



Full length article

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 comorbidity 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.

1. 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

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

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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].

2. 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.

3. Study Design

3.1. 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.

3.1.1. 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.

3.1.2. 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].

3.1.3. 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.

4. Results

4.1. 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 (Fig. 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 1261 patients (726 in 2014–2015, 535 in 2015–2016). Fig. 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/uns subtypeable 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 2015–2016). 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).

4.2. 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).

4.3. 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%) (Fig. 1). One individual, whose second enrollment was excluded from analysis, was

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