

# Prevalence and Clinical Characteristics of Human Respiratory Syncytial Virus in Chinese Adults With Acute Respiratory Tract Infection

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Respiratory syncytial virus (RSV) is a leading cause of respiratory tract illnesses worldwide. Although the prevalence and clinical manifestations of the two subtypes, RSV-A and RSV-B, have been studied in some detail in infants and young children, they have not been determined in adults. To evaluate the prevalence of the RSV subtypes and disease severity between RSV-A and RSV-B infections in adults, nasal and throat swabs that were collected from patients  $\geq 15$  years old who sought medical care for acute respiratory infections at the Fever Clinic of the Peking Union Medical College Hospital in Beijing, China between May 2005 and April 2010. The samples were tested for RSV infection using PCR and sequencing analysis. RSV was detected in 95 (1%) of the adult patients, of whom 53 (55.8%) were positive for RSV-A and 42 (44.2%) for RSV-B. The incidence of RSV infections increased with age ( $\chi^2 = 37.17$ ,  $P = 1.66E-07$ ). Demographic data and clinical manifestations of RSV-A were similar to those of RSV-B. Although RSV-A and RSV-B co-circulated during the 2005–2006 and 2008–2009 seasons, RSV-A was predominant in the 2006–2008 seasons, whereas RSV-B was predominant in the 2009–2010 season. Upper respiratory tract infections were diagnosed in most RSV-infected patients ( $n = 80$ , 84.2%), and three patients suffered from pulmonary infection. This is the first study to provide data on the prevalence and clinical manifestations of RSV subgroups among Chinese adults with fever and acute illness, over five successive epidemic seasons. **J. Med. Virol.** 85:348–353, 2013. © 2012 Wiley Periodicals, Inc.

**KEY WORDS:** respiratory syncytial virus; acute respiratory tract infections; adults

## INTRODUCTION

Human respiratory syncytial virus (RSV) is the cause of many respiratory tract illnesses, particularly in infants and young children, leading to a large medical, and economic burden worldwide. RSV is an enveloped, single-stranded, negative-sense RNA virus belonging to the genus *Pneumovirus* of the *Paramyxoviridae* family. Based on its reactions with monoclonal antibodies and on the genetic characteristics of the attachment protein (the protein G), RSV can be divided into the subgroups A and B [Mufson et al., 1985]. Although RSV-A and -B can co-circulate in children in a community, the prevalence of each subgroup may shift yearly and can vary among different communities [Coggins et al., 1998; Scott et al., 2004; Arbiza et al., 2005; Sato et al., 2005; Deng et al., 2006;

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Zlateva et al., 2007; Shobugawa et al., 2009; Zhang et al., 2010].

In adults, RSV generally causes mild upper respiratory tract symptoms [O'Shea et al., 2007; Peter and James, 2007; Huang et al., 2009]. However, RSV infection produces severe respiratory tract illness in susceptible adult populations including in the elderly, the immunocompromised, and in those with severe underlying pathology [Falsey and Walsh, 2000; Johnstone et al., 2008]. It is not known if the prevalence of the RSV subgroups varies and if disease severity is similar between adults with RSV-A and RSV-B infections.

To evaluate the prevalence and clinical presentations of RSV infections in adults, reverse transcriptase PCR (RT-PCR) assays were performed on clinical specimens collected from patients  $\geq 15$  years old who sought medical care for acute respiratory infections at the Fever Clinic of the Peking Union Medical College Hospital in Beijing, China between May 2005 and April 2010. Epidemiological characteristics and clinical manifestations of the infection were also evaluated.

## MATERIALS AND METHODS

### Subjects and Clinical Samples

This study was part of a larger, long-term study of the prevalence of respiratory viral infections in Beijing, China [Ren et al., 2009; Xiang et al., 2010; Ren et al., 2011; Guo et al., 2012; Li et al., 2012; Xiang et al., 2012]. The study was approved by the Ethical Review Board of the Institute of Pathogen Biology, Chinese Academy of Medical Sciences. Written informed consent was obtained from each participant. Clinical specimens were collected from patients with acute respiratory infection when they first sought medical care (prior to their being admitted to a specific unit of the hospital) at the Fever Clinic of the Peking Union Medical College Hospital, a large comprehensive hospital for medical treatment, teaching, and scientific research in Beijing. According to the regulations for management of acute respiratory infection in China, all patients with acute fever must be screened at a Fever Clinic before being received by a specific medical department in a hospital. A total white-blood cell count less than  $10 \times 10^9/L$  may suggest the presence of viral infections [Ruuskanen et al., 2011]. Thus, to exclude typical bacterial infections and include potential viral infections, patients  $\geq 15$  years old were included in this study if they presented with: (1) acute fever (body temperature  $\geq 38^\circ C$ ); (2) white-blood cell count  $\leq 10 \times 10^9/L$ ; and (3) respiratory symptoms such as coughing and wheezing. On average, about 22 patients met these criteria each day during the study period. Every day during the study period, physicians blindly collected specimens from 5 to 10 patients meeting the enrollment criteria, without considering age, sex, ethnicity, and other symptoms. Nasal and throat swabs were collected from each patient, and both swabs were pooled in one tube

containing virus transport medium (VTM; Copan, Brescia, Italy). Sampling was performed every day from May 2005 to April 2010, except in July and November 2005. The samples were stored at  $-80^\circ C$  prior to being analyzed.

Physicians collected and recorded information from each recruited patient using a standardized questionnaire, which preserved anonymity of the patients. Information collected included demographic data, disease history, body temperature, antibiotic treatment or prophylaxis before visit, specific symptoms, physical signs, results of laboratory tests, chest X-rays, and preliminary clinical diagnosis. Collected information was placed into a database for statistical analysis. Disease severity was assessed according to the Guidelines for Surveillance of Severe Acute Respiratory Infections at Sentinel Hospitals (2011) issued by the Chinese Ministry of Health (<http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohjbyfkzj/s3577/201102/50590.htm>).

### Detection of RSV and Other Common Respiratory Viruses

Multiplex reverse transcriptase polymerase chain reaction (RT-PCR) or single RT-PCR assays were used to detect RSV and other viruses, including human parainfluenza virus, influenza virus, enterovirus, human coronaviruses (229E, NL63, HKU1, and OC43), metapneumovirus, adenovirus, and rhinovirus, as described previously [Ren et al., 2009]. Primers targeting the highly conserved fusion protein gene were used for RSV typing as described previously [Coiras et al., 2003]. RSV-A and -B were distinguished by the size of PCR products: 363 bp for RSV-A and 611 bp for RSV-B. Specific amplification of the fusion protein genes was confirmed by sequence analysis of the PCR products. An internal control was used to monitor efficient extraction and amplification of viral nucleic acids. Strict controls were also used during nucleic acid extraction and PCR analysis to monitor for cross-contamination.

### Statistical Analysis

Gender or age groups, prevalence by year, and demographic and clinical characteristics of the different RSV subgroups were compared using the chi-square test ( $\chi^2$  test). *P*-values  $< 0.05$  were considered statistically significant.

## RESULTS

### RSV Detection in Clinical Specimens

A total of 9,871 patients (4,547 males and 5,324 females) ranging from 15 to 97 years of age (median age of 30 years) were included in this study. RT-PCR analysis identified 95 (1%) patients (42 males and 53 females) positive for RSV. The detection rate did not differ significantly between males and females ( $\chi^2 = 0.13$ , *P* = 0.72). RSV-positive patients ranged in age from 17 to 83 years (median age of 40 years). Of

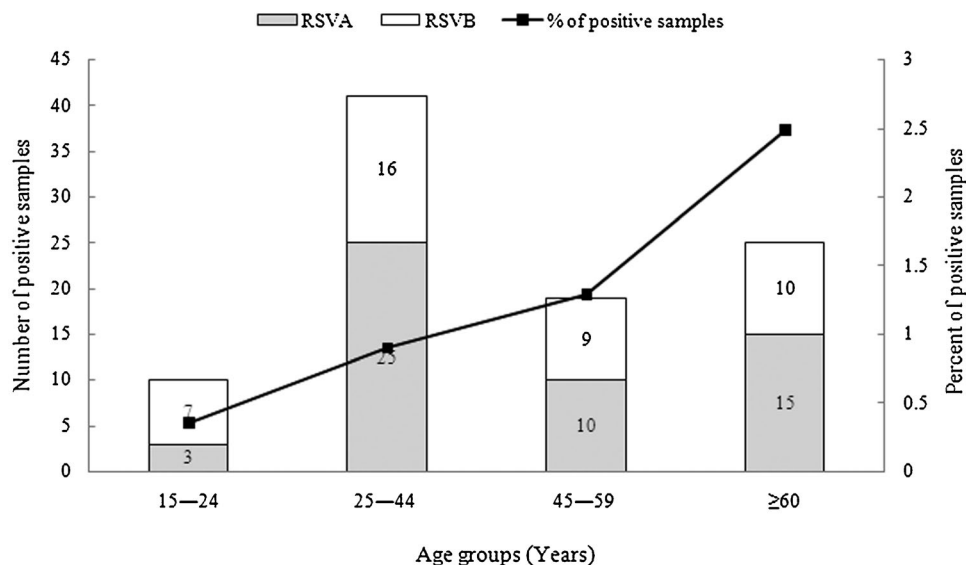


Fig. 1. Frequency of RSV detected in adult patients with fever and respiratory illness in Beijing, China. Numbers of RSV-A and RSV-B positive samples (columns) and percentage of total detection rate of RSV (line) are shown for each age group.

the RSV-positive patients, 53 (55.8%) tested positive for RSV-A and 42 (44.2%) for RSV-B (Fig. 1). RSV-positive patients were previously healthy, and none had co-morbidities.

The detection rate of RSV increased with age, with a significantly higher incidence in patients  $\geq 60$  years old than in other age groups ( $\chi^2 = 37.17$ ,  $P = 1.66E-07$ ). Incidence of RSV was about seven times higher in patients  $\geq 60$  years old (2.5%) than in patients 15-24 years old (0.4%; Fig. 1).

The rate of RSV infection fluctuated significantly each year throughout the study period and the detection rates are significantly higher in the 2009-2010 season than in other seasons ( $\chi^2 = 38.68$ ,  $P = 8.12E-08$ ). The rate decreased from 0.9% in the 2005-2006 season (May 2005 to April 2006) to 0.2% in the 2006-2007 season (May 2006 to April 2007). It then increased to 1.4% in the 2007-2008 season (May 2007 to April 2008), decreased to 1.1% in the 2008-2009 season (May 2008 to April 2009), and increased to 1.9% in the 2009-2010 season (May 2009 to April 2010).

RSV was most prevalent in November through March (73.7%), and was seldom detected in May through August (8.4%). The prevalence of RSV-A and RSV-B infections differed yearly (Fig. 2). RSV-A accounted for 100% of RSV infections in the 2006-2007 and 2007-2008 seasons. RSV-B accounted for 60% of the RSV infections in the 2005-2006 and 2008-2009 seasons and for 70% of the infections in the 2009-2010 season. RSV B was not detected from March 2006 through August 2008.

#### Co-Infection With RSV and Other Respiratory Tract Viruses

Co-infections with other respiratory viruses were detected in 23 (24.2%) of the RSV-positive patients.

Influenza virus was most frequently detected with RSV ( $n = 14$ , 14.6%), followed by human parainfluenza virus ( $n = 4$ , 4.2%), rhinovirus ( $n = 4$ , 4.2%), and adenovirus ( $n = 2$ , 2.1%). One patient was concomitantly infected with RSV-A, influenza virus B, and rhinovirus. Of the co-infected patients, 10 were positive for RSV-A and 13 were positive for RSV-B. The difference in co-infection rate was not significant between patients infected with RSV-A and RSV-B ( $\chi^2 = 1.86$ ,  $P = 0.17$ ).

#### Clinical Manifestations of Patients With RSV-A or RSV-B Infection

To characterize the clinical manifestations cause by each RSV subtype, only the clinical manifestations of patients with single RSV infections were analyzed (Table I). In addition to fever, the major symptoms of RSV single infections included pharyngeal congestion, headache, chills, myalgia, rhinorrhea, sore throat, and cough. Sixty patients (83.3%) were diagnosed with upper respiratory tract infections, and three patients (4.2%) were diagnosed with pulmonary infections. According to  $\chi^2$  analysis, median age, gender ratio, the rates at which clinical manifestations appeared, and diagnosis did differ significantly between patients infected with RSV-A and patients infected with RSV-B (Table I). Although patients infected with RSV-A reported a higher incidence of chills than patients infected with RSV-B, the difference was not statistically significant ( $\chi^2 = 3.18$ ,  $P = 0.07$ ).

#### DISCUSSION

Here, the prevalence of RSV infections was investigated in adult patients with acute respiratory

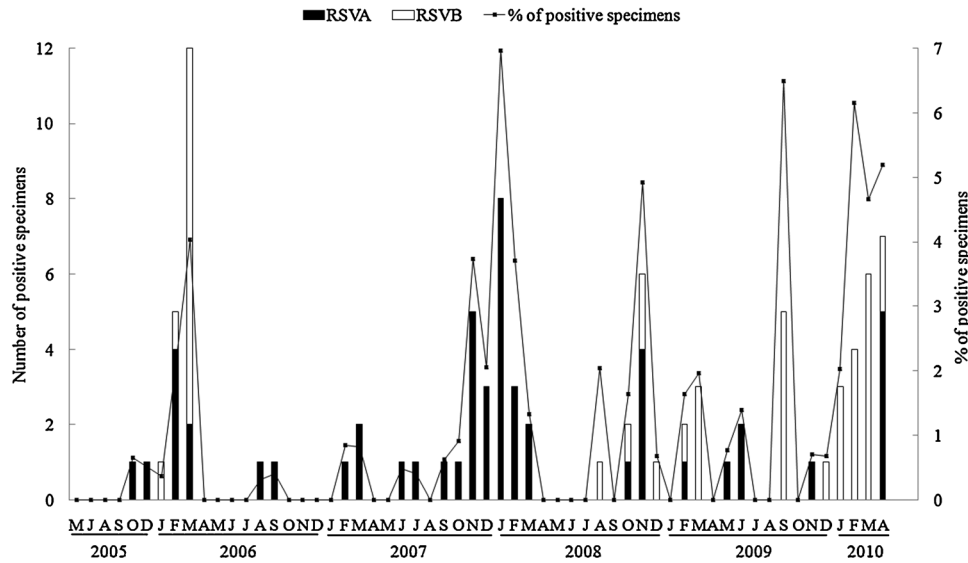


Fig. 2. Seasonal distribution of RSV-A and RSV-B in adults with fever and respiratory illness. RT-PCR analysis was used to detect the RSV-A and RSV-B subgroups in clinical samples. Numbers of RSV-A and RSV-B positive samples and percentage of total detection rate of RSV are shown for each indicated month.

infection when they first sought medical care at the Fever Clinic of the Peking Union Medical College Hospital in Beijing, China between May 2005 and April 2010. This is the first study that characterizes the incidence of RSV subgroups in Chinese adults with fever and respiratory illness. The results of this study indicate that RSV-A accounts for more cases of RSV infection (55.8%) than RSV-B (44.2%) in the study population. The ratio of RSV-A in this study is lower than that reported in Chinese children, in whom RSV-A accounts for 73.7% of the RSV infections in Beijing [Deng et al., 2006] and for 79.5% of the

RSV infections in Chongqing [Zhang et al., 2010]. Two factors may account for this disparity: (1) the subjects recruited in this study were adult outpatients, whereas those in other studies were mainly hospitalized children [Deng et al., 2006; Zhang et al., 2010]; and (2) samples were collected during different time periods. Zhang et al. [2010] collected nasopharyngeal aspirates from April 2006 to March 2009, whereas Deng et al. [2006] collected nasopharyngeal aspirates and throat swabs from November 2000 to March 2006.

This study also showed that the fluctuating prevalence patterns of the RSV subgroups in the study

TABLE I. Demographic and Clinical Manifestations Observed in RSV-Infected Adults

|  | RSV-A<br>(N = 43) | RSV-B<br>(N = 29) | P values |
|--|-------------------|-------------------|----------|
| Age, median (range)                    | 45 (18–83)        | 46 (20–75)        | 0.68     |
| Male                                   | 19 (44.2%)        | 13 (44.8%)        | 0.96     |
| Symptoms and signs                     |                   |                   |          |
| Pharyngeal congestion                  | 40 (93.0%)        | 26 (89.7%)        | 0.61     |
| Chills                                 | 36 (83.7%)        | 19 (65.5%)        | 0.07     |
| Headache                               | 32 (74.4%)        | 23 (79.3%)        | 0.63     |
| Myalgia                                | 30 (69.8%)        | 17 (58.6%)        | 0.33     |
| Rhinorrhea                             | 26 (60.5%)        | 17 (58.6%)        | 0.88     |
| Sore throat                            | 26 (60.5%)        | 16 (55.2%)        | 0.66     |
| Cough                                  | 23 (53.5%)        | 18 (62.1%)        | 0.47     |
| Sneezing                               | 19 (44.2%)        | 13 (44.8%)        | 0.96     |
| Expectoration                          | 16 (37.2%)        | 11 (37.9%)        | 0.95     |
| Rigors                                 | 6 (14.0%)         | 2 (6.9%)          | ND*      |
| Swelling of tonsils                    | 3 (7.0%)          | 3 (10.3%)         | ND       |
| Abnormal breath sounds on auscultation | 1 (2.3%)          | 0                 | ND       |
| Preliminary clinical diagnosis         |                   |                   |          |
| Upper respiratory tract infection      | 36 (83.7%)        | 24 (82.8%)        | 0.91     |
| Pulmonary infection                    | 1 (2.3%)          | 2 (6.7%)          | ND       |

\*ND, The group in which N < 5 was not included in statistical analyses.

population are similar to the patterns observed in children worldwide [Coggins et al., 1998; Scott et al., 2004; Arbiza et al., 2005; Sato et al., 2005; Zlateva et al., 2007; Shobugawa et al., 2009; Zhang et al., 2010]. In this study, RSV-A and RSV-B co-circulated during the 2005–2006 and 2008–2009 seasons. RSV-A was predominant in the 2006–2007 and 2007–2008 seasons, whereas RSV-B was predominant in the 2009–2010 season. Additionally, RSV infection appeared with an alternating high and low biennial rhythm in the study population. Similar rhythms have been observed in children from Beijing, China [Deng et al., 2006] and Chile [Avendaño et al., 2003]. The dominance of RSV-A and RSV-B has also been reported to alternate biennially in Japan [Sato et al., 2005]. A pattern in which RSV-A predominated for 2 years and RSV-B predominated for 1 year was reported in Chongqing, China [Zhang et al., 2010], Belgium [Zlateva et al., 2007], the United States [Coggins et al., 1998], and Kenya [Scott et al., 2004]. In Uruguay, two to four consecutive years of RSV-A predominance were followed by 1 year of RSV-B predominance [Arbiza et al., 2005]. Similarly, RSV-B predominance for 1 year was followed by 4 years of RSV-A predominance in Japan [Shobugawa et al., 2009].

Reports on differing virulence between RSV-A and RSV-B are controversial [van Drunen Littel-van den Hurk and Watkiss, 2012]. It has been shown that RSV-A is more likely than RSV-B to cause severe disease in hospitalized infants in two previous studies [McConnochie et al., 1990; Walsh et al., 1997]. In contrast, this study indicates that the clinical manifestations of RSV-A and RSV-B are very similar in Chinese adults with fever and respiratory illness. All of the RSV-positive patients identified in this study had mild acute respiratory infections. The disparity may be attributed to the subjects recruited. Hospitalized infants, who had severe respiratory infection even requiring mechanical ventilation, were recruited in the two previous studies [McConnochie et al., 1990; Walsh et al., 1997], whereas only adult outpatients with fever and acute respiratory illness were investigated in this study.

Additional caveats in interpreting the results of this study include the PCR analysis and the study group. The use of multiplex PCR rather than singleplex PCR to detect RSV in adults may not be optimal, as viral titers are considerably lower in adults than in infants. Limitations in the study population should also be considered. Because the outpatients could not be traced, patients who deteriorated due to worsening RSV infections may have been missed in the study, possibly resulting in an underestimate of disease severity. Additionally, due to the small number of RSV-positive patients in this study, a larger cohort of patients is needed to characterize the clinical manifestations of infections by each RSV subgroup. Although these points might be worth noting, they do not detract from the overall conclusions of this study.

Despite its limitations, this is the first study that provides data on the prevalence and clinical manifestations of RSV-A and RSV-B infections in Chinese adults with fever and acute illness over five successive epidemic seasons. Although the clinical manifestations of RSV-A and RSV-B are similar in this study, RSV-A infection occurs with higher frequency than RSV-B infection in Chinese adults with fever and respiratory illness. This research also highlights the alternating rhythm of RSV-A and RSV-B predominance and provides baseline data for the surveillance of RSV infection in China.

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