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VIA MEDICA

RESEARCH PAPER

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Comparison of clinical characteristics and outcomes between COVID-19 pneumonia and H1N1 influenza

Abstract

Introduction: The COVID-19 pandemic has been likened to the 2009 H1N1 influenza pandemic. We aim to study the similarities and differences between patients hospitalized with COVID-19 and H1N1 influenza in order to provide better care to patients, particularly during the co-circulation of Influenza A Subtype H1N1 and SARS-CoV-2.

Material and methods: A retrospective cohort study was conducted in order to compare clinical characteristics, complications, and outcomes of hospitalized patients with PCR-confirmed H1N1 influenza pneumonia and COVID-19 at a tertiary care center in Karachi, Pakistan.

Results: A total of 115 patients hospitalized with COVID-19 were compared with 55 patients with H1N1 Influenza A pneumonia. Median age was similar in both COVID-19 patients (54 years) and in patients with H1N1 influenza (59 years), but there was male predominance in COVID-19 patients (OR = 2.95; 95% CI: 1.12–7.79). Patients with COVID-19 pneumonia were 1.34 (95% CI: 1.14–1.62) times more likely to have a greater duration of illness prior to presentation compared to H1N1 influenza patients. COVID-19 patients were 4.59 times (95% CI: 1.32–15.94) more likely to be admitted to a general ward compared to H1N1 pneumonia patients. Moreover, patients with COVID-19 were 7.62 times (95% CI: 2.42–24.00) more likely to be treated with systemic steroids compared to patients with H1N1 pneumonia. The rate of nosocomial infections as well as mortality was similar in both H1N1 and COVID-19 pneumonia.

Conclusion: Our study found a male predominance and longer duration of illness in hospitalized patients with COVID-19 compared to H1N1 influenza patients but no difference in outcomes with either infection.

Key words: COVID-19, influenza A subtype H1N1, pneumonia

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Introduction

The COVID-19 pandemic, which initially started as an outbreak in the city of Wuhan in China, has presently infected more than 100 million people worldwide and has an estimated mortality of greater than 2 million [1]. Immediately after the pandemic was announced by the World Health Organization in March 2020, comparisons were drawn with the H1N1 Influenza A pandemic of 2009. In April 2009, numerous cases of severe pneumonia and influenza-like illness were reported by Mexican public health authorities in the town of La Gloria in the state of Veracruz. Shortly afterwards, similar cases were reported in California in the United States [2]. It was soon discovered that a new strain of the swine-origin influenza A (H1N1) flu had appeared in these countries. By the end of May 2009, 41 countries had reported 11,000 cases and 85 deaths and the WHO declared its first "Public Health Emergency of International Concern" (PHEIC) [3]. The 2009 swine flu pandemic lasted from January 2009 to August 2010 and was reported by the WHO to have caused nearly 18,500 deaths globally [3]. At present, worldwide cases of influenza-asso-

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ciated respiratory mortality have been occurring at a higher rate than what has been previously recorded [4]. According to CDC estimates, between April 2009 and April 2010, there were 60.8 million cases of H1N1 Influenza in the United States, with 12,500 deaths and a case fatality rate of 0.02% [5]. This is in contrast to the mortality rates reported with SARS-CoV-2 which have remained greater than 2% in most parts of the world [1]. Moreover, while the 2009 H1N1 pandemic caused deaths among primarily the young population, the majority of deaths in COVID-19 have occurred among the elderly [6].

Both the influenza virus and SARS-CoV-2 have similar modes of transmission (i.e. droplet and direct contact) but the incubation periods and rate of transmissibility differ significantly with SARS-CoV-2 having a longer duration of incubation and increased transmissibility [7]. The mechanism of viral pneumonia in COVID-19 is multifaceted with studies indicating that the viral infection is capable of producing an excessive immune reaction in the host. In some cases, there is extensive tissue damage with dysfunctional coagulation, which is also classified as a "cytokine storm" and can result in acute respiratory distress syndrome (ARDS) and multi-organ failure leading to death [8]. However, although ARDS is frequently observed in influenza pneumonia [9], the case fatality rate is lower than that of COVID-19 [10]. Similar to COVID-19, the most commonly reported symptoms of influenza included chills, cough, rhinorrhea, fever, sore throat, coryza, myalgia, shortness of breath, headache, dizziness, abdominal pain, decreased appetite, and malaise. The 2009 H1N1 strain also showed an increased number of people reporting vomiting and diarrhea as well [11, 12].

Although there have been some studies focusing on differences in symptomatology of seasonal influenza viruses, there are limited studies comparing clinical manifestations and complications of COVID-19 and Influenza A subtype H1N1, which share common clinical presentations. It is expected that there will be seasonal overlap of H1N1 Influenza A pneumonia and COVID-19 pneumonia, particularly between December and February. Hence, it is imperative to recognize the similarities and dissimilarities in order to provide better care to patients and identify those at increased risk for complications. Hence, we conducted this study to determine differences in clinical manifestations and complications between patients with H1N1 Influenza A pneumonia and COVID-19 requiring hospitalization at a tertiary care, academic medical center in Karachi Pakistan with a dedicated COVID-19 facility.

Material and methods

Study population and design

We conducted a retrospective cohort study of adult patients hospitalized with a RT-PCR-confirmed diagnosis of H1N1 Influenza pneumonia during seasonal outbreaks between the years 2017 and 2019 and patients hospitalized with RT-PCR confirmed COVID-19 during the outbreak from March 2020 onwards in a 700 bed tertiary care hospital in Karachi, Pakistan. Demographic and clinical characteristics of H1N1 influenza patients and COVID-19 patients including underlying medical and respiratory comorbidities, laboratory and radiological investigations, treatment, and complications during hospitalization were collected from hospital information management systems on a structured proforma.

Diagnosis of H1N1 influenza A and SARS-CoV-2

Nasopharyngeal swabs were processed for detection of the influenza virus by real-time reverse transcriptase polymerase chain reaction (RT-PCR) using the influenza virus PCR assay (Altona Diagnostics, GmbH). Nasopharyngeal swabs were processed for detection of SARS-CoV-2 virus by real-time reverse transcriptase polymerase chain reaction (RT-PCR) using the WHO protocol for the 2019 nCoV RT-PCR assay in March 2020. In May 2020, specimens were tested using the Cobas® SARS-CoV-2 RT-PCR assay (Roche Diagnostics, USA). A radiological diagnosis of pneumonia was made by evaluation of infiltrates observed on chest radiographs and/or CT of the chest. A multidisciplinary team of doctors including infectious disease consultants, pulmonologists, and internal medicine specialists were involved in the identification of cases and their management.

Ethical approval

This study received approval from the Aga Khan University Ethics Review Committee (ERC Reference Number: 2020-4908-10926). The requirement for informed consent was waived by the hospital ethics review committee as data was anonymized and no personal identifiers were collected.

Data analysis

We compared hospitalized H1N1 influenza patients with COVID-19 patients at a ratio of 1:2 in

order to improve statistical efficiency. Descriptive analysis was performed for demographic features with medians and interquartile ranges reported for quantitative variables such as age and length of hospital stay, as well as for frequencies (percentage) of qualitative variables such as gender, comorbid conditions, mortality, complications etc. The $\chi 2$ test of independence or the Fisher exact test was performed in order to compare factors between those with H1N1 influenza and those with COVID-19 pneumonia. Multivariable logistic regression analysis was performed in order to identify factors associated with COVID-19 pneumonia compared with H1N1 influenza. Subgroup analysis was performed using the Fisher exact test in order to compare those who died from COVID-19 to those who died from H1N1 influenza. STATA ver. 12.1 was used for data analysis and a p value ≤ 0.05 was considered to be significant.

Results

A total of 55 patients with H1N1 influenza A pneumonia were compared with 115 patients with COVID-19 who required hospitalization. The median age was similar in both COVID-19 patients (54 years) and in patients with H1N1 influenza (59 years). In COVID-19 patients, there was a male predominance with a male to female ratio of 3.26; the male to female ratio in H1N1 pneumonia was 0.66 ($p < 0.001$). Disaggregated data was evaluated for both COVID-19 and H1N1 influenza patients to determine gender differential across different age groups (Figure 1). Among H1N1 influenza patients, there were predominantly more females among younger age groups, but the male to female ratio became similar in patients with advanced age ($p = 0.036$). Overall, there were more females than males. On the other hand, in COVID-19 patients, there was a male predominance throughout all age groups ($p = 0.016$). The median duration of illness prior to presentation was 7 days (IQR 4–10) for COVID-19 compared to 5 days (IQR 3–5) for H1N1 influenza. The median CURB-65 Score was higher in patients with H1N1 influenza ($p < 0.001$). The most frequent comorbid conditions in both groups were diabetes and hypertension. However, there was a significantly greater number of patients with asthma and COPD in the H1N1 influenza group (Table 1). In terms of radiological findings, bilateral lung infiltrates were most commonly found on chest radiographs in both groups. However, a comparatively higher number of patients presented with bilateral lung involvement in H1N1 pneumonia than those with COVID-19 pneumonia (92% *vs* 75%, $p = 0.006$). In terms of laboratory parameters, the median procalcitonin levels were similar but the median neutrophil to lymphocyte ratio (NLR) was slightly higher in patients with H1N1 influenza than in COVID-19 patients (6.84 *vs* 4.10, $p = 0.077$). However, the median CRP was higher in patients with COVID-19 pneumonia than in those with H1N1 pneumonia (72.6 *vs* 65, $p = 0.347$), although this was not statistically significant. The majority of patients with H1N1 pneumonia required admission to either a special care unit or intensive care unit as opposed to those with COVID-19 pneumonia (Table 2). Thirty-three percent of patients with H1N1 pneumonia required invasive ventilation as compared to 15.6% with COVID-19 pneumonia ($p = 0.011$). All patients with H1N1 influenza received oseltamivir for treatment. Patients with COVID-19 were more likely to be treated with systemic steroids compared to patients with H1N1 influenza (60% *vs* 40%, $p = 0.014$). 98% of patients with H1N1 influenza received antibiotics concomitantly compared to 55% of patients with COVID-19. Among complications, 40% of patients with H1N1 influenza had acute kidney injury compared to 20% of COVID-19 patients ($p = 0.01$). The rate of nosocomial infections was similar in both H1N1 and COVID-19 pneumonia ($n = 10$ in COVID-19 and $n = 8$ in H1N1 influenza). In both groups, the most common organisms were multi-drug resistant *Acinetobacter sp*. ($n = 6$), *Pseudomonas aeruginosa* ($n = 4$), and methicillin-resistant *Staphylococcus aureus* (MRSA) ($n = 4$). Moreover, *Aspergillus* species were isolated in lower respiratory tract specimens of seven patients ($n = 4$ in the H1N1 influenza group and $n = 3$ in the COVID-19 group) with the most common species being *Aspergillus flavus* (6/7 patients). Mortality and length of hospitalization was similar in both groups (Table 2).

In multivariable logistic regression analysis, it was found that patients with COVID-19 pneumonia were 1.34 (95% CI: 1.14–1.62) times more likely to have a greater duration of illness prior to presentation compared to H1N1 influenza patients. Moreover, there was a male predominance in COVID-19 (OR = 2.95; 95% CI: 1.12–7.79) compared to H1N1 influenza pneumonia. Patients with COVID-19 were 4.59 times (95% CI: 1.32–15.94) more likely to be admitted to an inpatient setting compared to those with H1N1 pneumonia. Furthermore, patients with COVID-19 pneumonia were 7.62 times (95% CI: 2.42–24.00) more likely to be treated with systemic steroids compared to H1N1 pneumonia patients.

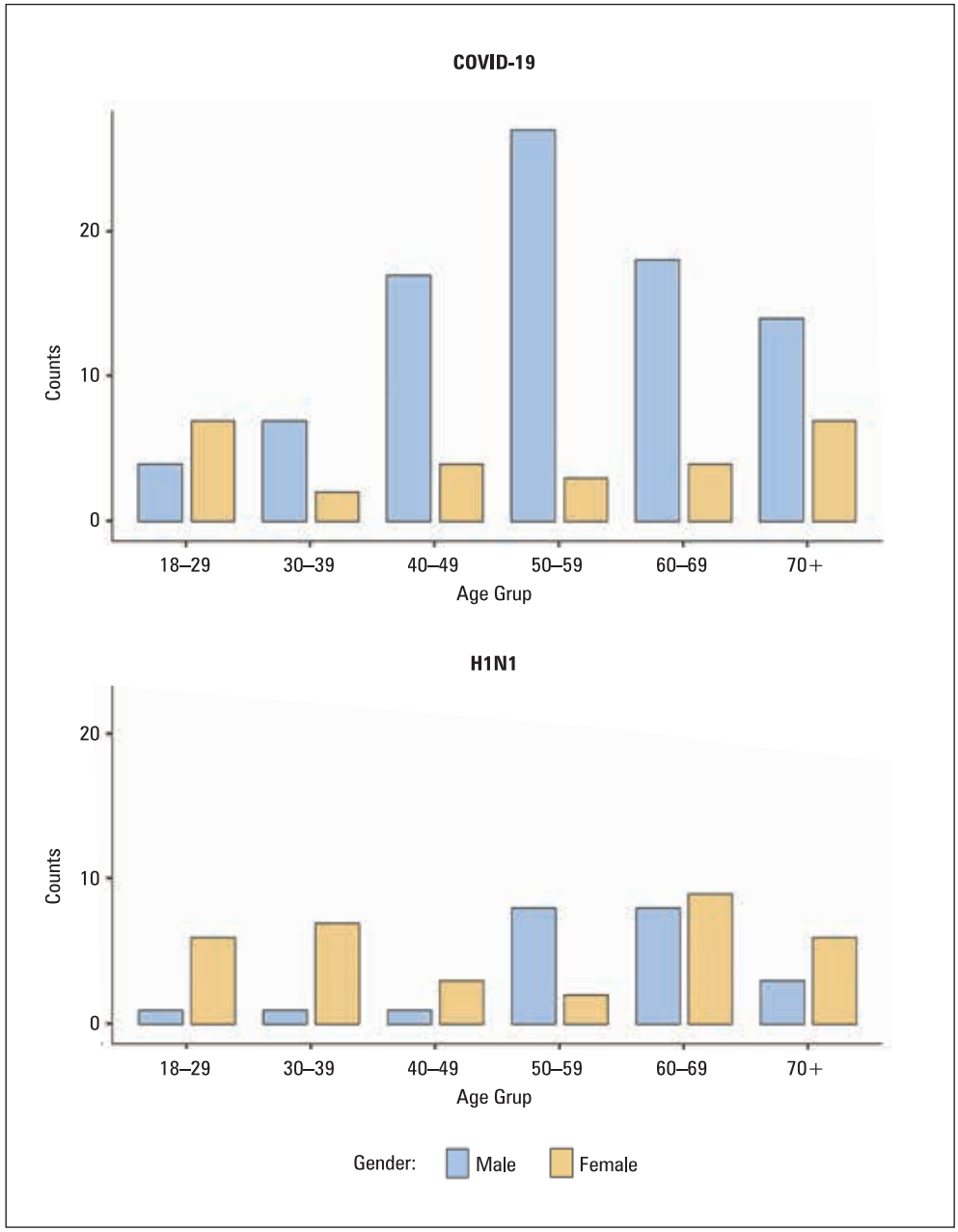

Figure 1. Gender differential by age group in COVID-19 pneumonia patients compared with H1N1 influenza patients

A subgroup analysis of mortality in patients in both groups showed that 12 out of 13 patients who died from COVID-19 were male, whereas mortality from H1N1 influenza was equally distributed (n = 5 each). The median age of mortality in COVID-19 patients was 62 years (IQR: 55–70) as compared to 56 years (IQR: 43–63) in patients with H1N1 influenza. The majority of patients from both groups had been admitted to the ICU and had required invasive ventilation ($p < 0.001$) prior to mortality. The cause of death was ARDS in the majority of those who died from both COVID-19 (11/13) and H1N1 influenza (9/10). Four out of 13 patients who died from COVID-19 and two out of 10 patients with H1N1 pneumonia also had a NSTEMI. Among all the patients who died in both groups, increases in NLR ($p=0.013$) and CRP (0.039) were significantly associated with mortality.

Discussion

Our study highlights similarities and differences between COVID-19 and H1N1 influenza pneumonia. There was a significant male predominance amongst patients with COVID-19 which

Table 1. Baseline characteristics of patients with COVID-19 pneumonia compared to H1N1 influenza A pneumonia

Characteristics	COVID-19 (n = 115)	H1N1 (n = 55)	P value
Median age (IQR) in years	54 (43–65)	59 (36–65)	0.951
Median CURB score (IQR)	1 (0–2)	2 (1–2)	< 0.001
Median Duration of Illness (IQR) in days	7 (4–10)	5 (3–5)	< 0.001
Gender			
Male	88 (76.5)	22 (40.0)	< 0.001
Female	27 (23.5)	33 (60.0)	
Comorbidities			
Diabetes	43 (37.4)	24 (43.6)	0.436
Hypertension	41 (35.7)	24 (43.6)	0.316
COPD	0 (0.0)	8 (14.6)	< 0.001
Coronary artery disease	18 (15.7)	6 (10.9)	0.406
Obesity	1 (0.9)	5 (0.1)	0.014
CVA	4 (3.5)	2 (3.6)	0.958
Malignancy	6 (5.2)	2 (3.6)	0.649
Immunosuppression	1 (0.9)	4 (7.3)	0.038
Asthma	1 (0.9)	7 (12.7)	0.002
ILD	0 (0.0)	2 (3.6)	0.103
CLD	3 (2.6)	1 (1.8)	0.750
CKD	8 (6.9)	3 (5.4)	0.710
Radiological findings			
Unilateral	9 (7.9)	2 (3.6)	0.507
Bilateral	86 (75.4)	51 (92.7)	0.006
Laboratory investigations			
Median procalcitonin (IQR)	0.129 (0.06–0.43)	0.74 (0.18–3.9)	0.564
Median creatinine (IQR)	1 (0.8–1.3)	1.2 (0.9–1.5)	0.521
Median CRP mg/L (IQR)	72.65 (21.83–179.87)	65.8 (23.2–152.1)	0.347
NLR			
< 3	38 (33.0)	10 (18.2)	0.044
≥ 3	77 (67.0)	45 (81.8)	

CKD — chronic kidney disease; CLD — chronic liver disease; COPD — chronic obstructive pulmonary disease; CVA — cerebrovascular accident; ILD — interstitial lung disease; IQR — interquartile range

is consistent with data reported from other parts of the world [13]. As opposed to this, there was almost equal gender distribution in H1N1 pneumonia [12]. Also, it was notable that hospitalization was required in similar age groups for both infections. This is in contrast to earlier reports from the 2009 H1N1 pandemic where there was greater severity among younger age groups who developed infection with influenza A subtype H1N1 [5]. However, this is similar to the seasonal influenza outbreaks reported from different parts of the world where greater severity is observed in elderly populations [14]. In our study, there was a longer duration of illness prior to presentation in patients with COVID-19 compared to H1N1 influenza patients. Tang *et al.* reported a similar difference of duration in patients requiring hospitalization with COVID-19 patients having a relatively protracted course and becoming critically ill later than those with influenza [15]. It has been postulated that this variance may be due to the difference in the distribution of virus entry receptors because the influenza A virus binds to α2, 6-linked sialic acid receptors, expressed throughout the respiratory tract and likely responsible for the short incubation period. On the other hand, the receptor actively involved in SARS-CoV-2 is the ACE2 protein

Table 2. Outcomes and Complications of patients with COVID-19 pneumonia in comparison to patients with H1N1 influenza A pneumonia

Variables	COVID-19 (n = 115)	H1N1 (n = 55)	P value
Type of admission			
ICU	17 (14.8)	15 (27.3)	0.051
SCU	42 (36.5)	30 (54.6)	0.026
Ward	56 (48.7)	10 (18.2)	< 0.001
Management			
Vasopressors	17 (14.8)	13 (23.6)	0.157
Non-invasive ventilation	30 (26.1)	20 (36.4)	0.169
Invasive ventilation	18 (15.6)	18 (32.7)	0.011
Systemic steroids	69 (60.0)	22 (40.0)	0.014
Antibiotics	63 (54.8)	54 (98.2)	< 0.001
Oseltamivir	1 (0.9)	55 (100.0)	< 0.001
Complications			
ARDS	27 (23.5)	17 (30.9)	0.301
Septic shock	16 (13.9)	13 (23.6)	0.115
MODS	11 (9.6)	13 (23.6)	0.014
Nosocomial infection	13 (11.3)	6 (10.9)	0.939
AKI	24 (21.1)	22 (40.0)	0.01
NSTEMI	10 (8.7)	9 (16.4)	0.138
Outcome			
Recovered	96 (88.1)	41 (80.4)	0.197
Mortality	13 (11.9)	10 (19.6)	
Unknown	6 (5.2)	4 (7.3)	
Median length of stay (IQR)	7 (4–10)	6 (4–10)	0.911

AKI — acute kidney injury; ARDS — acute respiratory distress syndrome; ICU — intensive care unit; SCU — special care unit; MODS — multi-organ dysfunction syndrome; NSTEMI — non-ST elevation myocardial infarction

predominantly found on alveolar epithelial cells which accounts for the longer incubation period of COVID-19 infection [16]. In the current study, almost all patients with H1N1 pneumonia and the majority of patients with COVID-19 had bilateral lung involvement on chest radiograph imaging at presentation. Studies have shown that although chest radiographs can be quite similar, computed tomography scans can show certain key differences such as the presence of pleural effusion and bronchiectasis in H1N1 influenza pneumonia that would otherwise not be seen during infection with COVID-19 [17, 18]. As opposed to H1N1, COVID-19 can present with normal chest radiographs as well as strictly unilateral chest involvement [19]. The study did not find any specific laboratory marker which was helpful in distinguishing between either infection and this is in agreement with previous studies published which compared the two infections, although their amount is limited [20]. Serial monitoring of laboratory parameters such as serum procalcitonin, C-reactive protein, and neutrophil to lymphocyte ratio may be able to elicit differences as per the study conducted by Mei *et al.* [21]

We found no difference in mortality in patients who required hospitalization for COVID-19 and H1N1 pneumonia. Studies have reported similar prognoses in patients with either infection [15]. The overall proportion of patients receiving systemic steroids was higher in both groups. However, patients with COVID-19 were more likely to be treated with steroids compared to H1N1 in our current study. This is also similar to other studies reporting use of systemic steroids in the treatment of these infections [15]. As per the Cochrane review in 2019, a greater

number of patients with COVID-19 were treated with steroids as compared to influenza patients because patients with influenza who received steroids as adjunctive treatment had a greater risk of mortality compared to those who did not receive steroid treatment. This was potentially due to the increased incidence of hospital-acquired infections [22]. However, the RECOVERY trial for COVID showed mortality benefit with the use of steroids [23]. The immunosuppressive effects of steroids may have implications on the development of nosocomial infections. In our study, patients developed these infections more often (11% of all patients) than those in other studies. Although the rate of nosocomial infections was similar in both groups, patients with H1N1 were more likely to be treated with antibiotics in addition to oseltamivir as opposed to COVID-19 patients, which is similar to other studies [24]. This study had some limitations. It was a single center, retrospective study. However, to the best of our knowledge, it is the first to describe important common characteristics of both COVID-19 and H1N1 influenza infections and may be helpful in providing care to patients in the setting of these viral outbreaks.

Conclusion

Our study highlights the difficulty in distinguishing these infections clinically. The only difference that stood out was the comparatively prolonged duration of illness prior to hospitalization in COVID-19 patients. Hence, patients may require screening with PCR in the setting of an influenza-like illness to diagnose/rule out influenza A subtype H1N1 and/or SARS--CoV2. Moreover, treatment with steroids can potentially lead to an increase in the number of opportunistic and superimposed infections and needs to be cautiously administered in the subset of COVID-19 patients requiring oxygen support and/or in patients with ARDS. Our study did not find any difference in mortality despite the availability of treatment for H1N1 influenza in advanced stages of the disease and despite the use of steroids in COVID-19. Hence, we recommend implementing and using strategies focusing on prevention for influenza (i.e. immunization) and measures such as universal masking and social distancing for COVID-19.

Conflict of interest

None declared.

References:

1. Worldometer. COVID-19 Coronavirus Pandemic. 2020. Available online: www.worldometers.info/coronavirus/. [Last accessed: 27.01.2021].
2. Smith GJD, Vijaykrishna D, Bahl J, et al. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. Nature. 2009; 459(7250): 1122–1125, doi: 10.1038/nature08182, indexed in Pubmed: 19516283.
3. World Health Organization. Swine influenza 2009. Available online: www.who.int/mediacentre/news/statements/2009/h1n1_20090425/en/. [Last accessed at: 27.01.2021].
4. Iuliano AD, Roguski KM, Chang HH. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet. 2018; 391: 1285–1300, doi: 10.1016/S0140-6736(17)33293-2, indexed in Pubmed: 29248255.
5. Prevention CfDC. 2009 H1N1 Pandemic (H1N1pdm09 virus). 2019. Available online: www.cdc.gov/flu/pandemic-resources/2009-h1n1-pandemic.html. [Last accessed: 27.01.2021].
6. Karageorgopoulos DE, Vouloumanou EK, Korbila IP, et al. Age distribution of cases of 2009 (H1N1) pandemic influenza in comparison with seasonal influenza. PLoS One. 2011; 6(7): e21690, doi: 10.1371/journal.pone.0021690, indexed in Pubmed: 21747947.
7. Wang Q, Zhang T, Zhu H, et al. Characteristics of and public health emergency responses to COVID-19 and H1N1 outbreaks: a case-comparison study. Int J Environ Res Public Health. 2020; 17(12), doi: 10.3390/ijerph17124409, indexed in Pubmed: 32575492.
8. Ragab D, Salah Eldin H, Taeimah M, et al. The COVID-19 cytokine storm; what we know so far. Front Immunol. 2020; 11: 1446, doi: 10.3389/fimmu.2020.01446, indexed in Pubmed: 32612617.
9. Li SH, Hsieh MJ, Lin SW, et al. Outcomes of severe H1N1 pneumoniae: A retrospective study at intensive care units. J Formos Med Assoc. 2020; 119(1 Pt 1): 26–33, doi: 10.1016/j.jfma.2019.02.006, indexed in Pubmed: 30852002.
10. World Health Organization. Q&A: influenza and COVID-19 — similarities and differences. 2020. Available online: www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-similarities-and-differences-covid-19-and-influenza. [Last accessed: 27.01.2021].
11. Shen C, Tan M, Song X, et al. Comparative analysis of early-stage clinical features between COVID-19 and influenza a H1N1 virus pneumonia. Front Public Health. 2020; 8: 206, doi: 10.3389/fpubh.2020.00206, indexed in Pubmed: 32574297.
12. Cao B, Li XW, Mao Yu, et al. Clinical features of the initial cases of 2009 pandemic influenza a (H1N1) virus infection in China. N Engl J Med. 2009; 361(26): 2507–2517, doi: 10.1056/NEJMoa0906612, indexed in Pubmed: 20007555.
13. Haitao Tu, Vermunt JV, Abeykoon J, et al. COVID-19 and sex differences: mechanisms and biomarkers. Mayo Clin Proc. 2020; 95(10): 2189–2203, doi: 10.1016/j.mayocp.2020.07.024, indexed in Pubmed: 33012349.
14. Dabanch J, Perret C, Najera M, et al. Age as risk factor for death from pandemic (H1N1) 2009, Chile. Emerg Infect Dis. 2011; 17(7): 1256–1258, doi: 10.3201/eid1707.101398, indexed in Pubmed: 21762580.
15. Tang X, Du RH, Wang R, et al. Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1. Chest. 2020; 158(1): 195–205, doi: 10.1016/j.chest.2020.03.032, indexed in Pubmed: 32224074.
16. Zayet S, Kadiane-Oussou NJ, Lepiller Q, et al. Clinical features of COVID-19 and influenza: a comparative study on Nord Franche-Comte cluster. Microbes Infect. 2020; 22(9): 481–488, doi: 10.1016/j.micinf.2020.05.016, indexed in Pubmed: 32561409.
17. Yin Z, Kang Z, Yang D, et al. A comparison of clinical and chest CT findings in patients with influenza a (H1N1) virus infection and coronavirus disease (COVID-19). AJR Am J Roentgenol. 2020; 215(5): 1065–1071, doi: 10.2214/AJR.20.23214, indexed in Pubmed: 32452731.
18. Schoen K, Horvat N, Guerreiro NFC, et al. Spectrum of clinical and radiographic findings in patients with diagnosis of

H1N1 and correlation with clinical severity. BMC Infect Dis. 2019; 19(1): 964, doi: 10.1186/s12879-019-4592-0, indexed in Pubmed: 31718571.
19. Zhao W, Zhong Z, Xie X, et al. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicenter study. AJR Am J Roentgenol. 2020; 214(5): 1072–1077, doi: 10.2214/AJR.20.22976, indexed in Pubmed: 32125873.
20. Ozaras R, Cirpin R, Duran A, et al. Influenza and COVID-19 coinfection: Report of six cases and review of the literature. J Med Virol. 2020; 92(11): 2657–2665, doi: 10.1002/jmv.26125, indexed in Pubmed: 32497283.
21. Mei Y, Weinberg SE, Zhao L, et al. Risk stratification of hospitalized COVID-19 patients through comparative studies of laboratory results with influenza. EClinicalMedicine. 2020; 26: 100475, doi: 10.1016/j.eclinm.2020.100475, indexed in Pubmed: 33089115.
22. Lansbury LE, Rodrigo C, Leonardi-Bee Jo, et al. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev. 2019; 2(2): CD010406–e9e106, doi: 10.1002/14651858.CD010406.pub3, indexed in Pubmed: 30798570.
23. Dexamethasone in hospitalized patients with COVID-19. New England Journal of Medicine. 2021; 384(8): 693–704, doi: 10.1056/nejmoa2021436.
24. Barlow GD. BSAC Council. Swine flu and antibiotics. J Antimicrob Chemother. 2009; 64(5): 889–894, doi: 10.1093/jac/dkp313, indexed in Pubmed: 19740909.