*Original Article*

# Risk factors of prolonged hospital stay in children with viral severe acute respiratory infections

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## Abstract

Introduction: Severe acute lower respiratory infections (SARIs) are one of the major causes of morbidity and mortality in young children, especially in developing countries. The present study focused on detection of risk factors for prolonged hospital stays among children with viral SARIs.

Methodology: A sentinel surveillance study was conducted at Cairo University Hospital (CUH) between February 2010 and May 2011. Nasopharyngeal (NP) and oropharyngeal (OP) swabs were collected from all children admitted with SARIs. Viruses were identified using reverse transcription polymerase chain reaction (RT-PCR).

Results: Out of 1,046 children, 380 (36%) were positive for one or more viruses; these included respiratory syncytial virus (RSV) (22.9%), adenovirus (6.2%), parainfluenza viruses (PIVs1-3) (5.1%), human metapneumovirus (HMPV) (4.5%), influenza A (1.4%), and influenza B (0.6%). Viral etiology was mainly detected in children under one year of age (88.9%). Prolonged length of stay was independently associated with the presence of cyanosis and underlying chronic illness (OR 7.4, CI: 1.8-30.32 [p = 0.005], OR 2.5, CI: 1.36-4.64 [p = 0.004], respectively). Virus type did not affect the length of hospital stay (p > 0.05). Oxygen therapy was required in 91% of the patients. A total of 43 patients (11.6%) required intensive care admission. Twenty-one patients (5.5%) died, and 15 of them (71.4%) had an underlying chronic illness.

Conclusions: The study demonstrated the important burden of respiratory viruses as a cause of SARI in hospitalized children in a tertiary Egyptian hospital. Cyanosis and underlying chronic illness were significantly associated with prolonged length of stay.

**Key words:** respiratory viruses; children; SARI; prolonged stay.

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## Introduction

Acute respiratory infections (ARIs) are a leading cause of morbidity, hospitalization, and mortality among children worldwide, particularly in developing countries and in young children under five years of age [1]. The most frequently implicated viruses among hospitalized children are respiratory syncytial virus (RSV), human metapneumovirus (hMPV), influenza A and B viruses, parainfluenza viruses (PIV1-2-3), and adenoviruses [2-4]. Other commonly implicated causes are human rhinoviruses, human corona viruses, enteroviruses, and human bocavirus [5-9]. Seasonality is one of the features of respiratory viruses, and geographical variation related to temperature, rainfall, and relative humidity have been identified in epidemiological studies [10,11].

The epidemiology of respiratory viral infections in developing countries, including Egypt, is not well studied. The present study focused on detection of risk factors for prolonged hospital stay among children with viral SARI, including demographic and clinical characteristics of patients, and the type and seasonality of different respiratory viral pathogens causing acute lower respiratory infection (ALRI).

## Methodology

*Study design, study setting, and population*

A sentinel surveillance study was conducted at - two tertiary care hospitals belonging to Cairo University Pediatric Hospital, with a total bed capacity of 800 beds, between February 2010 and May 2011. All children who were hospitalized in pediatric

intensive care units (PICUs) and pediatric wards with the World Health Organization (WHO)'s case definition for severe acute respiratory infections (SARIs) were enrolled [12].

The enrollment criteria consisted of an acute respiratory infection with onset during the previous seven days requiring hospitalization that included either history of fever and/or current fever ≥ 38°C or current hypothermia < 35.5°C and at least one of ab normal breath sounds, tachypnea (according to age), cough, or respiratory distress (nasal flaring, chest indrawing, grunting).

An enrollment form was used to collect the following data from enrolled patients: demographic data including age, gender, and residence; clinical data including number of days of symptoms prior to admission; symptoms and signs of respiratory distress; core temperature and respiratory rate on admission; presence of an underlying chronic illness; need for and duration of oxygen therapy; need for and duration of ICU admission; need for and duration of ventilation; radiographic and laboratory diagnostic data; total duration of hospitalization; and outcome.

*Outcome measurement and definitions*

Children with ALRI were classified as having pneumonia when they had respiratory distress, crackles on physical examination, and chest radiographic evidence of pneumonic infiltrates. Children under two years of age with wheezing and signs of air trapping on radiograph were considered to have bronchiolitis [4]. Prolonged length of stay (PLOS) was defined as > 10 days, which is beyond the 75th percentile of hospital stays. Presence of suspected bacterial infection was defined as a core temperature > 38.5°C and a band count > 10%.

Univariate analysis was done to determine the association between PLOS and various demographic and clinical characteristics. A multivariate analysis was done using a logistic regression model to determine factors associated with PLOS. Variables statistically significant in the univariate analyses were included in the model.

*Ethics*

Informed verbal consent was obtained from the parents or guardians of all the patients. The study design conformed to the Revised Helsinki Declaration of Bioethics [13] and was approved by the Scientific Ethics Committee of Department of Pediatrics, Faculty of Medicine of Cairo University.

*Sample collection*

Nasopharyngeal (NP) and oropharyngeal (OP) swabs were obtained from each patient on admission by trained personnel using standard operating procedures as described by the WHO (2009), and both swabs were placed in a 15 mL falcon tube containing 2 mL of viral transport medium (VTM). NP and OP swabs in VTM were kept at 4°C for no more than 24 hours and were then stored at -70°C until testing.

*Molecular identification of respiratory viruses*

Total nucleic acid (TNA) was extracted from the NP/OP swabs by the automated KingFisher Flex Magnetic Particle Processor (Thermo Scientific, Waltham, USA) using MagMAX Total Nucleic Acid Isolation Kit (Cat No. AM 1840, Applied Biosystems, Foster City, USA) according to the manufacturer's instructions. All the viral targets were amplified using specific primers and probes produced by the Center of Disease Control and Prevention (CDC), Atlanta, USA, and following standard protocol for quantitative reverse transcription PCR detection.

Detection of influenza viruses was conducted in the Cairo University Hospital laboratory and confirmed by the Naval Medical Research Unit No.3 (NAMRU-3) laboratory. For the detection of influenza viruses, viral RNA was extracted from the NP/OP swabs using Qiagen Viral RNA Extraction Kit in the automated QiaCube system (Qiagen, Venlo, Netherlands) following the manufacturer's instructions. The samples were screened for the presence of influenza A and B using the CDC kit for influenza following CDC protocol [14]. For all the samples, the human RNAse P gene (RP) was used as an internal positive control to ensure proper sample collection and handling as described by the CDC protocol. The influenza A and influenza B primer and probe set were designed for universal detection of type A and type B influenza viruses. Influenza A-positive samples were all typed according to the CDC protocol to the following types: pandemic influenza 2009 A(H1N1), seasonal H1, and H3. Further typing of H5a and H5b was done at the NAMRU-3 laboratory.

Testing for adenovirus, human parainfluenza viruses 1, 2, and 3 (hPIV), respiratory syncytial virus (RSV), and human meta-pneumovirus (hMPV) was done at NAMRU-3 laboratory by RT-qPCR using CDC specific primers and probes and following a CDC protocol for the detection of non-influenza viruses. Samples were considered positive to the viral target if the amplification curve crossed the threshold line before cycle 40. All clinical samples had to be

positive for RP, with a Ct value ≤ 37, for validation. A positive control for each virus was added to each run to ensure adequate amplification of the target genes.

*Statistics*

Data were coded and entered using the statistical package SPSS version 16 (IBM Corp, Armonk, New York, United States). Data were summarized using median (range) for quantitative variables and number and percent for qualitative variables. Comparison between groups was done using the Chi-square test for qualitative variables, independent sample *t* test for normally distributed quantitative variables, while the Mann-Whitney U test was used for quantitative variables that are not normally distributed. Multivariate stepwise logistic regression analysis was done for predictors for prolonged length of stay.The logistic regression model included variables that were significant by univariate analysis. P < 0.05 was considered significant.

## Results

*Study population and clinical presentation*

One or more viral pathogens were detected in 380 (36.33%) out of 1,046 enrolled children. The demographic and clinical characteristics on admission of the 380 children with viral SARIs are shown in Table 1. Nasal flaring, cough, fever ≥ 38ºC, chest indrawing, wheezing, and grunting were the most prevalent signs among the patients (93%, 87.4, 75%, 71.6%, 51.6, and 48.6%, respectively). The predominant chest radiographic findings were infiltrates and consolidations. Evidence of co-existing bacterial infection was present in 45 patients (11.8%), and an underlying medical condition was present in 41.1% of patients.

Statistically significant differences were found regarding the presence of cough, nasal flaring, and chest indrawing among children under one year of age, children between one and five years of age, and children over five years of age (p = 0.000, 0.000, and 0.002, respectively) (Table 2).

*Hospital course*

The median duration of hospital stay in our study was 7 days (range 2-120 days). Twenty-two percent of the patients diagnosed with viral lower respiratory tract infections had a PLOS of > 10 days, which is beyond the 75th percentile of the median length of stay. Admission of 87.1% of patients was to pediatric wards. Data of supplemental oxygen therapy, ICU admission, and mechanical ventilation are shown in Table 3. Out of a total of 380 patients with viral ALRIs, 21 patients (5.5%) died, 16 of whom were admitted to the PICU and required a ventilator (Table 2). Fifteen of the patients who died had an underlying chronic illness (71.4%). All the patients who died were under one year of age.

*Predictors of prolonged hospital stay*

By univariate analysis comparing patients with viral respiratory tract infections who had a PLOS with those who did not, a statistically significant association was found between PLOS and the following factors: clinical presentation with lethargy (p = 0.008), cyanosis (p = 0.003), having any underlying chronic illness (p = 0.000), and having an underlying chronic cardiac disease (p = 0.021). No association was found with the type of virus, co-infection with other viruses, or seasonality (p = 0.599, 1.000, and 0.067, respectively). By stepwise multivariate logistic regression analysis, the presence of cyanosis on admission and the presence of an underlying chronic illness were independent risk factors for PLOS (OR 7.4, CI 1.802-30.315 [p = 0.005], OR 2.502, CI 1.350-4.639 [p = 0.004], respectively).

*Viral etiologies, age distribution, and seasonality*

Respiratory viruses were detected in 380 patients. RSV was the most frequently detected virus (240/1,046; 22.9%), followed by adenovirus (65/1,046; 6.2%), parainfluenza viruses (53/1,046; 5.1%), human metapneumovirus (48/1,046; 4.5%), influenza A – which were all swine flu (H1N1) – (15/1,046; 1.4%), and influenza B (7/1,046; 0.6%). Infections caused by one virus accounted for 31.8% (333/1,046) of cases. Infection with multiple viruses (viral co-infection) was found in 4.5% (47/1,046); dual infections were identified in most cases, while infection with three different respiratory pathogens was found in one child only. RSV was the most frequent virus involved in co-infections, followed by adenovirus (Table 4). The presence of infection with multiple viruses was not significantly associated with a PLOS (p = 0.602).

The incidence of viral infections and co-infections was higher in children under one year of age (88.9%), followed by children between one and five years of age (7.9%) and by children over five years of age (3.2%) (Figure 1). Distribution of viruses among age groups is shown in Table 5.

**Table 1.** Characteristics of children hospitalized with viral lower respiratory tract infections

| | |
|---|---|
| **Age** | |
| Years, median (range) | 0.42 (0.01-14.00) |
| **Gender** | **Number (%)** |
| Male | 213 (56) |
| Female | 167 (44) |
| **Diagnosis on admission** | **Number (%)** |
| Pneumonia | 320 (84.2) |
| Bronchiolitis | 60 (15.8) |
| **Clinical Presentation** | **Number (%)** |
| Nasal flaring | 344 (93.0) |
| Cough | 332 (87.4) |
| Fever | 282 (75.0) |
| Chest indrawing | 265 (71.6) |
| Wheezes | 196 (51.6) |
| Grunting | 180 (48.6) |
| Refusal of feeds | 106 (29.2) |
| Vomiting | 41 (11.3) |
| Lethargy | 32 (8.8) |
| Cyanosis | 28 (7.4) |
| Convulsion | 16 (4.4) |
| **Symptomatic days prior to admission** | 4 (1-45) |
| **Admission temperature (ºC, range)** | 38.0 (36.0-41.0) |
| **Types of chronic illness (number [%])** | 155 (41.1) |
| Chronic respiratory illness | 27 ( 17.4) |
| Chronic cardiac disease | 79 ( 51.0) |
| Chronic neurologic disease | 36 ( 23.2) |
| Other chronic disease | 13 (8.4) |
| **Hospital stay (days)** | 7 (2-120) |
| **Blood profile** | **Number (%)** |
| Thrombocytopenia | 22 (8) |
| Leucopenia | 30 (10.9) |
| Leucocytosis | 14 (5.1) |
| Bandemia (>10%) | 45 (11.8) |
| **Chest X-ray findings** | **Number (%)** |
| Normal | 9 (2.4) |
| Infiltrates | 182 (47.9) |
| Consolidation | 178 (46.8) |
| Effusion | 3 (0.8) |
| Cavitation | 2 (0.5) |

**Table 2.** Clinical presentation of the patients by age group

| **Clinical symptoms and signs** | **< 1 year (290)** | **1-5 years (80)** | **> 5 years (10)** | **P value** |
|---|---|---|---|---|
| Nasal flaring | 264 | 75 | 5 | 0.000 |
| Cough | 242 | 80 | 10 | 0.000 |
| Fever | 216 | 62 | 8 | 0.777 |
| Chest indrawing | 204 | 59 | 2 | 0.002 |
| Wheezes | 145 | 46 | 5 | 0.491 |
| Grunting | 140 | 37 | 3 | 0.510 |
| Refusal of feeds | 91 | 23 | 1 | 0.332 |
| Vomiting | 25 | 7 | 0 | 0.623 |
| Lethargy | 25 | 6 | 1 | 0.935 |
| Cyanosis | 13 | 1 | 1 | 0.257 |
| Convulsions | 12 | 3 | 1 | 0.645 |

**Table 3.** Hospital course of viral positive ALRI children

| Hospital course | |
|---|---|
| Oxygen therapy, number (%) | 336 (91.1) |
| Duration of oxygen therapy, days (median range) | 3 (1-44) |
| ICU admission, number (%) | 43 (11.6) |
| Duration of ICU admission, days (median range) | 6 (1-23) |
| Mechanical ventilation, number (%) | 27 (7.3) |
| Duration of mechanical ventilation, days (median range) | 6 (1-21) |
| Death, number (%) | 21 (5.5) |

**Table 4.** Identified viral etiologies

| Viral causes | Single infection, number | Co-infection, number | Total positive, number |
|---|---|---|---|
| RSV | 204 | 36 | 240 |
| Parainfluenza | | | 53 |
| PIV-1 | 2 | 1 | 3 |
| PIV-2 | 2 | 0 | 2 |
| PIV-3 | 39 | 9 | 48 |
| hMPV | 42 | 6 | 48 |
| Adeno | 36 | 29 | 65 |
| Flu A (H1N1) | 8 | 7 | 15 |
| Flu B | 1 | 6 | 7 |
| Total | 333 | 47 | 380 |

**Table 5.** Age specific incidence of viral infections in the study

| Viruses detected | < 1 year (290) N (%) | 1-5 years (80) N (%) | > 5 years (10) N (%) | Total positive cases | *P value |
|---|---|---|---|---|---|
| RSV | 220 (91.7) | 16 (6.7) | 4 (1.7) | 240 | 0.041 |
| hPIV-1 | 2 (66.7%) | 0 | 1 (33.3%) | 3 | 0.010 |
| hPIV-2 | 0 | 2 (100) | 0 | 2 | 0.000 |
| hPIV3 | 46 (95.8) | 1 (2.1) | 1 (2.1) | 48 | 0.241 |
| hMPV | 41 (85.4) | 4 (8.3) | 3 (6.2) | 48 | 0.416 |
| Adeno | 54 (83.1) | 9 (13.8) | 2 (3.1) | 65 | 0.148 |
| Flu A (H1N1) | 11 (73.3) | 1 (6.7) | 3 (20.0) | 15 | 0.001 |
| Flu B | 7 (100) | 0 | 0 | 7 | 0.642 |
| Co-infections | 42 | 3 | 2 | 47 | 0.835 |

*P < 0.05 was considered significant

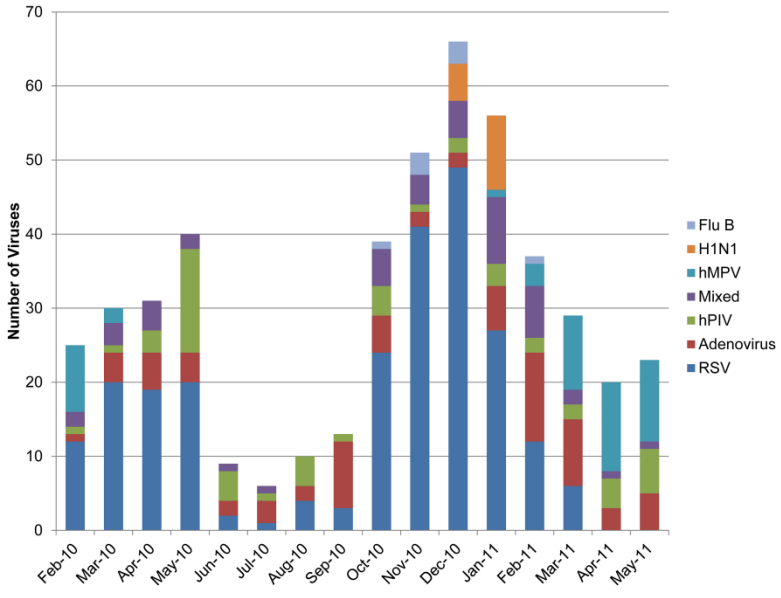


**Figure 1.** Monthly distribution of all viruses in the study

The monthly distribution of viruses is shown in Figure 1. RSV, adenovirus, and PIV3 infections were detected throughout the year. The peak incidence of RSV occurred in the cold months, especially November and December, with very low incidence in the summer. Adenovirus infection peaked in late winter and spring, while the peak incidence of PIV infections was in the spring. HMPV infections occurred in late winter and spring. Influenza infections occurred in the cold months. Co-infection with multiple viruses was detected throughout the year, peaking in the cold months (Figure 1).

## Discussion

We identified a viral etiology in 36.3% of patients hospitalized with SARI. RSV was the most predominant respiratory virus with a prevalence of 22.9%. The overall incidence is comparable to previous studies conducted in other developing countries [15-17] and to studies conducted in Middle Eastern countries [18-20]. The predominance of RSV is in concordance with the assertion that this virus is the single most frequently identified lower respiratory tract pathogen in hospitalized infants and young children worldwide [21-24].

Adenovirus was the second most frequently detected virus in the current study and was responsible for 6.2% of viral lower respiratory tract infection-related hospitalizations. These results are in concordance with previous studies from Ghana [17] and Saudi Arabia [19], in which adenovirus was the second most frequently detected virus following RSV infection. However, other studies carried out in Saudi Arabia [18,20] showed that parainfluenza was the second most frequently detected virus following RSV. In Kuwait, Hijazi *et al*. [25] identified RSV as the most frequent viral pathogen in children with lower respiratory tract infections, followed by influenza and parainfluenza.

Our study recorded a 5.1% prevalence of PIV infections with the predominant type being PIV-3. Similar hospital-based studies have been reported in other developing countries [17,26,27].

Influenza viruses, including pandemic H1N1 virus, were less frequently identified in patients, accounting for only 2% of cases, and they were mostly in children under one year of age. A similar low prevalence of influenza viruses has been previously reported among hospitalized children in Ghana and Thailand [17,28]. The low prevalence of influenza in this study may be explained by the fact that only patients with SARI needing admission were included in our study. Patients with mild respiratory symptoms did not undergo diagnostic testing for viral infections; they were treated in outpatient clinics and were not enrolled.

The incidence of viral co-infection in the current study was 4.5%, which was lower than that reported in other studies [29-32]. RSV was most frequently involved in co-infections, followed by adenovirus. Interestingly, the viruses most commonly involved in co-infections were the viruses with the highest incidence. The differences in the incidence of co-infection may reflect geographic differences or differences in etiologic agents [33,34] or diagnostic methods [35]. Co-infection of influenza with other viruses was detected in 13 cases, mainly with RSV. This is in contrast to the results of Tanner *et al*., who reported that the pandemic strain of influenza A(H1N1) was notable in that it was the least likely to be co-detected with another respiratory virus [36].

In Cairo, the climate is a hot desert climate [37], but often with high relative humidity (~50%–60%). Wind storms can be frequent, bringing Saharan dust into the city during the months of March and April. The climate of Egypt is characterized by a hot season from May to October and a cool season from November to April. The temperatures are hot or very hot on summer days and warm or mild on winter days, but warm on summer nights and cool on winter nights. Rainfall is sparse and only happens in the colder months, but sudden showers cause harsh flooding [38].

In this study, RSV infections occurred throughout the year, with clusters in cold months and peak incidence in November and December. Similarly, in a previous study done in the United Arab Emirates, RSV activity was detected throughout the year with a predominance during cooler months with an associated relative humidity (RH) between 50% and 60% [39]; however, in India, RSV identifications were most frequent in the fall and winter, continued at a lower level throughout the year, and increased during the rainy season in July and August [40]. RSV seasonality in this study differs from a previous study conducted between December 2006 and November 2007 in Egypt by Fattouh *et al*. [41], who recorded that 97.1% of RSV infections occurred between December and February. Differences existed in the design of the studies and in the laboratory methods, as they used immunoflourescent assay (IFA) to detect viruses, while we used RT-PCR for virus detection. Adenovirus infections occurred throughout the year, with clusters in cold months. These results matched those reported in India [40] and Kuala Lumpur, Malaysia [11].

Viral infections occurred mostly in children one year of age and younger (88.9%), followed by children between one and five years of age (7.9%) and children over five years of age (3.2%). This is consistent with the age distribution of viral ALRI reported in developing countries [15-17,40-43] and Middle Eastern countries [18,20,24]. However, we did not identify a significant association between PLOS and the type of virus or seasonality. The median duration of hospitalization of children with viral lower respiratory tract infection in our study was 7 days (range, 2-120 days), and 22% of the patients had a PLOS. Similarly, a study examining the viral etiologies of acute respiratory infections among hospitalized Vietnamese children found that the median duration of hospitalization was 6 days, and 25% of patients were hospitalized for more than 7 days [29].

Multivariate logistic regression analysis revealed that cyanosis at presentation and the presence of an underlying chronic illness were independent risk factors for PLOS in children with viral ALRI (OR 7.4, CI: 1.8-30.32 [p = 0.005], OR 2.5, CI: 1.36-4.64 [p = 0.004], respectively). These findings are consistent with those of Coffin *et al*. [46], who reported that cardiac and neurologic/neuromuscular diseases were independent risk factors for prolonged hospitalization among children hospitalized with laboratory-confirmed influenza. In another study, Wang *et al*. [47] found that there was a significant prolonged hospitalization attributable to RSV in patients with underlying chronic illness (median 9.5 days; range 1 to 47 days) compared to those without known risk factors (median 5 days; range 1 to 35 days; $p < 0.001$).

Similarly, Coffin *et al.* [44], found no association between prolonged LOS and influenza type.

Limitations of our study include a possible underestimation of viral etiologies of ALRI because testing for coronaviruses, bocaviruses, and rhinoviruses was not done, and these three viruses were previously detected in hospitalized patients [5-9]. Additionally, the prevalence of asymptomatic or very mild illness was not been included in the study, which may affect the overall prevalence of the studied viruses. It is also possible that the pattern of viral infections varies in other governorates with differing climates. However, the hospital is a tertiary hospital and accepts referrals from many governorates.

## Conclusions

Viruses are a major cause of SARIs in hospitalized children under one year of age. PLOS was significantly associated with cyanosis on presentation and with the presence of underlying chronic diseases, which underscores the importance of early recognition and categorization of these children as a high-risk group on their first visit to an emergency department or outpatient clinic, for prompt management and follow-up.

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