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Respiratory syncytial virus hospitalization in middle-aged and older adults

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Abstract

Background—The importance of Respiratory Syncytial Virus (RSV) is increasingly recognized in hospitalized adults, but mainly in those ≥ 65 years.

Objectives—We sought to describe the epidemiology and clinical severity of RSV compared to influenza in hospitalized adults ≥18 years.

Study Design—Adults hospitalized with acute respiratory illnesses (ARI) of ≤10 days duration were prospectively enrolled from two Michigan hospitals during two influenza seasons. Collected specimens were tested for RSV and influenza by real-time, reverse transcription polymerase chain reaction (RT-PCR). Viral load and subtype were determined for RSV-positive specimens. We evaluated factors associated with RSV and outcomes of infection using multivariable logistic regression. RSV-positive patients were separately compared to two reference groups: RSV-negative and influenza-negative, and influenza-positive patients.

Results—RSV was detected in 84 (7%) of 1259 hospitalized individuals (55 RSV-B, 29 RSV-A). The highest prevalence was found in 50-64 year olds (40/460; 8.7%); 98% of RSV cases in this age group had at least one chronic comorbidity. RSV detection was associated with obesity (OR: 1.71 95% CI: 0.99-3.06, p=0.03). Individuals with RSV were admitted to the hospital later in their illness and had a higher median Charlson comborbidity index (3 vs 2 $p < 0.001$) compared to those with influenza. Clinical severity of RSV-associated hospitalizations was similar to influenza-associated hospitalizations.

Discussion—In this study we observed the highest frequency of RSV-associated hospitalizations among adult 50-64 years old; many of whom had chronic comorbidities. Our results suggest the potential benefit of including these individuals in future RSV vaccination strategies.

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Keywords

RSV; influenza; hospitalization; adults; acute respiratory illness

Background

Respiratory Syncytial Virus (RSV), commonly regarded as a childhood infection, is also an important contributor to respiratory illness among adults [1–8]. However, unlike influenza, in which serious morbidity has been clearly recognized for years, the relative impact of RSV infection in adults has more recently gained widespread recognition [9,10]. While primary RSV infections in infancy can result in severe disease, subsequent infections are often comparatively mild. Incomplete immunity results in continued susceptibility to reinfection through life. For example, we recently detected RSV in 4% of acute respiratory illnesses (ARI) in community dwelling adults 18-49 years old [11]. Current vaccine development efforts have identified prevention of severe RSV-associated illness in older adults, particularly those resulting in hospitalization, as a priority. Estimates of the frequency and severity of these RSV-associated hospitalizations have varied considerably, with some earlier studies using antibody titer rather than molecular methods to document infection. Most previous studies of RSV-associated hospitalization have concentrated on those 65 years of age and older, with five to ten percent of hospitalizations for ARI due to RSV infection [2,5,12–17]. Older adults with underlying cardiopulmonary disease such as chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) have been shown to be at particular risk [2,18].

Because of these findings, and the known role of influenza in causing hospitalization, studies of RSV in hospitalized adults have often used influenza positive illnesses as a frame of reference. This was particularly true with regards to efforts to distinguish between symptoms of severe RSV and severe influenza prior to the availability of rapid, point-of-care diagnostics. RSV infections have been reported to present less frequently with fever and more frequently with wheezing, but otherwise can be difficult to distinguish clinically from influenza and, for that matter, from other viral respiratory illnesses [1,12]. In some studies, these comparative evaluations have found the frequency of RSV hospitalization to rival that of influenza in highly influenza vaccinated populations [1,3,4,12].

Objectives

Establishing the burden of severe RSV has added urgency given the accelerating development of RSV vaccines; a major issue for vaccination programs will be identifying target populations for rational use. We sought to characterize the frequency and clinical severity of RSV among hospitalized adults ≥18 years, overall and by subtype, for two respiratory illness seasons in two large Southeast Michigan hospitals.

Study Design

Study Design

We used specimens and data from a prospective study of adults hospitalized with ARI meeting a standardized case definition [19]. The ongoing, case-test negative study was designed to estimate influenza vaccine effectiveness (VE) in the prevention of influenza-associated hospitalization. Patients ≥18 years old hospitalized with ARI at one of two hospitals were prospectively identified from November 2014-March 2015 and November 2015-April 2016. These hospitals are two large tertiary care centers in Michigan serving primarily suburban (Hospital A) and urban (Hospital B) populations. Chief complaints and admission diagnoses for all new admissions were screened for evidence of an ARI of ≤10 days duration. Patients or a proxy/surrogate provided written informed consent to participate. This study was approved by the Institutional Review Boards at the University of Michigan Medical School and Henry Ford Health System.

Data collection

At enrollment, consented patients self-reported demographic characteristics, subjective health, frailty [20–22], influenza vaccination, and illness onset date via structured interviews with study staff. Throat and nasal swab specimens were collected and combined in universal transport media.

Electronic medical records (EMR) were reviewed to document evidence of COPD, CHF and other chronic conditions, for calculation of the Charlson Comorbidity Index (CCI) [23,24] and for determination of body mass index (BMI) [25]. Obesity was defined as a BMI ≥ 30. Measures of clinical severity were also collected from the EMR including: length of stay, admission to and duration of stay in the intensive care unit (ICU), requirement for invasive (e.g. intubation) and non-invasive (e.g. BiPAP/CPAP) mechanical ventilation, and discharge disposition.

Laboratory testing

Collected respiratory specimens were tested for RSV and influenza by real-time reverse transcription PCR (RT-PCR) using primers, probes, and a testing protocol developed by the CDC Division of Viral Diseases and Influenza division, respectively [26]. RSV positive specimens were subsequently quantified and subtyped using published methods [27]. Quantification was standardized using known quantities of plasmid-based standards containing the amplicon, and results were expressed in log copies/ml of media. All specimens were also tested for RNase P to assess sample quality [28].

Statistical analyses

Analyses were restricted to data from the first RSV-positive enrollment of an individual or the first overall enrollment if no RSV-positive episodes were identified. Characteristics and clinical outcomes of participants with RSV were compared to RSV-negative, influenza-negative subjects and, separately, to influenza-positive subjects using Chi-square, Fisher's exact test, or Wilcoxon rank-sum tests, as appropriate. P-values less than 0.05 were considered statistically significant for all analyses.

We determined risk factors associated with detection of RSV and assessed the association between RSV detection and extended length of stay (≥3 days) using regression models; comparison groups were defined similarly to the unadjusted analysis. Multivariable logistic regression models were used to analyze patient demographics and clinical outcomes, controlling for BMI, CCI, age ≥65 years, study site, study year, and time from illness onset to admission. All logistic models used Firth's regression with profile-likelihood confidence intervals, p-values were calculated as Wald's p-values. All analyses were performed using SAS software version 9.4.

Results

Detection of RSV and Influenza

1306 patients hospitalized for ARI were enrolled in the study between November 2014-March 2015 and November 2015-April 2016 (Figure 1). Subsequent enrollments of individuals enrolled multiple times (n=42) and subjects with missing or inconclusive influenza testing results (n=3) were excluded, resulting in a study population of 1,261 patients (726 in 2014-2015, 535 in 2015-2016). Figure 1 presents RSV and influenza epidemic curves by season. Overall, RSV was detected in 86 (7%) and influenza was detected in 236 patients (19%). Two individuals had co-detection of RSV and influenza in the same specimen [1 with RSV-B/unsubtypeable influenza A and 1 with RSV-A/Influenza A(H1N1)pdm09] and were excluded from further analysis. Overall study enrollment was lower in the second year of the study (726 in 2014-2015 and 535 in 3015-2016). The proportion of RSV detections was also lower in the second year (8% in 2014-2015 and 5% in 2015-2016, while the proportion of influenza infections remained consistent in both years (19% in 2014-2015 and 19% in 2015-2016).

RSV and influenza hospitalizations by participant characteristics

Nearly two-thirds of RSV cases detected in this study were among adults 18-64 years of age (n=56). The age-specific proportion of RSV detection (Table 1) was 4% among those 18-49, 9% among those 50-64, and 7% among those 65 years old and older (p = 0.06). In contrast, influenza was identified slightly less frequently in the middle age group (16%) than in older (20%) and younger adults (20%). Overall, 1118 (88%) of all enrolled patients had a CCI ≥1, indicating the presence of at least one major comorbid condition. On average, patients with RSV had a higher median CCI than patients with influenza (3 vs 2, p < 0.001). After stratifying by age group (Table 2), we further found that the higher average CCI of patients with RSV was specific to those 50-64 years old (median 4 vs 2, p =0.001). The median time from illness onset to admission among RSV-positive patients was 3 days (IQR: 2-4) and the median time from onset to specimen collection was 4 days (IQR: 3-6). Individuals with RSV had a longer interval from illness onset to admission (p=0.006) and to specimen collection (p=0.003) than individuals with influenza (Table 1).

RSV subtyping & viral load

Among the 84 identified RSV infections, 29 were RSV-A and 55 were RSV-B; RSV-B predominated in 2014-2015 (n=49; 82%) and RSV-A predominated in 2015-2016 (n=19; 76%) (Figure 1). One individual, whose second enrollment was excluded from analysis, was

hospitalized twice with RSV-B detected in specimens collected 29 days apart. Neither participant characteristics nor illness outcomes differed significantly between subtypes (Table 3). There was also no significant difference in time from illness onset to specimen collection by subtype.

Viral loads were obtained for 81 of 84 RSV-positive samples and are presented in table 4. Median viral load was 4.34 (IQR: 3.54-5.23; range: 1.95-7.86) log10 copies/ml. Median viral load of RSV-A infections was significantly lower than RSV-B infection [3.42 (2.93-4.06) vs 4.86 (4.00-5.44) log10 copies/ml; p<.0001]. We did not observe associations between viral load and increasing age, CCI, or BMI, in an analysis adjusting for time between illness onset and sample collection. The median viral load did not differ significantly for RSV-positive cases hospitalized for ≥3 days compared to those with a shorter length of stay [4.34 (3.69-5.23) vs 4.43 (3.33-5.33) $\log_{10}$ copies/ml; p=0.95]. Similarly, viral load did not differ for patients requiring mechanical ventilation or admission to the ICU, compared to those who did not.

RSV-positive compared with influenza-positive and RSV-negative, influenza-negative patients

1174 (94%) patients with complete data for all covariates were included in multivariable logistic regression models comparing RSV-positive patients to RSV-negative, influenza positive and, separately, RSV-negative, influenza-negative patients. After adjusting for potential confounders, RSV detection was associated with obesity (OR 1.71, 95% CI: 0.99-3.06; p=0.03) when compared to RSV-negative, influenza-negative patients (Table 5). In analyses comparing individuals with RSV to those with influenza, obesity was not significantly associated with RSV detection but participants admitted to the hospital later in their course of illness were more likely to have RSV than influenza (OR 1.16 95% CI: 1.03-1.30 per illness day; p=0.02) (Table 6).

Clinical severity of RSV hospitalizations

Sixty-six percent of RSV-positive participants were admitted for ≥3 days, compared to 54% of influenza-positive participants (p = 0.048). Mechanical ventilation was required in 6 (7%) individuals with RSV. Five individuals with RSV (6%) were admitted to the ICU. There were no in-hospital deaths among the RSV group, 2 in the influenza group (1%) and 13 in the RSV-negative, influenza-negative group (1%). In multivariable analysis controlling for age, CCI, study site, year, and time from illness onset, no significant differences were found between RSV and influenza with respect to these clinical indicators of severity (Table 7).

Discussion

Adults ≥65 years old have long been the focus of targeted efforts to reduce the burden of hospitalization due to severe respiratory illness. Even now that yearly influenza vaccination recommendations have been extended to adults of all ages, efforts still continue to improve vaccines for older individuals including the introduction of high dose formulations. Thus, it is no surprise that recent initiatives to develop an RSV vaccine for adults have targeted those 60-65 years and older. However, in this study conducted over two respiratory seasons in two

different hospitals, we have demonstrated that a substantial proportion of RSV infections was detected in younger adults. We also observed that patients with RSV had a higher median CCI than patients with influenza, and that this association was driven by individuals in the 50-64 year old age group. This may suggest that influenza infection results in hospitalization for a relatively healthier group of adults 50-64 years old while RSV infection is more likely to result in hospitalization for those with multiple chronic conditions. A similarly designed study conducted in France over 3 seasons found that RSV cases were more likely to have cancer or be on immunosuppressive therapy than influenza cases [10]. Our findings provide evidence in support of focused development of RSV vaccines and therapies targeted toward an expanded age group of adults, particularly those 50-64 and those of any age with chronic comorbidities.

This study was conducted, in part, during the 2014-2015 respiratory illness season, which was notable for the circulation of an antigenically drifted influenza strain and unusually high numbers of hospitalizations for influenza-associated ARI [29]. Even in this context, we found RSV to be associated with a substantial proportion of ARI hospitalizations among adults of all ages. A number of previous studies of RSV in adults have enrolled an older study population [1,2,12,30,31]. An exception was a recent US study examining RSV in medically attended illnesses of all severities [32] which extended down to age 50, as well as previous studies from the United Kingdom that examined visits to general practitioners among individuals of all ages [33]. Modeling studies suggest a modest burden of RSV-associated medical visits, but little burden of hospitalizations, in those 18-49 years, especially for those with underlying risk conditions [6].

Much effort has been dedicated to comparing the clinical severity of RSV and influenza [1,3,4,12,17,34]. As with previous studies, we found that morbidity due to RSV in this adult population was comparable to that of influenza, as defined by need for mechanical ventilation and ICU admission; albeit in relatively few patients with severe endpoints. Importantly, this study was conducted in communities where influenza vaccination was common. Recent results from case-test negative studies, including the 2014-2015 season of this study, have suggested that influenza vaccine may be more effective in preventing severe rather than mild infections [19,35,36], thus our estimates of influenza severity may be reduced accordingly. While the occurrence of severe morbidity was comparable to that of influenza in this study, we were unable to adequately compare age-specific effects on severity between the two diseases due to sample size. We also observed that individuals with RSV were admitted later in their illness, on average, than individuals with influenza. While not significant in multivariable analyses, this finding could suggest a slower overall progression to acute illness for RSV versus influenza, as has been found in challenge studies [37].

We found that the predominant RSV subtype, as determined through molecular methods, varied from year to year. This is a pattern that has been observed elsewhere in studies of community-based RSV epidemiology [38,39]. In our modern era of rapid molecular methods, the rapid determination of RSV subtype is potentially significant on two fronts: early prediction of disease burden in a given season and eventual monitoring of RSV vaccine effectiveness. It is well-established that varied strains of influenza A are associated with

differing disease burden and morbidity [1,40] and require the selection of type-specific vaccine strains. Our analysis, unlike previous work in children [41,42], did not find any evidence of a corresponding difference in morbidity by RSV strain type. The antigenic target of RSV vaccines currently in development is fairly well conserved between the subtypes [43]; nevertheless, it remains to be seen to what degree subtype variability in RSV will present challenges for a broadly effective vaccine.

Our current data suggest that there is more hospitalization attributable to RSV in younger adults than has been previously thought, and that most of these individuals have underlying risk conditions. Our study was conducted only among hospitalized individuals and, therefore, does not provide population-based incidence rates. Still, more than 67% of RSV identifications were in individuals under 65 years of age, suggesting the potential benefit of including these individuals in future RSV vaccination strategies. The fact that most have multiple underlying conditions makes it possible to target vaccination programs similar to the strategies used for influenza vaccination in countries without have a universal recommendation.

Acknowledgments

Conflict of Interest Declaration

REM, ETM and ASM report a grant from MUGAS outside the current work. ETM reports grants from Merck and Pfizer outside the current work. ASL reports grants from the Doris Duke Charitable Foundation outside the current work. ASM reports grants and personal fees from Sanofi-Pasteur, and personal fees from Novartis and Protein Sciences outside the submitted work

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Disclaimer

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Key points

RSV-associated hospitalizations were highest among adults 50-64 years and those with chronic illness, suggesting these individuals should be targeted in future RSV vaccination strategies.

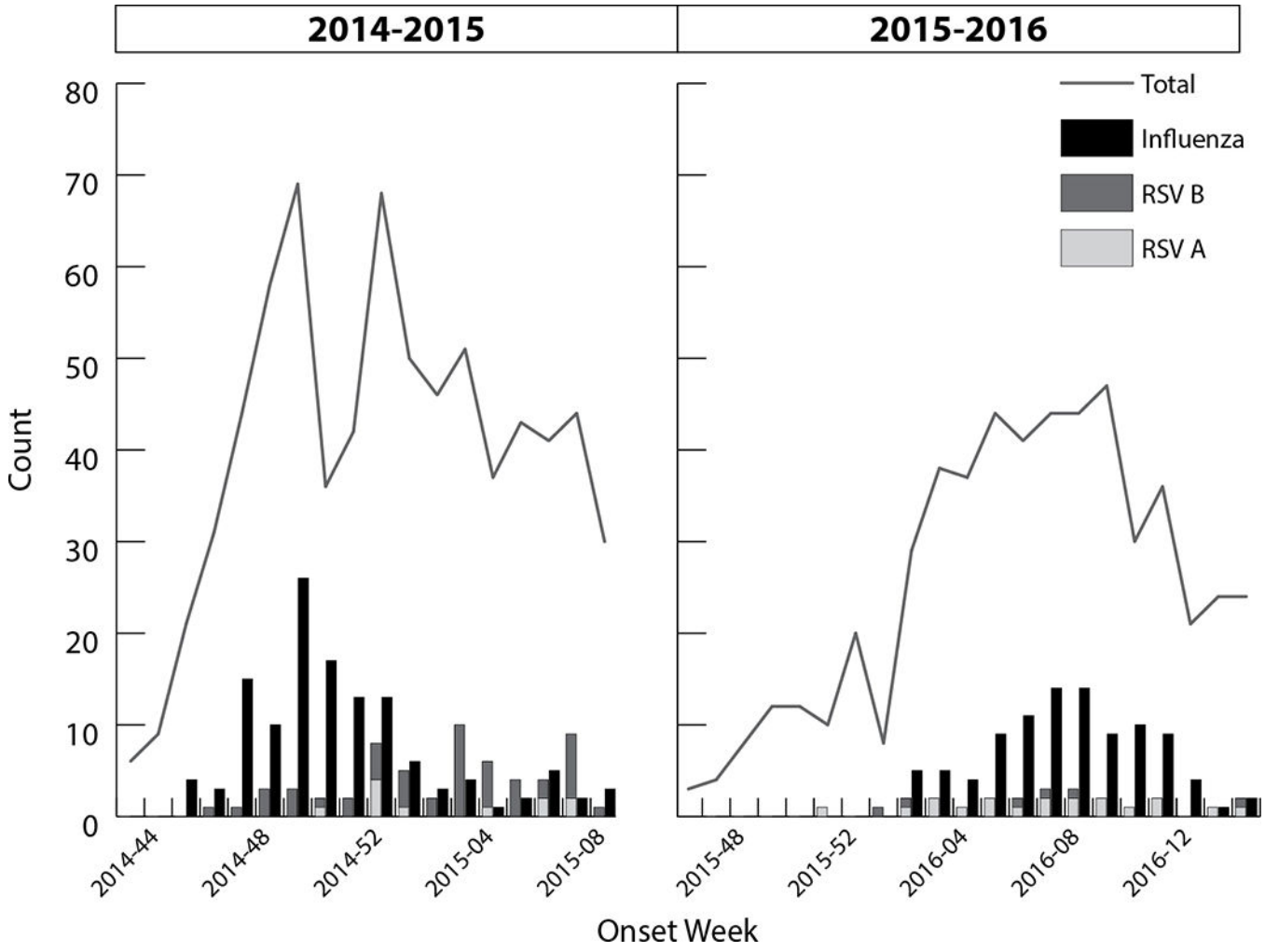

Figure 1. Respiratory Syncytial Virus (RSV) and influenza detections and total number of specimens collected in adults hospitalized with acute respiratory illness (ARI) over two seasons

[a] 2014-2015 season: 62 RSV positive specimens, 11 RSV-A and 50 RSV-B. 136 Influenza positive specimens, 116 (85%) influenza A/H3N2. One individual was coinfected with RSV-B and unsubtypeable influenza A and was excluded from further analyses.

[b] 2015-2016 season: 25 total RSV positive specimens, 19 RSV-A and 6 RSV-B. 100 influenza positive specimens, 89 (89%) influenza A/H1N1. One individual in 2015-2016 was coinfected with RSV-A and influenza A/H1 and was excluded from further analyses.

Table 1

Frequency of hospitalizations associated with respiratory syncytial virus (RSV), influenza, and RSV-negative, influenza-negative acute respiratory infection (ARI) by participant characteristics.

	Row Totals	RSV-positive (n=84)[a]	Influenza-positive (n=234)[a]	RSV-negative & Influenza-negative (n=941)
Age group, n (%)[b]				
18-49	372	16 (4.3)	75 (20.2)	281 (75.5)
50-64	461	40 (8.7)	75 (16.3)	346 (75.1)
≥65	426	28 (6.6)	84 (19.7)	314 (73.7)
BMI, n (%)[c]				
Normal/underweight	351	19 (5.4)	67 (19.1)	265 (75.5)
Overweight	311	18 (5.8)	55 (17.7)	238 (76.5)
Obese	547	46 (8.4)	103 (18.8)	398 (72.8)
Charlson score, n (%)[d]				
0	141	6 (4.3)	36 (25.5)	99 (70.2)
1	301	15 (5.0)	70 (23.3)	216 (71.8)
2	179	16 (8.9)	37 (20.7)	126 (70.4)
≥3	637	47 (7.4)	91 (14.3)	499 (78.3)
CHF, n (%)[d]	404	25 (6.2)	54 (13.4)	325 (80.4)
COPD, n(%)[d]	769	58 (7.6)	133 (17.3)	578 (75.1)
Frailty score, n(%)[e]				
0	267	23 (8.6)	57 (21.3)	187 (70.0)
1	308	24 (7.8)	56 (18.2)	228 (74.0)
2	261	8 (3.1)	54 (20.7)	199 (76.2)
3	186	11 (5.9)	34 (18.3)	141 (75.8)
4/5	198	15 (7.6)	22 (11.1)	161 (81.3)
Hospital B, n (%)	556	43 (7.7)	107 (19.2)	406 (73.0)
Time to admission in days, med (IQR)	–	3 (2-4)	2 (1-3)[f]	2 (1-4)
Time to specimen collection in days, med (IQR)	–	4 (3-6)	3 (2-5)[f]	4 (2-6)
Antiviral prescribed, n (%)	267	15 (5.6)	160 (59.9)	92 (34.5)
Antiviral prescribed before study specimen collection, n (%)	184	12 (6.5)	110 (59.8)	62 (33.7)
Influenza vaccination (any), n(%)[g]	792	57 (7.2)	116 (14.6)	619 (78.2)

Abbreviations: BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IQR, interquartile range

[a] Two individuals were coinfected with RSV and influenza and excluded from analyses.

[b] Chi-square p-value for frequency of detection by age group: 0.06 among RSV-positive; 0.40 among influenza positive; and 0.85 among RSV-negative, influenza-negative hospitalizions.

[c] 50 individuals were missing data on body mass index (BMI) – 40 RSV-negative/influenza-negative, 1 RSV-positive, 9 influenza-positive.

[d] 1 RSV-negative/influenza-negative individual was missing data on comorbid conditions.

[e] 39 individuals missing data on frailty score – 25 RSV-negative/influenza-negative, 3 RSV-positive, 11 influenza-positive.

[f] P-value from Wilcoxon rank-sum test comparing RSV-positive and influenza-positive ARI for time to admission (0.003) and time to specimen collection (0.006)

[g] 64 individuals with vaccination status unknown – 49 RSV-negative/influenza-negative, 3 RSV-positive, 12 influenza-positive.

Table 2

Frequency of RSV subtype by participant characteristics

	RSV-A positive (n=29)	RSV-B positive (n=55)	p-value
Age group			0.54
18-49	4 (13.8)	12 (21.8)	
50-64	16 (55.2)	24 (43.6)	
≥65	9 (31.0)	19 (34.6)	
Male sex	12 (41.4)	21 (38.2)	0.78
BMI, median (IQR)	31.45 (25.13-43.01)	32.00 (26.08-37.46)	0.53
BMI categories, n (%)[a]			0.82
Underweight/normal (18.5-24.99)	7 (25.0)	12 (21.8)	
Overweight (25-29.99)	5 (17.9)	13 (23.6)	
Obese (≥ 30)	16 (57.1)	30 (54.6)	
Charlson score, n (%)			0.41
0	1 (3.5)	5 (9.1)	
1	3 (10.3)	12 (21.8)	
2	7 (24.1)	9 (16.4)	
≥3	18 (62.1)	29 (52.7)	
Time to specimen collection from onset day, median (IQR)	5 (3-6)	4 (3-6)	0.97
Time to admission from onset day, med (IQR)	3 (2-4)	3 (2-4)	0.64
Hospital B, n (%)	12 (41.4)	31 (56.4)	0.19
Year, n (%)			<0.0001
2014-2015	11 (37.9)	49 (89.1)	
2015-2016	18 (62.1)	6 (10.9)	
Viral load (log10 copies/ml), median (IQR)[b]	3.42 (2.93-4.06)	4.86 (4.00-5.44)	<0.0001

Abbreviations: BMI, body mass index; IQR, interquartile range

[a] P-value from Kruskal-Wallis test.

[b] Results from linear regression model adjusted for time between illness onset to specimen collection (in days).

Table 3

Median (IQR) Charlson Comorbidity Index (CCI) among respiratory syncytial virus (RSV)-positive and influenza-positive hospitalizations, stratified by age-group

	RSV-positive	Influenza-positive	p-value[a]
18-49 years	1 (1-2)	1 (1-2)	0.97
50-64 years	4 (2-6)	2 (1-5)	0.001
65+ years	3 (2-5)	2 (1-5)	0.34

Abbreviations: IQR, interquartile range

[a]P-value from Wilcoxon rank-sum test

Table 4

Median respiratory syncytial virus (RSV) viral load by participant characteristics and regression coefficients and 95% confidence intervals (CI) from linear regression models

Independent variable	Viral load (log10 copies/ml), median (IQR)	p-value[a]	Adjusted linear regression models[b], β (95% CI)	p-value
Age group		0.79		
18-49	4.36 (3.86-5.54)		Ref	
50-64	4.59 (3.31-5.40)		−0.20 (−0.98-0.57)	.45
≥65	4.29 (3.54-4.86)		−0.31 (−1.13-0.51)	.60
BMI		0.23		
Underweight/normal (18.5-24.99)	5.00 (3.90-5.73)		Ref	
Overweight (25-29.99)	4.10 (3.18-4.75)		−0.70 (−1.55-0.15)	.11
Obese (≥ 30)	4.55 (3.53-5.24)		−0.30 (−1.02-0.41)	.40
Charlson score		0.07		
0	4.33 (4.03-6.06)		Ref	
1	5.06 (4.05-5.33)		0.36 (−0.86-1.59)	.56
2	3.91 (3.53-4.41)		−0.84 (−2.05-0.38)	.17
≥3	4.59 (3.28-5.40)		−0.18 (−1.28-0.91)	.74

Abbreviations: BMI, body mass index

[a] P-value from Kruskal-Wallis test.

[b] All models include the independent variable listed and viral load as the dependent variable adjusted for time between illness onset to specimen collection (in days).

Table 5

Factors associated with RSV hospitalization compared to RSV-negative, influenza-negative hospitalization in unadjusted and adjusted logistic regression models.

	RSV compared to RSV-negative and influenza-negative				
	Unadjusted OR (95% CI)[a]	**Adjusted OR (95% CI)[a,b]**	**P[c]**	**Adjusted OR (95% CI)[a,b]**	**P[c]**
BMI					
Underweight/normal (18.5-24.99)	Ref		Ref		
Overweight (25-29.99)	1.06 (0.54-2.05)	.53	1.08 (0.55-2.11)	.49	
Obese (≥ 30)	1.59 (0.93-2.81)	.06	1.71 (0.99-3.06)	.03	
Charlson score					
0	Ref		Ref		
1	1.10 (0.44-3.03)	.40	0.73 (0.29-2.05)	.25	
2	2.00 (0.81-5.52)	.09	1.23 (0.48-3.51)	.28	
≥3	1.46 (0.67-3.73)	.63	0.92 (0.40-2.46)	.86	
Age group					
18-49	Ref		Ref		
50-64	1.99 (1.12-3.70)	.04	1.77 (0.97-3.36)	.10	
≥65	1.55 (0.84-2.95)	.71	1.45 (0.75-2.86)	.75	
Hospital B	1.38 (0.89-2.16)	.16	1.40 (0.88-2.10)	.15	
Year (2015-2016)	0.52 (0.32-0.84)	.01	0.53 (0.31-0.87)	.01	
Time to admission, d	1.08 (0.98-1.18)	.12	1.07 (0.97-1.17)	.17	

Abbreviations: BMI, body mass index

[a] Firth penalized logistic regression models with profile-likelihood confidence intervals.

[b] Adjusted for BMI, Charlson score, age, study site, year, and time from illness onset to admission.

[c] Wald p-values.

Table 6

Factors associated with RSV hospitalization compared to influenza hospitalization unadjusted and adjusted logistic regression models.

	RSV compared to Influenza			
	Unadjusted OR (95% CI)[a]	**P[c]**	**Adjusted OR (95% CI)[a,b]**	**P[c]**
BMI				
Underweight/normal (18.5-24.99)	Ref		Ref	
Overweight (25-29.99)	1.15 (0.55-2.40)	.80	1.01 (0.47-2.18)	.66
Obese (≥ 30)	1.56 (0.85-2.91)	.15	1.38 (0.73-2.66)	.25
Charlson score				
0	Ref		Ref	
1	1.24 (0.47-3.57)	.18	0.84 (0.30-2.54)	.11
2	2.47 (0.93-7.26)	.17	1.76 (0.63-5.36)	.26
≥3	2.92 (1.25-7.83)	.01	1.87 (0.76-5.20)	.08
Age group				
18-49	Ref		Ref	
50-64	2.46 (1.29-4.83)	.01	1.87 (0.93-3.84)	.05
≥65	1.54 (0.79-3.10)	.96	1.16 (0.56-2.45)	.57
Hospital B	1.24 (0.76-2.05)	.39	1.25 (0.73-2.14)	.42
Year (2015-2016)	0.55 (0.32-0.93)	.03	0.57 (0.32-0.99)	.05
Time to admission, days	1.16 (1.04-1.31)	.01	1.16 (1.03-1.30)	.02

Abbreviations: BMI, body mass index

[a] Firth penalized logistic regression models with profile-likelihood confidence intervals.

[b] Adjusted for BMI, Charlson score, age, study site, year, and time from illness onset to admission.

[c] Wald p-values.

Table 7

Clinical outcomes of respiratory syncytial virus (RSV)-positive, RSV-negative and influenza-negative, and influenza-positive hospitalization.

	N, (%)			Adjusted logistic regression models OR (95% CI)[a]			
	RSV-positive (n=84)	**RSV-negative & influenza-negative (n=941)**	**Influenza-positive (n=234)**	**RSV vs RSV-negative, influenza-negative**	**P-value[c]**	**RSV vs Influenza**	**p-value[c]**
LOS ≥ 3 days[b]	56 (66.7)	593 (63.2)	127 (54.3)	1.12 (0.70-1.84)	.64	1.53 (0.90-2.67)	.13
ICU admission	5 (6.0)	89 (9.5)	19 (8.1)	0.76 (0.28-1.73)	.56	0.88 (0.29-2.31)	.79
Mechanical ventilation[d]	6 (7.1)	116 (12.3)	24 (10.3)	0.65 (0.26-1.41)	.32	0.65 (0.23-1.63)	.38

Abbreviations: OR, odds ratio; CI, confidence interval; LOS, length of stay; ICU, intensive care unit

[a] Firth penalized logistic regression models with profile-likelihood confidence intervals, adjusted for age ≥65, categorized Charlson score (0, 1, 2, ≥3), site, year, and time from illness onset to admission (in days).

[b] 2 RSV-negative/influenza-negative individuals were missing data on LOS.

[c] Wald p-values.

[d] Any mechanical ventilation (invasive or noninvasive). 1 RSV-negative/influenza-negative individual was missing information on mechanical ventilation status.