002
Viral Infection						
Influenza	0.33	(0.12–0.89)	0.028	0.78	(0.64–0.95)	0.014
RSV	1.55	(1.00–2.39)	0.051	1.02	(0.94–1.11)	0.591
Rhinovirus	0.86	(0.65–1.14)	0.306	0.85	(0.78–0.93)	0.000
Adenovirus	1.53	(1.12–2.09)	0.007	0.98	(0.78–1.23)	0.861
Interactive effects (scale)						
Influenza and age in months (multiplicative)	1.07	(0.98–1.16)	0.135	1.03	(1.02–1.06)	0.001
Influenza and age in months (additive [RERI])	0.05	(0.01–0.09)	0.012			
RSV and age in months (multiplicative)	0.91	(0.86–0.97)	0.003			
RSV and age in months (additive [RERI])	−0.15	(−0.3–0.01)	0.042			
Adenovirus and age in months (multiplicative)				1.02	(1.01–1.05)	0.036
Adenovirus and age in months (additive [RERI])						

ICU, intensive care unit; RR, risk ratio; RERI, relative excess risk owing to interaction; RSV, respiratory syncytial virus.
[a]Small area-level measure of household deprivation derived from variables collected at the 2013 national census (NZDep2013 Index of Deprivation) [24].
[b]Preterm birth defined as <37 weeks of gestational age. Low birth weight defined as birth weight <2500 g.

(Table 2). The overall risk of ICU admission was also higher in hospitalisations where ADV (RR = 1.53; 95% CI 1.12–2.09) or RSV (RR = 1.55; 95% CI 1.00–2.39) was detected, while detection of influenza was associated with a decreased risk of ICU admission (RR 0.33; 95% CI 0.12–0.89).

We detected significant interactions for age with RSV or influenza infections (Table 2). RSV and age had a significant negative interaction ($P < 0.05$), meaning the decrease in ICU admission risk with age was more pronounced among children with RSV than those without RSV infection. Among children aged <5 months, those with RSV had a higher predicted probability of ICU admission compared with children without RSV. For children aged 6–24 months, the predicted probability of ICU was inverse that of younger children – higher among children without RSV compared with RSV-positive children (Fig. 2A, Supplementary Fig. S2).

In contrast, the influenza and age interaction was positive ($P < 0.05$). The predicted probability of ICU admission associated with influenza remained relatively flat across ages; whereas, those without influenza decreased over age. Consequently, for children aged >16 months, the predicted probability of ICU admission was higher for those with influenza compared with those without influenza infection (Fig. 2B, Supplementary Fig. S3). No significant interactions were found between age and ADV, rhinovirus or multiple viruses on ICU admission risk.

Long length of hospital stay: main and interactive effects of age and virus

Age had a significant main effect, with a decrease in LOS for every month increase in age (RR 0.97; 95% CI 0.96–0.97) (Table 2) after adjusting for ethnicity, SES, single and co-infection with virus and underlying conditions. Children born prematurely and/or with a low birth weight had an increased risk of longer LOS (RR 1.15; 95% CI 1.05–1.27), as did those with a pre-existing respiratory conditions (RR 1.20; 95% CI 1.11–1.30) or with cardiovascular, immune, renal or hepatic conditions (RR 1.68; 95% CI 1.39–2.04) (Table 2). The main effects of influenza (RR = 0.78; 95% CI 0.64–0.95) and rhinovirus (RR = 0.85; 95% CI 0.78–0.93) were associated with a decreased LOS.

We detected a significant interactive effect between age and either influenza or ADV infection on LOS (Table 2). Both influenza and ADV infections had positive interactions with age ($P < 0.05$), meaning the predicted LOS for children with either infection remained elevated across ages; whereas, LOS decreased over age in hospitalisations without these infections. Among children aged >8 months old, those positive for influenza had a longer predicted LOS compared with those without influenza (Fig. 3A). Apart from the first month of life, ADV hospitalisations had a higher predicted LOS compared with those without ADV (Fig. 3B). No significant interactions were found between age and RSV, rhinovirus or multiple virus detections on LOS.

Discussion

In this hospital-based study in New Zealand, we found 83% of children <2 years hospitalised with ALRI to be positive for at least one respiratory virus. Younger age and underlying conditions were associated with a higher risk of ICU admission and longer hospital stay among children. Additionally, we found important joint effects on these outcomes between age in months and whether the detected virus was RSV, influenza or ADV.

Overall, RSV infections were associated with a higher risk of ICU admission that decreased with age. In contrast, influenza infection did not increase the risk of ICU admission or LOS overall, but was associated with an increased risk of both outcomes among older children. Finally, ADV was shown to be associated with an increased risk of ICU admission and longer LOS regardless of age. If these associations are causal, they identify specific age groups within the first 2 years of life that would most benefit from viral-specific interventions such as antiviral treatments and vaccinations.

Previous studies have reported similar main effects for age [7, 13], underlying conditions [8, 9] and viruses [5, 14, 30] on ALRI-associated ICU admission and/or LOS; however, such a detailed examination of the combined effects of age in months and laboratory-confirmed viral effects on disease severity outcomes is a novel approach in the current study. Similar to other studies [5, 14, 31], RSV was the most common cause of ALRI in our seasonal study accounting for almost half of the hospitalisations, and caused more severe disease in the youngest children. We show hospitalised children <5 months to be at the greatest risk of severe disease outcomes due to RSV, and that this risk decreased rapidly with age in months. The reasons for the association between risk of severe RSV disease and very young age has been well established through immunological investigations [32–34]. Our results, ascertained from a large hospital-based study, support these findings and highlight the potential value of an RSV maternal vaccine or passive immunoprophylaxis. They also emphasise the importance of extended protection among new RSV preventative strategies to at least 5 months of age among infants in order to protect them from the most severe RSV disease.

In contrast, the risk of ICU admission and/or longer LOS among ALRI cases remained comparatively low for influenza and did not decrease significantly with age. In fact, influenza increased the risk of ICU admission and longer LOS among older hospitalised children (ICU: aged 16–23 months and LOS: 8–23 months). Our findings indicate that although the risk of severe disease following hospitalisation is relatively low for influenza, this risk does not change dramatically with age and may contribute more to severe outcomes among children older than 8–16 months than in very young children. Other studies from the New Zealand, UK and USA have found influenza hospitalisations and infections to be concentrated in children over 6 months of age [5, 35, 36] and to decline after 2 years of life [35]. As the most severe outcomes associated with influenza among children appear to also be concentrated in a narrow age range of >6 months to <2 years, influenza vaccination and early anti-viral treatment of children in this age group would likely provide the greatest benefit in controlling influenza-associated severe outcomes.

ADV infection among ALRI hospitalisations in children was also found to be a significant risk factor for ICU admission and a longer LOS compared with non-ADV respiratory infections for most ages (Fig. 3B). We hypothesise that the association of ADV with disease severity in our study was driven by an ADV-7 outbreak in Auckland during 2015 [37]. ADV-7 has been shown to have greater virulence than other ADV strains [38, 39] and contributed a larger proportion of ADV in ICU (Table 1). Since only a small number of our ADV isolates were sub-typed, we are unable to confirm this association and encourage further research in the area.

Finally, although rhinovirus was present in more than 20% of cases admitted to ICU or with prolonged hospital stay, it did not
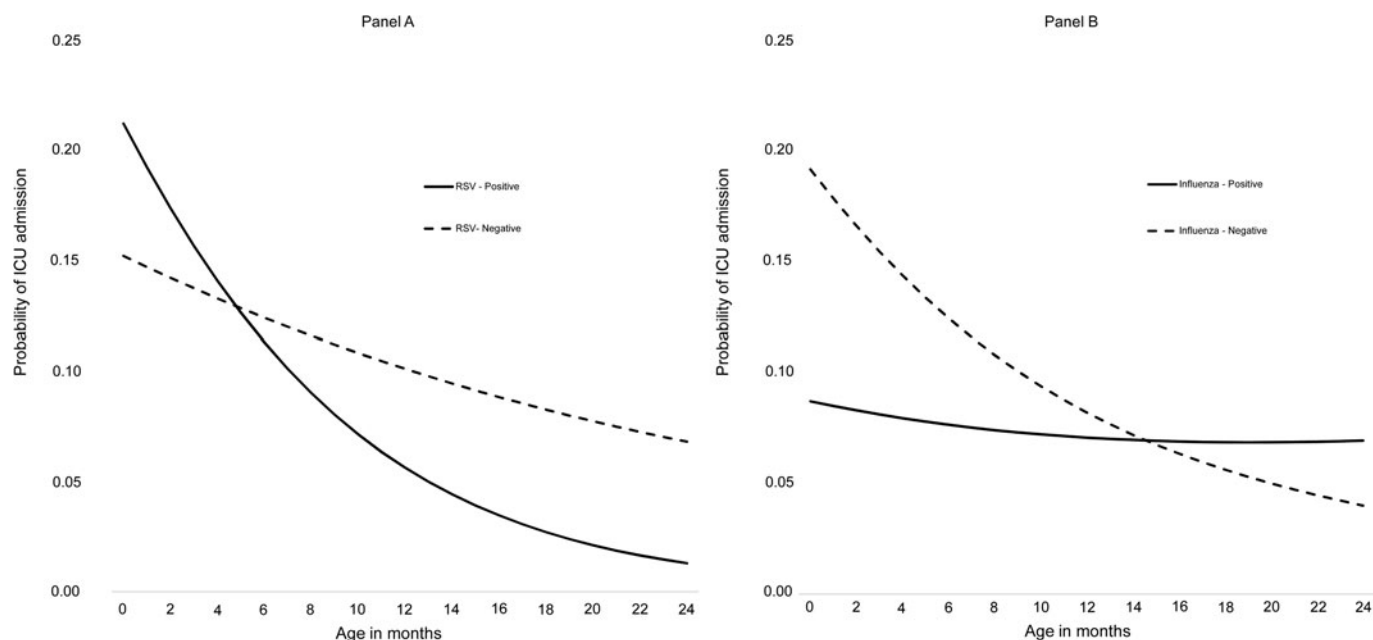
Fig. 2. Probability of ICU admission by age in months and RSV (A), influenza (B) positivity status among children aged <2 years hospitalised with acute lower respiratory infections, Auckland, New Zealand, 2012–2015.
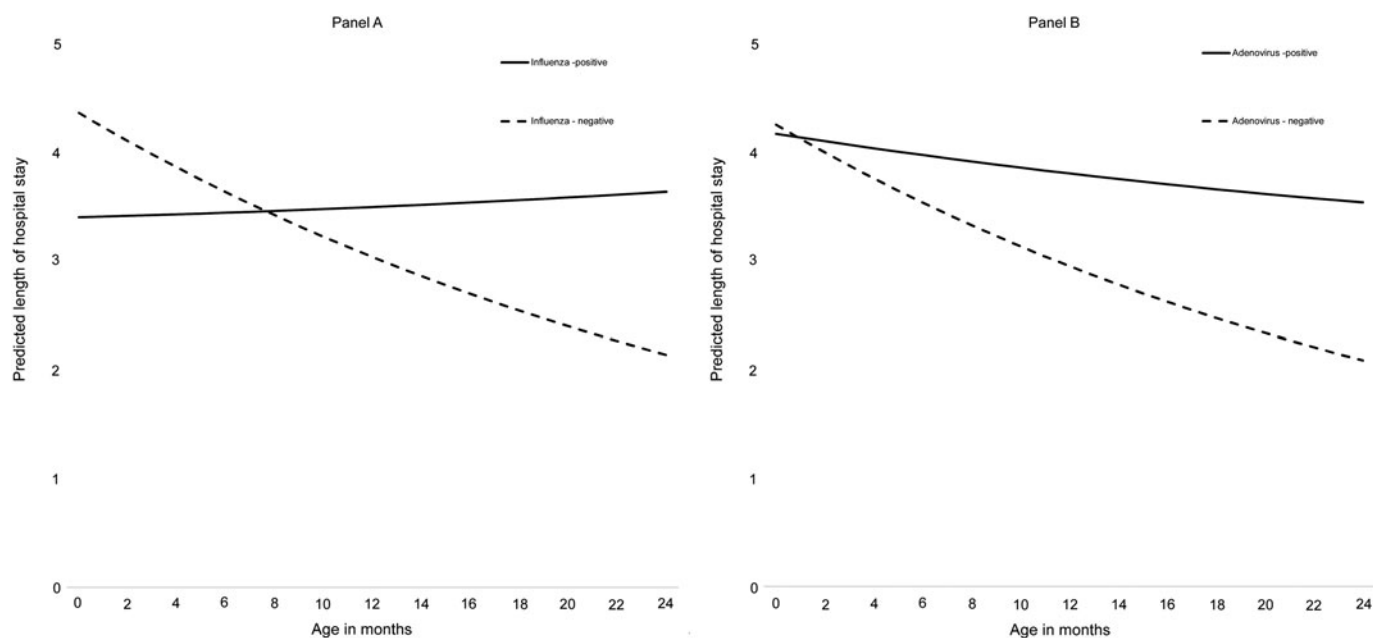

Fig. 3. Predicted length of hospital stay by age in months and influenza (A) or adenovirus (B) positivity status among children aged <2 years hospitalised with acute lower respiratory infections, Auckland, New Zealand, 2012–2015.

present as a significant risk factor for ALRI severity nor did it display an age-associated effect. The role of rhinovirus as a pathogen is unclear [30, 40]. Considering the wide genetic diversity of rhinovirus, investigation of specific rhinovirus sub-types would appear necessary to further understand its role in ALRI severity.

Limitations of our study are: first, the very low level of influenza vaccination coverage in our study population, which prevented us from including it as an exposure variable in our analysis. Second, although we had robust laboratory data, we had limited information on viral subtypes and bacterial pathogens, hence were unable to investigate their specific roles on severe ALRI. Third, precautionary clinician practices could be driving some of the outcomes, particularly ICU admission; however, by investigating both ICU and LOS, we hoped to capture a realistic picture of ALRI severity. Finally, while supportive therapies such as oxygen supplies and mechanical ventilation would have also been informative outcomes to investigate, the equipment and criteria used to provide such care changed during the

course of our study period and prevented us from including them in our analysis. Strengths of this study include its large prospective design over multiple seasons with systematic identification of cases and testing for a number of respiratory viruses across a broad spectrum of ALRIs. The use of national health data to validate our measures prevented bias from self-report and allowed adjustment for important demographic factors.

Conclusions

To our knowledge, this study is the first to examine both independent main and interactive effects of child age and respiratory virus on the risk of severe ALRI outcomes. By doing so, we are able to elucidate more clearly the relationship between age and specific viruses on the risk of severe ALRI. We found very young children (<5 months) to be at the highest risk from RSV-associated severe outcomes while children >8 months were at greater risk from influenza. Our findings suggest that in controlling severe ALRI among children <2 years, RSV-specific interventions would benefit children <5 months the most, while influenza vaccination and anti-viral treatment among children >6 months to <2 years would likely have a significant impact in reducing influenza-associated severe outcomes.

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