The Underrecognized Burden of Respiratory Syncytial Virus Among Infants Presenting to US Emergency Departments

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Introduction

Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract illness (LRI) in infants and young children and one of the most frequently detected respiratory viruses among hospitalized children.[1] In the United States, the RSV season generally occurs between November and March; however, season onset and offset, duration, and peak can have considerable regional and local variability.[2]

Many infants infected with RSV develop mild upper respiratory tract disease that resolves uneventfully in 8 to 15 days. However, pneumonia and bronchiolitis are apparent in up to 40% of children on their initial RSV infection.[3] RSV disease is often not diagnosed as there is debate whether RSV testing of infants with bronchiolitis changes management. The American Academy of Pediatrics, in their bronchiolitis management guidelines, specifically does not recommend RSV testing.[3] Although results are rapidly available with antigen testing, the lack of sensitivity and specificity limits its usefulness[4]; cell culture and virus isolation lack sensitivity and are expensive, and results are not available for days.[5] Although reverse transcription polymerase chain reaction (RT-PCR) is the most sensitive test available for RSV detection during peak and off-peak seasons,[1] it is infrequently used in the emergency department (ED) setting owing to the expense and lack of available results while the child is in the ED.[1] Given the limitations of routine diagnostic testing for RSV, it is likely that RSV in the ED setting is underrecognized. The objective of this analysis was to compare the prevalence of RSV assessed by RT-PCR with that of primary International Classification of Diseases, Ninth Revision (ICD-9) diagnosis among infants presenting to US EDs with LRI or apnea.

Materials and Methods

This post hoc analysis examined data collected from a previous prospective, active-surveillance study of RSV illness in infants younger than 12 months who presented to 31 US EDs with LRI or apnea during 2 RSV seasons (2006-2008).[6] LRI was diagnosed based on the presence of bronchiolitis, pneumonia, wheezing, rales, retractions, or a new infiltrate. Infants receiving RSV prophylaxis were excluded from the analysis. Data were reported from 31 sites in 23 states in season 1, and from 27 sites in 20 states in season 2.

Nasal swab samples for RT-PCR testing were collected each season during 3 surveillance periods, the peak RSV season (January 15-February 15) and the 2 shoulder seasons outside the traditional RSV period (September 1-October 31 and April 1-May 31). RSV-specific RT-PCR (Gen-Probe/Prodesse, Waukesha, WI) was performed at a central laboratory as previously reported.[6] Discharge ICD-9 codes were determined from medical records. Providers were not aware of the PCR results at the time of discharge. For all ICD-9 discharge codes reported, the RSV positivity rate by PCR was calculated during peak and shoulder intervals. Conversely, among those that tested positive for RSV by study PCR testing, the proportion with an RSV-specific ICD-9 code was calculated. RSV-specific ICD-9 discharge codes included 079.6 (RSV), 466.11 (acute bronchiolitis due to RSV), and 480.1 (pneumonia due to RSV).

Results

International Classification of Diseases, Ninth Revision discharge codes and PCR testing results were available for 1100 and 3070 infants during the peak and shoulder

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periods, respectively. The percentage of infants testing positive for RSV by RT-PCR was 62% (678/1100) during the peak seasons and 20% (620/3070) during the shoulder seasons. As expected, RSV positivity by RT-PCR was high (87%) among those infants with RSV-specific ICD-9 diagnoses.

Among nonRSV-specific discharge diagnoses reported in at least 10 infants, RSV positivity (by RT-PCR) was highest during the peak RSV season among those with otitis media (80%, 8/10), acute bronchiolitis (74%, 71/96), and acute bronchiolitis due to other infectious organisms (59%, 239/403). During the shoulder seasons, RSV positivity was highest for acute bronchiolitis (33%, 45/135), acute bronchiolitis due to other infectious organisms (26%, 110/432), and other dyspnea and respiratory abnormalities (24%, 28/118; Figure 1A). Across the peak and shoulder seasons combined, ICD-9 discharges for acute bronchiolitis (50%, 116/231) and acute bronchiolitis due to other infectious organisms (33%, 455/1393) had the highest RSV positivity (Figure 1A).

Among those with RT-PCR–confirmed RSV, only 35% (237/678) and 25% (155/620) during peak and shoulder seasons, respectively, had an RSV-specific ICD-9 diagnosis assigned at discharge. The most common ICD-9 discharge codes assigned to infants with RT-PCR–confirmed RSV during the peak season were acute bronchiolitis due to other infectious organisms (35%, 239/678) and acute bronchiolitis due to RSV (34%, 230/678; Figure 1B). During the shoulder seasons, the frequency of acute bronchiolitis due to other infectious organisms (35%, 216/620) was similar to that for the peak season, but acute bronchiolitis due to RSV was less common (23%, 143/620; Figure 1C).

Discussion

In this study, RSV disease in infants younger than 12 months in the ED was not often identified in discharge diagnoses. This underrecognition of RSV disease was present during both peak and shoulder seasons, presumably due to limited RSV testing. Even among infants with RSV-specific ICD-9 discharge codes, 13% were RT-PCR negative. This may imply that either a false-positive RSV rapid antigen test arose or that some infants were never tested for RSV, despite being assigned an RSV-specific ICD-9 code on discharge. A large proportion of infants with a discharge diagnosis of bronchiolitis due to other infectious organisms had RT-PCR–confirmed RSV. Although this study did not assess the presence of coinfection with other viruses, previous studies in similar populations have shown a coinfection rate of approximately 10%.[7] The diagnosis of bronchiolitis due to other infectious organisms implies that providers had ruled out RSV; the high RSV positivity rates among these infants may be due to false-negative rapid antigen tests conducted in the ED, or indiscriminate use of the ICD-9 code of bronchiolitis due to other infectious organisms. Additionally, the fact that the proportion of RSV-positive infants diagnosed with RSV bronchiolitis was lower in the shoulder seasons relative to peak season may reflect providers' lower likelihood of testing for RSV outside of the typically defined November to March season. Infants positive for RSV by RT-PCR were rarely discharged with an RSV-specific ICD-9 code during the peak season. This may be, in part, because of decreased RSV testing during the peak season compared with the onset and offset seasons. A general failure to accurately identify RSV as the causal agent of disease in hospital discharge codes is corroborated by a study of US children younger than 5 years who were tested for RSV independent of their discharge diagnosis in the inpatient and outpatient setting.[8] In the inpatient hospital setting, only 45% were diagnosed with an RSV-associated illness; among RSV-positive children in the outpatient setting, 3% had an RSV diagnosis.[8] These differences between observed RSV testing practices in the inpatient and outpatient settings may be partially explained by more severe illness in the inpatient setting and the predominance of older children 2 to 5 years of age in the outpatient setting.[8]

The clinical symptoms of RSV infection are similar to those produced by other respiratory pathogens,[3] which likely contributes to the underrecognition of the true burden of RSV disease. A 2004 survey of ED and laboratory directors from hospitals across the United States indicated that testing for RSV was ordered primarily to aid in diagnosis, prognosis, and treatment.[9] One cannot discount the value for physicians and parents in knowing which viruses are making their patient or child ill. Increased testing for RSV should be considered given the frequency of RSV disease diagnosed as otitis media, dyspnea, wheezing, and croup, especially during the shoulder seasons. Additional benefits of rapid RT-PCR testing for RSV in the ED may include improved patient care and decreased costs such as decreased length of time in ED or hospital, decreased antibiotic use, decreased number of laboratory tests ordered, and the difficult-to-measure comfort for the parents and doctors of having a specific diagnosis. A recent Cochrane review[10] regarding the use of viral testing in the ED concluded that it may reduce antibiotic usage but did not go on to recommend routine testing as the results did not reach statistical significance due to lack of power. A retrospective study of 30 US children's hospitals found that RSV testing was associated with

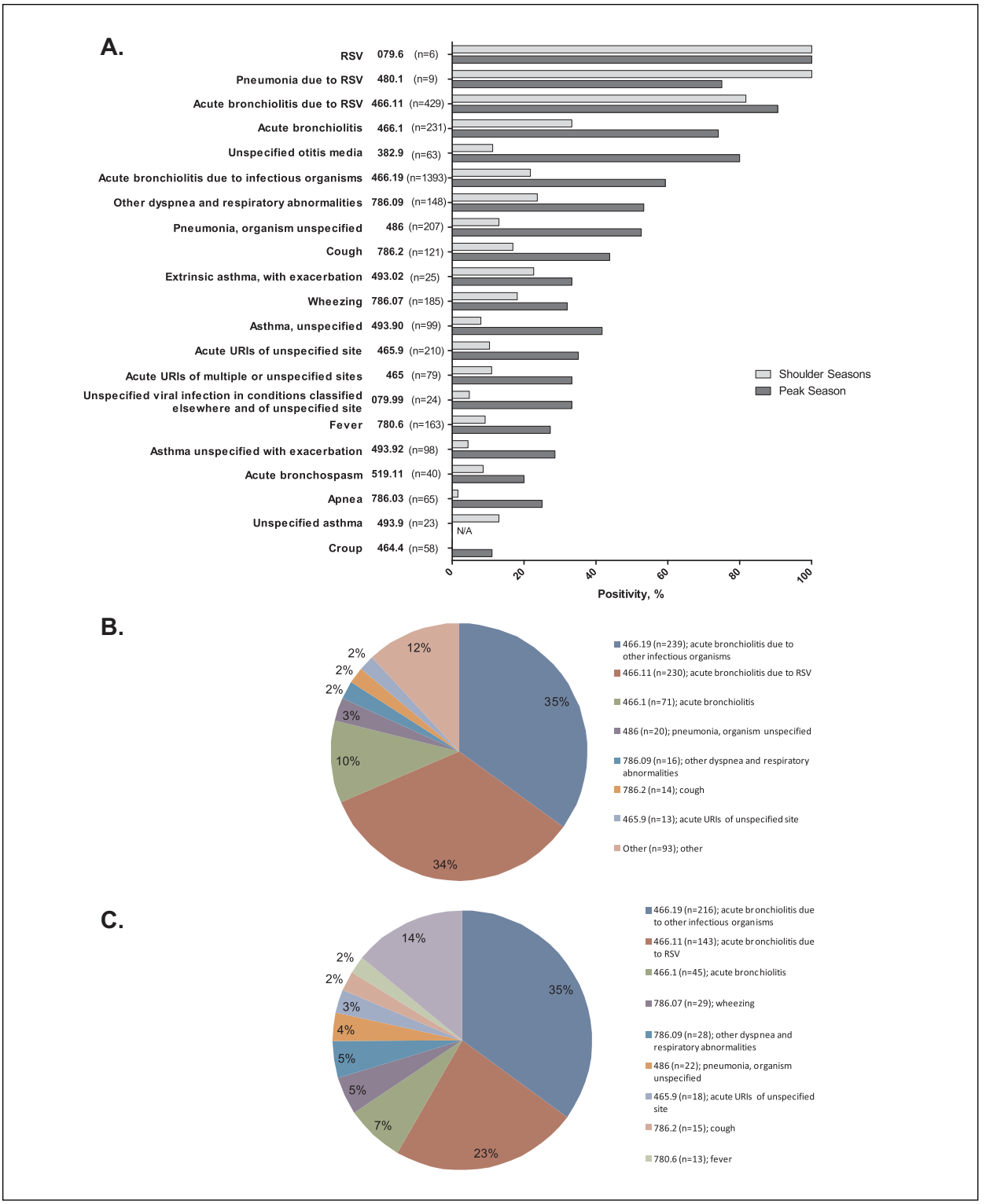

Figure 1. The percentage of (A) infants testing positive for RSV within each ICD-9 discharge code category. Codes are ordered by cumulative positivity (ie, shoulder and peak seasons combined). Discharge diagnoses among children testing positive for RSV by PCR during the (B) peak and (C) shoulder seasons.[a]

Abbreviations: ICD-9, International Classification of Diseases-Ninth Revision; N/A, not available because there were no cases during period; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; URI, upper respiratory tract infection.

[a]ICD-9 codes specific to RSV or those reported in >20 patients are presented.

decreased use of antibiotics, which in children younger than 12 months was statistically significant.[11]

Although RT-PCR, first introduced in the mid-1990s, has not been the traditional or predominant method for RSV screening, RT-PCR use in hospitals has been steadily increasing over recent RSV seasons, progressing to >20% of reported tests in 2011.[12] In clinical and research settings, the use of RT-PCR testing for respiratory illness has been associated with improved sensitivity and specificity compared with antigen detection and can be performed in 2 to 4 hours.[1] Thus, improving the accuracy of testing in the ED may result in more precise estimates of the true burden of RSV disease. In this study, RSV diagnosis by RSV-specific ICD-9 code did not correlate well with RSV positivity as diagnosed by PCR. This underscores the need for accurate and timely PCR testing being made more widely available. More widespread use of PCR has the potential of allowing us to gain a more accurate assessment of the true burden of RSV disease.

Authors' Note

Xionghua Wu was an employee of MedImmune at the time of study conduct and analysis.

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