Research Article

iMedPub Journals
www.imedpub.com

Journal of Biomedical Sciences
ISSN 2254-609X

2020
Vol.9 No.4: 41

Respiratory Pathogens in Pediatric Patients in Saudi Arabia: Seasonal Variation and Epidemiological Distribution?

Saleh Al Harbi[1,2*], Sumayyah Ahmed Nezar Kobeisy[1], Omer Mohammed Akbar Hossain[1], Khalid Mohammed Abadullah Faruqi[1], Bayan Yassin Sayed[1], Ibrahim Hussain Ali Muzaffar[1], Shahd Sameer Majdali[1] and Hisham Abudulmalik Essa[1]

[1]Soliman Fakeeh Hospital, Jeddah, Saudi Arabia

[2]Umm Al-Qura University, Mecca, Saudi Arabia

***Corresponding author:** Saleh Al Harbi

salharbi@fakeeh.care

Department of Pediatrics, Dr. Soliman Fakeeh Hospital, Jeddah, Saudi Arabia

Citation: Harbi SA, Kobeisy SAN, Hossain OMA, Faruqi KMA, Sayed BY, et al. (2020) Respiratory Pathogens in Pediatric Patients in Saudi Arabia: Seasonal Variation and Epidemiological Distribution. J Biomedical Sci Vol.9 No.4:41

Abstract

Background: Acute respiratory tract infections remain one of the most common causes for pediatric visits to primary care providers, emergency departments and pediatric hospitalizations. Multiplex Polymerase Chain Reaction (mPCR) testing allows for rapid detection of pathogens in as little as six hours and some kits can test as many as 20 pathogens at a time.

Objective: The aim of this study is to explore the incidence, seasonal distribution, relationship with C-Reactive Protein (CRP), and epidemiological association of various respiratory pathogens among the pediatric age group.

Methodology: A retrospective study was conducted at Dr. Soliman Fakeeh Hospital in Jeddah, Saudi Arabia to analyze the results of the Respiratory Film Array Panel taken via nasopharyngeal swabs from December 2018 to December 2019 in the pediatric age group. Data was collected and analyzed using IBM SPSS Version 20.

Results: 534 patient's files were reviewed for multiplex PCR nasopharyngeal samples. Age group and pathogen coinfection or monoinfection was statistically significant (x2 (8, N=534)=21.304, p=0.006). There was a statistical significance between age group and enterovirus (F (2.792, 115.875)=3.186, p=0.013), respiratory syncytial virus (F (1.939, 35.065)=7.312, p=<0.0001), rhinovirus (F (2.792, 115.875)=3.186, p=0.013) and influenza B (F (0.831, 23.903)=4.600, p=0.001).

Conclusion: Studies in Saudi Arabia and the Middle East in general are limited regarding the various pathogens that cause acute respiratory tract infection in the pediatric age group. This is a ground break study that sheds light on the seasonal variation, age presentation, association of CRP with various pathogens and incidence of not only viral but bacterial organisms as well by the use of mPCRr.

Keywords: Multiplex PCR; Pediatrics; Respiratory infection

Received: December 11, 2020; **Accepted:** December 19, 2020; **Published:** December 31, 2020

Introduction

Acute respiratory tract infections remain one of the most common causes for pediatric visits to primary care providers, emergency departments, and pediatric hospitalizations [1-3]. However, they serve as a diagnostic dilemma for clinicians due to the nonspecific symptoms of the various pathogens, whether viral or bacterial, that cause them [4-5]. Investigative lab tests, chest radiographs, and antibiotics have been unnecessarily ordered for children in treating upper and lower respiratory tract infections [1-3]. Traditional microbiological testing of organisms such as culture or direct immunofluorescence can take days or involve a time-consuming process with minimal yield. Multiplex Polymerase Chain Reaction (mPCR) testing allows for rapid detection of pathogens in as little as six hours and some kits can test as many as 20 pathogens at a time [5-6]. The mPCR technique has been found to decrease the burden on healthcare systems by reducing demand for chest radiographs and antibiotics and improving isolation measures [7].

In the Middle East, and specifically Saudi Arabia, limited research has been conducted regarding the incidence and epidemiological features of the various pathogens causing respiratory tract infections [8-9]. The aim of this study is to explore the incidence, seasonal distribution, relationship with C-Reactive Protein (CRP), and epidemiological association of various respiratory pathogens among the pediatric age group.

Methodology

A retrospective study was conducted at Dr. Soliman Fakeeh Hospital in Jeddah, Saudi Arabia to analyze the results of the Respiratory film array panel taken via nasopharyngeal swabs from December 2018 to December 2019. Nasopharyngeal swab samples for all the involved study subjects were obtained by trained health care workers during the hospital visit, which was then analyzed by the BioFire film array respiratory panel.

The collection of medical records for analysis was approved by the Dr. Soliman Fakeeh Hospital Institutional Review Board (DSFH IRB). A total of 534 pediatric patient's files, between the ages of 0 to 15 years of age, were reviewed on the hospital information system, YASASII, to extract initial C-Reactive Protein (CRP), nasopharyngeal swab results, age, and season of presentation. Patients were divided into the following age groups: infants were divided into those that were 0-6 months and those that were >6-12 months of age, toddler (>12 months to 36 months), preschool (37 months to five years) and school-age (more than five years of age). CRP was considered to be high at a value ≥ 5.0 mg/L. Data was collected and analyzed using IBM SPSS Version 20. Pearson Chi-square, Fisher's exact appropriate tests, and Likelihood Ratio Chi Statistics were applied to measure variable independence. The Bonferroni correction was used in post hoc testing of the data. The strength of association was determined by the Phi correlation coefficient. ANOVA was used to compare the means of the sample. The level of significance, (p-value), was taken at <0.05.

Results

During the study period, 534 patient's files were reviewed for multiplex PCR nasopharyngeal samples. The average age of those studied was 2.8 years while the minimum age was 10 days and the maximum age being 15 years. 18.5% were in the 0-6 month age group, 12.2% in the >6-12 month group, 40.6% were toddlers, 14% were preschoolers and 14.6% were of school age. The most common age included were three years olds (44/534). Positive mPCR swabs were found in 68.7% (367 samples) and 52.0% (191/367) had other pathogen coinfection with a total of 600 positive pathogens overall. Age group and pathogen coinfection or mono-infection was statistically significant (x^2 (8, N=534)=21.304, p=0.006). Post hoc testing using the Bonferroni adjustment to correct the significant value to p=0.003 revealed that significance for pathogen coinfection was statistically significant among toddlers (p=0.0007). However, there was no statistical significance between the age group and the number of pathogens found on mPCR (F (4, 529)=0.322, p=0.863). Frequencies of positive swabs and pathogen infections across age groups are demonstrated in **Figure 1**.

The most commonly identified pathogens were the enterovirus (33.3%) and the human rhinovirus (33.3%) across all age groups. Respiratory Syncytial Virus (RSV) was most common amongst 0-6 months old (53.6%), adenovirus was most prevalent among the toddlers and preschoolers (66.7%), human metapneumovirus was most common amongst toddlers (46.4%) and influenza B was most evident in those above 5 years of age (40%). Other pathogens that were found on the multiplex PCR panel are displayed in **Table 1**. **Figure 2** displays the distribution of pathogens across age groups. There was a statistical significance between age group and enterovirus (F (2.792, 115.875)=3.186, p=0.013), respiratory syncytial virus (F (1.939, 35.065)=7.312, p=<0.0001), rhinovirus (F (2.792, 115.875)=3.186, p=0.013) and influenza B (F (0.831, 23.903)=4.600, p=0.001). The Games Howell Post Hoc testing revealed that both rhinovirus and enterovirus were statistically significant in those >12-36 months (p=0.042), RSV in those 0-6 months (p=0.017) and influenza B in those >12-36 months (p=0.036) and those more than 5 years of age (p=0.010).

Elevated CRP was found in 71% of study participants (379/534). The average CRP was 37.8 with a standard deviation of 58.0, a minimum of 0.0, and a maximum of 370.6. High CRP was found in 73.1% (122/167) of those with negative nasopharyngeal PCR results, 69.9% (123/176) of those with mono pathogen infection, and 71% (134/191) of those with pathogen coinfection. However, there was no significance between CRP level and the number of pathogens found on the multiplex PCR nasopharyngeal swab results (x^2 (2, N=534)=0.514, p=0.774). CRP level was significant for adenovirus (x^2 (1, N=534)=8.866, p=0.003) and influenza B (x^2 (1,N=534)=17.538, p=<0.0001). Adenovirus was positively associated with high CRP levels (ϕ=0.129=p=0.003) while those with influenza B virus were negatively associated with high CRP (ϕ=-0.181, p<0.0001). Elevated CRP levels associated with various pathogens and the Positive Predictive Values (PPV) are displayed in **Table 2**.

Regarding the seasonal presentation, 46.6% of patients with positive swabs presented during the spring, followed by 37.5% during the winter, 15% in the summer and only 0.9% in the fall. Most cases (84.3%) of enterovirus and rhinovirus infection presented during the spring and winter seasons. Most cases of RSV infection presented during the winter (27/40). **Table 3** demonstrates the seasonal distribution of the various pathogens. Positive seasonal association with pathogens was statistically significant for adenovirus (G^2 (3, N=534)=11.076, p=0.011),(ϕ =0.141, p=0.014), respiratory syncytial virus (G^2 (3, N=534)=24.563, p< 0.0001),(ϕ =0.225, p<0.0001), coronavirus OC43 (G^2 (3, N=534)=13.656, p=0.003),(ϕ =0.141, p=0.014), *Parainfluenza* virus type 1 (G^2 (3, N=534)=8.307,p=0.040),(ϕ =0.314,p<0.0001) and coronavirus 229e (G^2 (3, N=534)=11.487, p=0.009),(ϕ =0.179,p=0.001).

Table 1: Respiratory panel pathogens on multiplex PCR.

Respiratory Panel Pathogen	n(%)
Enterovirus	178/534 (33.3)
Rhinovirus	178/534 (33.3)
Adenovirus	48/534 (9.0)
Respiratory Syncytial Virus	40/534 (7.5)
Human metapneumovirus	33/534 (6.2)
Influenza B	26/534 (4.9)
Parainfluenza type 3	25/534 (4.7)
Coronavirus oc43	23/534 (4.3)
Influenza A h1-2009	14/534 (2.6)
Coronavirus hku1	7/534 (1.3)
Parainfluenza virus type 4	6/534 (1.1)
Mycoplasma pneumonia	4/534 (0.7)
Influenza A h3	3/534 (0.6)
Bordatella pertussis	3/534 (0.6)
Coronavirus 229e	3/534 (0.6)
Chlamydia pneumonia	2/534 (0.4)
Influenza a h1n1	2/534 (0.4)
Parainfluenza virus type 1	2/534 (0.4)
Coronavirus nl63	2/534 (0.4)
Human parechovirus	1/534 (0.2)

Table 2: Elevated CRP among pathogens.

Respiratory Panel Pathogen	n(PPV)
Enterovirus	130/178 (73.0)
Rhinovirus	130/178 (73.0)
Adenovirus	43/48 (89.6)
Respiratory Syncytial Virus	25/40 (62.5)
Human metapneumovirus	20/33 (60.6)
Influenza B	9/26 (34.6)
Parainfluenza type 3	17/25 (68.0)
Coronavirus oc43	16/23 (69.6)
Influenza A h1-2009	9/14 (64.3)
Coronavirus hku1	4/7 (57.1)
Parainfluenza virus type 4	3/6 (50.0)
Mycoplasma pneumonia	4/4 (100.0)
Influenza A h3	3/3 (100.0)
Bordatella pertussis	1/3 (33.3)
Coronavirus 229e	2/3 (66.7)
Chlamydia pneumonia	2/2 (100.0)
Influenza a h1n1	1/2 (50.0)
Parainfluenza virus type 1	2/2 (100.0)
Coronavirus nl63	1/2 (50.0)
Human parechovirus	1/1 (100.0)

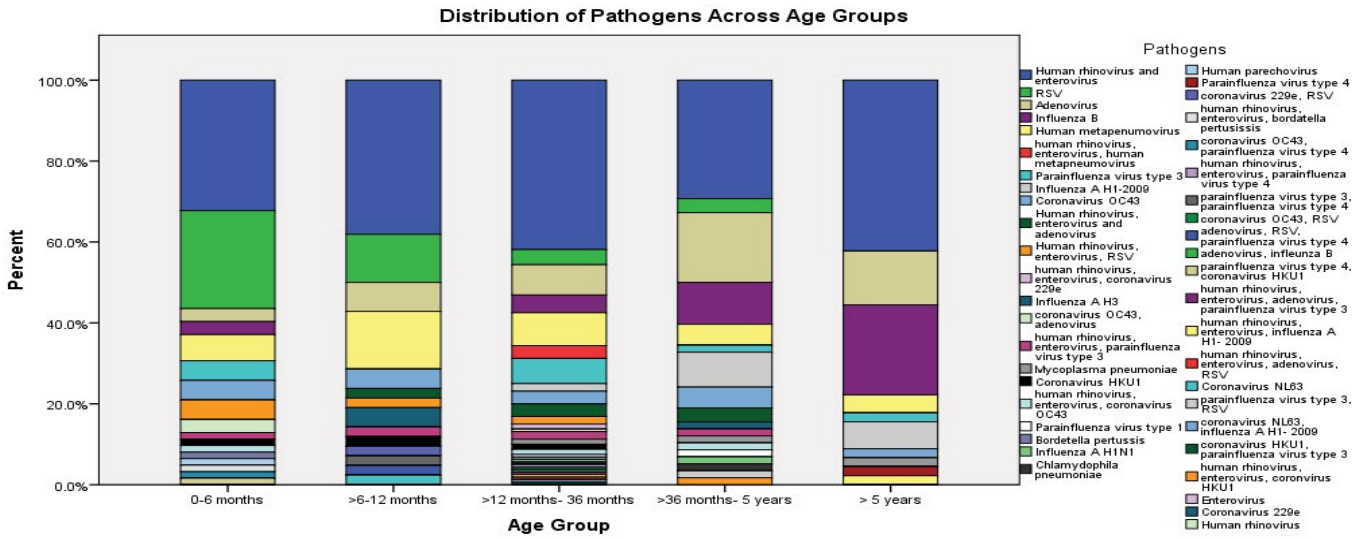

Figure 2 Distribution of pathogens across age groups.

Post hoc testing using the Bonferroni adjustment to correct the significant value to p=0.0063 showed that adenovirus and coronavirus OC43 were significant during the spring (p=0.0013 and 0.0012 respectively). RSV was significant during spring (p=0.0044), fall (p=0.0055) and winter (p=0.00004). *Parainfluenza* virus type 1 was found to be statistically significant during the fall (p<0.000) while coronavirus 229e was significant during the summer (p=0.00004). The temporal distribution of pathogens across age groups can be visualized in **Figure 3**.

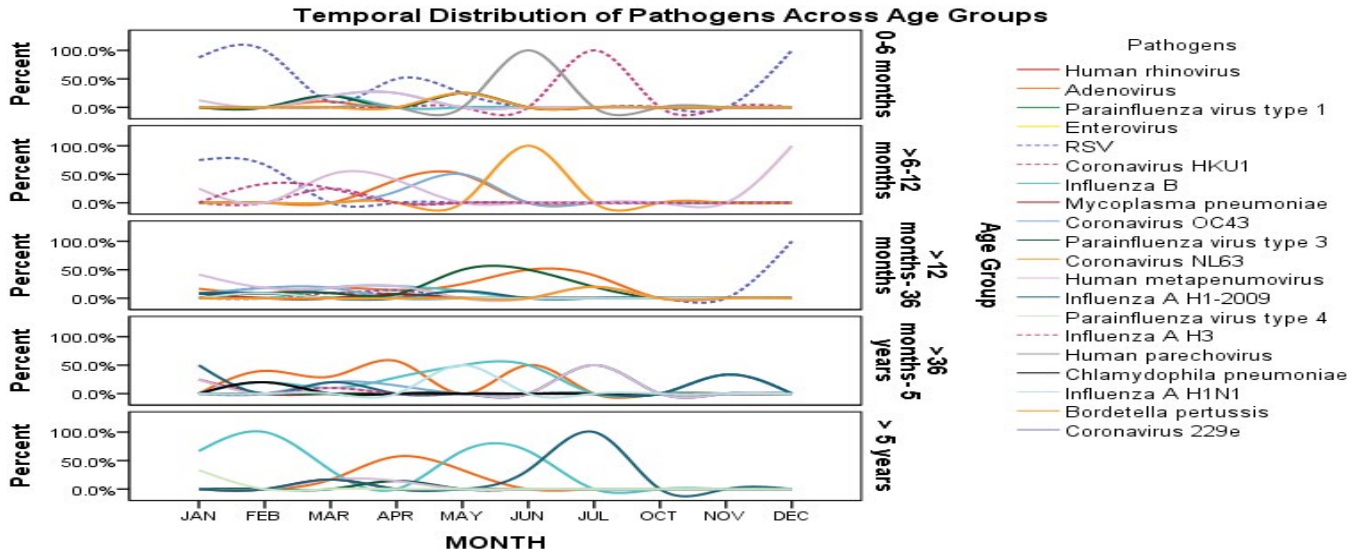

Figure 3 Temporal distribution of pathogens across age groups

Table 3: Seasonal distribution of pathogens.

Pathogen	Spring	Summer	Fall	Winter
Enterovirus	73/178	27/178	1/178	77/178
Rhinovirus	73/178	27/178	1/178	77/178
Adenovirus	33/48	4/48	0/48	11/48
Respiratory Syncytial Virus	10/40	1/40	240	27/40
Human metapneumovirus	18/33	2/33	0/33	13/33
Influenza B	16/26	3/26	0/26	7/26
Parainfluenza type 3	12/25	3/25	2/25	8/25
Coronavirus oc43	18/23	0/23	0/23	5/23
Influenza A h1-2009	4/14	3/14	1/14	6/14
Coronavirus hku 1	5/7	1/7	0/7	1/7
Parainfluenza virus type 4	2/6	0/6	0/6	4/6
Mycoplasma pneumonia	2/4	0/4	0/4	2/4
Influenza A h3	2/3	0/3	0/3	1/3
Bordatella pertussis	1/3	2/3	0/3	0/3
Coronavirus 229e	0/3	3/3	0/3	0/3
Chlamydia pneumonia	0/2	0/2	0/2	2/2
Influenza a h1n1	1/1	0/1	0/1	1/1
Parainfluenza virus type 1	1/2	0/2	1/2	0/2
Coronavirus nl63	0/2	1/2	0/2	1/2
Human parechovirus	0/1	1/1	0/1	0/1

Discussion

In children less than 5 years of age, acute respiratory tract infections account for the single most cause of mortality and disability worldwide especially in developing countries where mortality reaches 4 million children per year [10-11]. Of those included in the study, 85.4% were less than five years of age with a positivity rate of 68.8% amongst all study participants. A little more than a third of those that had positive mPCR swab results had multiple pathogen coinfection (35.8%). Around 48% of total positive mPCR swabs were only positive for one pathogen, 41% for dual infection, 10% for three organisms, and only 0.5% were found to have four organisms. These results are similar to frequencies in other studies that showed the most common coinfection to be two organisms and the least as four organisms [2, 12-13].

Although only the toddler age group was significant for pathogen coinfection using the adjusted Bonferroni correction (p=0.0007), 46.7% of preschoolers had pathogen mono-infection (p=0.0065) and 25.6% of school-age children had pathogen coinfection (p=0.043). Age and the occurrence of pathogen coinfection were also found to be significant in the GENRES cohort conducted in Spain for children aged 12-48 months and in a UK cohort for those 12-24 months of age [14].

There were many variations of pathogen co-infection among those studied. Research has shown that the most common age group for pathogen coinfection are children less than 5 years old, while other studies have specified that the 6 month to 2 years age group is more susceptible to coinfection than other age groups [15]. The most common combination was simultaneous infection with the human rhinovirus and enterovirus across all age groups (37.9%). The enterovirus and more specifically, the human rhinovirus, are respiratory viruses that have the ability to contribute to a simultaneous infection and are very common pathogens [15-17]. The most common mono-infection was adenovirus (9%), followed by RSV and human metapneumovirus (7.6% each) and influenza B (6.8%). All other mono-infection and pathogen coinfection frequencies were less than 5%. Approximately two-thirds of those found to have adenovirus were between one and five years of age. More than half of those found to have RSV were between 0-6 months of age. Human metapneumovirus was most

common amongst toddlers (46.4%) and influenza B was most evident in those above five years of age (40%). A French study found that RSV was more frequent in children less than the age of three, adenovirus was more common in 6 months to 3-year-olds and influenza was more common in adults than children [18].

The majority of those with mono pathogen infection and with pathogen coinfection had elevated CRP (69.9% and 71% respectively). This rate is similar to reported ranges in the literature of around 68-85% of those with respiratory infections have elevated CRP levels [19]. However, there was no significance between CRP level and the number of pathogens found on the multiplex PCR nasopharyngeal swab results ($p=0.774$). CRP level was significant for adenovirus ($p=0.003$) and influenza B ($p=<0.0001$). Adenovirus has been described in the literature to be associated with elevated CRP levels as was found in this study [20]. Interestingly, influenza B was negatively associated with an elevated CRP level ($p<0.0001$). This is comparable to a study that found that out of 117 children diagnosed with influenza B, 85% had a CRP level of less than 20 mg/L [21].

Although Saudi Arabia is an arid climate, there seemed to be a seasonal variation in pathogen presentation. 46.6% of patients with positive swabs presented during the spring, 37.5% during the winter, 15% in the summer, and only 0.9% in the fall. Most cases (84.3%) of enterovirus and rhinovirus infection presented during the spring and winter seasons. Most cases of RSV infection presented during the winter (27/40). Research has suggested that globally, RSV tends to occur more frequently during the respective winter months of each geographic location [22].

Limitations of this study include that it is a retrospective study and that clinical information and management plan regarding antibiotic use and exposure to chest radiography has not been included. This study also focuses on data from one hospital in Jeddah, Saudi Arabia, and does not include other centers or cities in the country that may use other mPCR techniques, and therefore the positivity rates may be different.

Conclusion

Studies in Saudi Arabia and the Middle East in general are limited regarding the various pathogens that cause acute respiratory tract infection in the pediatric age group. This is a ground break study that sheds light on the seasonal variation, age presentation, association of CRP with various pathogens, and incidence of not only viral but bacterial organisms as well by the use of mPCR. Further studies are needed to assess the use of antibiotics and radiation exposure in children presenting with viral acute respiratory tract infections.

Acknowledgments

The authors would like to thank all volunteers who helped in distributing the questionnaire among the study participants.

Conflicts of Interests

The other authors have no conflicts of interest to disclose.

Funding

No funding was secured for this study.

References

1 Thornton HV, Blair PS, Lovering AM, Muir P, Hay AD (2015) Clinical presentation and microbiological diagnosis in paediatric respiratory tract infection: A systematic review. Br J Gen Pract 65: e69-e81.

2 Kholy AA, Mostafa NA, Ali AA, Soliman MM, El-Sherbini SA, et al. (2016) The use of multiplex PCR for the diagnosis of viral severe acute respiratory infection in children: A high rate of co-detection during the winter season. Eur J Clin Microbiol Infect Dis 35: 1607-1613.

3 Doan Q, Enarson P, Kissoon N, Klassen TP, Johnson DW (2014) Rapid viral diagnosis for acute febrile respiratory illness in children in the emergency department. Cochrane Database Syst Rev 2014: CD006452.

4 Pierce VM, Elkan M, Leet M, Mcgowan KL, Hodinka RL (2011) Comparison of the Idaho Technology FilmArray System to Real-time PCR for detection of respiratory pathogens in children. J Clin Microbiol 50: 364-371.

5 Krause JC, Panning M, Hengel H, Henneke P (2014) The role of multiplex PCR in respiratory tract infections in children. Dtsch Arztebl Int 111: 639-45.

6 Poritz MA, Blaschke AJ, Byington CL, Meyers L, Nilsson K, et al. (2011) Correction: FilmArray, an automated nested multiplex PCR system for multi-pathogen detection: Development and application to respiratory tract infection. PLoS ONE 6: e26047.

7 Subramony A, Zachariah P, Krones A, Whittier S, Saiman L (2016) Impact of multiplex polymerase chain reaction testing for respiratory pathogens on healthcare resource utilization for pediatric inpatients. J Pediatr 173: 196-201

8 Al-Ayed MS, Asaad AM, Qureshi MA, Ameen MS (2014) Viral etiology of respiratory infections in children in southwestern Saudi Arabia using multiplex reverse-transcriptase polymerase chain reaction. Saudi Med J 35: 1348-1353.

9 Albogami SS, Alotaibi MR, Alsahli SA, Masuadi E, Alshaalan M (2018) Seasonal variations of respiratory viruses detected from children with respiratory tract infections in Riyadh, Saudi Arabia. J Infect Public Health 11: 183-186.

10 Bellos A, Mulholland K, O'brien KL, Qazi SA, Gayer M, et al. (2010) The burden of acute respiratory infections in crisis-affected populations: A systematic review. Confl Health 4: 1-3.

11 Hann F, Woolcock A, Black R, Cripps A, Foy H, et al. (1999) Introduction: Acute respiratory tract infections-The forgotten pandemic. Clin Infect Dis 28: 189-191.

12 Bierbaum S, Forster J, Berner R, Rücker G, Rohde G, et al. (2013) Detection of respiratory viruses using a multiplex real-time PCR assay in Germany, 2009/10. Arch Virol 159: 669-676.

13 Bonzel L, Tenenbaum T, Schroten H, Schildgen O, Schweitzer-Krantz, et al. (2008) Frequent detection of viral coinfection in children hospitalized with acute respiratory tract infection using a real-time polymerase chain reaction. Pediatr Infect Dis J 27: 589-594.

14 Cebey-López M, Herberg J, Pardo-Seco J, Gómez-Carballa A, Martinón-Torres N, et al. (2015) Viral Co-infections in pediatric patients hospitalized with lower tract acute respiratory infections. PLoS One 10: e0136526.

15 Pinky L, Dobrovolny HM (2016) Coinfections of the respiratory tract: Viral competition for resources. PLoS One 11: e0155589.

16 Leung TF, To MY, Yeung AC, Wong YS, Wong GW, et al. (2010) Multiplex molecular detection of respiratory pathogens in children with asthma exacerbation. Chest 137: 348-354.

17 Kusel MM, Klerk NH, Holt PG, Kebadze T, Johnston SL, et al. (2006) Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life. Pediatr Infect Dis J 25: 680-686.

18 Visseaux B, Collin G, Ichou H, Charpentier C, Bendhafer S, et al. (2017) Usefulness of multiplex PCR methods and respiratory viruses' distribution in children below 15 years old according to age, seasons and clinical units in France: A 3 years retrospective study. PLoS One 12: e0172809.

19 Jeon J, Rheem I, Kim JK (2017) C-reactive protein and respiratory viral infection. Korean J Clin Lab Sci 49: 15-21.

20 Appenzeller C, Ammann RA, Duppenthaler A, Gorgievski-Hrisoho M, Aebi C (2002) Serum C-reactive protein in children with adenovirus infection. Swiss Med Wkly 132: 345-350.

21 Peltola V, Ziegler T, Ruuskanen O (2003) Influenza A and B virus infections in children. Clin Infect Dis 36: 299-305.

22 Bloom-Feshbach K, Alonso WJ, Charu V, Tamerius J, Simonsen L, et al. (2013) Latitudinal variations in seasonal activity of influenza and Respiratory Syncytial Virus (RSV): A Global Comparative Review. PLoS One 8: e54445.