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Influenza in the immediate post-pandemic era: A comparison with seasonal and pandemic influenza in hospitalized patients

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ABSTRACT

Background: Comparative data on severity and treatment of seasonal, pandemic and post-pandemic influenza virus infections are scarce.
Objectives: To systematically analyze characteristics of hospitalized patients with influenza in the post-pandemic period compared to seasonal and pandemic influenza.
Study design: Clinical and virological data of patients hospitalized in a tertiary referral hospital with post-pandemic influenza (2010–2011) were compared with those during seasonal influenza epidemics (2007–2009) and the influenza A(H1N1)pdm09 pandemic (2009–2010).
Results: 82 patients were admitted during the post-pandemic period, compared to 85 during the pandemic and 60 during seasonal influenza epidemics. No differences were observed in the occurrence of complicated illness and the need for intensive care. However, radiographic pneumonia was significantly more often diagnosed in patients with influenza A(H1N1)pdm09 compared to patients with seasonal influenza A (25% versus 71% in pandemic, $p = 0.004$, and 55% in post-pandemic, $p = 0.047$). Oseltamivir was more frequently prescribed in post-pandemic and pandemic patients compared to previous influenza seasons (48.9% resp. 76.5% versus 6.5%, $p < 0.0001$). During the post-pandemic period, patients with influenza B were significantly less often treated with oseltamivir compared to patients with influenza A (27.0% versus 48.9%, $p = 0.043$), although the course of illness in patients with influenza B was comparable with influenza A. No upsurge of oseltamivir resistance was observed.
Conclusions: In our center, severity of illness was comparable for all influenza seasons, although more radiographic pneumonia was diagnosed in patients with influenza A(H1N1)pdm09. Despite the increased use of oseltamivir, no increase in oseltamivir resistance was detected.

1. Background

In March 2009 a novel influenza A H1N1 virus 'influenza A(H1N1)pdm09' emerged and rapidly spread around the world causing the first pandemic of this century. Although severe illness and death have been reported, it was mostly regarded as a relatively mild disease, with a course of illness comparable to seasonal influenza.[1–4] Historically, influenza in the immediate post-pandemic period has been known to be able to cause severe morbidity and mortality.[5] Indeed, some countries reported a more severe influenza season in 2010–2011 compared to the pandemic waves.[6] However, data based on systematic analysis of the impact of influenza in the post-pandemic period are scarce.

2. Objectives

In order to compare the characteristics of influenza in hospitalized patients in the post-pandemic period to those with seasonal and pandemic influenza, we systematically collected clinical information of patients hospitalized in a tertiary referral hospital with influenza from 2007 to 2011.

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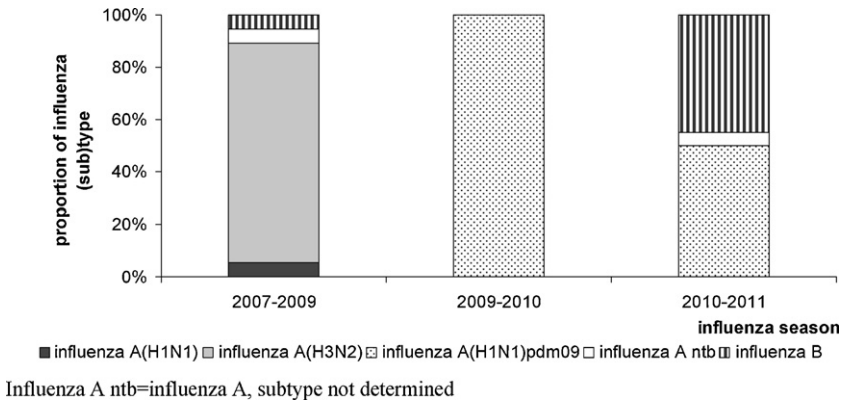

Fig. 1. Influenza (sub)type distribution during influenza seasons 2007–2011.

3. Study design

3.1. Study population

A retrospective observational study was conducted in all patients with influenza infection hospitalized in the University Medical Center Groningen (UMCG) from August 2007 till July 2011. Patients with acute respiratory illness were tested; only patients with real-time PCR (RT-PCR) confirmed influenza were included in the study. The UMCG is a large tertiary referral hospital with over 1300 beds in the northern region of the Netherlands. Patients were divided into three cohorts: patients with seasonal influenza (August 2007–May 2009), patients with pandemic influenza (June 2009–July 2010) and those with influenza during the first post-pandemic season (August 2010–July 2011). We compared clinical, epidemiological and virological data of patients with confirmed influenza A separately from those with influenza B infection.

3.2. Clinical data and definitions

Clinical information was gathered using a standardized questionnaire, including clinical symptoms, underlying chronic illness, medical complications, and treatment. Influenza vaccination history was initially included in the questionnaire, however because this was poorly documented in patients records, it had to be excluded for analysis. Complications were listed as pulmonary (pneumonia, respiratory insufficiency, pneumothorax, other pulmonary symptoms) or extra-pulmonary (renal failure, sepsis, neurological symptoms). Radiographic findings were classified into infiltrates, pleural effusion, interstitial abnormalities and pneumothorax. Bacterial co-infection was defined by isolation of a significant pathogen in respiratory or blood samples of a patient within 3 days before or after the detection of influenza. Time from onset of symptoms to admission and to sample date was calculated for each patient.

3.3. Laboratory methods

Nasopharyngeal swabs or nasopharyngeal aspirates were taken for the detection of respiratory viruses by a laboratory developed RT-PCR as has been described before.[7,8] In 11% of patients, sputum was used. Identification of influenza types and subtypes during 2007–2011 was performed as described elsewhere.[9–12] In short, RNA was isolated using the NucliSense EasyMag (bioMérieux, Lyon, France), or Magna Pure LC Total Nuclei Acid Isolation kit with external lysis protocol (Roche Diagnostics, Indianapolis, USA). Both influenza A and influenza B were detected by generic RT-PCR assay targeting the matrix gene. Multiple primers were used for screening and subtyping (Table 1). All influenza A(H1N1) positive samples were subsequently screened for the presence of the H275Y mutation in the neuraminidase gene (N1 nomenclature), conferring full resistance to oseltamivir.[12]

3.4. Statistical analysis

Statistical analyses were performed using SPSS version 18.0 (Chicago, USA). Interseasonal comparisons were tested using Mann Whitney *U* test and Fisher's exact test for continuous variables. Dichotomous variables were tested using χ^2 test. The effect of age on outcome was analyzed using multinomial logistic regression, for which each cohort was divided in two groups: patients under the age of 15 and those above. *P* values $\leq$0.05 were considered as statistically significant.

4. Results

A total of 227 patients with confirmed influenza were included in the study: 60 patients during the pre-pandemic seasons (47 with influenza A, of which 33 with influenza A(H3N2)), 85 during the pandemic (all influenza A(H1N1)pdm09), and 82 in the post-pandemic period (45 with influenza A(H1N1)pdm09, 37 with influenza B) (Fig. 1). For analysis, the pre-pandemic seasons (2007–2009) were compiled as no significant differences were observed with regard to patients' characteristics, course of illness and clinical outcomes (data not shown).

4.1. Influenza A

Characteristics of patients with influenza A are summarized in Table 2. No significant differences were observed in gender ratio, although there was a tendency toward more male patients admitted during the pandemic and post-pandemic period (57.6% and 55.6% versus 42.7% during seasonal influenza, $p = 0.11$ resp. $p = 0.30$) Age distribution among patients with seasonal, pandemic and post-pandemic influenza A differed significantly (Table 3). Forty percent of patients hospitalized with seasonal influenza A were aged under 4 years, significantly more than during the post-pandemic period (20%, $p = 0.03$). During the pandemic, a shift toward young adolescents was observed: almost 25% of patients with pandemic influenza A were aged 5–14 years, significantly more than during seasonal and post-pandemic influenza. In the post-pandemic period more patients aged 15–64 years were admitted (71%) compared to patients with seasonal influenza (38%, $p = 0.002$) and with pandemic influenza (45%, $p = 0.004$).

Table 1
Primers used for screening and identification of influenza viruses used in this study (with adjustments from April 2011 onwards).

Target	Aim	Primer	Oligotide sequence 5′ ⇒ 3′ and labels
InfA	Screening	INFA-asense-TM	CAAAGCGTCTACGCTGCAGTCC
		infA-probe-2	FAM-TTTGTGTTCACGCTCACCGTGCC-BHQ1
	04/18/11	INFA-sense-TM	AAGACCAATCCTGTCACCTCTGA
InfB	Screening	INFB-sense-TM	GAGACACAATTGCCTACCTGCTT
		INFB-asense-TM	TTCTTTCCCACCGAACCAAC
		INFB-probe-TM	TET-AGAAGATGGAGAAGGCAAAGCAGAACTAGC-EDQ
	04/18/11	infb-NSfwdB	GRACAACATGACCACAACACAAAT
		infb-NSrevB	CACTCCARAATTCCTGCTTCAAA
		infb-NSprobeB	DRAGONFLY-CGGGAGCAACCAATGCCACCATAAA-BHQ2
H1N1	Identification	H1-RF1162	GAATAGCCCCACTACAATTGGGTAA
		H1-RF1163	GTAATTCGCATTCTGGGTTTCCT
		H1-RF1164	FAM-AAGATCCATCCGGCAACGCTGCA-BHQ1
	04/18/11	H1-fwd1	CCAAAGTATGTCAGGAGTGCAAAAT
		H1-fwd2	CCAAAGTATGTCAGGAGTACAAAAT
		H1-rev	CCTTCAATGAAACCGGCAAT
		H1-probe	FAM-TGGTTACAGGACTAAGGAACATCCCATCCA-BHQ1
H3N2	Identification	H3-RF1358	GATGTGTACAGAGATGAAGCATTAAACA
		H3-RF1359	TAGGATCCAATCTTTGTATCCTGACTT
		H3-RF1360	YY-AGCTCAACACCTTTGATCTGGAACCGG-BHQ1
		H3prb2	YY-AGCTCAACGCCTTTGATCTGGAACCGG-BHQ1
	04/18/11	H3-fwd	GGGAAAAGCTCAATAATGAGATCAG
		H3-rev	TTGGGAATGCTTCCATTTGG
		H3-probe	DRAGONFLY-TGCACCCATTGGCAAATGCAATTC-BHQ2
		H3-probe2	DRAGONFLY-TGCACCTATTGGCAAATGCAATTC-BHQ2
H1N1pdm09	Identification	MexFlu-H1-fwd	GGAAAGAAATGCTGGATCTGGTA
		MexFlu-H1-rev	ATGGGAGGCTGGTGTTTATAGC
		MexFlu-H1-pr	DRAGONFLY-TGCAATACAACTTGTCAGACACCCAAGGG-BHQ2
	04/18/11	SwN1-fwd	ACATGTGTGTGCAGGGATAACTG
		SwN1-rev	TCCGAAAATCCCACTGCATAT
		SwN1-probe	FAM-ATCGACCGTGGGTGTCTTTCAACCA-BHQ1
H1N1 H274Y	Resistance	FluAN1-H275F	CCGCCTCGTACAAAATCTTCAAGA
		FluAN1-H275R	CAGTGTCTGGGTAACAGGAACATT
		FluAN1-H275	VIC-CTCATAATGAAAATTG-MGBNFQ
		FluAN1-H275Y	FAM-CCTCATAATAAAAATTG-MGBNFQ
H1N1pdm09 H274Y	Resistance	panN1-H275a	TGCACACACATGTGATTTCACTAG
	04/18/11	panN1-275Hp	FAM-TTATCACTATGAGGAATG-BHQ1
		panN1-275Yp	DRAGONFLY-TTATTACTATGAGGAATG-BHQ2
		panN1-H275s	CAGTCGAAATGAATGCCCCTAA

Table 2
Overview of influenza A cohorts as described in this study.

	Seasonal influenza A ($n=47$)	Pandemic influenza A ($n=85$)	Post-pandemic influenza A ($n=45$)
Influenza A subtypes (absolute numbers)			
H1N1	7	0	0
H3N2	33	0	0
H1N1nv	0	85	41
Non typable influenza A	7	0	4
Male gender (%)	42.6	57.6	55.6
Median age in years (IQR)	21.3 (1.1–59.5)	14.2 (4.6–48.5)	49.8[*] (14.9–59.5)
Underlying medical condition (%)	87.2[**]	70.6	80.0
Timespan, median in days (IQR)			
From symptom onset to admission	2.5 (1.0–4.0)	2.0 (1.0–4.0)	1.0[¶] (0.0–3.0)
From symptom onset to sample date	4.0[†] (2.0–6.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)
Hospital length of stay	8.0 (5.0–14.0)	6.0 (2.0–14.5)	6.0 (3.0–20.5)
Received oseltamivir therapy (%)	6.5	76.5[§]	48.9
Resistance to oseltamivir (absolute numbers)	4	4	1
Admitted to ICU (%)	25.5	29.4	22.2
Experienced complications (%)	38.3	49.4[‡]	40.0
Death (absolute numbers)	3	7	3

IQR = interquartile ranges.
[*] $p=0.004$ post-pandemic influenza A versus pandemic influenza A.
[**] $p=0.03$ seasonal influenza A versus pandemic influenza A.
[¶] $p=0.03$ post-pandemic influenza A versus seasonal influenza A.
[†] $p=0.02$ seasonal influenza A versus pandemic influenza A, $p=0.008$ seasonal influenza A versus post-pandemic influenza A.
[§] $p<0.0001$ pandemic influenza A and post-pandemic influenza A versus seasonal influenza A, $p=0.001$ pandemic influenza A versus post-pandemic influenza A.
[‡] $p=0.2$ pandemic influenza A versus seasonal influenza A.

The course of illness in patients with influenza A was similar for all seasons. No significant differences were observed in the occurrence of complicated illness and the need for admission to the intensive care unit (ICU), also after adjustment for the differences in age distribution (Table 2). During all seasons, patients were admitted to the hospital within a median time of 3 days after onset of symptoms, independent of the presence of complicated illness or necessity for ICU admittance. No differences in duration of

Table 3
Age distribution in patients with seasonal, pandemic and post-pandemic influenza A.

	Seasonal influenza A ($n=22$)	Pandemic influenza A ($n=44$)	Post-pandemic influenza A ($n=11$)
0–4 years	40.4%	21.7%	20.0%*
5–14 years	6.4%	24.7%**	4.4%
15–64 years	38.3%	44.7%	71.1%†
>65 years	14.9%§	3.5%	4.4%

* $p=0.03$ post-pandemic influenza A versus seasonal influenza A.
** $p=0.004$ pandemic influenza A versus post-pandemic influenza A, $p=0.009$ pandemic influenza A versus seasonal influenza A.
† $p=0.002$ post-pandemic influenza A versus seasonal influenza A, $p=0.004$ post-pandemic influenza A versus pandemic influenza A.
§ $p=0.02$ seasonal influenza A versus pandemic influenza A.

hospitalization were seen; only complicated illness was associated with a longer hospital stay ($p<0.0001$, data not shown). In patients admitted during the pandemic and post-pandemic period, respiratory samples for the detection of influenza were taken significantly more rapidly compared to patients admitted in previous influenza seasons.

Chronic underlying illness was significantly less present in patients with pandemic influenza A compared to those with seasonal influenza A (70.6% versus 87.2%, $p=0.03$). However, when adjusted for age, no significant differences of comorbidities were detected among the three influenza periods in patients over 15 years. In both the pandemic and post-pandemic period, comorbidities were significantly less present in patients under the age of 15: 59.1% with pandemic influenza A ($p=0.025$) and 54.4% with post-pandemic influenza A ($p=0.044$) compared to 86.4% of patients with seasonal influenza A.

The most remarkable differences however were seen in oseltamivir treatment: oseltamivir was more frequently prescribed in pandemic patients compared to previous influenza seasons (76.5% versus 6.5%, $p<0.0001$). In the post-pandemic period, prescription rates diminished although still more patients received antiviral therapy compared to those with seasonal influenza A (48.9% versus 6.5%, $p<0.0001$). These differences remained after adjustment for the differences in age distribution.

During the pandemic, patients not treated with oseltamivir were significantly younger, had less chronic underlying illness, were admitted to the hospital later in the course of illness and had to stay hospitalized relatively shortly compared to those who were treated with oseltamivir. Also, patients not treated with oseltamivir were less frequently admitted to the ICU (Table 4). During the post-pandemic period however, these differences between patients with and without oseltamivir treatment were not observed. Despite the strong increase in oseltamivir treatment, no increase in oseltamivir resistance was detected. During the seasonal influenza period, all oseltamivir resistant influenza A were subtyped as influenza A(H1N1), as was expected considering reports of emerging oseltamivir-resistant seasonal influenza A(H1N1) since 2007.[13] During the pandemic and post-pandemic period, four out of five patients developed oseltamivir resistance while being treated with oseltamivir; one patient was infected with primarily oseltamivir resistant influenza A(H1N1)pdm09.

Chest radiographs were performed in 68%, 67% and 76% of patients with seasonal, pandemic and post-pandemic influenza A respectively. Radiographic abnormalities were reported in similar frequencies in pandemic and post-pandemic influenza A (60% and 59%), more than in seasonal influenza A (37.5%) although statistical significance could not be reached. Compared to seasonal influenza A however, radiographic pneumonia (25% in seasonal influenza A) was more often diagnosed in patients during the pandemic (71%, $p=0.004$) and post-pandemic period (55%, $p=0.047$). No significant differences were seen in isolated bacterial pathogens between all influenza seasons. Also, no difference was seen in the prescription rate of antibiotics: during all seasons approximately 70% of patients were treated with antibiotics.

4.2. Influenza B

In the study period, 50 patients were included with confirmed influenza B infection, 13 during pre-pandemic seasons, and 37 during the post-pandemic period. No differences were seen in patients' characteristics and course of illness between patients with post-pandemic influenza B compared to those with seasonal influenza B. The clinical characteristics of patients with influenza B were remarkably similar to those with influenza A (Table 5). However, during the post-pandemic period, patients with influenza B were significantly less often treated with oseltamivir compared to patients with influenza A (27.0% versus 48.9%, $p=0.043$). Patients with post-pandemic influenza B were admitted later in the course of illness (median 3 versus 2.5 days, $p=0.028$) and were also tested later for the presence of influenza (median 4 versus 3 days, $p=0.006$).

5. Discussion

Our study is one of the first to systematically assess the clinical, epidemiological and virological characteristics of patients with post-pandemic influenza. Influenza in the post-pandemic period, including both influenza A and influenza B, was in our center equally severe as the pandemic in terms of the number of patients admitted. The course of illness in patients with influenza A was comparable for all seasons, indicating no increased severity of influenza A(H1N1)pdm09 compared to other influenza A subtypes. Besides, patients with influenza B displayed similar clinical characteristics as those with influenza A. However, several aspects are noteworthy.

The age distribution of patients admitted with influenza differed significantly in the three study periods. Patients with seasonal influenza displayed the well known age distribution with relatively more infections in the young (<4 years) and the old (> 65 years) compared to pandemic and post-pandemic periods. During the pandemic, a shift was noticed toward the school-aged and adolescent population, as has been described by others.[2,14,15] The relative lower risk of infection among older individuals has been explained by the presence of cross reactive antibodies due to exposure to circulating descendants of the 1918 H1N1 pandemic virus before 1957.[16] The majority of hospitalized patients in the immediate post-pandemic period were significantly older compared to those admitted during the pandemic. Children might have been less susceptible for serious infection during the post-pandemic period because of a relatively high attack rate during the previous pandemic influenza season or to persisting vaccine-induced immunity.[17]. In the Netherlands, vaccination strategy during the pandemic focused on risk groups and young children below the age of four. Vaccination coverage among children reached around 60% in the northern region of the Netherlands (personal communication B. Wolters, Municipal Health Service Groningen).

During all seasons patients were admitted relatively early in the course of illness. These findings suggest that serious illness is mainly due to effects of the influenza virus itself and not because

Table 4
Characteristics and course of illness in patients with and without oseltamivir treatment during pandemic influenza.

	Oseltamivir treatment $n = 65$	No oseltamivir $n = 20$	Significance, p-value
Age (median, years)	26.4	2.9	0.001
Underlying illness (% of patients)	78.5	45.0	0.004
ICU admittance (% of patients)	35.4	10.0	0.047
Complications (% of patients)	53.8	35.0	NS
Duration of illness at admission (median, days)	2.0	3.5	0.024
Length of hospital stay (median, days)	6.0	2.0	0.006

ICU = intensive care unit. NS = not statistically significant.

Table 5
Clinical characteristics, course of illness and treatment in patients with influenza B compared to seasonal and post-pandemic influenza A.

	Seasonal influenza A $n = 47$ (%)	Seasonal influenza B $n = 13$ (%)	Post-pandemic influenza A $n = 45$ (%)	Post-pandemic influenza B $n = 37$ (%)
Underlying illness	41 (87.2)	10 (76.9)	36 (80.0)	31 (83.3)
ICU admittance	12 (25.5)	4 (30.8)	10 (22.2)	10 (27.0)
Complications	18 (38.3)	6 (46.2)	18 (40.0)	17 (45.9)
Oseltamivir treatment	3 (6.4)	3 (23.1)	22 (48.9)	10 (27.0)*

* $p = 0.043$ post-pandemic influenza B versus post-pandemic influenza A.

of the occurrence of bacterial co-infection, although this is a well known complication of influenza. Still, more than two thirds of the patients during all seasons were treated with antibiotics. Although no significant differences were observed in severity of illness between the influenza seasons, more radiographic pneumonia was diagnosed during the pandemic and post-pandemic period. This is supported by in vitro data, which showed that influenza A(H1N1)pdm09 has an increased affinity for α2, 3-linked receptors on epithelial cells in the lower respiratory tract, in contrast to seasonal influenza subtypes.[18]

The majority of patients in our study had chronic underlying illness, regardless the season, emphasizing the impact of influenza in these high risk groups, and the importance of yearly influenza vaccination. Earlier reports recorded less comorbidities in patients admitted during the pandemic compared to other influenza seasons.[1,15] However, in our center, this was only observed in patients under the age of 15 years. During the post-pandemic period, a similar pattern was observed. These findings suggest that influenza A(H1N1)pdm09 can cause serious illness especially in previously healthy young patients. It probably also reflects the tertiary referral function of our hospital and might have biased our findings toward more complicated patients and more severe illness. However, the observed similarity in severity of illness between patients with seasonal and pandemic influenza is confirmed by a recent study in which the estimated burden of disease caused by pandemic influenza in the Netherlands, based on incidence, sequelae and mortality, was comparable with the burden of seasonal influenza.[19]

Another finding of our study is the frequency of oseltamivir treatment in patients with influenza infection. We observed a more than tenfold increase in the use of oseltamivir during the pandemic compared to seasonal influenza. This was probably at least partly due to national public health guidelines recommending treatment with oseltamivir in hospitalized patients, a phenomenon that very recently also has been described for the United States.[20] In contrast to the US-study however, where people above 65 years were less likely to receive antiviral agents, we found that especially relatively healthy, young children who were already ill for a couple of days and required only short term admission, did not receive oseltamivir. These findings suggest that during the pandemic these patients were admitted out of cautiousness rather than because of the seriousness of illness. During the post-pandemic period, oseltamivir was less frequently prescribed in patients with influenza A, although still significant differences remained compared with seasonal influenza. The reasons for this remain unclear. Compared to the pandemic, the use of oseltamivir was much less advocated by national guidelines or professional standards. Besides, influenza A(H1N1)pdm09 was by then generally regarded as causing relatively mild disease, possibly accounting for more reluctance among physicians to start antiviral treatment. The frequent use of oseltamivir did not lead to an upsurge of oseltamivir resistance of the influenza virus, suggesting that other mechanisms than antiviral pressure are responsible for the occurrence of resistance. This is not unknown for influenza, as in recent years the emergence of drug resistant influenza strains have been described in the absence of antiviral drug pressure, e.g. adamantine resistant influenza A(H3N2) since 2003 and oseltamivir resistant influenza A(H1N1) since 2007.[21]

Influenza B caused illness similar to influenza A, regardless the season. This is rather remarkable as previous studies showed that influenza A(H3N2) was associated with highest annual rates of influenza associated hospitalizations (with pneumonia, respiratory and circulatory hospitalizations as discharge diagnoses) compared to influenza A(H1N1) and influenza B.[22] Despite similarity in severity of illness, patients with influenza B during the post-pandemic period were less treated with oseltamivir compared to the patients with influenza A. This might be explained by the observation that patients with influenza B were admitted later in the course of illness. Treatment with oseltamivir can shorten the duration of illness when given early (within 48 h) in the course of illness.

A limitation of our study is the relative small amount of patients included, hospitalized in one single tertiary referral hospital. Larger studies in different patient populations are necessary to confirm our findings.

In conclusion, in our center, seasonal, pandemic and post-pandemic influenza showed many similarities with regard to patients' characteristics, severity of illness and clinical outcome. Influenza in the post-pandemic period led to an equally severe season in terms of number of patients admitted as compared to the pandemic. Although the use of oseltamivir became common practice, no increase in oseltamivir resistance was detected. Our findings particularly highlight the fact that influenza is an important cause of illness and death each year, and emphasizes the need for influenza vaccination.

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Competing interests

None declared

Ethical approval

Not required

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