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The impact of COVID-19 pandemic on surveillance of influenza and influenza-like viruses: a single center experience

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ABSTRACT

Aims: Influenza and the agents responsible for influenza-like illness (ILI) are a significant cause of upper and lower respiratory tract infections, with a notable pattern of seasonal incidence. The surveillance of influenza and agents causing ILI is important for the developmentof a prophylaxis approach and infection control. In the present study, we utilize the Reverse transcription-polymerase chain reaction (RT-PCR) method to identify the presence of influenza virus and other agents associated with ILI in nasopharyngeal smears obtained from patients exhibiting symptoms of influenza and ILI. The study sample included patients who were admitted to multiple clinics and intensive care units (ICU) of the Health Sciences University Ankara Training and Research Hospital in the period preceding, and in the initial months and first year following the coronavirus disease 2019 (COVID-19) outbreak. Throughthe comparisons made in the study, the intention is to gain a better understanding of the influence of the COVID-19 pandemic on other viral infectious agents transmitted via the respiratory tract.

Methods: Included in the study were 257 admitted to different wards and ICUs of our hospital due to symptoms of upper or lower respiratory tract infection and ILI between 2015 and 2021 (excluding data from 2017–2018). The study was conducted prospectively within the scope of the Global Influenza Hospital Surveillance Network project. Using sterile swabs, nasopharyngeal swab samples were collected from inpatients who provided informed consent for their participation in the study, and the samples were placed in a viral transport medium. The presence of influenza viruses (Influenza A, subtypes of Influenza A and Influenza B) and agents causing ILI (i.e. respiratory syncytial virus, coronavirus) was investigated with an RT-PCR approach.

Results: The most common symptoms among the 257 patients included in the study with pre-diagnoses of influenza and ILI were cough (82.2%), fever (67.7%), shortness of breath (66.1%) and myalgia (40%). The RT-PCR detected a viral agent in 60 (23.3%) of the 257 patients, whereas no agent could be detected in 197 (76.6%) patients. Furthermore, 51 (18.5%) tested positive for influenza virus, five (1.9%) for respiratory syncytial virus (RSV), and four (1.5%) for SARS-CoV-2. An analysis of the results within two distinct time frames, namely prior to the COVID-19 pandemic (2016–2017, 2019–prior to December 10, 2020) and during the COVID-19 pandemic (between December 11, 2020 and 2021), influenza viruses (influenza A H1N1 and influenza A H3N2), RSV and influenza type B were identified as the dominant viruses before the COVID-19 pandemic, while the predominant viruses were a single influenza strain and four SARS-CoV-2 variants during the COVID-19 pandemic.A significant difference was noted in the distribution of viruses between the two time frames – prior to the pandemic and during the pandemic. Of the patients, 199 (77.4%) were discharged with full recovery while 58 patients died (22.6%). Of the 58 patients that died, 25 were female (25/131 females) and 33 were male (33/126 males), 11 had tested positive for influenza virus andone for RSV, while no infectious agent could be identified in 46 patients.

Conclusion: The implementation of molecular testing methods for the identification of viral infectious agents among inpatients during influenza and ILI outbreaks, administering antiviral and prophylactic treatments targeting influenza, RSV and SARS-CoV-2 infections, and adopting infection control measures, could significantly decrease mortality and morbidity rates while mitigating the complications associated with these infectious agents.

Keywords: Influenza, influenza-like viruses, SARS-CoV-2, pandemic

INTRODUCTION

Influenza and influenza-like viruses are the most common causes of upper and lower respiratory tract infections in both adults and children.[1–3] Influenza, caused by highly contagious influenza viruses, is an acute respiratory tract infection that constitutes a substantial global threat, with an estimated 3–5 million people developing severe infections caused by seasonal flu viruses annually, leading to the death of 290,000–650,000 people around the world.[4]

The influenza-like viruses that are often mistaken for influenza viruses include rhinoviruses, respiratory syncytial virus (RSV), adenovirus, human parainfluenza viruses, human metapneumovirus, human bocavirus, coronaviruses and SARS-CoV-2, that last of which triggered the recent global pandemic.[1–5] These agents are significant causes of mortality and morbidity, particularly in children under the age of 5, older adults (65 years and above), immunocompromised patients and those with underlying chronic conditions.2,6–10 Influenza viruses

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undergo frequent antigenic mutations, and such changes lead to annual epidemics, prompting the production of new vaccines targeting specific virus strains and the regular vaccination of high-risk people each year. The surveillance of influenza viruses and influenza-like viruses is crucial for the identification of the predominant virus strain and for the planning of disease prevention and control activities, the early detection of outbreaks, and the planning of patient care and vaccination regimes.

The COVID-19 pandemic has had a profound impact on the lives of people around the world, prompting the implementation of comprehensive public health control measures, especially during the initial months of the pandemic, such as the avoidance of crowded places, lockdowns, restrictions on travel, emphasized hand hygiene practices, obligatory facemask use and social distancing. It is believed that these measures have had a comparable impact also on the influenza virus and other influenza-like viruses.

In the present study,an RT-PCR method is applied to investigate the presence of the influenza virus and other agents responsible for influenza-like illness (ILI) in nasopharyngeal smears obtained from patients exhibiting symptoms of influenza and ILI. Included in the study werepatients who were admitted to multiple clinics and ICUs of the Health Sciences University . Hospital during the period preceding, as well as in the initial months and the first year following the COVID-19 pandemic. The study results were examined within two distinct time frames, namely prior to the COVID-19 pandemic and during the COVID-19 pandemic, to gain a better understanding of the impact of the COVID-19 pandemic on other infectious agents transmitted via the respiratory tract.

METHOD

The study was carried out with the permission of Hacettepe University Faculty of Medicine Ethics Committee (Date: 21.12.2021, Decision No: 2021/21-48) as was authorized by the head physician, while written informed consent for their inclusion in the study was obtained from all patients. The study was conducted in accordance with good clinical practice guidelines. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study group comprised 257 patients who were admitted to different wards and ICUs of our hospital with symptoms of upper or lower respiratory tract infection and ILIs during the flu seasons (November–May) of 2015 and 2021 (excluding data from 2017–2018). ILI is defined as the presence of symptoms including fever (≥38°C), cough and sore throat.[11]

The study was conducted prospectively within the scope of the Global Influenza Hospital Surveillance Network project. The hospital records were examined daily and patients meeting the inclusion criteria were subjected to a bedside examination. The presence of flu-like symptoms was first enquired, followed by the demographic characteristics of the patients, clinical and laboratory findings, underlying conditions and the clinical course of the disease, and the forms displaying the vaccination status were completed.

Nasopharyngeal and/or pharyngeal smears were collected from the patients and sent to the contracted laboratory daily after placement in a viral transport medium (Virocult, Medical Ware& Equipment, UK) for the investigation of the influenza virus. The samples were stored at -20°C if not to be tested on the same day. An RT-PCR test was used for the identification and subtyping of influenza viruses. The nucleic acid extraction from the samples was carried out using an E21 Virus Mini Kit V2.0 (Qiagen, Germany). The samples were tested for the presence of influenza A, B and C viruses and other respiratory tract viruses (Enterovirus, Human coronavirus [229E/NL63], Human coronavirus (OC43), Human parainfluenza virus [1-4], Human metapneumovirus, Human bocavirus [types 1–4], Human respiratory syncytial virus A and B, Human adenovirus) using a multiplex influenza A, B and C kit (TibMolbiol, Germany) and a Bio-Rad CFX96 device (Bio-Rad, USA). Samples that tested positive for influenza viruses were further tested for the presence of influenza A H1 and H3 strains, and the influenza B Yamagata and Victoria subtypes using the CDC RT-PCR protocol. Analyses of SARS-CoV-2 were added to the study in 2020.

Statistical Analysis

IBM SPSS Statistics (Version 20.0. Armonk, NY: IBM Corp.) was used for the statistical analysis.A Chi-square test was used to determine the significance of the relationships between categorical variables. A p-value of ≤0.01 was considered statistically significant.

RESULTS

Nasopharyngeal smear samples were collected from 313 inpatients for the detection of influenza virus and other infectious viral agents. Of the patients, 132 (51.3%) were female and 125 (48.6%) were male, and the median age was 65.67 years. The most common symptoms in the study patients were cough (n=213, 82.8%), fever (n=174, 67.7%), shortness of breath (n=170, 67.7%) and myalgia (n=103, 40%).

The symptoms of the patients that reported flu-like complaints are presented in **Table 1**.

Of the 313 patients that underwent RT-PCR testing in the present study, 80 (26%) tested positive for influenza virus, five (1.9%) for RSV and four (1.5%) for SARS-CoV-2, while no viral agent could be identified in 224 patients

(70.6%). The distribution of PCR-positive and PCR-negative patient results by year presented in Table 2.

Table 1. Symptoms of patients reporting flu-like complaints

Symptoms	Number	%
Cough	213	82.8
Shortness of Breath	170	66.1
Fever	174	67.7
Myalgia	103	40

Table 2. Distribution of PCR-positive and PCR-negative patient results by year.

	PCR -positive patients n (%)	PCR -negative patients n (%)	Total
2015	11 (68.8)	5 (31.2)	16 (100)
2016	111 (79.9)	28 (20.1)	139 (100)
2019	2 (100)	0 (0)	2 (100)
2020	47 (63.5)	27 (36.5)	74 (100)
2021	26 (100)	0 (0)	26 (100)
Total	197	60	257 (100)

An examination of the monthly distribution of viral infectious agents showed that influenza virus, influenza A and B and RSV were the most common in the winter months (January–March), while SARS-CoV-2 was most commonly observed in April and May after March 11, 2020, when the first case of COVID-19 was identified in Turkey. The monthly distribution of viral agents is presented in Table 3.

The yearly distribution of viral agents is shown in Figure. The study period was divided into two distinct time frames: prior to the pandemic (2015-2016, 2016-2017, 2019 and before March 10, 2020) and during the pandemic (between March 11, 2020 and 2021).

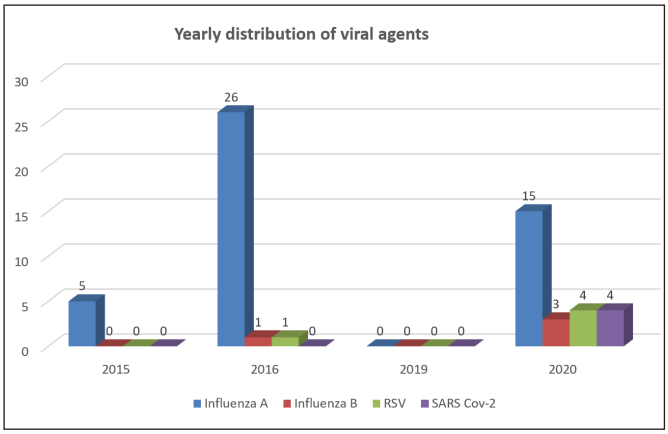

Figure. Most common viral agents by year

Influenza virus (influenza A H1N1 [n=16] and influenza A H3N2 [n= 12], RSV [n=5] and influenza B virus [n=4]) were predominant in the pre-pandemic period.

Only a single influenza virus was identified during the COVID-19 pandemic while SARS-CoV-2 was identified in four patients.

There was a significant difference in the distribution of viral agents between the pre- and peri-pandemic periods (Chi-square test; p=0.0001).

Of the sample, 199 (77.4%) were discharged with full recovery, whereas 58 patients (22.6%) died. Of the non-survivors, 25 were female (25/131 females) and 33 were male (33/126 males). Of those that died, 11 had tested positive for influenza virus and one for RSV, while no infectious agent could be identified in 46 patients. The median age was 77.46 years in the 58 non-survivors, 52 of whom (89.6%) had at least one comorbidity (i.e. diabetes mellitus, chronic kidney disease).

Of the total 257 patients (6.2%), 16 had received an influenza vaccination, among whom three were identified with the influenza virus based on the PCR testing of upper respiratory tract samples, and one of these died. The relationship between cause of death and influenza could not be identified due to a lack of detailed clinical data.

The clinical outcomes (death or discharge) did not differ significantly between the pre- and peri-pandemic periods (Chi-square test: p>0.05).

DISCUSSION

The objective of the present study was to analyze the yearly distribution of seasonal influenza viruses and other viral agents responsible for influenza-like illnesses (ILIs), and to evaluate the impact of the COVID-19 pandemic on the frequency of viral infectious agents following the first confirmed case of COVID-19 in Turkey on March 11, 2020.

The study examined the frequency of influenza and other viruses causing ILI in inpatients through the multiplex PCR testing of nasopharyngeal smear samples collected as part of the Global Influenza Hospital Surveillance Network project. The analysis was conducted for two distinct periods: before the COVID-19 pandemic and during the pandemic. An analysis of the two distinct

Table 3. Monthly distribution of viral agents

Agents	Months								Total (n)
	January	February	March	April	May	June	July	December	
Influenza A	33	1	4	0	0	0	0	9	47
Influenza B	0	1	2	0	1	0	0	0	4
RSV	1	3	0	0	0	0	0	1	5
SARS CoV-2	0	0	0	2	2	0	0	0	4
Total (n)	34	5	6	2	3	0	0	10	60

study periods (pre-pandemic, based on data from the 2015–2016, 2016–2017 2018–2019 and up to December 10, 2020, andthe peri-COVID-19 pandemic period, based on data from between December 11, 2020 and 2021) revealed influenza virus (influenza A H1N1 and influenza A H3N2, respectively), RSV and influenza B were to be predominant in the pre-pandemic period, whereas only a single influenza virus and four SARS-CoV-2 variants were the prevailing agents during the COVID-19 pandemic. A significant difference was noted in the distribution of viral agents between the two time frames.

The decrease in the frequency of the identification of the influenza virus and other agents responsible for ILIs may be attributable to the strict measures and restrictions imposed during the pandemic (the closure of schools, crowded workplaces and social establishments such as cafeterias, cinemas and restaurants), compliance with social distancing rules, wearing facemasks and hand hygiene, vaccinations against influenza and viral interference.

Studies conducted in the United States and Australia reported a decreased prevalence of the influenza virus during the COVID-19 pandemic. Although both SARS-CoV-2 and influenza viruses are transmitted through respiratory droplets, the lower transmission coefficient of the influenza virus compared to that of SARS-CoV-2 was suggested as the cause of the decrease in cases of influenza. Other factors contributing to the decrease in influenza cases during the pandemic include the reduced frequency of influenza testing compared to SARS-CoV-2 testing, the effectiveness of infection control measures implemented to combat COVID-19 in mitigating influenza transmission, and the potential influence of viral interference.[12–14]

Respiratory viruses are transmitted primarily through droplets, close contact, and through touching the mouth, nose or eyes with the hand after coming into contact with surfaces contaminated with the virus. Several studies have reported a decrease in the prevalence of other respiratory viruses that are transmitted primarily through droplets, such as influenza, RSV, coronaviruses, parainfluenza, adenoviruses and bocaviruses, attributing the decline to the restrictions and infection control measures implemented during the COVID-19 pandemic.[12,15]

Agca et al.[12] examined a total of 319 nasopharyngeal smear samples to investigate the epidemiological shift in prevalence of influenza and other respiratory viruses among patients during the COVID-19 pandemic, with positive tests recorded in 101 of the samples (31.7%). In all age groups, rhinoviruses and enteroviruses were identified as the most frequently encountered viral agents. During the initial years of the pandemic, a significant decrease was reported in the prevalence of influenza, declining from 17.3% to 2.3%, while no significant change was observed in the prevalence of the metapneumovirus during the same period. The authors suggested testing for other respiratory viruses, such as rhinoviruses/enteroviruses and metapneumovirus, in addition to SARS-CoV-2, for differential diagnoses, considering that the clinical presentation of such viruses can resemble COVID-19 and other respiratory tract infections.

In their study, Appak et al.16 analyzed a total of 4,770 respiratory samples to explore the monthly distribution of respiratory viruses and Mycoplasma pneumoniae from 2018 to 2021, and to assess the influence of the COVID-19 pandemic on the prevalence of respiratory viruses. The multiplex PCR method yielded a positive result in 2,603 out of the 4,770 samples analyzed (54.6%), coinfection in 474 samples (9.9%) and no specific agent in 2,167 samples (45.4%). In the same study, there were no identified cases of influenza A, influenza B or metapneumovirus during the COVID-19 pandemic, which were commonly encountered in previous years. On the other hand, rhinovirus was consistently identified as the most frequently encountered viral agent both before and during the pandemic. The study also identified respiratory syncytial virus as a coinfection in the last one month of the study period, which concurs with the findings of the present study, in which an influenza virus was identified in only one patient during the pandemic.

Seasonal influenza places a substantial burden on healthcare systems and can result in significant mortality and morbidity.[10] The implementation of national influenza prevention programs, along with the targeted vaccination of high-risk groups, has reduced the mortality rates associated with seasonal influenza significantly.[6,9,10]

A global influenza hospital surveillance network study carried out by Başaranoğlu et al.[1] in the Ankara province of Türkiye from 2016 to 2017 reported positive PCR test results for RSV in 145 out of the 917 patients (15.8%) analyzed. Among the cases with a positive RSV result, 1,322 were aged below 5 years, while 13 were aged above 5 years. Among those aged above 5 years, mortality was found to be associated with RSV in one out of two patients aged above 65 years. In the present study, influenza A was identified in 47 cases (18.5%) and influenza B in four cases (1.5%). Among the agents responsible for ILIs, RSV was detected in five cases (1.9%) and SARS-CoV-2 in four cases (1.5%). No specific agent could be identified in 197 of the 257 cases (76.6%). In the present study, the median age was 70.4 years among the five patients who tested positive for RSV using the PCR method (minimum 26 years, maximum 95 years). The median age of the 47

patients who tested positive for influenza A was 66.4 years (minimum 26 years, maximum 94 years). SARS-CoV-2 was also detected in a number of nasopharyngeal smear samples due to the study period (December 2019-April 2020), December 2020-May 2021) based on the date of the initial outbreak of the COVID-19 pandemic caused by SARS-CoV-2, in the city of Wuhan in China (December 31, 2019), and the date on which the first case of COVID-19 was identified in Türkiye (March 11, 2020). The clinical symptoms of COVID-19 resemble those of the influenza virus (i.e. fever, cough, shortness of breath, myalgia), and it is not possible to differentiate between the two infections based on the clinical manifestations, althoughthe lung involvement pattern observed in radiological imaging studies may sometimes be helpful in this regard – COVID-19 pneumonia is characterized by peripheral involvement in radiological imaging studies, whereas peribronchial involvement is common in influenza pneumonia.[17] That said, the isolation of the agent from respiratory samples is required for definitive diagnosis.

The clinical differentiation of viral infectious agents can be challenging due to the similarity of the associated symptoms in respiratory tract infections. To address this, various molecular diagnostic methods have been developed, including multiplex PCR and real-time PCR, and molecular tests based on respiratory tract syndromic panels.[18–21]

The main advantages of these tests include their ability to provide a rapid diagnosis, enabling the early initiation of treatment and prompt patient care, while their main disadvantages and challenges include their high cost, the lack of specified strategies for their optimum use and the challenges in the interpretation of the test results.[18]

In the present study, patients who tested positive for influenza were placed on antiviral therapy and droplet isolation measures were implemented. Those who tested positive for SARS-CoV-2 were started on COVID-19-focused therapies and transferred to wards designated for the care and follow-up of COVID-19 patients where appropriate infection control measures, including droplet and contact isolation precautions, were implemented. Patients who tested positive for other viral agents were started on symptomatic therapy and the appropriate infection control measures were implemented.

It has been reported that influenza vaccine scan reduce the prevalence of influenza infection by 75–80% in healthy patients, and the efficacy of the influenza vaccine in older adults, particularly those residing in nursing homes, in immunocompromised patients with underlying conditions or in those on immunosuppressive medication ranges from 40 to 60%.[22] Vaccination is considered the most effective preventive approach to the reductionof mortality and morbidity, and for the control of infections in older patients and those at high risk due to such underlying conditions as diabetes, chronic obstructive pulmonary disease (COPD), kidney and heart failure, malignancy and chronic collagen tissue disease.[6,22,23]

Of the 257 patients included in the present study, 16 (6.2%) had received the influenza vaccine, andof these, three tested positive for influenza virus during the PCR testing of upper respiratory tract samples, one of whom died. Due to a lack of detailed clinical data, the precise relationship between the cause of death and influenza could not be accurately determined in the present study.

The rate of patients that had received the influenza vaccine can be considered low in the present study (6.22%) when compared toprevious studies detailing vaccination rates in different risk groups. In a study carried out in Greece, Papaioannou et al.[23] reported an influenza vaccination rate of 34.8% among high-risk patients with such underlying conditions as chronic lung disease, chronic kidney disease, cardiovascular disease, diabetes, malignancy and neurological disease. The influenza vaccination rate was reported to be 57% among the older adult population in Japan, while in a Chinese study, a rate of 3.8% was reported among those aged 60 years and older. In Europe, an influenza vaccination rate of 45.5% has been reported for older adults, and 49.8% among those with a chronic condition.[24]

In a study carried out in Türkiye involving 155 patients, Özışık et al.[25] reported an influenza vaccination rate of 29.7% among 145 patients who were considered sufficiently high-risk for influenza vaccination. An influenza vaccination rate of 7.2% was reported in a study by Tanriover et al.[2] Given the low influenza vaccination rate (6.2%) observed in the present study, the authors recommend that individuals in high-risk groups should be actively encouraged to vaccinate for influenza, and that efforts should be made to convince those who are reluctant.

Demicheli et al.[26] reported that the influenza vaccine reduced the risk of influenza infection from 6% to 2.4%, and the risk of infection by influenza-like viruses from 6% to 3.5% in older adult patients.

Randomized and controlled studies as well as observational studies have suggested that vaccinating against influenza reduces the mortality and morbidity rates of adult patients with cardiovascular diseases,[5] although there have been several studies reporting that the influenza vaccine is effective in reducing influenza-

related morbidity, but has no effect on all-cause mortality.[7]

Influenza outbreaks are associated with increased mortality in winter months. The presence of a chronic disease and residing in a nursing home were identified as significant risk factors for the development of complications and increased mortality associated with influenza.[8]

In a study involving 774 inpatients carried out within the scope of the Global Influenza Hospital Surveillance Network, Tanrıover et al.[2] reported influenza positivity identified through the PCR testing of nasopharyngeal or oropharyngeal smear samples in 142 patients (18.4%), with the most commonly isolated influenza serotype being influenza A H1N1 PDM 09. Within the study, all older patients were reported to have at least one chronic underlying condition, the most common being cardiovascular disease, followed by chronic obstructive pulmonary disease. The rate of influenza vaccination among the study patients was reported to be 7.2%, and the same study reported that, regardless of the presence of influenza virus positivity, the clinical course was poorer in older patients, that half of the patients aged above 65 years required admission to the ICU, that one-third of the patients required the use of a mechanical ventilator, and that one-quarter of the patients died. The same study also reported ILIs to be associated with poorer clinical outcomes in older inpatients. The authors concluded the study with the suggestion that an influenza vaccination strategy could provide an opportunity to prevent deaths associated with ILI in older adults, and in adults with chronic conditions.

The present study has some limitations, including its retrospective design and the lack of long-term follow-up of the participants, which posed limitations on access to detailed clinical data, thereby hindering the assessment of the relationship between the cause of death and influenza and ILI. Furthermore, the patients were not tested for influenza or agents responsible for ILI between 2017 and 2018. Another limitation of the study, related to the assessment of the prevalence of viral agents, is the difference in the established periods before the pandemic (2015–2016, 2016–2017, 2019–December 10, 2020) and after the COVID-19 outbreak (between December 11, 2020 and 2021).

No significant difference was noted in the death and discharge rates recorded in the pre-pandemic period and after the COVID-19 outbreak.

The median age was 77.46 years in the 58 non-survivors, and 52 of these patients (89.6%) had at least one comorbidity (i.e. diabetes mellitus, chronic kidney disease).

CONCLUSION

The authors believe that the molecular testing for viral infectious agents of patients presenting with clinical symptoms suggestive of influenza and ILI, along with the administration of appropriate antiviral and prophylactic treatments targeting the specific agent, and the adoption of infection control measures to counter these agents, could decrease the mortality and morbidity rates associated with these infectious agents significantly.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hacettepe University Faculty of Medicine Ethics Committee (Date: 21.12.2021, Decision No: 2021/21-48).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Başaranoğlu ST, Bilgin E, Tanrıöver MD ve ark. İnfluenza benzeri hastalık nedeniyle yatırılan hastalarda respiratuvar sinsityal virüs infeksiyonu sıklığı ve mortaliteye etkisi: prospektif, çok merkezli gerçek yaşam verileri. *Flora.* 2018;23:172-178.
2. Tanriover MD, Bagci Bosi T, Ozisik L, et al. Poor outcomes among elderly patients hospitalized for influenza-like illness. *Curr Med Res Opin.* 2018;34:1201-1207.
3. Humiston SG, Pham TN. Influenza-Like Illness Diagnosis and Management in the Acute Care Setting. *Pediatr Emerg Care.* 2016;32:875-882.
4. World Health Organization. Influenza seasonal. Available online: https://www.who.int/health-topics/influenza-seasonal#tab=tab_1
5. Moriyama M, Hugentobler WJ, Iwasaki A. Seasonality of respiratory viral infections. *Annu Rev Virol.* 2020;7:83-101.
6. Yedlapati SH, Khan SU, Talluri S, et al. Effects of influenza vaccine on mortality and cardiovascular outcomes in patients with cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc.* 2021;10: e019636. doi: 10.1161/JAHA.120.019636
7. Gupta C, Sachdeva A, Khamar J, Bu C, Bartoszko J, Loeb M. Effectiveness of the influenza vaccine at reducing adverse events in patients with heart failure: A systematic review and meta-analysis. *Vaccine.* 2022;40:3433-3443.

8. 8.Muñoz MP, Soldevila N, Martínez A, et al. Influenza vaccine coverage, influenza-associated morbidity and all-cause mortality in Catalonia (Spain). *Vaccine.* 2011;29:5047-5052. doi: 10.1016/j.vaccine.2011.04.067
9. Ahmed AE, Nicholson KG, Nguyen-Van-Tam JS. Reduction in mortality associated with influenza vaccine during 1989-90 epidemic. *Lancet.* 1995;346(8975):591-595.
10. Soudani S, Mafi A, Al Mayahi Z, et al. A. A systematic review of influenza epidemiology and surveillance in the Eastern Mediterranean and North African Region. *Infect Dis Ther.* 2022;11(1):15-52. doi: 10.1007/s40121-021-00534-3. E
11. Centers for Disease Control and Prevention. https://www.cdc.gov/flue/weekly/overview.htm
12. Agca H, Akalin H, Saglik I, Hacimustafaoglu M, Celebi S, Ener B. Changing epidemiology of influenza and other respiratory viruses in the first year of COVID-19 pandemic. *J Infect Public Health.* 2021;14:1186-1190.
13. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic-United States, Australia, Chile, and South Africa, 2020. *Am J Transplant.* 2020;20:3681–3685.
14. Lee H, Lee H, Song KH, et al. Impact of public health interventions on seasonal influenza activity during the SARS-CoV-2 outbreak in Korea. *Clin Infect Dis.* 2020:ciaa672.
15. Kuitunen I, Artama M, Mäkelä L, Backman K, Heiskanen-Kosma T, Renko M. Effect of social distancing due to the COVID-19 pandemic on the incidence of viral respiratory tract infections in children in Finland during early 2020. *Pediatr Infect Dis J.* 2020;39:e423–427.
16. Appak Ö, Dinç F, Sayıner AA. COVID-19'un solunum yolu virüslerininprevalansına etkisi. 6. Ulusal Klinik Mikrobiyoloji Hibrid Kongresi, 20-24 Ekim 2021, Bildiri Özet Kitabı, p.17: SS-008.
17. Shi WY, Hu SP, Zhang HL, et al. Differential diagnosis of COVID-19 pneumonia from influenza A (H1N1) pneumonia using a model based on clinicoradiologic features. *Front Med (Lausanne).* 2021;8: 651556. doi: 10.3389/fmed.2021.651556
18. Ramanan P, Bryson AL, Binnicker MJ, Pritt BS, Patel R. Syndromic panel-based testing in clinical microbiology. *Clin Microbiol Rev.* 2017;31:e00024-17. doi: 10.1128/CMR.00024-17
19. Paz V, D'Agostino ML, Garibaldi F, Orellana R, Paniagua M, Santillán A. Multiplex PCR in the empirical antibiotic treatment of patients with SARS-CoV-2 and bacterial respiratory superinfection. *Infect Prev Pract.* 2022;4(3):100227. doi: 10.1016/j.infpip.2022.100227
20. Murphy CN, Fowler R, Balada-Llasat JM, et al. Multicenter evaluation of the biofirefilmarray pneumonia/pneumonia plus panel for detection and quantification of agents of lower respiratory tract infection. *J Clin Microbiol.* 2020;58:e00128-20. doi: 10.1128/JCM.00128-20.
21. Huang HS, Tsai CL, Chang J, Hsu TC, Lin S, Lee CC. Multiplex PCR system for the rapid diagnosis of respiratory virus infection: systematic review and meta-analysis. *Clin Microbiol Infect.* 2018;24: 1055-1063. doi: 10.1016/j.cmi.2017.11.018
22. Stiver G. The treatment of influenza with antiviral drugs. *CMAJ* 2003;168(1):49-56. 8.
23. Papaioannou A, Konstantinidi AE, Primikiri E, Asimakopoulou F, Aravantinos D, Mavromichali Z. Influenza vaccination rate among high risk group patients in primary health care in Greece. *Cent Eur J Public Health.* 2020; 28: 297-301. doi: 10.21101/cejph.a5237.
24. Ekici H, Buzgan T, Ekinci B, Kara F, Keskinkılıç B, Irmak H. Kronik hastalığı olan erişkinlerin 2015-2017 yılları arasında influenzaya karşı aşılanma durumları. *Turk Hij Den Biyol Derg.* 2022;79: 25-38.
25. Özışık L, Yekedüz E, Tanrıöver MD, Helvacı Ö, Başaran NÇ, Ünal S. Risk altındaki erişkinlerin pnömokok ve influenza aşılanma oranları ve aşıya karşı tutumları. *Flora.* 2016;21:15-20
26. Demicheli V, Jefferson T, Di Pietrantonj C. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev.* 2018;2:CD004876. doi: 10.1002/14651858.CD004876