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CHARACTERISTICS OF INFLUENZA INFECTION IN 2017 AND CURRENT PRACTICE: A RETROSPECTIVE STUDY AT A COLLEGE HOSPITAL IN JEDDAH.

INTESSAR SULTAN[1*], MONTASIR MOAMENA[2], AMMAR DEGNAH[2], BANDAR ALHARBI[2], HATIM ALHABI[2] AND ASSAD ALSAADI[2]

[1]Professor at IbnSina National College for Medical Studies, College of Medicine, Department of Medicine, Jeddah, SA.
[2] Intern at IbnSina National College for Medical Studies, College of Medicine, Jeddah, SA.

ABSTRACT

Saudi Arabia has recentlystarted a surveillance process for seasonal influenza outbreaks. Special interest should be given to the influenza-associated severe acute respiratory infection (SARI) to describe the epidemiological and clinical characteristics and current practice of influenza-associated SARI in 2017. A retrospective observational study was conducted at IbnSina National College Hospital in Jeddah in 2018. Review of medical records was done using checklists for in-patients who did rapid influenza diagnostic tests during 2017 using nasopharyngeal swabs and for whom coronavirus RT-PCR test was also performed by the "Saudi National Health Laboratory". Data collection included time of admission, demographic, clinical, and laboratory data, treatment, and outcome. Among 300 in-patients with fever, 31.3% had SARI due to influenza A rather than B but not H1N1 or MERS-CoV infection. SARI cases clustered during July and September ('Ramadan' and 'Hajj' periods). The risk of flu-related complications was high (45.7%) and included mostly children < 5 and presented mainly with pneumonia (21.3%). The main presentations were fever (83%), flu-like symptoms (41.9%), nonproductive cough (33%), dyspnea (25%), vomiting (14.9%), and abdominal pain (8.5%). Patients had lymphocytosis (27.7%) and neutropenia (20.2%).All received antiviral oseltamivir (16% received it late, 3.4% did not continue after discharge) and 90.4% received empirical antibiotics. All recovered completely with no ICU admission. Seasonal influenza A-associated SARI in 2017 in our hospital coincided with 'Ramadan' and 'Hajj' periods, presented with typical symptoms, and had a high risk of complications, especially pneumonia. It was amenable to antiviral therapy with a favorable outcome. Most patients received empirical antibiotics and a few did not receive proper antiviral therapy. Physicians should consider early antiviral treatment in patients with suspected SARI during influenza seasons. There is a need for national recommendations to guide antibiotic strategies and regimens in influenza-associated SARI.

KEYWORDS:*Epidemiological characteristics; Clinical characteristics; Influenza A, Influenza B; SARI, severe acute respiratory infection.*

INTESSAR SULTAN*
Professor at Ibn Sina National College for Medical Studies, College of Medicine, Department of Medicine, Jeddah, SA.

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INTRODUCTION

Influenza viruses A and B can cause significant human disease which ranges from mild self-limited symptoms to a severe acute febrile respiratory illness with significant morbidity and mortality, especially in high-risk patients. [1] Saudi Arabia deserves special consideration as influenza mostlypeaks during seasons of Hajj and Umrah, at the holy places in Mecca and Madinah.World Health Organization in 2017[2] emphasizes that early diagnosis and treatment of influenza virus infection improves outcome and reduces occurrence of severe cases and deaths. For surveillance purposes, influenza–like illness (ILI) is defined as an individual with acute respiratory infection with measured fever of ≥38°C, cough, and onset of symptoms within the last 10 days. [3] If the patient requires hospitalization, this is identified as "Severe Acute Respiratory Infection" (SARI). [3] WHO encourages health authorities to enhance their surveillance for SARI and to carefully review any unusual patterns of SARI or cases of pneumonia.[2]Influenza-associated SARI hospitalization rate has been studied in many countries[4–9]. However, rate estimate is limited by regional variation in risk factors, epidemiology, and health care practices. [6,8]Currently, the epidemiological and virological data on seasonal influenza viruses in Saudi Arabia is very deficient, especially from private section. Influenza virus surveillance was first introduced in Saudi Arabia after the outbreak of MERS-CoV in 2012. [10] For SARI, general or community hospitals (not the private hospitals) were chosen as the sentinel sites for surveillance. [3] Therefore, the present study was conducted to describe the epidemiologic and the clinical characteristics of influenza-associated SARI cases in 2017 with special emphasis on the current practice of managing such cases in a private college hospital in Jeddah.

METHODS

This retrospective descriptive study was conducted at the private "IbnSina National College Hospital" in Jeddah, Saudi Arabia from July to September 2018. The data was collected using checklists through reviewing medical files. First, the research team communicated with information technology personnel to have the list of file numbers of admitted patients who performed influenza workup during the year 2017. Second, files were selected by non-randomized convenient sampling according to the inclusion and exclusion criteria. Inclusion criteria included those of any age, any gender, and any nationality who were admitted to the hospital with fever under any diagnosis and performed full influenza workup including influenza A, B, H1N1, and Middle East Respiratory Syndrome Coronavirus (MERS CoV). Excluding criteria included out-patients and in-patients with incomplete data.For the purpose of diagnosis, the hospital policy entails that patients with suspected influenza should perform nasopharyngeal aspirate testing both in the local and the central laboratories. At the local laboratory, aspirates were tested using the commercially available rapid Influenza Diagnostic Tests (RIDTs) (SD influenza antigen A/B/A (H1N1) pandemic (SD standard diagnostic tests, INC)). RIDTs are antigen detection assays that can detect the viral antigens in 10-15 minutes with 50-70% sensitivity and 90% specificity without identifying influenza A subtypes. [11]The central laboratory – the "Saudi National Health Laboratory" tested the swabs for the MERS-CoV using real-time reverse transcription PCR test. [12] Any patient with positive influenza test was considered to have SARI because of the severity of symptoms that necessitated admission to the hospital. [3]Data extracted from medical records included: the date and time of admission from onset of the illness, demographic, clinical and laboratory data, associated medical conditions, pregnancy, treatment modalities, time of prescribing antimicrobial treatment from the onset of admission to treatment, results of culture and sensitivity, outcome, complications and short-term mortality in hospital. After data collection, the patients were divided into 2 groups: those with influenza and those with another non-influenza diagnosis.For influenza cases, the risk of developing flu-related complications was considered high if the patient was younger than 5 years, pregnant, a resident of long-term care, or an underlying medical condition (asthma, neurological and neurodevelopmental conditions, chronic lung, liver, renal or heart diseases, blood disorders, diabetes, immunosuppression and morbid obesity). [3] According to the center for disease control and prevention (CDC)[13], flu-related complications in this study were determined if any influenza patient had pneumonia, bronchitis, sinus/ear infections, exacerbation of asthma, or admission to ICU for any reason. The protocol of the study was approved by "IbnSina National College Ethical Review Board" and the patients' data was dealt with confidentiality.

STATISTICAL ANALYSIS

SPSS version 22 was used for statistical analysis and constructing figure 1 and Excel 2013 for constructing other figures. A descriptive analysis was performed on the patient's characteristics. Categorical and continuous data are reported as number (%), or median with the range (not normally distributed variables). Chi-squared tests were used to examine the differences in categorical variables, and non-parametric tests were applied to examine the differences in the non-normally distributed continuous variables. All statistical tests were two-sided, and a P-value less than 0.05 were considered significant.

RESULTS

Medical record files of 300 in-patients who had the influenza test done during the year 2017 were retrieved. None of them were Hajj or Umrah patients and all were residents in Jeddah. Figure 1 shows that influenza-associated SARI cases were detected in 94 patients (31.3%); mainly influenza A (29%), as influenza B was detected only in 2.3% of patients. None had H1N1 or MERS-CoV infection. The final diagnoses of non-influenza cases were mainly pneumonia (21.33%), upper respiratory tract infection (16%), gastritis/gastroenteritis (13.33%), typhoid (6%), and undiagnosed fever (4%). Figure 2 demonstrates the two peaks of new influenza cases during July and September 2017. The first peak in July coincided with the end of the month of "Ramadan" which started on the 27th of May and ended on the 24th of June. The second peak in September coincided with the "Hajj" period which roughly began in August and persisted for about 2 months.

Figure 1.

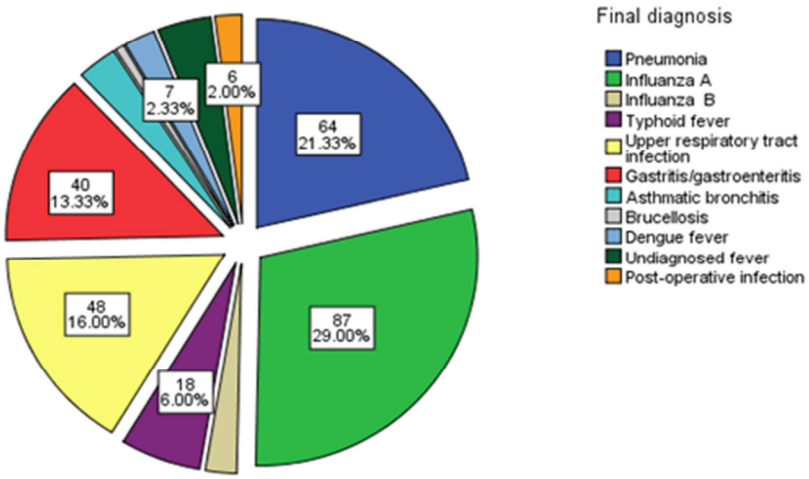

Figure 1
The final diagnosis of in-patients admitted with fever and got the rapid influenza diagnostic tests done (n=300).

Table 1 demonstrates the demographic characteristics of influenza cases. Children represented roughly 70% of cases (40.4% of them were <5), 51.1% were females, and 58.5% were Saudis. They were matched with that in non-influenza cases except in age groups where 82% of them were children (p=0.027). The risk of flu-associated complications among influenza cases was high (47.9%). Figure 3 shows the most common symptoms among influenza cases: fever (83%), flu- like symptoms (41.9%), cough (33%), and dyspnea (25%). Compared to non-influenza cases, patients with influenza showed significantly lower symptoms of vomiting (p=0.013) and diarrhea (p=0.035). In Table 2, 70.2% of SARI cases appeared unwell on admission with high fever (39°C (36-40)). Compared to non-influenza cases, they had more diastolic blood pressure (p=0.015) and weight (p=0.015). Laboratory results in Table 3 show that influenza cases had more significant neutropenia (20.2% vs 6.8%, p=0.001), lymphocytosis (27.7% vs 11.7%, p=0.047), but lower C-reactive protein (CRP) (6 vs 12.5, p=0.001) compared to those in non-influenza cases.

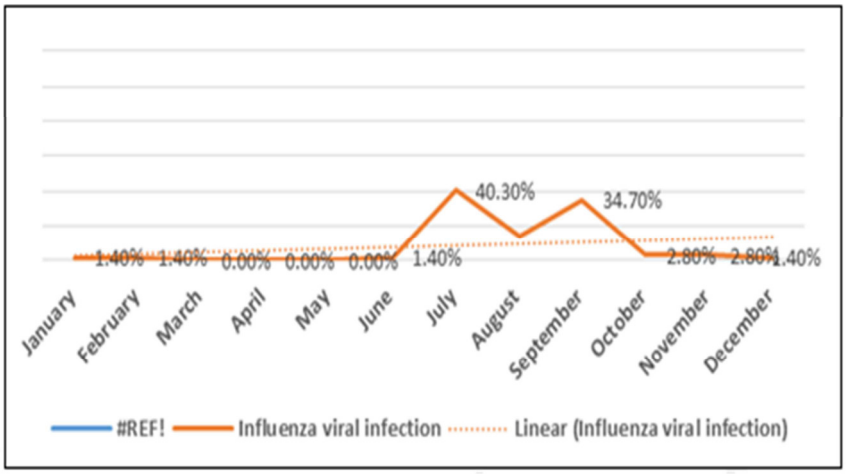

Figure 2
The 2 peaks of influenza severe acute respiratory infection in July and September 2017.

Table 1
Demographic characteristics of influenza-associated severe acute respiratory infection in comparison to non-influenza cases.

Variables.		Influenza cases (N=94).N (%).	Non-Influenza cases (N=206).N (%).	P*
Age group: years.	<5.	38 (40.4).	124 (60.2).	0.027.*
	5- <12.	28 (29.8).	45 (21.8).	
	12-<18	7 (7.4).	7 (3.4).	
	18-<65.	20 (21.3).	29 (14.1).	
	65 or older	1 (1.1).	1 (0.5).	
Gender	Males	46 (48.9).	103 (50).	0.864
	Females.	48 (51.1).	103 (50).	
Nationality.	Saudi.	55 (58.5).	130 (63.1).	0.448
	Non-Saudi	39 (41.5).	76 (36.9).	

P*: the significant difference between influenza and non-influenza cases (significant if p=<0.05).

Table 2
Clinical characteristics of influenza-associated SARI on admission in Comparison to non-influenza cases.

Variable.		Influenza cases (N=94). Median (range).	Non-Influenza cases (N=206). Median (range).	P*
Underlying medial disease: N (%).		7 (7.4)^	12 (5.9)	0.600
General condition: N (%).	Well.	28 (29.8)	59 (28.6)	0.839
	Unwell.	66 (70.2)	147 (71.4)	
Pulse: beats per min.		100 (77-140)	110 (74-138)	0.217
Temperature: °C.		39 (36-40)	39 (36-40)	0.454
Systolic Blood pressure: mmHg.		90 (70-180)	90 (65-170)	0.109
Diastolic blood pressure: mmHg.		60 (40-100)	60 (45-100)	0.045*
Weight: kg.		30 (3-80)	24 (5-82)	0.015*

P*: The significant difference between influenza and non-influenza cases (significant if p=<0.05).All cases had underlying chest disease.

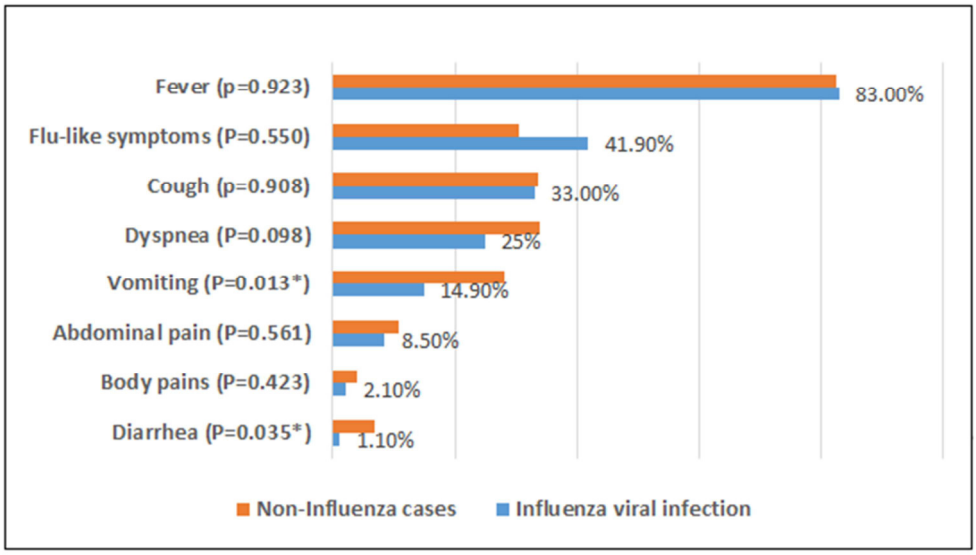

Figure 3

The presenting symptoms of influenza-associated severe acute respiratory infection in Comparison to non-influenza cases.

Table 3

Laboratory results of influenza-associated severe acute respiratory infection in comparison to non-influenza cases.

	Variables.	Influenza cases (N=94).n (%).	Non-Influenza cases (N=206).n (%).	P
Hemoglobin (median): g/dl.	Hemoglobin.	11.4 (9.5-16.5).	11.5 (8.5-15.6).	0.663.
White blood cells.	Normal.	78 (83).	159 (77.2).	0.028.*
	Leukocytosis.	11 (11.7).	44 (21.4).	
	Leukopenia.	5 (5.3).	3 (1.5).	
Lymphocytes.	Normal.	61 (64.9).	163 (79.1).	0.047.*
	Lymphocytosis.	26 (27.7).	24 (11.7).	
	Lymphopenia.	7 (7.5).	19 (9.2).	
Neutrophils.	Normal.	60 (63.8).	137 (66.5).	0.001.*
	Neutrophilia.	15 (16.0).	55 (26.7).	
	Neutropenia.	19 (20.2).	14 (6.8).	
Platelets.	Normal.	87 (92.6).	187 (90.8).	0.510.
	Thrombocytosis.	2 (2.1).	10 (4.9).	
	Thrombocytopenia.	5 (5.3).	9 (4.4).	
C-reactive protein: median mg/L (range).		6 (0-60).	12.5 (0-80).	0.001.*

P*: The significant difference between influenza and non-influenza cases (significant if p=<0.05).

In Table 4, 16% of influenza cases presented after 48 hours from the onset of illness. Their hospital stay ranged from 1 to 4 days with a median of only one day. Flu-related complications were mainly pneumonia (21.3%) and exacerbation of asthma (3.2%). The frequency of pneumonia did not differ between both influenza and non-influenza cases (p=0.255) and both occurred mainly in children less than 12 years. There was no admission to ICU for any reason and all influenza cases recovered completely. Influenza cases were initially managed similar to non-influenza cases (p=0.193). Anti-viral therapy was given to all influenza patients after getting the positive RIDTs even for those who presented after 48 hours of onset of fever (16%). Only 4.3% did not continue antiviral therapy after discharge. Antibiotics were continued on discharge in 79.8% (62.8% alone and with antiviral treatment in 17.0%).

Table 4

Admission, treatment, and outcome of influenza-associated severe acute respiratory infection in comparison to non-influenza cases.

Variables.		Influenza cases (N=94).N (%)	Non- Influenza cases (N=206).N (%).	P.
Time of admission from the onset of fever.	Within 48 hours.	79 (84).	182 (88.3).	0.304.
	After 48 hours.	15 (16).	24 (11.7).	
The median duration of admission: days.		1 (1-4).	2 (1-7).	0.184.
Flu-related complications.	**Pneumonia**	20 (21.3).	61 (29.6).	0.255.
	Exacerbated asthma	3 (3.2).	9 (4.4).	
Initial drugs in the hospital.	**Antibiotics**	85 (90.4).	182 (88.3).	0.193.
	Antiviral	94 (100).	0 (0).	
	Inotropes	1 (1.1).	1 (0.5).	
	Steroids	0 (0).	9 (4.4).	
The median time of prescribing antibiotics from the onset of admission to treatment: hours.		7.7 (1-23).	7.5 (0.5-23).	0.387.
Discharge medications.	Antibiotic.	59 (62.8).	189 (91.7).	0.000.*
	Antiviral.	74 (78.7).	0 (0%).	
	Both antibiotic and antiviral.	16 (17.0).	0 (0).	
	Neither.	4 (4.3).	17 (8.1).	
Outcome.	Improved.	94 (100.0).	203 (98.5).	0.240.
	Complicated.	0 (0).	3 (1.5).	

P*: The significant difference between influenza and non-influenza cases (significant if p=<0.05).

DISCUSSION

Influenza-associated SARI was found in 31.3% of admitted patients with fever during the year 2017 in a private hospital in Jeddah. None of the in-patients were positive for MERS-CoV or H1N1. The main viral agent of this season was influenza A (29%), it had 2 peaks, was amenable to antiviral therapy with oseltamivir and had a favorable outcome. Worldwide, outbreaks and epidemics of seasonal Influenza are caused mainly by influenza A or B in the winter season. The two peaks of 2017 seasonal Influenza A coincided with the end of the month of "Ramadan" and the "Hajj" period; where the travel to Mecca is the highest and the spread of respiratory viruses is common due to religious mass gatherings with possible emergence of resistant strains. [14] Jeddah is a port city in the Mecca region, and is the gateway for pilgrimages to Mecca. In another Saudi study of 1644 adults with community acquired pneumonia from January 2015 to December 2016[15]; 16.5% had influenza that peaked in October to December. Similar to the present study, absence of MERS-CoV infection was reported in the other study. But in contrast different incidences of influenza A (6.5%), H1N1 (7.3%), and influenza B (2.7%) were reported, probably because the previous study included those with influenza-associated pneumonia only. While the present study included residents of Jeddah city, absence of MERS-CoV infection was also documented in returning pilgrimages from Mecca to their different countries. [16-19]Epidemiologically, this seasonal influenza A-associated SARI affected mostly children (70%) of both gender equally and 58.5% of them were of Saudi nationality. They had a classic presentation with fever (83%), flu-like symptoms (41.9%), non-productive cough (33%), dyspnea (25%), vomiting (14.9%), and abdominal pain (8.5%); but few presented with diarrhea (1.1 %). These results did not differ from influenza presentation in other countries in 2017.[20]In this

study, 45.7% of influenza patients (mostly children younger than 5) had a high risk of flu-related complications which included mainly pneumonia in 21.3%. Interestingly, the frequency of pneumonia did not differ between both influenza and non-influenza cases (p=0.255) and both occurred mainly in children less than 12 years. Influenza–associated pneumonia may be primary, but is more commonly secondary to bacterial pneumonia. Influenza was recognized in a large epidemiological study to be the second most common viral pathogen inducing pneumonia in immune-competent adults. [21] The clinical characteristics, laboratory findings, and radiographic patterns of viral pneumonia are not unique. It resembles community-acquired pneumonia, and ranges from mild to severe disease. [22] Treatment should begin as soon as influenza pneumonia is suspected and before laboratory confirmation. Three neuraminidase inhibitors are FDA approved in 2014 for the treatment of influenza A and B in adults; oral oseltamivir, inhaled zanamivir and intravenous peramivir. [22]In this study, influenza cases received early antiviral therapy within 48 hours of presentation due to the rapid results of RIDTs within 15 min. However, 16% of cases received treatment later than 48 hours and 4.3% did not have their antiviral treatment among the discharge medications. All influenza virus-infected patients with or without pneumonia received early antibiotics within hours, together with oseltamivir antiviral therapy, and had a generally good response with short median hospitalization for only one day. C-reactive protein (CRP) like other inflammatory markers can be used to differentiate between bacterial and viral infection. On the other hand, CRP level has been shown to be negatively associated with prognosis of influenza virus infection. [23] In the current study, influenza cases were characterized by a lower level of CRP compared with non-influenza cases which could serve as a marker of both viral etiology and good prognosis. The main limitation of this study was its retrospective observational study design with no causal inference. Researchers had no access to travel history or data for immunization directly from patients. The second limitation was the use of RIDTs that cannot identify influenza subtypes and have possible false negative tests because of their low sensitivity (50-70%). It is recommended that all hospitalized patients with suspected SARI should be tested with high sensitivity and specificity molecular assays tests. [2,3] However, in this study, influenza diagnosis is not confirmed by other diagnostic tests. Finally, generalization of our results applies only for admitted patients with influenza-associated SARI.

CONCLUSION

Seasonal influenza-associated SARI in a private hospital in Jeddah during 2017 was common (31.3%), and affected mostly children (70%) of both gender equally. It had a classic presentation, coincided with “Ramadan and Hajj” periods and was amenable to antiviral therapy with a favorable outcome. The most common risk groups were children less than 5 years old and those with underlying chest disease. Pneumonia was detected in 21.3% of cases; probably due to either primary viral infection or secondary bacterial infection, or even mixed. Most patients received early antibiotics even after diagnosis of viral infection and 16% received antiviral therapy after 48 hours of presentation. Physicians should consider early antiviral treatment for all influenza-associated SARI cases. In addition, early use of antibiotics should also be considered especially in the presence of pneumonia. There is a need to have clear national guidelines for the use of antibiotic therapy in influenza cases to guide physicians during influenza pandemics, especially in areas that receive millions of pilgrimages, like the Mecca region.

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AUTHOR CONTRIBUTION STATEMENT

Professor Intessar Sultan was the supervisor of the research. MontasirMoamena, AmmarDegnah, Bandar Alharbi, HatimAlhabi, and Assad Alsaadi were involved in writing the research proposal, conducting the review of the literature, collecting and entering the research data, analyzing the research data, and drafting the publication manuscript.

CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, et al. Seasonal Influenza in Adults and Children—Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(8):1003–32. DOI: 10.1086/598513
2. World Health Organization Influenza (seasonal). Geneva: WHO; 2018. Available from: https://www.who.int/ith/diseases/influenza_seasonal/en/
3. Infection prevention and control guidelines for seasonal influenza in healthcare setting Ministry of Health – Kingdom of Saudi Arabia. Riyadh: Ministry of health. Seasonal Influenza; 2017. Available from: https://www.moh.gov.sa/en/CCC/StaffRegulations/Influenza/Documents/IPCGuidelines-for-Seasonal-Influenza.pdf
4. Kwofie TB, Anane YA, Nkrumah B, Annan A, Nguah SB, Owusu M. Respiratory viruses in children hospitalized for acute lower respiratory tract infection in Ghana. Virol J. 2012;9(1). DOI: 10.1186/1743-422x-9-78
5. Al-Shehri MA, Sadeq A, Quli K. Bronchiolitis in Abha, Southwest Saudi Arabia: viral etiology and predictors for hospital admission. West Afr J Med. 2006;24(4). DOI: 10.4314/wajm.v24i4.28193
6. Broor S, Parveen S, Bharaj P, Prasad VS, Srinivasulu KN, Sumanth KM, et al. A Prospective Three-Year Cohort Study of the Epidemiology and Virology of Acute Respiratory Infections of Children in Rural India. PLoS One. 2007;2(6):e491. DOI: 10.1371/journal.pone.0000491
7. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010;375(9730):1969–87. DOI: 10.1016/s0140-6736(10)60549-1
8. Khor C-S, Sam I-C, Hooi P-S, Quek K-F, Chan Y-F. Epidemiology and seasonality of respiratory viral infections in hospitalized children in Kuala Lumpur, Malaysia: a retrospective study of 27 years. BMC Pediatr. 2012;12(1). DOI: 10.1186/1471-2431-12-32
9. Uduman SA, Ijaz MK, Kochiyil J, Mathew T HM. Respiratory syncytial virus infection among hospitalized young children with acute lower respiratory illnesses in Al Ain, UAE. J Comm Dis. 1996;28(4):245–52. Available from: https://europepmc.org/abstract/med/9057448
10. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus ADME, Fouchier RAM. Isolation of a Novel Coronavirus from a Man with Pneumonia in Saudi Arabia. N Engl J Med. 2012;367(19):1814–20. DOI: 10.1056/nejmoa1211721
11. Merckx J, Wali R, Schiller I, Caya C, Gore GC, Chartrand C, et al. Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection Compared With Reverse Transcriptase Polymerase Chain Reaction. Ann Intern Med. 2017;167(6):394. DOI: 10.7326/m17-0848
12. Corman VM, Müller MA, Costabel U, Timm J, Binger T, Meyer B, et al. Assays for laboratory confirmation of novel human coronavirus (hCoV-EMC) infections. Eurosurveillance. 2012;17(49). DOI: 10.2807/ese.17.49.20334-en
13. People at high risk of developing serious flu–related Complications. Center for disease control and prevention. Georgia, USA; 2018. Available from: https://www.cdc.gov/flu/about/disease/high_risk.htm
14. Memish ZA, Al-Rabeeah AA. Health conditions of travellers to Saudi Arabia for the pilgrimage to Mecca (Hajj and Umra) for 1434 (2013). J Epidemiol Glob Health. 2013;3(2):59–61. DOI: 10.1016/j.jegh.2013.03.001
15. Al-Tawfiq JA, Rabaan AA, Hinedi K. Influenza is more common than Middle East Respiratory Syndrome Coronavirus (MERS-CoV) among hospitalized adult Saudi patients. Travel Med Infect Dis. 2017;20:56–60. DOI: 10.1016/j.tmaid.2017.10.004
16. Koul PA, Mir H, Saha S, Chadha MS, Potdar V, Widdowson M-A, et al. Influenza not MERS CoV among returning Hajj and Umrah pilgrims with respiratory illness, Kashmir, north India, 2014–15. Travel Med Infect Dis. 2017;15:45–7. DOI: 10.1016/j.tmaid.2016.12.002
17. Gautret P, Charrel R, Benkouiten S, Belhouchat K, Nougairede A, Drali T, et al. Lack of MERS Coronavirus but Prevalence of

Influenza Virus in French Pilgrims after 2013 Hajj. Emerg Infect Dis. 2014;20(4):726–8. DOI: 10.3201/eid2004.131708

18. Aberle JH, Popow-Kraupp T, Kreidl P, Laferl H, Heinz FX, Aberle SW. Influenza A and B Viruses but Not MERS-CoV in Hajj Pilgrims, Austria, 2014. Emerg Infect Dis. 2015;21(4):726–7. DOI: 10.3201/eid2104.141745
19. Memish ZA, Assiri A, Almasri M, Alhakeem RF, Turkestani A, Al Rabeeah AA, et al. Prevalence of MERS-CoV Nasal Carriage and Compliance With the Saudi Health Recommendations Among Pilgrims Attending the 2013 Hajj. J Infect Dis. 2014;210(7):1067–72. DOI: 10.1093/infdis/jiu150
20. Yang Y, Zhong H, Song T, He J, Guo L, Tan X, et al. Epidemiological and clinical characteristics of humans with avian influenza A (H7N9) infection in Guangdong, China, 2013–2017. Int J Infect Dis. 2017;65:148–55. DOI: 10.1016/j.ijid.2017.07.021
21. Community-Acquired Pneumonia Requiring Hospitalization. N Engl J Med. 2015;373(24):2380–2. DOI: 10.1056/nejmc1511751
22. Dandachi D, Rodriguez-Barradas MC. Viral pneumonia: etiologies and treatment. J Investig Med. 2018;66(6):957–65. DOI: 10.1136/jim-2018-000712
23. Vasileva D, Badawi A. C-reactive protein as a biomarker of severe H1N1 influenza. Inflamm Res. 2018;68(1):39–46. DOI: 10.1007/s00011-018-1188-x