Viral aetiology of influenza-like illnesses and severe acute respiratory illnesses in Morocco, September 2014 to December 2016

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Background There is a scarcity of information on the viral aetiology of influenza-like illness (ILI) and severe acute respiratory infection (SARI) among patients in Morocco.

Methods From September 2014 to December 2016, we prospectively enrolled in-patients and outpatients from all age groups meeting the World Health Organization (WHO) case definition for ILI and SARI from 59 sentinel sites. The specimens were tested using real-time monoplex reverse-transcription polymerase chain reaction method for detecting 16 relevant respiratory viruses.

Results At least one respiratory virus was detected in 1423 (70.8%) of 2009 specimens. Influenza viruses were the most common, detected in 612 (30.4%) of processed samples, followed by respiratory syncytial virus (RSV) in 359 (17.9%), human rhinovirus (HRV) in 263 (13.1%), adenovirus (HAdV) in 124 (6.2%), parainfluenza viruses (HPIV) in 107 (5.3%), coronaviruses (HCoV) in 94 (4.7%), human bocavirus (HBoV) in 92 (4.6%), and human metapneumovirus (HMPV) in 74 (3.7%). From 770 samples from children under 5 years old, RSV (288, 36.6%), influenza viruses (106, 13.8%), HRV (96, 12.5%) and HAdV (91, 11.8%) were most prevalent. Among 955 samples from adults, Influenza viruses (506, 53.0%), and HRV (167, 17.5%) were most often detected. Co-infections were found in 268 (18.8%) of 1423 positive specimens, and most (60.4%) were in children under 5 years of age. While influenza viruses, RSV, and HMPV had a defined period of circulation, the other viruses did not display clear seasonal patterns.

Conclusions We found that RSV was predominant among SARI cases in Morocco, particularly in children under 5 years of age. Our results are in line with reported data from other parts of the world, stating that RSV is the leading cause of lower respiratory tract infections in infants and young children.

Acute respiratory tract infections (ARIs) are a major public health problem that leads to higher morbidity and mortality worldwide, with the highest burden of disease in developing countries. Young children, the elderly, the chronically ill, and immunocompromised persons are at imminent risk [1]. ARIs are the leading cause of death among children under five years of age and are responsible for 19% of deaths and around 8% of all disabilities [2,3]. Practically, 13% of deaths reported in Moroccan children under five years old in 2012 were caused by ARIs [4].

The etiological agents for acute respiratory infections include bacteria, viruses, and fungi [5]. Viruses are responsible for around 80% of respiratory infections. They are responsible for upper respiratory infections (rhinitis, laryngotracheitis) and for potentially severe lower respiratory infections (bronchitis, bronchiolitis, and pneumonia) [6]. Several viruses
are implicated in respiratory tract infections, including influenza viruses (Flu A/B), respiratory syncytial virus (RSV), human adenoviruses (HAdV), human coronaviruses (HCoV), human rhinovirus (HRV), parainfluenza viruses (PIVs), and human metapneumovirus (HMPV) [7].

While influenza is considered the most common cause of viral respiratory infections among older adults [8], RSV is recognized as the main viral pathogen in children [9]. RSV infections are responsible for most cases of severe symptoms such as bronchiolitis, asthma exacerbation and pneumonia, and lead to higher hospitalization rates [10]. Other non-influenza viruses may cause respiratory tract infections with similar symptoms and clinical features. Thus, identifying the aetiological agent is usually difficult without laboratory testing [11].

Although Morocco's influenza surveillance system was established in 1996 [12], little data are available on the circulation of other respiratory viruses. To address this gap, virological data from the country's existing influenza surveillance system was used to investigate the characteristics and circulation of respiratory viruses in patients with acute respiratory infections either admitted in hospitals or seen at out-patient clinics in Morocco from 2014 to 2016.

**METHODS**

**Study design and case definition**

A sentinel-based influenza surveillance system was established by health authorities in the country in 1996 [12]. The country's respiratory surveillance network includes two concomitant components. While the outpatient influenza-like illness (ILI) surveillance system accepts patients attending health facilities with mild symptoms of fever ≥38°C and cough with an onset of >10 days [13], the severe acute respiratory infection (SARI) surveillance system takes hospitalized patients with SARI with fever ≥38°C and cough with a symptom onset within the same period [13].

SARI virological surveillance is conducted throughout the year in eight public general hospitals located in the country's main regions. All patients who meet the WHO case definition of SARI are recruited and relevant epidemiological data are recorded by medical staff. The ILI virological surveillance system conducts specimen collection and data recording from the first five cases meeting the WHO's case definition for ILI daily in eight out-patient public clinics and fifty private physicians located in nine main cities across the country.

The study period lasted from September 1, 2014, to December 31, 2016.

**Sample and data collection**

Nasopharyngeal (NP) and oropharyngeal (OP) specimens were collected from all patients fulfilling ILI or SARI case definitions. Tubes of viral transportation medium (ViCUM®) containing specimens were conserved at 4°C at the health services and were sent to the National Influenza Center within two days. A standardized form with patient-specific information (medical history, clinical symptoms, and demographic and epidemiological data) was completed by physicians or health workers.

**Nucleic acid extraction**

Total nucleic acids were extracted automatically from 400 μL of samples, using a High Pure Viral Nucleic Acid Kit and iPrep instrument, according to the manufacturer's instructions (Lifetechnologies, Carlsbad, USA). After that, ribonuclease P (RNase P) was considered as the internal control during specimen extraction. 100μL of extracted nucleic acids were stored at -70°C until processing.

**Real-time reverse transcriptase PCR**

Detection of 16 respiratory viruses was performed in 5μL volume using Invitrogen® Superscript III Platinum® One-step Reverse transcription polymerase chain reaction (RT-PCR), amplification and reaction conditions were made with an ABI 7500 Fast Sequence Detection System® in accordance with the protocols developed by Centers for Disease Control and Prevention (CDC; Atlanta, GA) and provided as part of a material transfer agreement that ensures privacy and non-publication.

**Statistical analysis**

To describe the temporal distribution of positive cases, we aggregated results obtained by real-time RT-PCR by calendar month and week. Demographic, clinical, and virological data for all enrolled patients were entered
RESULTS

Demographic characteristics

From September 1, 2014, to December 31, 2016, NP and OP swabs were collected from 2009 patients meeting the WHO’s case definition for ILI and SARI from all age groups from 59 sentinel sites. 1187 (59%) specimens were collected from ILI and 822 (41%) from SARI sentinel sites. A slightly higher proportion of specimens belonged to female than to male patients (51.3% vs 48.7%). The patients’ mean age in years was 23.78 years (SD±23.8) and the median age was 16.00 years (IQR=0.08-99.00).

A total of 740 patients (36.8%) were younger than 5 years, 842 (41.9%) were aged between 5-24 years, 273 (13.6%) were aged between 25-64 years, while 127 (6.4%) were older than 65 years (Table 1). More than half of the specimens were collected from two of the eight sentinel regions, Fes-Meknes (n=753, 37.5%) and Rabat-Sale-Kenitra (n=555, 27.6%). Although patients were enrolled for this study throughout the year, most specimens were collected during the fourth and first quarters of the season (October-April).

Virus detection

A total of 1423 of 2009 specimens tested for both ILI and SARI were positive for at least one virus, resulting in a 70.8% detection rate. Among all positive specimens, a single infection occurred in 1155 (81.2%) patients while co-infections were detected in 268 (18.8%) patients. Dual, triple, and quadruple co-infections occurred in respectively 237 (16.7%), 28 (2.0%) and 3 (0.2%) patients.

Influenza was the most common virus, detected in 612 patients (30.5%) positive specimens, followed by RSV (n = 359, 17.9%), HRV (n = 263, 13.1%), HAdV (n = 124, 6.2%), PIVs (n = 107, 5.3%), HCoVs (n = 94, 4.7%), human bocaviruses (HBoVs) (n = 92, 4.6%), and HMPV (n = 74, 3.7%) (Table 2). While 44.3% (P<0.001) of influenza positives were detected in patients over 5 years of age with mild symptoms, positive RSV (42.4%; P<0.001) and HAdVs (13.0%; P<0.001) detections were mostly observed during SARI infection in children under 5 years with respectively of positive detections of these two viruses in this age category (Table 3).

The number and rates of positive specimens stratified by virus and clinical symptom (Table 4) showed that fever (55.2%; P=0.013), rhinitis (16.5%; P<0.001), headache (21.4%; P<0.001) and sore throat (23.7%; P<0.001) were more often reported in patients infected with influenza A/B compared to those infected with other viruses. Cough was the most reported clinical sign for all prevalent viruses, especially for RSV-positive cases (90.8%; P<0.001).

Table 1. Demographic characteristics of patients with influenza-like illness (ILI) and severe acute respiratory infections (SARI), Morocco, 2014-2016

| Region (sentinel sites) | N = 1187 | N = 822 | N = 2009 |
|------------------------|----------|---------|----------|
| Beni Mellal-Khenifra   | 99 (8.3) | 88 (10.7)| 187 (9.3) |
| Fes-Meknes             | 458 (38.6)| 295 (35.9)| 753 (37.5) |
| Laayoune-Dakhla        | 2 (0.2)  | 2 (0.2)  | 4 (0.2)   |
| Marrakesh-Safi         | 60 (5.1) | 5 (0.6)  | 65 (3.2)  |
| Oriental (Oujda)       | 52 (4.3) | 51 (6.2) | 103 (5.1) |
| Rabat-Sale-Kenitra     | 284 (24) | 271 (33.0)| 555 (27.6) |
| Souss-Massa (Agadir)   | 99 (8.3) | 99 (12.1)| 198 (9.9) |
| Tanger-Tetouan         | 133 (11.2)| 11 (1.3)  | 144 (7.2) |

Table 2. Frequencies of virus detections by age category in Morocco, September 2014 – December 2016

| Virus     | N = 1187 | N = 822 | N = 2009 |
|-----------|----------|---------|----------|
| ≤5 years  |          |         |          |
| Flu A/B   | 106 (13.8)| 506 (53.0)|          |
| RSV       | 282 (36.6)| 77 (8.1)  |          |
| HAdV      | 91 (11.8) | 33 (3.5)  |          |
| HRV       | 96 (12.5) | 167 (17.5)|          |
| HMPV      | 36 (4.7)  | 38 (4.0)  |          |
| HBoV      | 56 (7.3)  | 36 (3.8)  |          |
| HPIV-1    | 20 (2.6)  | 10 (1.0)  |          |
| HPIV-2    | 8 (1.0)   | 6 (0.6)   |          |
| HPIV-3    | 29 (3.8)  | 25 (2.6)  |          |
| HPIV-4    | 4 (0.5)   | 5 (0.5)   |          |
| HCoV-229E | 6 (0.8)   | 9 (0.9)   |          |
| HCoV-NL63 | 20 (2.6)  | 18 (1.9)  |          |
| HCoV-HKU1 | 5 (0.6)   | 14 (1.5)  |          |
| HCoV-OC43 | 11 (1.4)  | 11 (1.2)  |          |

Flu A/B – influenza viruses, HCoV-229E – human coronavirus 229E, HCoV-NL63 – human coronavirus NL63, HCoV-HKU1 – human coronavirus HKU1, HCoV-OC43 – human coronavirus OC43, HAdV – human adenovirus, HMPV – human metapneumovirus, HPIV-1– parainfluenza virus 1, HPIV-2 – parainfluenza virus 2, HPIV-3 – parainfluenza virus 3, HPIV-4 – parainfluenza virus 4, RSV – respiratory syncytial virus

*Percentage of viruses detected equals the number of positives from each group/total number of positives.
Seasonal distribution

During the observation period, the study of seasonality showed that viral circulation extends throughout the year. However, there was a concomitant circulation of influenza and RSV viruses from November to April, with peaks during the months of December-March. HAdVs and HRV circulated throughout the year with peaks during the winter months. Other viruses often circulated during the cold season with sporadic cases throughout the year (Figure 1).

Table 3. Prevalence (n, %) of the viruses frequently related to respiratory infections by age category and origin of specimens, Morocco, September 2014 – December 2016

| Virus   | Total | ILI | SARI | P-value |
|---------|-------|-----|------|---------|
| Inf A/B | <5 y, N = 740 | >5 y, N = 1242 | <5 y, N = 203 | >5 y, N = 972 | <5 y, N = 537 | >5 y, N = 270 | <0.001 |
| RSV     | 282 (38.1) | 73 (5.9) | 54 (26.6) | 63 (6.5) | 228 (42.4) | 10 (3.7) | <0.001 |
| HAdV    | 91 (12.3) | 33 (2.6) | 21 (10.3) | 25 (2.6) | 70 (13.0) | 8 (2.9) | <0.001 |
| HRV     | 96 (12.9) | 164 (13.2) | 15 (7.3) | 128 (13.2) | 81 (15.1) | 36 (13.3) | 0.225 |

ILI – influenza-like illnesses, SARI – severe acute respiratory illness, Inf A/B – influenza A and B, RSV – respiratory syncytial virus, HAdV – human adenovirus, HRV – human rhinovirus

*Some variables from age have not been included in the analysis owing to incomplete data.

Table 4. Number and rates of positive specimens by virus and clinical symptom, Morocco, September 2014 – December 2016

| Symptom    | RSV (n = 359) | INF A/B (n = 612) | HRV (n = 263) | HAdV (n = 124) |
|------------|---------------|-------------------|---------------|----------------|
| Cough      | 326 (90.8)    | 509 (83.2)        | 231 (87.8)    | 104 (83.8)     |
| Fever >38  | 176 (49.0)    | 338 (55.2)        | 121 (46.0)    | 66 (53.2)      |
| Rhinitis   | 20 (5.6)      | 101 (16.5)        | 28 (10.6)     | 10 (8.0)       |
| Sore throat| 52 (14.5)     | 145 (23.7)        | 39 (14.8)     | 14 (11.3)      |
| Headache   | 25 (6.9)      | 131 (21.4)        | 31 (11.8)     | 9 (7.2)        |

Figure 1. The incidence of the predominant respiratory viruses detected in Morocco, from September 2014 to December 2016. HAdV – human adenovirus, HMPV – human metapneumovirus, HPIV-3 – parainfluenza virus 3, RSV – respiratory syncytial virus, Inf A/B – influenza virus A and B, HRV – human rhinovirus.
DISCUSSION

In this study, we detected influenza and other respiratory viruses using RT-PCR in 2009 samples collected during the 2014/2016 influenza seasons through a sentinel-based influenza surveillance system. Among these samples, 1423 (70.8%) specimens were positive for at least one virus, which is consistent with the results from other studies with positivity rates between 63% to 75% [14-16].

According to WHO guidelines, the collection of patients' specimens should be done rapidly after symptom onset, ideally within 7 days, and the specimens should reach the laboratory as soon as possible after collection [17]. It should be noted that viruses are generally detectable in throat swabs of most patients from the onset of symptoms until the end of the second week [17]. In our study, 72.0% (P=0.005) of the positive samples were taken in the first week following the onset of the symptoms.

The findings also showed that Flu A/B (n=612, 35.5%), RSV (n=359, 20.8%), HRV (n=263, 15.2%), and HAdV (n=124, 7.2%) were the most common viruses detected. The representativeness of other viruses ranged from 5.3% to 0.5%. This is corroborated by one study [18], while others mentioned HRVs or HRSV as the most predominant viruses [14,16]. There are several explanations for these differences. First, the infection rates may be specific to geographic areas, size, type of sampling method, and study period. Second, detection methods and PCR primers may differ from one study to another, making it difficult to directly compare data. Other studies can clarify this question by evaluating the sensitivity and specificity of the different detection methods used [14,19].

Although influenza viruses were detected in all age groups, the proportion of positive cases for Flu A/B was comparatively higher in patients older than 5 years, especially in mild infections (88.7%; P<0.001), which was consistent with similar studies conducted on adults that found influenza virus as the leading cause of ILLs among adults and that HRV was the second most common cause of ILLs in this category of age [15,18,20].

The most frequent viral pathogen in patients under five years old with SARI was RSV, followed by HAdV, HRV, and Flu A/B, as found in several studies [14,16,18,21-24].

The prevalence of RSV in children under 5 years of age with SARI was 42.4% (P<0.001), which is high compared to data from other studies, which ranges from 18% to 34% [14,18,25]. This high prevalence of RSV infection among children can be attributed to the nosocomial spread of the virus within paediatric care units during the high circulating season of RSV. Despite the lack of data to support this hypothesis, some authors pointed to RSV as the major cause of annual nosocomial outbreaks, especially among the children admitted to paediatric units [26]. RSV infection is also recognized as a predominant problem in the elderly, especially among adults older than 65 years with chronic heart disease, asthma, lung disease, and immunocompromised patients. Despite the low number of patients recruited among adults over 65 years in this study, the prevalence of RSV infection was 7.1% in this age category, which is consistent with research suggesting a prevalence of RSV of approximately 5%-10% per year in the elderly [27].

Several studies [28-30] have revealed that the proportion of infections due to HAdVs was increasing. Indeed, in this present study the prevalence of HAdVs in SARIs among children under 5 years old was (13.0%; P<0.01). This finding suggests that HAdVs was a significant pathogen of severe respiratory infections in hospitalized children.

Co-infections were observed in 18.8% (268/1423) of samples, which is coherent with rates reported in the literature ranging from 10% to almost 40% [31,32].

The samples co-infected with RSV and another virus constitute 45.9% (123/268) of the total mixtures. A 60.4% (162/268) co-infection rate was detected in children under 5 years old, which is consistent with several studies that suggest co-infections were significantly more widespread in paediatrics [31-34]. This is probably due to the children’s undeveloped immune system associated with the absence of respiratory virus infection history (primary infection with more than one virus at time) or RSV possibly facilitating the reinfection of the respiratory tract system by other viruses. Drew et al. [33] reported 85.7% of coinfections with RSV in children under 5 years old. Moreover, findings from other studies indicated that severe clinical cases were more common in patients with coinfections, particularly with RSV co-infections, which may increase the severity of the disease in children [34-36].

While influenza viruses, RSV, and HCoVs showed a seasonal peak during the winter season in temperate regions, HRV, HMPV, HBoV, and HAdV display no discernible seasonal patterns and can be considered all-year viruses [37].
In Morocco, the circulation of influenza viruses peaks in the period from October through April [12]. The detection rates for RSV and HMPV increased during the winter season and predominated along with influenza viruses. HRVs and HAdVs tend to circulate during the fall months, while HCoVs, PIVs and HBoV were circulating all over the year with no distinct seasonal patterns.

Our study has some limitations. First, specimen collection is limited to patients who fulfil the standard ILI/SARI symptoms according to World Health Organization ILI/SARI case definition, which may have excluded many viral infections and resulted in an underestimation of the detection rates of respiratory virus infections. Second, the small sample size did not allow a thorough investigation of the association between clinical and epidemiological characteristics and risk factors in relation to detected pathogens. Moreover, to establish the seasonality of the respiratory viruses circulating patterns, more time-series data analyses are required over 3 to 5 years periods.

CONCLUSIONS

Our findings facilitate a better understanding of the characteristics and circulating patterns of respiratory viruses in patients with ILI or SARI in Morocco over the period of 2014-2016. While Influenza viruses are the most frequently detected respiratory viruses among outpatient adults, RSV remain the most important viral aetiological agent causing both mild and severe acute respiratory infections among children under 5 years old.

The co-circulation of several respiratory pathogens that cause infection with often similar symptoms requires greater vigilance and regular updating of the national epidemiological and virological surveillance system. Further research is needed to better understand respiratory viral epidemiology in our country, which may be useful for clinicians interested in developing the sequencing of emerging viruses. The combination of virological data issued from WGS and epidemiological data will provide precious information for public health decision-making to better manage potential epidemics and minimize socio-economic damage.

Ethical approval: The protocol was approved by the Ministry of Health for the objective of conducting surveillance of respiratory diseases with epidemic potential, in which participants remain anonymous, and therefore did not require an assessment of the ethics committee or IRB approval. Verbal consent was obtained from all patients.

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REFERENCES

1 Hodinka RL. Respiratory RNA viruses. Microbiol Spectr. 2016;4. Medline: 27726802 doi:10.1128/microbiolspec.DMIH2-0028-2016
2 Denny FW Jr. The clinical impact of human respiratory virus infections. Am J Respir Crit Care Med. 1995;152:S4-12. Medline:7551411 doi:10.1164/ajrccm/152.4_Pt_2.S4
3 Shann F, Woolcock A, Black R, Cripps A, Foy H, Harris M, et al. Introduction: acute respiratory tract infections-the forgotten pandemic. Clin Infect Dis. 1999;28:189-91. Medline:10064223 doi:10.1086/515107
4 World Health Statistics. 2014. WHO.int. Available: https://apps.who.int/iris/bitstream/handle/10665/112738/9789240692671_eng.pdf. Accessed: 10 December 2021.
5 Bluuyan GS, Hassain MA, Sarker SK, Rahat A, Islam MT, Haque TN, et al. Bacterial and viral pathogen spectra of acute respiratory infections in under-5 children in hospital settings in Dhaka city. PLoS One. 2017;12:e0174488. Medline:28346512 doi:10.1371/journal.pone.0174488
6 Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet. 2010;375:1545-55. Medline:20399493 doi:10.1016/S0140-6736(10)60206-1
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REFERENCES

7 Zimmerman RK, Rinaldo CR, Nowalk MP, Gk B, Thompson MG, Moebling KK, et al. Influenza and other respiratory virus infections in outpatients with medically attended acute respiratory infection during the 2011-12 influenza season. Influenza Other Respir Viruses. 2014;8:397-405. Medline:24852890 doi:10.1111/irv.12247

8 Kodama F, Nace DA, Jump RLP. Respiratory Syncytial Virus and Other Non influenza Respiratory Viruses in Older Adults. Infect Dis Clin North Am. 2017;31:767-90. Medline:29079159 doi:10.1016/j.idc.2017.07.006

9 El-Hajje MJ, Moulin F, Suremain N. Respiratory syncytial virus in hospitalized children, A 3-year study. Presse Med. 2008;37:37-43. Medline:18061394 doi:10.1016/j.pmed.2007.06.023

10 Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med. 2001;344:1917-28. Medline:11419430 doi:10.1056/NEJM200106213442407

11 Njouom R, Yekwa EL, Cappy P, Vabret A, Boisser P, Rouset D. Viral etiology of influenza-like illnesses in Cameroon, January-December 2009. J Infect Dis. 2012;206:529-35. Medline:23169968 doi:10.1086/652753

12 Barakat A, Ihsanm H, Benkarroum A, Cherkaozi I, Benmamoun A, Youbi M, et al. Influenza surveillance among outpatients and inpatients in Morocco, 1996-2009. PLoS One. 2011;6:e24579. Medline:21931764 doi:10.1371/journal.pone.0024579

13 Fitzner J, Qasmieh S, Mounts AW, Alexander B, Besselaar T, Briand S, et al. Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. Bull World Health Organ. 2018;96:122-8. Medline:29403115 doi:10.2471/BLT.17.194514

14 Kim JK, Jeon J, Kim JW, Rheem I. Epidemiology of Respiratory Viral Infection Using Multiplex RT-PCR in Cheonan, Korea (2006-2010). J Microbiol Biotechnol. 2013;23:267-73. Medline:23412071 doi:10.4103/1212.12050

15 Razanajatovo NH, Richard V, Hoffmann J, Reynolds J-M, Razafitrimo GM, Randremanana RV, et al. Viral etiology of influenza-like illnesses in Antananarivo, Madagascar, July 2008 to June 2009. PLoS One. 2011;6:e17579. Medline:21390235 doi:10.1371/journal.pone.0017579

16 Marciel S, Khabaj H, Jroundi I, Barakat A, Mahraoui C, Kettani S, et al. Epidemiology and diagnosis of the severe acute viral respiratory infections in patients admitted at IBN Sina University Hospital Rabat- Morocco. Disord. 2018;2:1-6.

17 Collecting, preserving and shipping specimens for the diagnosis of avian influenza A(H5N1) virus infection: guide for field operations. WHO.int. Available: https://apps.who.int/iris/handle/10665/69392. Accessed: 20 June 2022.

18 Çiçek C, Arslan A, Karakuş HS, Yalaz M, Saz EU, Pululkuç H, et al. Prevalence and seasonal distribution of respiratory viruses in patients with acute respiratory tract infections, 2002-2014. Mikrobiyol Bul. 2015;49:188-200. Medline:26167819 doi:10.5578/mb.9024

19 Bellet N, Carrero E, Perosa A, Watanabe A, Arruda E, Granato C. Acute respiratory infection and influenza-like illness viral etiologies in Brazilian adults. J Med Virol. 2008;80:1824-7. Medline:18718327 doi:10.1002/jmv.21295

20 Al-Romaihi HE, Smatti MK, Ganesan N, Nadeem S, Farag E, Coyle PV, et al. Epidemiology of respiratory infections among adults in Qatar (2012-2017). PLoS One. 2019;14:e0218097.

21 Kwofie AB, Anane YA, Nkrumah B, Annan A, Ngua A, Owosu M. Respiratory viruses in children hospitalized for acute lower respiratory tract infection in Ghana. Virol J. 2012;9:78. Medline:22490105 doi:10.1186/1743-422X-9-78

22 Uduman SA, Ijaz MK, Kochiyil J, Mathew T, Hossam MK. Respiratory syncytial virus infection among hospitalized young children and adults in Qatar (2012-2017). PLoS One. 2019;14:e0218097.

23 Bellei N, Carraro E, Perosa A, Watanabe A, Arruda E, Granato C. Acute respiratory infection and influenza-like illness viral etiologies in Brazilian adults. J Med Virol. 2008;80:1824-7. Medline:18718327 doi:10.1002/jmv.21295

24 Al-Romaihi HE, Smatti MK, Ganesan N, Nadeem S, Farag E, Coyle PV, et al. Epidemiology of respiratory infections among adults in Qatar (2012-2017). PLoS One. 2019;14:e0218097.

25 Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The Burden of Respiratory Syncytial Virus Infection in Young Children. N Engl J Med. 2009;360:588-98. Medline:19196675 doi:10.1056/NEJMoa0804877

26 Miñarí-Galinovic G, Gvarda-Bricic D. Nosocomial respiratory syncytial virus infections in children’s wards. Diagn Microbiol Infect Dis. 2000;37:237-46. Medline:10974574 doi:10.1016/S0732-8893(00)00154-1

27 Falsay AR, Falsey EE. Respiratory Syncytial Virus Infection in Elderly Adults. Drugs Aging. 2005;22:577-87. Medline:16038573 doi:10.2165/00025212-200522070-00004

28 Tang LF, Wang TL, Tang HF, Chen ZM. Viral pathogen of acute lower respiratory tract infection in China. Indian Pediatr. 2008;45:971-5. Medline:19129564

29 Jin Y, Zhang R-F, Xie Z-P, Yan K-L, Gao H-C, Song J-R, et al. Newly identified respiratory viruses associated with acute lower respiratory tract infections in Lanzhou, China, from 2006 to 2009. Clin Microbiol Infect. 2012;18:74-80. Medline:21767329 doi:10.1111/j.1469-0691.2011.03541.x

30 Ampuero JS, Ocaña V, Gómez J, Gamero ME. Adenovirus Respiratory Tract Infections JG. in Peru. PLoS One. 2012;7:e46988. Medline:23056519 doi:10.1371/journal.pone.0046988

31 Richter J, Panayiotou RC, Tryfonos C, Koptides D, Kolionu M, Kalogirou N, et al. Aetiology of acute respiratory tract infections in hospitalised children in Cyprus. PLoS One. 2016;11:e0147041. Medline:26761647 doi:10.1371/journal.pone.0147041

32 Mandelja Y, Procop G, Richter S, Worley S, Liu W, Esper F. Dynamics and predisposition of respiratory viral co-infections in children and adults. Clin Microbiol Infect. 2021;27:631.e1-6. Medline:32540470 doi:10.1016/j.cmi.2020.05.042

33 Drews AL, Atmár RL, Glezen WP, Baxter BD, Piedra PA, Greenberg SB. Dual respiratory virus infections. Clin Infect Dis. 1997;25:1421-9. Medline:9431390 doi:10.1086/516137

34 Richard N, Komurian-Pradel F, Javouhey E, Perret M, Rajaharison A, Bagnaud A, et al. The impact of dual viral infection in infants admitted to a pediatria intensive care unit associated with severe bronchiolitis. Pediatr Infect Dis J. 2008;27:213-7. Medline:18277932 doi:10.1097/INF.0b13e31815b4935
35 Cho HJ, Shim S-Y, Son DW, Sun YH, Tchah H, Jeon I-S. Respiratory viruses in neonates hospitalized with acute lower respiratory tract infections: Respiratory viruses in neonates. Pediatr Int. 2013;55:49-53. Medline:22978535 doi:10.1111/j.1442-200X.2012.03727.x

36 Wu X, Wang Q, Wang M, Su X, Xing Z, Zhang W, et al. Incidence of respiratory viral infections detected by PCR & QPCR in adult patients with community-acquired pneumonia: a meta-analysis. Respiration. 2015;89:343-52. Medline:25791384 doi:10.1159/000369561

37 Moriyama M, Hugentobler WJ, Iwasaki A. Seasonality of Respiratory Viral Infections. Annu Rev Virol. 2020;7:83-101. Medline:32196426 doi:10.1146/annurev-virology-012420-022445