

**REVIEW**

# Etiology of acute viral respiratory infections common in Pakistan: A review

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**Summary**

Respiratory infections, especially those of the lower respiratory tract, remain a foremost cause of mortality and morbidity of children greater than 5 years in developing countries including Pakistan. Ignoring these acute-level infections may lead to complications. Particularly in Pakistan, respiratory infections account for 20% to 30% of all deaths of children. Even though these infections are common, insufficiency of accessible data hinders development of a comprehensive summary of the problem. The purpose of this study was to determine the prevalence rate in various regions of Pakistan and also to recognize the existing viral strains responsible for viral respiratory infections through published data. Respiratory viruses are detected more frequently among rural dwellers in Pakistan. Lower tract infections are found to be more lethal. The associated pathogens comprise respiratory syncytial virus (RSV), human metapneumovirus (HMPV), coronavirus, enterovirus/rhinovirus, influenza virus, parainfluenza virus, adenovirus, and human bocavirus. RSV is more dominant and can be subtyped as RSV-A and RSV-B (BA-9, BA-10, and BA-13). Influenza A (H1N1, H5N1, H3N2, and H1N1pdm09) and Influenza B are common among the Pakistani population. Generally, these strains are detected in a seasonal pattern with a high incidence during spring and winter time. The data presented include pneumonia, bronchiolitis, and influenza. This paper aims to emphasise the need for standard methods to record the incidence and etiology of associated pathogens in order to provide effective treatment against viral infections of the respiratory tract and to reduce death rates.

**KEYWORDS**

Acute viral respiratory infections, Bronchiolitis, children, developing countries, enteroviruses, epidemiology, etiology, HMPV, incidence, Influenza, Pakistan, Pneumonia, rhinoviruses, RSV, Viral respiratory infections

## 1 | INTRODUCTION

Respiratory tract infections (RTI) can be defined as the infection in any part of the respiratory tract. RTIs can be further classified as upper

tract respiratory infections (UTRI) and lower tract respiratory infections (LTRI). The infections of the upper tract are most common and include rhinitis, croup, sinusitis, pharyngitis, epiglottitis, and laryngitis. The infections of the lower tract are more fatal and include

**Abbreviations:** ALRI, Acute lower respiratory tract infection; ARI, Acute respiratory infections; HMPV, Human metapneumovirus; LRTI, Lower respiratory tract infection; qPCR, Quantitative polymerase chain reaction; RSV, Respiratory syncytial virus; RTI, Respiratory tract infection; RT-PCR, Real-time polymerase chain reaction; URTI, Upper respiratory tract infection

pneumonia, bronchitis, bronchiolitis, and influenza.<sup>1</sup> Acute respiratory infections (ARI) are tremendous cause of health problems and mortality in emerging countries.<sup>2</sup> In South Asia, 48 of every 1000 children died before the age of five.<sup>3</sup> Pakistan is currently ranked as the sixth most populous country with the population of 199 million.<sup>4</sup> It is estimated that about 20% to 30% of all deaths of children under 5 years of age are because of respiratory infections in Pakistan.<sup>5</sup> This paper comprises an introduction to viral respiratory infections, common genotypes of viruses associated with respiratory infections in different regions of Pakistan, and data from surveys led from 2007 onwards.

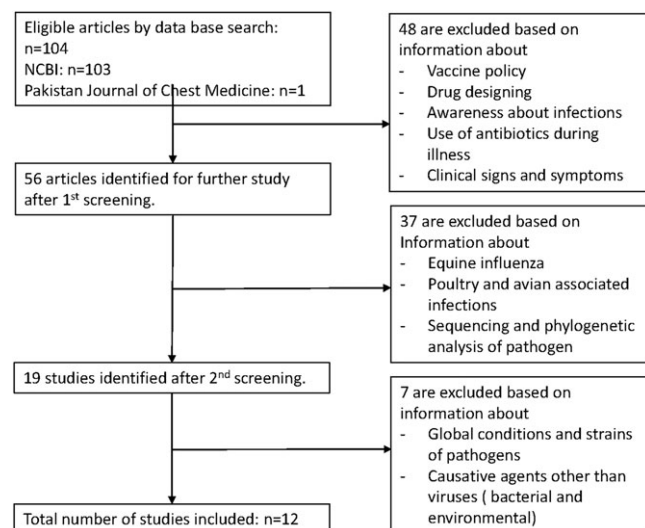
## 2 | METHODOLOGY

### 2.1 | Literature search strategy

A literature review was conducted to identify the published studies having data of viral respiratory infections in Pakistan. To perform the literature review, we searched the PubMed database for articles published between 2000 and 2018, using the key terms “viral respiratory infections,” “influenza,” “pneumonia,” “bronchiolitis,” “common cold,” combined with the terms “morbidity,” “mortality,” “fatality,” “epidemiology,” “etiology,” “genotypes,” “developing countries,” “South Asia,” “Pakistan,” “prevalence,” “incidence” for articles published in English. Titles and abstracts of publications were reviewed, and articles containing data of viral respiratory infections from Pakistan were included. Studies were evaluated by all team members (Figure 1).

### 2.2 | Inclusion and exclusion criteria

The inclusion criteria for studies were study of respiratory infections caused by viruses, data from Pakistan, publications from the year 2000 onwards in English language, and there was no restriction on subject age and gender (Figure 1). The exclusion criteria were bacterial infections, information about countries other than Pakistan, and infections of non-human species.



**FIGURE 1** Flow chart showing the process of literature selection for the review

## 3 | RESULTS

We initially identified 104 electronic articles from NCBI and Pakistan Journal of Chest Medicine that met our original search strategy. Figure 1 identifies the strategy used to screen articles for this review. After obtaining and evaluating each article, 12 articles were incorporated, and 92 were excluded. Out of 12 included articles, seven (including four for bronchiolitis and one for influenza) were about viral strains which were responsible for causing pneumonia in children and in older adults, and five were about surveillance and epidemiology of viral strains that cause influenza (Table 1). The excluded articles were related to vaccine policies, drug designing for eradication purpose of infection, raising awareness, clinical symptoms of infections, infections caused by bacterial and environmental influences, and had information about the global status of infections.

### 3.1 | Included studies

The characteristics of the articles included in this systematic review of the literature are shown in Table 1.

### 3.2 | Etiology

Viral etiology of LTRIs includes respiratory syncytial virus (RSV) and parainfluenza virus 3 among Pakistani population.<sup>6</sup> According to a study, enterovirus/rhinovirus, coronavirus, parainfluenza virus, adenovirus, and human Bocavirus were also found to be associated with respiratory infections particularly with viral pneumonia.<sup>7</sup> RSV was labeled as a dominant causative agent of lower RTI in a research conducted in a tertiary care healing center of Gilgit Baltistan where RSV genotypes were detected in 75 out of 105 children <2 years of age suffering from ARIs during the winter season from December 2011 to March 2012. The 75 identified strains were typed as 71 strains of RSV-A and four strains of RSV-B.<sup>8</sup> Another study employed 1941 samples, analyzed by real time polymerase chain reaction (RT-PCR) for RSV infection. Twenty four percent of samples were positive, and out of these positive, 22% were subtyped RSV-B. Three genotypes of RSV-B—BA-9, BA-10, and BA-13—were isolated.<sup>9</sup> Throat swabs were tested by RT-PCR. Nineteen percent of cases were identified as RSV associated infections. RSV appeared to be more incident from August to October and highest in September. Susceptibility increased in rainy seasons.<sup>10</sup> HMPV was detected in 7% of the cases in the above scenario, most of which were children under 1 year of age.<sup>11</sup>

The results of a surveillance study conducted during January 2008 and December 2011 determined influenza A as a causative agent of infection in a great number of people. A total of 6258 samples were analyzed by RT-PCR assay, out of which 1489 samples were positive for influenza virus. Seventy-two percent of which were influenza A, and 28% were influenza B. Among influenza A, three strains were identified. These strains were A/H1N1, A/H3N2, and A/H1N1pdm09.<sup>12</sup> The results of another hospital-based study confirmed the viral association with ALRI. The study was conducted in two hospitals of twin cities of Pakistan from November 1986 to

**TABLE 1** Distribution of viral pathogens responsible for RTIs across Pakistan, studies from 2000 to 2018

Reference Publication	Year of Publication	Study Duration	Geographical Location	Infection Studied	Cases Studied	Age Group	Viral Genotypes
13	2000	November 1986-March 1988	Rawalpindi, Islamabad	ALRIs	553 out of 1492	>60 months	RSV, parainfluenza 3, influenza A&B, adenovirus
17	2005	October 1999-April 2000	Rawalpindi, Islamabad	Pneumonia, bronchiolitis	80 infected out of 391	2 months-3 years	RSV
27	2008	October-December 2008	Peshawar (KPK)	Influenza	5 (4 confirmed, 1 asymptomatic)	22-33 years	Influenza A/H5N1
28	2011	2006-07	Northwest Frontier Province (KP)	Influenza	20 (4 confirmed, 7 likely, 9 possible)	25-35 years	Influenza A/H5N1
29	2012	2009-10	Not specified	Influenza	497 out of 1287	Not specified	Influenza A/(H1N1)pdm09 (n = 262), B (n = 180), A(H3N2) (n = 6), non-typed influenza A viruses (n = 49)
19	2013	17 August 2009-16 September 2011	Karachi	Pneumonia (n = 13), bronchiolitis (n = 4), URTI (n = 3), Asthma (n = 2), other syndromes (n = 1)	812 enrolled, 27 positive, 4 deaths	>5 year	Influenza A/(H1N1)pdm09 (n = 27) (H3 in 7 children) 1 untyped
8	2013	2011-2012	Gilgit-Baltistan	ARIs	80 out of 105	<2 years	RSVA genotype-A1/GA2 (n = 71), RSVB genotype-BA (n = 04), influenza A (n = 05), HMPV (n = 04)
12	2013	Jan 2008- Dec 2011	Islamabad, KP, Punjab and Baluchistan	ILI, SARI	1489 out of 6258	≥65	Influenza A (n = 1066; A/H1N1 25, A/H3N2 169 A/(H1N1)pdm09 872), influenza B (n = 423)
18	2013	Nov 2010-Sep 2011	Karachi	Pneumonia, influenza	169	6 weeks- 2 years	HMPV (n = 24), influenza A/H1N1 (n = 08), non-typed A (n = 01), RSV (n = 30)
9	2017	Mar 2011-April 2012	Islamabad	ALRI, Pneumonia, UTRI-bronchiolitis	117 out of 155	6 weeks-2 years	RSVA (n = 69), RSVB (n = 35), influenza A (n = 38), influenza B (n = 11), HMPV (n = 08), adenovirus (n = 13) [single virus (n = 67), 2 pathogens (n = 45), up to 3 (n = 5) cases]
6	2016	Not specified	Rawalpindi	LTRI	72 out of 150	<10 years	Parainfluenza virus 3 (n = 27), RSV (n = 27), influenza A (n = 15), influenza B (n = 3)
20	2016	Oct 2015-Feb 2016	Peshawar	Pneumonia	37 out of 145	4 < 20 years > 33	Influenza A/H1N1
7	2016	Oct 2011-June 2014	Matiari (Sindh)	Pneumonia	204 out of 692	<2 years	RSV (n = 13), influenza B (n = 04), HMPV (n = 05), enterovirus/rhinovirus (n = 119), human coronavirus (n = 21), parainfluenza virus (n = 33), adenovirus (n = 08), human Boca virus (n = 01)
10	2017	Aug 2009-June 2012	Karachi	ARI, Pneumonia (n = 87), bronchiolitis (n = 89), asthma (n = 31), URI (n = 20)	227 out of 1150	<5 years	RSV
16	2017	Oct 2010-April 2013	Not specified	ALRI; ILI (n = 295), SARI (n = 177)	472 out of 1941	<5 years	RSVA (n = 367), RSVB genotype-BA (n = 105)
30	2017	Dec 2015-Jan 2016	North West Pakistan	Influenza	11 out of 37	40.46 (±15.27) years	Influenza A/(H1N1)pdm09
11	2018	Aug 2009-June 2012	Karachi	ARI Pneumonia (n = 29), bronchiolitis (n = 18), asthma (n = 19), URI (n = 10)	84 out of 1150	<5 years	HMPV

March 1988. A total of 1492 nasopharyngeal aspirates were analyzed. The patients enrolled were presented with wheezing, cough, high breathing rate, and chest retraction. Results indicated the viral etiology in 37% of the cases, of which 33% of the total (and 89% of cases with viral etiology) were resulted positive for RSV. Other pathogens identified were parainfluenza 3, influenza A&B, and adenovirus. RSV also showed peak activity in cold and showery weather from December to February.<sup>13</sup>

## 4 | DISCUSSION

### 4.1 | Pneumonia

Pneumonia is an ARI of the lower tract particularly the lungs. It is a fatal disease and can be viral, bacterial, or fungal. Viral pneumonia is commonly caused by RSV. Children under 5 years of age are more susceptible for pneumonia which was responsible for killing 920 136 (16%) children worldwide in 2015.<sup>14</sup> Every year, almost 200 million cases of viral pneumonia occur, which affects children and adults equally.<sup>15</sup> Common symptoms include cough, high-temperature fever, wheeze, runny nose, and nasal congestion.<sup>9,16</sup> In 2017, UNICEF assessed 64% of children under age 5 indicating the symptoms of pneumonia in Pakistan.<sup>3</sup>

A study employing 391 cases of pneumonia showed the dominant behavior of RSV. It was conducted in Armed Forces Institute of Pathology from October 1999 to April 2000. Nasopharyngeal aspirates were collected from different pediatric units of Rawalpindi and Islamabad for analysis purpose. Eighty samples showed positivity for RSV with a clear peak activity in winter season.<sup>17</sup> Another study conducted in Karachi from August 2009 to September 2011 reported 13 out of the 27 cases diagnosed with pneumonia which were positive for influenza A(H1N1)pdm09.<sup>18</sup> One more study was conducted during November 2010 and September 2011 in Karachi, Pakistan. All of the children were admitted because of severe pneumonia, out of which 18% were diagnosed with viral pneumonia. Throat swabs were analyzed using RT-PCR. Out of 169 children, 24 were detected with human metapneumovirus (HMPV), 9 with influenza A and 30 with RSV. Nine out of 169 admitted patients (aged 6 weeks to 2 years) with pneumonia were diagnosed positive for influenza A virus, out of which eight tested positive for H1N1 strain.<sup>19</sup> According to a descriptive study from Lady Reading Hospital Peshawar, conducted during October 2015 and February 2016, out of 145 suspected cases, 37 were selected on the basis of various factors including age, gender, residence, hypoxia, pregnancy status, symptoms, positivity to PCR, fatality, ventilation support, and radiological findings. All of the cases were tested positive for H1N1 strain of influenza A.<sup>20</sup> In 2016, one more study was conducted in the rural district of Matiari in Sindh, Pakistan. Nasopharyngeal swabs were collected from identified cases of pneumonia. The analysis was done by using multiplex RT-PCR. A total of 817 newborns were enrolled and 49 enrolled for 2 years; 77.8% (179/230) were positive for any of the following: RSV, influenza virus, HMPV, enterovirus/rhinovirus, coronavirus, parainfluenza virus, adenovirus, and human Bocavirus. The incidence of 11.9 per 100

children was observed for laboratory-confirmed viral pneumonia; 51.7% of patients were detected with Enterovirus/rhinovirus, 8.3% with parainfluenza virus type 3, and 5.7% with RSV.<sup>7</sup> Bashir and colleagues conducted a detailed study during March 2011 to April 2012 in two hospitals of Islamabad, Pakistan; 75% of cases among children aged less than 2 years were viral. Samples were analyzed using RT-PCR. Major pathogens included 44% RSV-A, 23% RSV-B, 24.5% influenza A, 7% influenza B, 8.4% adenovirus, and 5.2% HMPV. RSV-A and RSV-B association was detected more commonly during 2 to 6 months of age, while influenza A was estimated as more common in 2.1 to 6-month age group.<sup>9</sup> RSV association with kids between the ages of one and 5 years old suffering from pneumonia and asthma was the most widely recognized finding of a 3-year study conducted in Karachi from August 2009 to June 2012. In older children between the ages of one and 5 years old, pneumonia and asthma were the most widely recognized findings.<sup>10</sup> In another study conducted by the group, the cases were characterized by pneumonia followed by bronchiolitis.<sup>11</sup>

### 4.2 | Bronchiolitis

Bronchiolitis is an acute viral infection, characterized by the inflammation of bronchioles. It is a contagious infection of the lower respiratory tract, and incidence is high during the winter season. It is more common in immuno-compromised individuals.<sup>21</sup> Key pathogens associated with the condition of bronchiolitis include influenza virus, RSV, coronavirus, adenovirus, and rhinovirus.<sup>22</sup>

A study conducted in Armed Forces Institute of Pathology from October 1999 to April 2000 estimated the association of RSV with bronchiolitis in 20% of the cases. A total of 391 nasopharyngeal aspirates from Rawalpindi and Islamabad were analyzed using direct immunofluorescence. Children aged between 2 months and 3 years were enrolled for study. Results pointed out the significant increase of about 50% in activity of RSV in winter.<sup>17</sup> Another study conducted in Agha Khan University Hospital, Karachi identified 27 positive cases for influenza A(H1N1)pdm09. This study was conducted from August 2009 to September 2011. Total of 812 children were enrolled, out of which 3.3% resulted positive with viral etiology. Four of the admissions diagnosed were of bronchiolitis. The samples were tested using RT-PCR. The results of this study estimated 15% fatality rate.<sup>18</sup> Association of key viral pathogen RSV and influenza virus was identified in children under 2 years of age hospitalized with bronchiolitis during March 2011 and April 2012 in Islamabad, Pakistan. Major pathogens involved were RSV-A, RSV-B, influenza A, influenza B, adenovirus, and HMPV. Cases involving dual and even multiple pathogens were also identified.<sup>9</sup> Children less than 5 years of age conceded with intense respiratory contaminations (ARI) were enlisted for another study conducted at Aga Khan University Hospital, Karachi. This study spanned the duration of 3 years from August 2009 to June 2012. RT-PCR was done for RSV testing by using throat swabs. Out of 1150 children selected, RSV was recognized among 223 (19%). The most noteworthy rate of RSV identification was in infants under 3 months of age (48/168, 29%), which represented 22% of all RSV distinguished. Most normal determination in RSV positive babies (<12 months of

age) was bronchiolitis trailed by pneumonia whereas in other study, 7% (84 out of 1150) of the cases were identified with the presence of HMPV, 67% (56 out of 84) of which were children under 1 year of age, and these cases were characterized by bronchiolitis trailed by pneumonia.<sup>10,11</sup>

### 4.3 | Influenza

Influenza or flu is an acute and contagious viral infection of the respiratory tract.<sup>23</sup> Influenza viruses are RNA viruses belonging to family orthomyxoviridae. Influenza A and influenza B are the two key viral strains blamable for inflicting infection, a transmissible respiratory illness in humans. Additionally, Zika virus infection also seems to be the reason behind the influenza-like illness in certain cases.<sup>24</sup> In 2009, the rapid worldwide spread of an emerging reassorted strain, influenza A(H1N1)pdm09, was detected in the USA along with Mexico. This condition pushes WHO to raise the pandemic alert. This pandemic mainly affected 214 countries and killed 18 449 people.<sup>25</sup> In 2008, about 28 000 to 111 500 deaths of children aged under 5 years due to influenza-related infections were estimated around the globe. In developing countries, that ratio is around 99%.<sup>26</sup>

The first human case of influenza A/H5N1 virus infection from Pakistan was restricted to a cluster of four brothers. Evidence of these cases suggested the occurrence of the transmission chain. It began with a poultry culling operation that was carried out in late October 2007. It was performed in the response to a laboratory-confirmed outbreak in a poultry breeding farm located near Abbottabad in the then North West Frontier Province (now KhyberPakhtun Khawa). Thirteen people performed in this operation. One of those was a 25-year-old Livestock Production officer, who became the index case. This was the initial transmission that was from poultry to human. This was followed by next three generations of human to human transmission because of long and intimate contact among brothers.<sup>27</sup>

In another evidence of human to human spread in KhyberPakhtun Khawa, 20 positive cases for A/H5N1 influenza were identified in October 2007. One subject had poultry infected H5N1 virus, other eight patients got an infection by human-to-human-transmission. However, 12 patients did not show any epidemiological relation with group of other eight patients.<sup>28</sup> In June 2009, the first case with A (H1N1)pdm09 influenza infection was documented. Between 27th April 2009 and 31st August 2010, 1287 suspected cases were analyzed by means of RT-PCR. Influenza A (H1N1)pdm09 were detected in 262 samples from Pakistan. While others exhibited combinations of influenza A (unknown type), influenza B, and influenza A/H3N1.<sup>29</sup> According to another study conducted in a tertiary care hospital throughout December 2015 until the end of January 2016, patients with cough, nasal congestion, wheezing, and chest pain were likely to develop complications of RTI and were suspected for influenza A/H1N1 and severe acute respiratory illness (SARI). Samples from 36 patients were obtained and analyzed by qPCR. Out of 11 patients, seven were confirmed with the presence of influenza A/H1N1pdm09 strain. Three patients died because of further respiratory complications.<sup>30</sup>

## 5 | CONCLUSION

The results of literature review acknowledged numerous gaps in the availability of data. Reportedly, lower tract infections have high fatality rate. Particularly in the countryside communities of Pakistan, the occurrence of respiratory viruses is more periodic and common especially in children under 2 years of age. Evaluation of reported data has identified several pathogens involved in causing respiratory infections. Pathogens involved include RSV, HMPV, enterovirus/rhinovirus, coronavirus, influenza virus, parainfluenza virus, adenovirus, and human Bocavirus. Especially, RSV is a major respiratory pathogen as reported by cited articles with both RSV-A and RSV-B, circulating in Pakistan. It is responsible for causing the death of children and infants. Three genotypes of RSV-B, BA-9, BA-10, and BA-13, are observed. Influenza A (H1N1, H5N1, H3N2, and H1N1pdm09) and influenza B are common among Pakistani natives. Despite the fact that influenza strains keep circulating during the whole year but usually causes seasonal pandemics with high occurrence during winter and spring period. A number of diseases are associated with respiratory tract. However, available data include pneumonia, bronchiolitis, and influenza. Pneumonia is common among children whereas every year 2 to 3 episodes of influenza are commonly observed. Bronchiolitis is not common. On the other hand, such high mortality rate is also because of the inadequate awareness and lack of disease control strategies.

### CONTRIBUTION

Z.F. conceived and designed the study. R.N., U.J., A.U., and S.A. collected the data and wrote the manuscript. Z.F. and A.G. finalized the draft and supervised the study. All authors discussed the results and contributed to the final manuscript.

### CONFLICT OF INTEREST

None declared.

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