

Viral agents causing acute lower respiratory tract infections in hospitalized children at a tertiary care center in Saudi Arabia

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ABSTRACT

الأهداف: معرفة ثقل واهمية الفيروسات التنفسية عند الاطفال السعوديين المنومين ومصابين بالتهاب الجهاز التنفسي السفلي الحاد.

الطريقة: أجريت هذه الدراسة بأثر رجعي خلال الفترة من يناير 2005م إلى ديسمبر 2010م حيث تمت الدراسة في قسمي الأطفال والمختبرات الميكروبيولوجي في مستشفى الملك خالد الجامعي في المملكة العربية السعودية حيث تم جمع سوائل الأنف حلقية من 643 طفل وخضعت لفحص المناعة المضئ وذلك للكشف عن الفيروسات التالية الفيروس التنفسي الخلوي، وفيروس الغدة، وفيروس الانفلونزا، وفيروس نظير الانفلونزا.

النتائج: من بين 643 طفل مصاب بالتهاب الرئوي التنفسي السفلي تم الكشف عن وجود الفيروسات في 309 حوالي (48.1%) من العينات وكانت نتيجة تصنيف الفيروسات كالتالي: الفيروس التنفسي الخلوي (95.5%) 295 ، ونظير الانفلونزا (1.2%) 8، وفيروس الغدة (0.3%) 2، وفيروس الانفلونزا أ (0.3%) 2، وفيروس الانفلونزا ب (0.3%) 2. كان الفيروس التنفسي الخلوي يسود (75%) من الأطفال الأقل من سنة في العمر ووجد أن الأطفال اليافعين والذكور هم أكثر عرضة للإصابة بمرض شديد وقد ظهرت أغلب الحالات في فصل الشتاء. من 309 عينة وجد التهاب القصيبات في (81.2% n=251) ووجد أيضا التهاب رئوي في (14.2% n=44) ($p < 0.0001$).

خاتمة: تشكل الفيروسات سبب رئيسي في حدوث الالتهاب الرئوي السفلي عند الأطفال في السعودية حوالي (48.1%) من الحالات. فيروس التنفسي الخلوي يعتبر أكثر فيروس مسبب للمرض (95.5%)، ووجد أن الأطفال الأكثر عرضة للإصابة بالمرض هم الأطفال الذين تقل أعمارهم عن سنة ونسبة إصابتهم بالتهاب القصيبات أكثر من إصابتهم بالالتهاب الرئوي.

Objectives: To determine the load and importance of respiratory viruses in hospitalized Saudi children with acute lower respiratory tract infections (ALRIs).

Methods: A retrospective study was performed in the Departments of Pediatrics, Pathology/Microbiology, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia from January 2005 to December 2010. Nasopharyngeal aspirates were collected from 643 children with ALRI. Viruses were detected by direct immunofluorescence, respiratory syncytial virus (RSV), adenovirus (ADV), type 1 to 3 parainfluenza viruses (PIV), and type A and B influenza virus (flu).

Results: Of the 643 children with ALRI, viruses were detected in 309 (48.1%) specimens. The viruses that were identified included RSV (n=295, 95.5%), PIV (n=8, 1.2%), ADV (n=2, 0.3%), flu A (n=2, 0.3%), and flu B (n=2, 0.3%). The RSV was predominated in 231 (75%) children less than one year of age. Only younger age and male gender were associated with severe illness. The peak frequency of the viruses detected was in the winter. Of the 309 virus positive samples, bronchiolitis was detected in 81.2% (n=251), and pneumonia in 14.2% (n=44) ($p < 0.0001$).

Conclusion: Viruses are an important cause of ALRIs in Saudi children constituting approximately 48.1% of the total cases. The RSV is the most common pathogen (95.5%) causing ALRIs. Most of the children were younger than one year of age, and were more likely to present with bronchiolitis than pneumonia.

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Acute lower respiratory tract infection (ALRIs) is a leading cause of morbidity and mortality among children in developing countries. In these countries, it causes 19% of all deaths among children younger than 5 years, and 8.2% of all disability.¹ Little is known regarding the epidemiology of respiratory viruses causing ALRI in the Kingdom of Saudi Arabia (KSA). The aim of this study is to determine the prevalence of respiratory viruses, age distribution, clinical manifestations, risk factors, and seasonal occurrence of respiratory viruses in children younger than 17 years old, and hospitalized with ALRIs.

Methods. This retrospective study was conducted at the Departments of Pediatric, and Pathology/Microbiology, King Khalid University Hospital, Riyadh, KSA between January 2005 to December 2010. The charts of all children admitted with ALRIs (n=643; 344 males, 299 females) were reviewed. Our inclusion criteria included hospitalized children younger than 17 years with clinical diagnosis of ALRIs. We recorded the gender, age, direct immunofluorescence assays results, and treatment type for each patient. A diagnosis of bronchitis, bronchiolitis, or pneumonia at discharge was considered as ALRI. Clinical factors such as prematurity, pre-existing diseases such as immune deficiency, chronic lung disease, congenital heart disease, and congenital anatomical abnormalities were also recorded. Nasopharyngeal aspirates (NPA) were collected from each patient. Direct immunofluorescence assays were performed as per the manufacturer's instructions (IMAGEN, Oxoid, Cambridgeshire, United Kingdom) to identify the following respiratory viruses: respiratory syncytial virus (RSV); adenovirus (ADV); type 1 to 3 parainfluenza viruses (PIV), and type A and B influenza virus (flu).

Statistical analysis. All data were encoded on Microsoft Excel 2007 version and exported to Predictive Analytics Software (PASW) version 18 (IBM-SPSS Inc, Chicago, IL, USA) for analysis. Descriptive data were presented as mean, standard deviation, and percentages. Continuous data were analyzed using the independent t-test, and categorical data were analyzed using the Chi-square test. Statistical results were considered significant when $p < 0.05$.

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Results. During the 6-years study, 643 hospitalized cases of ALRI were investigated. Among all samples, respiratory viruses were detected in 309 samples. The overall detection rate was 48.1%. Of the positive samples, RSV was identified most frequently with 295 cases, which accounted for 95.5% of the total viral agents. Other viruses detected were PIV (1.2%, ($p < 0.0001$), flu (0.3%, $p = 0.1240$), and ADV (0.3%, $p = 0.992$). Coinfection with 2 kinds of virus was not identified in those samples. During these 6 years, the proportion of viral etiology ranged from 37.9% in 2008 to 69% in 2007 ($p = 0.0200$). In this study, some differences in the prevalence rates were noticed in each year, with the predominance of RSV virus identified from ALRIs as shown in Table 1. The age distribution of ALRIs by specific virus is shown in Table 2. Most viral infections occurred in the first 3 years of life (n=287 cases). Approximately 245 cases were younger than one year. The highest rate of RSV infection was identified in infants during the first 6 months of life ($p < 0.03$). The monthly distribution of respiratory tract viruses is shown in Figure 1. All viruses were detected through the year. The RSV was detected in each month, and peaked in the winter. Most of the admissions occurred in the months of January (n=94), February (n=82), and March (n=38). The number of males (n=344) was slightly more than females (n=299) with a ratio of 1.34:1. The association between clinical diseases and specific agents is shown in Table 3. Of the 309 virus positive samples, bronchiolitis was detected in 264 (85%), and pneumonia in 45 (14.5%). The RSV was the most often causative agent of both diseases (bronchiolitis in 251 and pneumonia in 44) ($p < 0.0001$). To assess the effects of host factors on the development of an acute respiratory infection specifically from RSV as compared with other causes, we compared the results of children with respiratory infections who were RSV-positive with those who were RSV-negative. In this study, although the number of the children with non RSV with underlying disease was higher than those with RSV, there was no significant statistical difference ($p = 0.0001$). Also, this study showed a high percentage of using antibiotics in both groups (RSV and non RSV) but it was of no statistical importance ($p = 0.0001$) (Table 4). The degree of severity of ALRIs was evaluated by the number of intensive care admissions. In this study, 41 patients required admission to the intensive care ward, and bronchiolitis was diagnosed in 35 patients. Of those, 29 patients were found to be with RSV positive test.

Discussion. Acute lower respiratory tract infections are the main causes of morbidity and mortality. In

Table 1 - The frequency of virus detection carried out by direct immunofluorescence assay between 2005-2010 in a study conducted at the Departments of Pediatric, and Pathology/Microbiology, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

Virus	2005 (n=63)	2006 (n=137)	2007 (n=113)	2008 (n=116)	2009 (n=112)	2010 (n=102)	Total (N=643)	P-value
RSV	26	60	72	43	45	49	295 (45.9)	0.0200
ADV		1	1				2 (0.3)	0.992
<i>Flu</i>								
Type A			1	1			2 (0.3)	0.1240
Type B		2					2 (0.3)	0.1240
<i>PIV</i>							8 (1.2)	
Type 1								
Type 2								
Type 3	2		4			2	8 (1.2)	<0.0001
Total	28 (41.3)	63 (45.9)	78 (69)	44 (37.9)	45 (40.2)	51 (50)	309 (48.1)	

n (%), RSV - respiratory syncytial virus, ADV - adenovirus, Flu - influenza virus, PIV - parainfluenza virus

Table 2 - The frequency of virus detection in acute lower respiratory tract infection among different age groups in a study conducted at the Departments of Pediatric, and Pathology/Microbiology, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

Variables	RSV	ADV	Flu		PIV		
			Type A	Type B	Type 1	Type 2	Type 3
<i>Gender</i>							
Male	146	2	1	2			4
Female	149		1				4
<i>P-value</i>							
<i>Age</i>							
<6 months	170	2	2	2			5
≥6-12 months	61						
>1-3 years	42						3
≥3-6 years	8						
>6-12 years	6						
13-14 years	8						
Total	295	2	2	2			8

RSV - respiratory syncytial virus, ADV - adenovirus, Flu - influenza virus, PIV - parainfluenza virus

Table 3 - The association between clinical diseases and specific agents found in a study conducted at the Departments of Pediatric, and Pathology/Microbiology, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

Virus	Bronchiolitis (n=404)	Pneumonia (n=224)	P-value
RSV	251	44	<0.0001
ADV	2	0	0.5403
<i>Flu</i>			
Type A	2	0	0.5403
Type B	2	0	0.5403
<i>PIV</i>	1	1	0.9980
Type 1			
Type 2			
Type 3	6	0	0.0937

RSV - respiratory syncytial virus, ADV - adenovirus, Flu - influenza virus, PIV - parainfluenza virus

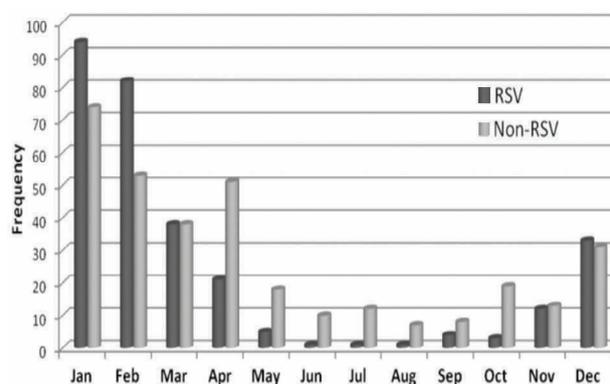


Figure 1 - The monthly distribution and frequency of respiratory tract viruses. RSV - respiratory syncytial virus

Table 4 - Clinical characteristics of children under 17 years of age with or without respiratory syncytial virus (RSV) infections.

Variables	n	RSV n=295	Non RSV n=348	P-value
<i>Gender</i>				
Male	344	146	198	0.0681
Female	299	149	150	
<i>Age</i>				
<6 months	342	170	172	0.0395
>6-12 months	131	61	70	0.9218
>1-3 years	91	42	49	0.9980
>3-6 years	29	8	21	0.0554
>6-12 years	32	6	26	0.0016
13-17 years	18	8	10	0.9980
<i>Underlying conditions</i>				
B. asthma + HAAD	155	44	111	0.0001
Premature	48	24	24	0.4519
Immunodeficiency	2	1	1	0.9980
Cardiac problem	25	13	12	0.5463
<i>Down syndrome</i>	11	5	6	0.9980
Other	11	2	9	0.0730
Others	45	16	39	0.0105
<i>Treatment</i>				
Antibiotic	474	193	281	0.0001
Steroids	298	130	168	0.3027

B. asthma - bronchial asthma, HAAD - hyperactive airway disease

under-developed countries the mortalities in children were accounted for 33-50%, mostly in those children less than 5 years of age.² Viruses are not only a very important cause of ALRIs, it also responsible for a significant percentage of childhood deaths. The most important viruses are the RSV, influenza virus type A and B, PIV 1 to 3, and ADV.³ There is very little information on the epidemiology of the respiratory viruses causing ALRIs in children in this region.^{4,5} Data on the viral etiology of ALRIs in developing countries showed the detection rate varies between 22-55% depending on the method used.^{6,7}

In our study, viruses were identified in 48.1% of children as sole infectious agents. These results agree with reports from other authors.^{8,9} In most studies performed in developed and developing countries, RSV was found to be the predominant viral cause of ALRIs in childhood, being responsible for 27-90% of hospitalized cases.^{5,10-12} Similarly in the present study, RSV was the major viral pathogens accounting for approximately 45.8% of the ALRI, and 95.5% of the total viral agents. In most studies, males were more commonly affected than females, and the male to female ratio was between 1.5 and 1.8.¹³ In our study, the gender ratio was approximately 1.34:1 (344 males, 299 females). We also examined differences in virus types among the different age groups, most viral infections occurred during the first 3 years of life, the infection rate was highest in children aged <6 months, with a secondary peak at one to 3 years. The rate of RSV was significantly higher in infants during the first 6 months of life than in any other age group ($p<0.03$). Also flu A/B, PIV 3, and ADV were most frequently detected in children <6 months. These results of our study corresponded with other studies of ALRI in developing countries in which age incidence of ALRI in our study was comparable to those observed in other countries, that is, children aged under one year being the most affected.¹⁴⁻¹⁶

Previous studies have demonstrated the association of viral infection and climate.^{2,4,17} We analyzed the seasonality of viral ALRI in children, and almost all viruses were detected through the year. The RSV was detected in each month, and peaked during winter months. Most of the admissions occurred in the months of January (n=168), February (n=135), and March (n=76). Sawadkahi et al¹⁸ in their study reported that RSV is responsible for a large number of hospital admissions during winter and spring. Out of 70 children with RSV infection, 31 patients (44.3%) were referred to the hospital during the first month of winter.¹⁸ Bronchiolitis and pneumonia are the most common manifestations of viral lower respiratory tract infections

in infants. In one study,¹⁹ bronchiolitis accounted for 16% of the cases and pneumonia for 34.6%. In our study, the major clinical syndromes associated with RSV infection were bronchiolitis (n=251), and pneumonia (n=44) ($p<0.0001$). Although RSV infection is the most important viral cause of severe acute lower respiratory tract infection, only a small proportion of children infected with this virus develop severe disease. In one study,²⁰ it was found that severe lower respiratory syndromes associated with RSV infection commonly includes pneumonia and bronchiolitis.

In our study, 41 out of 643 patients (6%) required admission to the intensive care ward, and bronchiolitis was diagnosed in 35 patients. Of those, 29 were positive with RSV. In another study, 56 out of 70 of their patients (83%) had mild disease, not requiring admission to hospital, and 20% of their patients (n=14) had moderate to severe infection requiring admission to a general ward and intensive care unit. The RSV infection was the most common virus isolated in those children.²¹ Risk factors for severe RSV infection have been identified in some studies. Infants who are premature, have chronic lung disease, congenital heart disease, or immunodeficiency disorders, or have underlying metabolic or neuromuscular disorders are at increased risk for developing especially severe RSV disease.²²⁻²⁴ In our study, we have specifically focused on congenital heart disease, prematurity, immune deficiency and syndrome as risk factors of severe RSV and non RSV bronchiolitis and pneumonia. However, only a younger age and male gender were identified to be independently associated with severe illness requiring hospitalization in the intensive care. Previous reports have found that multiple logistic-regression analyses revealed that none of these potential risk factors, independently correlated with more severe illness among patients with severe RSV and non RSV infection, only prematurity and a young age were independent risk factors for hospitalization.²⁵⁻²⁷ Despite being viral infections, our study pointed to a high frequency in the use of injected antibiotics (74.7%) of children with RSV (n=193), and non RSV (n=281, $p=0.0001$). In one study,²³ antibiotics were administered upon admission for most of the patients (69.5%). In another study,²⁷ 60.5% of RSV and ADV positive children received antibiotics after admission. The prescribing of antibiotics may be due to viral illnesses being mistaken with bacterial infection. Corticosteroids are commonly prescribed for treating RSV bronchiolitis, however, no study has proven their therapeutic efficacy. In our study, corticosteroids were prescribed for 46% of children with RSV and non RSV ALRI. In one study,²⁷ corticosteroids were prescribed for 40% of children with ADV, and 26% with RSV.

Our analysis is based on a retrospective study and has some limitations. First, the small sample size may indicate that other positive results of NPA for ALRIs infections went undetected. Second, measurements of clinical variables were obtained from a clinical chart review that may be incomplete.

In conclusion, despite the above limitations, our study has shown that viral infection is a very important cause of ALRI in our area. The RSV is an important pathogen in our community, and has significant impact in pediatric hospitalization. A continued multi-center surveillance may help in a better understanding of the epidemiology of respiratory viral infections, and may be used for monitoring respiratory viruses involved in ALRI, also it improves the orientation of therapeutic and preventive measures, avoids unnecessary use of and antibiotics, and helps control hospital infection.

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