Wiener klinische Wochenschrift
The Central European Journal of Medicine

Is there a clinical difference between influenza A and B virus infections in hospitalized patients?

Results after routine polymerase chain reaction point-of-care testing in the emergency room from 2017/2018

Mario Karolyi · Erich Pawelka · Simon Daller · Caroline Kaczmarek · Hermann Laferl · Iulia Niculescu · Birte Schrader · Christian Stütz · Alexander Zoufaly · Christoph Wenisch

Summary

Purpose The clinical presentation, complications and mortality in molecularly confirmed influenza A and B infections were analyzed.

Methods This retrospective observational single-centre study included all influenza positive patients older than 18 years who were hospitalized and treated at the flu isolation ward during 2017/2018. The diagnosis was based on point-of-care tests with the Alere™.

Results Of the 396 patients tested positive for influenza, 24.2% had influenza A and 75.8% influenza B. Influenza A patients were younger (median age 67.5 years vs. 77 years, $p < 0.001$), were more often smokers (27.7% vs. 16.8%, $p = 0.021$), had chronic pulmonary diseases more frequently (39.6% vs. 26.3%, $p = 0.013$), presented with a higher body temperature (38.6 °C vs. 38.3 °C, $p = 0.004$), leucocyte count (8 G/L vs. 6.8 G/L, $p = 0.002$), C-reactive protein (CRP) level (41 mg/l vs. 23 mg/l, $p < 0.001$) and had dyspnea more often (41.7% vs. 28%, $p = 0.012$). Influenza B patients had an underlying chronic kidney disease in 37% vs. 18.8% ($p < 0.001$) and presented with vomiting on admission more frequently (21.7% vs. 11.5%, $p = 0.027$). Influenza A patients were admitted for 8 days vs. 7 days ($p = 0.023$). There were no differences in the rate of complications; however, 22 (5.6%) patients died during the hospital stay. The in-hospital mortality was higher in influenza A patients (8.3% vs 4.7%, $p = 0.172$).

Conclusion Some differences were found between influenza A and B virus infections but symptoms were overlapping, which necessitates polymerase chain reaction point-of-care testing for accurate diagnosis. Influenza A was a more severe disease than influenza B during the period 2017/2018.

Keywords Respiratory infection · Elderly · Flu · POCT · Seasonal

M. Karolyi · Dr. E. Pawelka (✉) · H. Laferl · I. Niculescu ·
A. Zoufaly · C. Wenisch
Department for Infectious Diseases,
Kaiser-Franz-Josef-Hospital (KFJ),
Kundratstraße 3, 1100 Vienna, Austria
erich.pawelka@wienkav.at

S. Daller · C. Kaczmarek · B. Schrader · C. Stütz
Medical University Vienna (MUW),
Spitalgasse 23, 1090 Vienna, Austria

Introduction

Influenza infections occur in seasonal outbreaks during the winter period related to cold or humid weather conditions and are associated with an excess hospitalization and an increase in overall mortality [1, 9]. Due to a lack of accurate diagnostic tools in the past the cause of death might often have been inaccurate and the influenza-associated mortality underestimated [1, 2, 8]. While studies show pneumonia and influenza excess mortality during influenza seasons, the all-cause mortality in the same period is also 3.8 times higher [1]. High virulence and insufficient vaccination response result in up to 10^9 cases of influenza virus infections yearly [3–5]. Until recently laboratory tests for influenza diagnosis have been reserved for monitoring epidemics and clinical trials. This lack of confirmation renders the diagnosis relying on clinical parameters often inaccurate since the manifestations of influenza may vary greatly depending on patient characteristics, especially age and comorbidities [2, 6]. Particularly in

high-risk hospitalized patients the diagnosis may be missed due to exacerbation of symptoms of pre-existing diseases or atypical presentation bearing the risk of inadequate treatment [7–9].

The increased availability of point-of-care testing (POCT) assists with the diagnosis of influenza virus infections during epidemic seasons. While rapid diagnostic tests (RDT) based on immunoassays have limited use due to low sensitivity [10, 11] polymerase chain reaction (PCR) POCT devices allow a simple, rapid, cost-effective and accurate means of diagnosis [12–15]. This ensures correct management of influenza virus infections including prompt initiation of antiviral treatment, preventing onward transmission and avoiding overuse of antibiotics [16–20]. With POCT being widely available, recent studies showed similar influenza virus positive samples for patients presenting with various typical as well as atypical clinical manifestations at emergency departments [8, 9].

Since real world information of molecularly confirmed influenza infections in hospitalized patients is missing a retrospective analysis of patient history, symptoms on admission, complications and mortality was conducted to identify any differences in hospitalized influenza A and B patients after implementing routine PCR testing prior to admission to influenza wards.

Methods

Study design and influenza management

This retrospective observational single center study was carried out at the flu isolation ward of the infectious diseases department of the Kaiser-Franz-Josef-Hospital in Vienna, Austria. The department consists of 2 wards with 28 beds each and an intensive care unit with 10 beds. The hospital has an isolation policy for influenza positive patients. Patients presenting at the emergency department with influenza-like illness undergo POCT for influenza virus infections with the Alere™ i Influenza A & B assay (Alere, Waltham, MA, USA) performed by trained professionals. The Alere™ i Influenza A & B assay uses rapid nucleic acid amplification and was chosen as it produces reliable results within 15 min [12–15]. The time until the test result is available is an essential factor in this organizational setting. Influenza virus positive patients who needed in-patient treatment were transferred directly to the isolation ward. Whether a patient had to be admitted to this ward or could be treated on an outpatient basis had to be decided by the physician at the emergency department. The study was approved by the local ethics committee (Approval number EK 18-106-VK) and due to the retrospective nature of this study informed consent was not necessary.

Data gathering and statistical analysis

Data were collected from patient medical files. The information was double entered into a MS Excel sheet (Microsoft, Redmond, WA, USA), anonymized and verified for accuracy. The patient medical files included demographic information, laboratory results, symptoms, information about treatment and underlying medical conditions. All patients older than 18 years who tested positive for influenza virus infections with the Alere™ i Influenza A & B assay and needed in-patient care at the isolation ward within the influenza season 2017/2018 (October 2017–April 2018) were included in this retrospective evaluation. Patients who required immunosuppression due to organ transplantation or had undergone stem cell transplantation were not included. The 30-day and 90-day follow-up evaluations were carried out by telephone calls. Baseline characteristics were tabulated with proportions for categorical variables or median (Md) and interquartile range (IQR) for not normally distributed metric variables. Cross-tables, χ^2-test and Fisher's exact test (where applicable) were carried out to identify differences between influenza type and dichotomous categorical variables. For non-normally distributed variables Mann-Whitney U-tests were calculated to test for differences in metric variables. The study is exploratory and retrospective, therefore the alpha-level was not corrected for multiple tests. A two-sided $p < 0.05$ was considered statistically significant. After importing the MS Excel sheet all analyses were made with SPSS 25 (IBM, Armonk, NY, USA) for Mac OS (Apple, Cupertino, CA, USA).

Definition of variables and diagnosis

Fever was defined as a body temperature ≥38 °C, measured by via ear thermometers. Respiratory insufficiency was defined as the need for oxygen by any kind of device (e.g. nasal cannula, masks). The need for oxygen was assessed by the treating physician. Pneumonia was defined as a consolidation and/or opacity on a radiological image (mostly X-ray) accompanied by elevated inflammation markers and/or fever. Rhabdomyolysis was defined as a creatinine kinase (CK) level above 1000 U/l. Heart failure was defined by new onset or worsening of peripheral edema and/or congestion on X-ray in patients with history of chronic heart failure and without any other cause. Acute kidney injury was defined as an increase of creatinine level by 0.3 mg/dl from the baseline kidney function within 48 h or an increase of ≥1.5 times the baseline presumed to have occurred with the previous 7 days due to the current episode of illness. In cases of a missing creatinine baseline the acute kidney injury was retrospectively assessed by comparing the creatinine level on admission and on the day of discharge, which was assumed to be the baseline function. Symptoms, such as diarrhea, vomiting, ab-

Table 1 Patient characteristics

	Total (N = 396)	Influenza A (n = 96)	Influenza B (n = 300)	p-value[a]
Sex				0.578
Female (%)	213 (53.8)	54 (56.3)	151 (53)	
Male (%)	183 (46.2)	42 (43.8)	141 (47)	
Vaccination status				0.802
Unknown (%)	192 (48.5)	–	–	
Known (%)	204 (51.5)	–	–	
Not vaccinated (%)	164/204 (80.4)	40 (81.6)	124 (80)	
Vaccinated (%)	40/204 (19.6)	9 (18.4)	31 (20.3)	
Age median (years) IQR (years)	75.5 (63–84)	67.5 (54–79)	77 (67–85)	<0.001[b]
History of:				
Chronic kidney disease (%)	122 (30.8)	18 (18.8)	111 (37)	<0.001
Chronic pulmonary disease (COPD, asthma) (%)	117 (29.5)	38 (39.6)	79 (26.3)	0.013
Diabetes (%)	104 (26.3)	24 (25)	80 (26.8)	0.734
Current smokers (%) [374][d]	73 (18.4)	26 (27.7)	47 (16.8)	0.021
Any tumor (%)	69 (17.4)	18 (18.8)	51 (17)	0.694
Atrial fibrillation (%)	67 (16.9)	10 (10.4)	57 (19)	0.051
Dementia (%)	49 (12.4)	9 (9.4)	40 (13.3)	0.305
Myocardial infarction (%)	47 (11.9)	6 (6.3)	41 (13.7)	0.051
Stroke (%)	45 (11.4)	7 (7.3)	38 (12.7)	0.147
Congestive heart failure (%)	37 (9.3)	7 (7.3)	30 (10)	0.427
Peripheral artery disease (%)	26 (6.6)	2 (2.2)	24 (8)	0.055[c]
Charlson comorbidity score[e] Median (IQR) [355][d]	1 (0–3)	1 (0–3)	1 (0–3)	0.734[b]

IQR interquartile range, *COPD* chronic obstructive pulmonary disease
[a]*p*-values derived from χ^2-tests if not otherwise noted
[b]Mann-Whitney U-test
[c]Fisher's exact test
[d]Not all information was available for each patient on admission, in such cases the available values per variable are given in square brackets
[e]The updated version of the Charlson comorbidity score [31] was used. The score ranges from 0 to 24

sence of fever or acute heart failure were considered as atypical because they are primarily not indicative of influenza virus infections.

Results

Patient characteristics

The study population consisted of 396 people. The distribution between influenza A and influenza B positive patients was unequal with influenza B being the more common infection. Gender distribution was equal in both groups. The vaccination status was not known for all patients. There were no differences in vaccination rates between the two influenza groups. Patients who tested positive for influenza A were significantly younger than influenza B positive patients. Significantly more patients in the influenza A group had a history of a chronic pulmonary disease and were current smokers. Patients with influenza B suffered significantly more often from chronic kidney disease. No differences were found in the proportion of patients with atrial fibrillation, myocardial infarction,

peripheral artery disease, history of congestive heart failure, diabetes, stroke, dementia and tumors and no differences in the Charlson comorbidity score were found. For details see Table 1.

Symptoms on admission

The symptoms with which the patients presented at this hospital are listed in Table 2 and sorted from the most common to the least common. Fever, cough and malaise were the three most common symptoms with no differences between the two influenza types. Patients with influenza A had a higher body temperature and a higher number of patients suffered from high grade fever defined as a body temperature ≥39 °C (41.5% vs. 27.6%, *p* = 0.037). More patients with influenza A suffered from dyspnea, whereas vomiting was reported more frequently in influenza B patients. No differences were found in the symptoms on admission between influenza A and B in the proportion of cough, malaise, abrupt onset of symptoms, muscle ache, diarrhea, cognitive impairment, thoracic pain,

Table 2 Symptoms

	Total (N = 396)	Influenza A (n = 96)	Influenza B (n = 300)	p-value[a]
Fever (≥38 °C) (%)	271 (69.2)	71 (75.5)	200 (67.3)	0.133
Temperature (°C) Md (IQR)	–	38.6 (37.98–39.3)	38.3 (37.6–39.0)	0.004
Cough (%)	258 (65.2)	67 (69.8)	191 (63.7)	0.273
Malaise/prostration (%)	243 (61.4)	57 (59.4)	186 (62)	0.646
Rales (%)	147 (37.1)	43 (44.8)	104 (37.4)	0.074
Dyspnea (%)	124 (31.3)	40 (41.7)	84 (28)	0.012
Vomiting (%)	76 (19.2)	11 (11.5)	65 (21.7)	0.027
Abrupt onset (<12 h) (%)	67 (16.9)	15 (15.2)	52 (17.3)	0.698
Muscle ache (%)	64 (16.2)	17 (17.7)	47 (15.7)	0.636
Diarrhea (%)	60 (15.2)	16 (16.7)	44 (14.7)	0.634
Cognitive impairment (%)	48 (12.1)	8 (8.3)	40 (13.3)	0.191
Headache (%)	43 (10.9)	15 (15.6)	28 (9.3)	0.085
Thoracic pain (%)	38 (9.6)	10 (10.4)	28 (9.3)	0.754
Coryza (%)	36 (9.1)	5 (5.2)	31 (10.3)	0.155[b]
Incontinence (%)	34 (8.6)	7 (7.3)	27 (9)	0.631
Epigastric pain (%)	31 (7.8)	5 (5.2)	26 (8.7)	0.272[b]
Chills (%)	30 (7.6)	4 (4.2)	26 (8.7)	0.147
Sore throat (%)	20 (5.1)	7 (7.3)	13 (4.3)	0.247

Md median, *IQR* interquartile range
[a]*p*-values derived from χ^2-tests if not otherwise noted
[b]Fisher's exact test

coryza, rales, headache, incontinence, epigastric pain, chills and sore throat. For details see Table 2.

Laboratory parameters on admission

Laboratory parameters were analyzed on admission for every patient (Table 3). Patients with influenza A had a significantly higher leucocyte count and a higher C-reactive protein (CRP) level on admission. In contrast patients with influenza B presented with a higher creatinine level and therefore a lower estimated glomerular filtration rate (eGFR) No differences were found in the level of creatinine kinase (CK), lactate dehydrogenase (LDH), alanine aminotransferase (ALAT), bilirubin and oxygen saturation (O_2).

Complications and duration of stay

Patients with influenza A had a significantly longer length of hospital stay. No differences were found for the following complications: pneumonia, respiratory failure, acute kidney injury, rhabdomyolysis, intensive care unit (ICU) admission rate, acute heart failure and myocardial infarction. For details see Table 4.

Mortality

In total 22 out of 396 patients (5.6%) died during the stay at hospital. There was no effect of the influenza type on the in-hospital mortality or the impact of the influenza type on the 30-day and the 90-day mortality.

The 90-day mortality increased further to 9.4%. For details see Table 5.

Treatment

In both groups similar numbers of patients received oseltamivir (influenza A vs. B, 55.5% vs. 59.5%, $p = 0.476$). The time from symptom onset to start of antiviral treatment between patients with influenza A (7.3% <24 h, 29.2% 24–48 h, 16.7% >48 h, 46.9% no treatment) and B (13.3% <24 h, 27.3% 24–48 h, 14% >48 h, 45.3% no treatment) was similar ($p = 0.438$). The decision to prescribe oseltamivir was made by the treating physician based on the time of symptom onset and the disease severity. In the season examined it was not common at this ward to treat every hospitalized patient with oseltamivir.

There was no relationship between treatment with oseltamivir and the rate of complications or in-hospital mortality. Patients who were treated with oseltamivir had a longer in-hospital stay (7 days, IQR 6–9 vs. 6 days, IQR 4.5–9, $p = 0.011$). Antibiotics were given to 44.8% of influenza A patients and 36% of influenza B patients ($p = 0.123$).

Discussion

This study showed various differences in the clinical presentation and complication rates in hospitalized patients with influenza A and B. Patients with influenza A tended to be younger and were more likely to have dyspnea and higher fever. Patients with

Table 3 Laboratory parameters of the patients on admission

Name (unit) [n]	Influenza A (n = 96) Md (IQR)	Influenza B (n = 300) Md (IQR)	p-value[a]
Leukocytes (G/L)	8 (6–11.5)	6.8 (4.9–9.2)	0.002
CRP (mg/L)	41.1 (20.5–87.5)	22.95 (9.5–54)	<0.001
Thrombocytes (G/L)	195.5 (159–253)	185 (143–283)	0.091
CK (U/L) [347][b]	119 (68–243)	119 (73–216)	0.948
LDH (U/L) [211][b]	238 (201–311)	233 (202–289)	0.549
ALAT (U/L) [355][b]	25 (18–49)	24 (17–37)	0.165
Creatinine (mg/dl) [395][b]	0.96 (0.72–1.20)	1.04 (0.85–1.39)	0.004
eGFR (ml/min) [394][b]	74.06 (48.7–90)	57.98 (42.22–78.35)	<0.001
Bilirubin (mg/dl) [358][b]	0.46 (0.32–0.66)	0.45 (0.31–0.66)	0.730
O2 saturation (%) [271][b]	95 (91–97)	95 (92–97)	0.464

CRP C-reactive protein, *CK* creatinine kinase, *LDH* lactate dehydrogenase, *ALAT* alanine aminotransferase, *eGFR* estimated glomerular filtration rate, *O2* oxygen, *Md* median, *IQR* interquartile range
[a]p-values derived from Mann-Whitney U-test
[b]Not all laboratory parameters were available for each patient on admission. In such cases the available values per variable are given in square brackets

influenza B had atypical presentations more often including vomiting and a partial absence of respiratory symptoms, which are classically associated with influenza. Mortality rates tended to be numerically higher in influenza A versus B. In previous studies comparing demographic attributes of patients with influenza A and B, a higher age for patients with influenza A was described although this may vary according to influenza A strains. Patients with H3N2 were shown to be older than influenza B patients while patients with H1N1 tended to be younger than patients with influenza B [21–23]. A French study by Chagvardieff et al. analyzed patients presenting at an emergency department and similarly to the present results influenza B patients were significantly older [24]. The age difference therefore seems to depend on the study population as well as the dominant influenza A subtype. Unfortunately, no information was available about influenza subtypes in the current population; however, during the season concerned influenza A/H1N1 and influenza B/Yamagata were the dominant subtypes in Austria [25]. It has been shown that patients with influenza A suffered more often from chronic diseases, such as asthma, chronic obstructive pulmonary disease, diabetes and cardiovascular disorders [22, 27]. Furthermore, patients with influenza A were more likely to be smokers. In patients suffering from influenza B infections chronic kidney disease was more frequent. A non-statistically significant trend towards a higher proportion of atrial fibrillation, myocardial infarction and peripheral artery disease in the history of patients with influenza B was observed in this study population, which could be explained by the higher mean age of this group. In this population influenza A patients presented with a higher body temperature and with dyspnea statistically more often. Influenza B infections were associated with vomiting. A Japanese study with adults who consulted a medical center

with influenza infections combined gastrointestinal symptom (e.g. nausea, diarrhea, epigastric pain) with one parameter and showed that they are more common in influenza B. Matching the present findings they also showed a higher body temperature in influenza A infected patients [26]. Other studies with a younger population and outpatient treatment did not show any differences in clinical presentation [21, 23].

A study of 2791 hospitalized patients reported a higher rate of ICU admission, ARDS, mechanical ventilation and pneumonia in influenza pdmH1N1 patients compared to H3N2 and influenza B patients although this study included children as well and represented a much younger study population [27]. In this study the rate of ICU admission and respiratory failure was higher in influenza A but this did not reach statistical significance. Pneumonia was the most common complication (24%) and equal in both groups. There was a trend towards a higher proportion of acute kidney injury in the influenza B group, which probably could be attributed to the higher age, higher amount of chronic kidney disease and vomiting as a common symptom in this population. Despite the fact that the influenza A patients were younger, they had a longer median in-hospital stay (8 days vs. 7 days). This might reflect the fact that patients with influenza A were sicker and had a prolonged recovery.

The overall in-hospital mortality rate for both groups was 5.6% with a numerically but not statistically significantly higher mortality rate in the influenza A group (8.3% for influenza A vs. 4.7% for influenza B, p = 0.172). Other studies of hospitalized patients described a similar mortality rate (3.7–5.2%) without differences between influenza A and B virus infections [27, 28, 32]. Of the studies one analyzed community and healthcare-acquired influenza infections and described an in-hospital mortality rate of

Table 4 Complications

	Total (N = 396)	Influenza A (n = 96)	Influenza B (n = 300)	p-value[a]
Pneumonia (%)	95 (24)	23 (24)	72 (24)	0.993
Respiratory failure (%)	77 (19.4)	22 (22.9)	55 (18.3)	0.323
Acute kidney injury (%)	48 (12.1)	7 (7.3)	41 (13.8)	0.092
Rhabdomyolysis (%)	31 (7.8)	7 (7.5)	24 (8.1)	0.870
ICU admission (%)	19 (4.8)	6 (6.3)	14 (4.3)	0.444
Acute heart failure (%)	15 (3.8)	4 (4.2)	11 (3.7)	0.765[b]
Myocardial infarction (%)	4 (1)	1 (1)	3 (1)	1.000[b]
Duration of hospitalization in the isolation ward (days) Md (IQR)	7 (5–9)	8 (6–9)	7 (5–8)	0.023[c]

ICU intensive care unit, *Md* median, *IQR* interquartile range
[a]p-values derived from χ^2-tests if not otherwise noted
[b]Fisher's exact test
[c]Mann-Whitney U-test

Table 5 In hospital, 30-day and 90-day mortality

	Total	Influenza A	Influenza B	p-value[a]
In-hospital mortality (%)	22/396 (5.6)	8 (8.3)	14 (4.7)	0.172
30-day mortality				
From all patients (%)	27/396 (6.8)	–	–	–
From all patients followed up (%)	27/383 (7.0)	9 (9.6)	18 (6.2)	0.271
90-day mortality				
From all patients (%)	36/396 (9.1)	–	–	–
From all patients followed up (%)	36/383 (9.4)	10 (10.6)	26 (9)	0.636

[a]p-values derived from χ^2-tests

10%. The reason for this discrepancy is not known but may be due to the dominance of H3N2, which caused approximately 60% of the influenza infections in this study [33]. In the present population influenza B accounted for 75% of the infections and most of the influenza A infections were most likely caused by H1N1 [25]. In this study the 90-day mortality increased further to 9.4% with no difference between influenza A and influenza B, which represented a twofold increase in mortality. This was not surprising as there is an increased risk for complications leading to death after influenza infections as previously described [29].

The strength of this study is that it focused on hospitalized patients, so any immediate complications could be tracked, especially pneumonia, acute kidney injury, acute heart failure and death which are of great interest and a potential healthcare burden. In addition, efforts were made to assess mortality in the months after influenza infection. There are several limitations of this study. Almost 75% were infected with influenza B therefore the results may not be generalized to influenza A dominant seasons. The study did not differentiate between H1N1 and H3N2 and analyzed the two strains as one group. The symptoms on admission were not collected via a standardized questionnaire which may explain why mild common influenza-like symptoms, such as sore throat and coryza were underreported, especially in patients presenting with severe symptoms, such as dyspnea to the emergency department. There was no standardized testing for specific laboratory results which is why some parameters were missing.

While the three most common symptoms (fever, malaise/prostration, cough) were according to typical manifestations described in textbooks [30] the frequently described abrupt onset was not nearly as common in the setting of hospitalized patients with influenza. It is remarkable that gastrointestinal complaints, acute kidney injury and acute heart failure were the leading symptoms.

In conclusion, this study identified various differences in the presentation and medical history between patients infected with influenza A and B; however, symptoms were overlapping and definite differentiation on mere clinical parameters was not reliable. The use of PCR-POCT for accurate diagnosis seems to be necessary.

References

1. Simonsen L, Clarke MJ, Williamson GD, et al. The impact of influenza epidemics on mortality: introducing a severity index. Am J Public Health. 1997;87:1944–50.
2. Govaert TM, Dinant GJ, Aretz K, et al. The predictive value of influenza symptomatology in elderly people. Fam Pract. 1998;15:16–22.

3. Girard M, Cherian T, Perikov Y, et al. A review of vaccine research and development: human acute respiratory infections. Vaccine. 2005;23(50):5708–24.

4. Haviari S, Bénet T, Saadatian-Elahi M, et al. Vaccination of healthcare workers: a review. Hum Vaccines Immunother. 2015;11(11):2522–37.

5. Paules CI, Sullivan SG, Subbarao K, et al. Chasing seasonal influenza—the need for a universal influenza vaccine. N Engl J Med. 2018;378(1):7–9.

6. Monto AS, Gravenstein S, Elliott M, et al. Clinical signs and symptoms predicting influenza infection. Arch Intern Med. 2000;160:3243–7.

7. Cate TR. Clinical manifestations and consequences of influenza. Am J Med. 1987;82:15–9.

8. Monmany J, Rabella N, Margall N, et al. Unmasking influenza virus infection in patients attended to in the emergency department. Infection. 2004;32:89–97.

9. Casalino E, Antoniol S, Fidouh N, et al. Influenza virus infections among patients attending emergency department according to main reason to presenting to ED: a 3-year prospective observational study during seasonal epidemic periods. PLoS ONE. 2017;12(8):e182191.

10. Bouscambert M, Valette M, Lina B. Rapid bedside tests for diagnosis, management, and prevention of nosocomial influenza. J Hosp Infect. 2015;89:314–8.

11. Chartrand C, Leeflang MM, Minion J, et al. Accuracy of rapid influenza diagnostic tests: a meta-analysis. Ann Intern Med. 2012;156:500–11.

12. Bell J, Bonner A, Cohen DM, et al. Multicenter clinical evaluation of the novel Alere I Influenza A&B isothermal nucleic acid amplification test. J Clin Virol. 2014;61:81–6.

13. Hurtado JC, Mosquera MM, de Lazzari E, et al. Evaluation of a new, rapid, simple test for the detection of influenza virus. BMC Infect Dis. 2015;15:44.

14. Van Nguyen JC, Camelena F, Dahoun M, et al. Prospective evaluation of the Alere I Influenza A&B nucleic acid amplification versus Xpert Flu/RSV. Diagn Microbiol Infect Dis. 2016;2016(85):19–22.

15. Nie S, Roth RB, Stiles J, et al. Evaluation of Alere i Influenza A&B for rapid detection of influenza viruses A and B. J Clin Microbiol. 2014;52:3339–44.

16. Vanhems P, Benet T, Munier-Marion E. Nosocomial influenza: encouraging insights and future challenges. Curr Opin Infect Dis. 2016;29:366–72.

17. Trabattoni E, Le V, Pilmis B, et al. Implementation of Alere i Influenza A & B point of care test for the diagnosis of influenza in an emergency department. Am J Emerg Med. 2017;36(6):916–21.

18. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med. 2014;2:395–404.

19. Leibovici L, Paul M. Should we recommend neuroaminidase inhibitors for influenza? Clin Microbiol Infect. 2014;20:979–80.

20. Andrews D, Chetty Y, Cooper BS, et al. Multiplex PCR point of care testing versus routine, laboratory-based testing in the treatment of adults with respiratory tract infections: a quasi-randomised study assessing impact on length of stay and antimicrobial use. BMC Infect Dis. 2017;17:671.

21. Mosnier A, Caini S, Daviaud I, et al. Clinical characteristics are similar across type A and B influenza virus infections. PLoS ONE. 2015;10(9):e136186.

22. Hinds AM, Bozat-Emre S, Van Caeseele P, et al. Comparison of the epidemiology of laboratory-confirmed influenza A and influenza B cases in Manitoba, Canada. BMC Public Health. 2015;15(1):35.

23. Irving SA, Patel DC, Kieke BA, et al. Comparison of clinical features and outcomes of medically attended influenza A and influenza B in a defined population over four seasons: 2004–2005 through 2007–2008. Influenza Other Respir Viruses. 2012;6(1):37–43.

24. Chagvardieff A, Persico N, Marmillot C, et al. Prospective comparative study of characteristics associated with influenza A and B in adults. Med Mal Infect. 2018;48(3):180–7.

25. https://www.virologie.meduniwien.ac.at/wissenschaft-forschung/virus-epidemiologie/influenza-projekt-diagnostisches-influenzanetzwerk-oesterreich-dinoe/vorhergehende-saisonen/saison-20172018/. Accessed 27 Nov 2018.

26. Kaji M, Watanabe A, Aizawa H. Differences in clinical features between influenza A H1N1, A H3N2, and B in adult patients. Respirology. 2003;8(2):231–3.

27. Chaves SS, Aragon D, Bennett N, et al. Patients hospitalized with laboratory-confirmed influenza during the 2010–2011 influenza season: exploring disease severity by virus type and subtype. J Infect Dis. 2013;208(8):1305–14.

28. Chung JY, Hsu CC, Chen JH, et al. Geriatric influenza death (GID) score: a new tool for predicting mortality in older people with influenza in the emergency department. Sci Rep. 2018;8:9312.

29. Musher DM, Abers MS, Corrales-Medina VF, et al. Acute infection and myocardial Infarction. N Engl J Med. 2019;380(2):171–6.

30. Kasper DL, Fauci AS, Hauser SL, et al. Harrison's principles of internal medicine. 19th ed. New York: McGraw-Hill; 2015. Ebook Version 1.0

31. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson Comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173:676–82.

32. Topoulos S, Giesa C, Gatermann S, et al. Analysis of acute respiratory infections due to influenza A, B and RSV during an influenza epidemic 2018. Infection. 2019; https://doi.org/10.1007/s15010-018-1262-x.

33. Hagel S, Ludewig K, Moeser A, et al. Characteristics and management of patients with influenza in a German hospital during the 2014/2015 influenza season. Infection. 2016;44(5):667–72.