Estimation of influenza activity in Vojvodina (Serbia) for five consecutive influenza seasons

Procena aktivnosti influence u Vojvodini (Srbija) tokom pet uzastopnih sezona nadzora nad gripom

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Abstract

Background/Aim. After pandemic 2009/10 influenza season, influenza A (H1N1)pdm09, A(H3N2) and B viruses have continued to circulate in the population. The aim of this study was to describe the epidemiological and virological characteristics of influenza and evaluate values of proposed case definitions of influenza like illness (ILI), severe acute respiratory illness (SARI) and acute respiratory distress syndrome (ARDS) for detecting laboratory-confirmed influenza cases in Vojvodina. **Methods.** We conducted a descriptive epidemiological study using surveillance reports and laboratory data from October 2010 to May 2015 (five surveillance seasons). **Results.** Out of 1,466 samples collected, 720 (49.1%) were laboratory confirmed as influenza. Influenza A infection was more frequently detected than influenza B infection. Using the case definition of ILI was a good predictor for influenza confirmation ($p < 0.05$) during 5 influenza seasons. The predominant age-range of patients with confirmed influenza A (42.2%) and B (43.0%) infections was 30 to 64, but the patients aged from 15 to 29 years were more likely to have influenza A ($p = 0.0168$). In the period from December to January, influenza A (17.8%) was more frequently registered than influenza B (7.6%). The highest number of deaths (19/38) and hospitalized patients (128/402) was registered during the last influenza season (2014/15). The immunosuppressed patients with confirmed influenza infection were more likely to have influenza B than influenza A ($p = 0.0110$). **Conclusion.** Our results indicate that influenza surveillance should be continued and expanded in order to fully assess the burden of the disease in given population.

Key words:
influenza, human; serbia; epidemiology; virology; diagnosis, differential.

Apstrakt

Uvod/Cilj. Nakon pandemijske 2009/10 sezone nadzora nad gripom, virusi influence tipa A (H1N1)pdm09, A(H3N2) i tipa B nastavili su da cirkulišu u populaciji. Cilj ovog istraživanja bio je da se opišu epidemiološke i virusološke karakteristike virusa influence i da se proceni vrednost predloženih definicija slučaja oboljenja sličnih gripu (OSG), teške akutne respiratorne bolesti (TARB) i akutnog respiratornog distres sindroma (ARDS) za otkrivanje laboratorijski potvrđenih slučajeva virusa influence u Vojvodini. **Metode.** Sprovedena je deskriptivna epidemiološka studija upotrebom podataka iz izveštaja u nadzoru i laboratorijskih podataka u periodu oktobar 2010–maj 2015. godine (pet sezona nadzora). **Rezultati.** Od ukupno 1 466 prikupljenih uzoraka, laboratorijska potvrda virusa influence dobijena je kod 720 (49,1%). Infekcija prouzrokovana virusom influence tipa A je češće detektovana u odnosu na onu izazvanu virusom influence tipa B. Korišćene definicije slučaja OSG su bile dobar prediktor za laboratorijsku potvrdu virusa influence ($p < 0,05$) tokom svih pet sezona nadzora. Infekcije virusom gripa tipa A i B najčešće su dokazivane kod bolesnika starosti 30–64 godine (42,2% i 43,0%), a bolesnici starosti 15–29 godina imali su veće šanse da obole od virusa gripa tipa A nego tipa B ($p = 0,0168$). U periodu od decembra do januara virus influence tipa A (17,8%) češće je registrovan nego virus influence tipa B (7,6%). Najveći broj smrtnih slučajeva (19/38) i hospitalizovanih zbog gripa (128/402) registrovan je tokom poslednje sezone nadzora nad gripom (2014/15). Imunokompromitovani bolesnici sa potvrđenim gripom imali su veće šanse da obole od virusa gripa tipa B nego tipa A ($p = 0,0110$). **Zaključak.** Naši rezultati ukazuju na to da je za potpuniju procenu opterećenja populacije virusom influence neophodno nastaviti i proširiti nadzor nad gripom.

Ključne reči:
grip; srbija; epidemiologija; virologija; dijagnoza, diferencijalna.

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Introduction

Influenza is a common seasonal illness causing epidemics worldwide [1]. Influenza surveillance provides information on virus activity and basis for early warning of an upcoming epidemic or pandemic period [2].

Influenza A and influenza B viruses are responsible for recurrent epidemics in humans. Influenza A has more significant impact on public health because of its faster evolution and diverse host range [3].

It is known that influenza A(H1N1)pdm09, A(H3N2) and B viruses continue to circulate in population after the pandemic period. A number of reports from different countries have documented the burden of influenza in the post-pandemic period [4].

Surveillance of influenza at the European level has been conducted since 1996 [5]. According to the model of surveillance conducted in Slovenia [6], sentinel surveillance of influenza like illness (ILI) and acute respiratory infection (ARI) was introduced in the Autonomous Province (AP) of Vojvodina (the northern region of Serbia) in the period 2004/05 (pilot study) and continued for the following 4 influenza seasons. Thanks to the results of this quality surveillance, newly established national influenza surveillance throughout the Republic of Serbia, has been conducted since 2009 [7].

Also, since 2010/11 influenza season along with surveillance of ILI, surveillance of severe acute respiratory infection (SARI) and acute respiratory distress syndrome (ARDS) among hospitalized patients was implemented in Vojvodina [7].

There are very limited data on the contribution of influenza virus to the burden of outpatients and hospitalized patients in Vojvodina. A five-year surveillance study was carried out in Vojvodina to estimate the influenza activity during the post-pandemic period.

Methods

A retrospective study was conducted. We analysed data from Vojvodina surveillance of influenza among outpatients (with ILI) and in hospitalized patients (with SARI and/or ARDS). Surveillance data from the period from October 2010 to May, 2015 were analyzed. We characterized the epidemiology, virology and the predictor values of proposed case definitions to detect influenza virus infection based on our results. The surveillance data were collected for the whole influenza season (from the calendar week 40 of the given year to the calendar week 20 of the following year) [7, 8].

Sentinel surveillance

From 2010 to 2015 seasons, approximately 168.000 inhabitants, each year were required to report the weekly number of ILI cases aggregated by age group to a local public health centres which were then aggregated at Vojvodina level. From 2010 to 2015, sentinel surveillance covered between 5.2% and 15.8% of total Vojvodina population and included between 89 to 135 sentinel physicians who observed

influenza seasons. In the surveillance of ILI, only outpatiens in Health Centres of Vojvodina were covered. From 2010 to 2013 sentinel sites have included počulation of 19 municipalities in Vojvodina, while since 2013 sentinel surveillance was expanded in all of 45 municipalities of Province. The World Health Organization (WHO) and national recommendations, we observed five age groups (0–4, 5–14, 15–29, 30–64 and ≥ 65). General practitioners and paediatricians were included in the network of sentinel physicians and they reported the number of new cases of ILI in their weekly population reference. Also, sentinel physicians electronically entered the data of new cases of ILI weekly and regularly sent samples for virological confirmation to the WHO National Influenza Centre, the Centre for Virology of the Institute of Public Health of Vojvodina in Novi Sad [7].

Hospitalizations – SARI and ARDS surveillance

As previously described in detail [7], the hospital coordinators of SARI and ARDS surveillance from all 15 acute care hospitals in Vojvodina sent daily reports on each hospitalized SARI and/or ARDS case to the district coordinators of influenza infection in local departments of public health. Individual reports on the hospitalized cases with SARI and/or ARDS were registered in a computer database in the local departments of public health and in the Institute of Public Health of Vojvodina.

We included patients of all ages who were hospitalized in the intensive care units and high dependency units (severe form of infections), general/internal medicine, pediatric medicine, infectious disease wards and respiratory disease wards in Vojvodina.

Inclusion criteria

The inclusion criteria for the study were clinical diagnosis of ILI, SARI and ARDS. In accordance with the WHO criteria, a case definition as a basis for physicians to collect specimens were following: ILI cases were defined as those with a sudden onset of fever (> 38°C) and cough/sore throat within seven days of the onset, while the inclusion criteria for the SARI patients was defined as presence of an acute respiratory illness with the onset during the previous seven days, and who required overnight hospital admission on the basis of history of fever or measured fever of 38°C, cough, and shortness of breath or difficulty in breathing [9, 10].

ARDS cases were defined as acute onset of bilateral infiltrates on the chest radiograph; arterial oxygen tension partial pressure of oxygen (PaO$_2$)/fraction of inspired oxygen (FiO$_2$) ratio < 27 kPa and absence of cardiac failure or left atrial hypertension (assessed clinically, echocardiographically or with invasive monitoring) and required invasive ventilation [11–13].

Laboratory diagnosis

The reference laboratory for virological surveillance of influenza was WHO National Influenza Center, the Centre for Virology of the Institute of Public Health of Vojvodina in Novi Sad [14].

The nasal and throat swabs samples were collected from all patients in Vojvodina who meet the ILI, SARI or ARDS case definition. Once samples were collected, swabs were put in the Viral Transport Media, stored at 4 °C, and then transported to the Centre for Virology and kept at -20 °C. The transport of the samples to the laboratory was organized on a daily basis by local departments of public health. The case data, including demographic and clinical information, were collected on a questionnaire/laboratory form from all patients from whom a swab was collected.

Swab samples from the patients were tested for influenza A (H1N1)pdm09, influenza A (H3N2) and influenza B (without further determination of B/Yamagata-like and B/Victoria-like) virus infection using real-time polymerase chain reaction (RT-PCR) as described previously [15].

The results were analysed using the Applied Biosystems 7500 Software version 2.0.6, and the interpretation of the data was done according to WHO guidelines [16]. Immediately after the testing was finished, the results of the laboratory tested samples were sent to the Institute of Public Health of Serbia, local departments of public health, the sentinel/hospital physicians, and to the patients [7].

Statistical analysis

Using the above-mentioned methodology [7], we calculated weekly incidence rate of ILI in Vojvodina and weekly age-specific incidences of ILI for the monitored age groups were measured per 100,000 of population.

The epidemic threshold of incidence of 246.3/100,000 was determined in the previous 5 pre-pandemic sentinel seasons on the basis of weekly incidence rate of ILI value [7].

To study the evolution of the influenza activity and hospitalization rate during the influenza surveillance seasons, the ILI incidence rates per week and weekly hospitalization rates (number of hospital admissions) were compared for five seasons. Univariate analysis was performed to determine a degree of significance of proposed case definitions related to the laboratory confirmation of the influenza virus. Stepwise logistic regression analysis was performed to determine which case definitions had predicted influenza infection. Odd ratios (OR) and their 95% confidence intervals (CI) were calculated for each variable in the logistic regression model. Comparisons of the influenza A and B virus subtypes distribution by sex, age, proposed case definitions, monthly notified cases and underlying conditions were analysed by Fisher's exact test. Differences were considered statistically significant at $p < 0.05$. Statistical analysis was done by using SPSS version 21 software.

Results

Figure 1 (a-d) shows the distribution of influenza type/subtype among all laboratory confirmed cases of influenza. For the five infleunza seasons, the highest value of weekly ILI incidence rate was accompanied by the highest number of confirmed influenza cases. Except the 2013/14 influenza season, when influenza B was not detected, each year, influenza A and B viruses cocirculated. A total of 720 samples were identified as influenza A or B positive. Among

the positive cases, 288 (40.0%) were influenza A (H1N1)pdm09, 253 (35.1%) were influenza A (H3N2), 158 (21.9%) were influenza B, while 3.0% of all influenza cases were influenza A without subtypes (these samples had low viral loads that were below the threshold of detection with subtype-specific reagents). The majority of influenza A (H1N1)pdm09 positive samples were detected in the 2010/11 influenza season. In this season, the highest percentage (79.2%; 80/101) of influenza A (H1N1)pdm09 was registered between weeks 4 and 7. The highest proportion of influenza A (H3N2) specimens were registered in the last influenza season (2014/15) when laboratory confirmed 90 cases of influenza A (H3N2) and 20 cases (22.2%) was registered only in the 9/2015 week. During the study period, a total of 158 cases of influenza B were registered and most of influenza B samples were confirmed during 2012/13 influenza season (63.9%; 101/158). In the same influenza season, we registered the highest weekly incidence rate of ILI (712.3/100,000 inhabitants) in the 9/2013 week.

The physician sentinel network data regarding hospitalized cases of influenza and data from virological surveillance for 2010–2015 are presented in the Figure 2. During the study period (2010–2015), the highest weekly incidence rates of ILI were registered during the 2010/11 and 2012/13 influenza seasons. The lowest values of weekly incidence rate were registered in the 2013/14 influenza season. Observed by clinical diagnosis, the majority of cases of SARI and ILI patients with influenza, were registered during the 2012/13 and 2014/15 influenza seasons, respectively. Only during the 2011/12 season we did not detect influenza patients with clinical diagnosis of ARDS.

In the observed period, 1,466 specimens from patients with ILI, SARI or ARDS, were tested for influenza by RT-PCR, and 720 samples were identified as influenza A or B positive (49.1%). Among all the case definitions, the case definition of ILI was a good predictor for influenza confirmation ($p < 0.05$) during five seasons. According to observations regarding each seasons, the patients with SARI or ARDS were more likely to be negative than positive for influenza after testing or were not significantly different ($p > 0.05$) in predicting influenza laboratory confirmation (Table 1).

The duration of the epidemic period was 8 weeks in 2010/11, 3 weeks in 2011/12 and 6 consecutive weeks during 2012/13 and 2014/15. There was no epidemic period in the 2013/14 influenza season, because weekly incidence rate of ILI were below the epidemic threshold.

A total of 38 influenza-associated deaths were reported during the study period. The highest number of deaths (19/38) and number of hospitalized patients (128/402) with influenza were registered during the 2014/15 influenza season, when influenza A (H3N2) (37.8%) and A (H1N1)pdm09 (35.2%) were almost equally present among the confirmed influenza cases. The highest hospitalization rate by week (6.6/100,000) were equally registered during the 2012/13 influenza season (influenza B predominant) as well as during the last one 2014/15. No influenza-associated deaths were reported to us and only 4 patients with influenza were hospitalized during the 2011/12 influenza season when influenza A (H3N2) was predominant (Table 2).
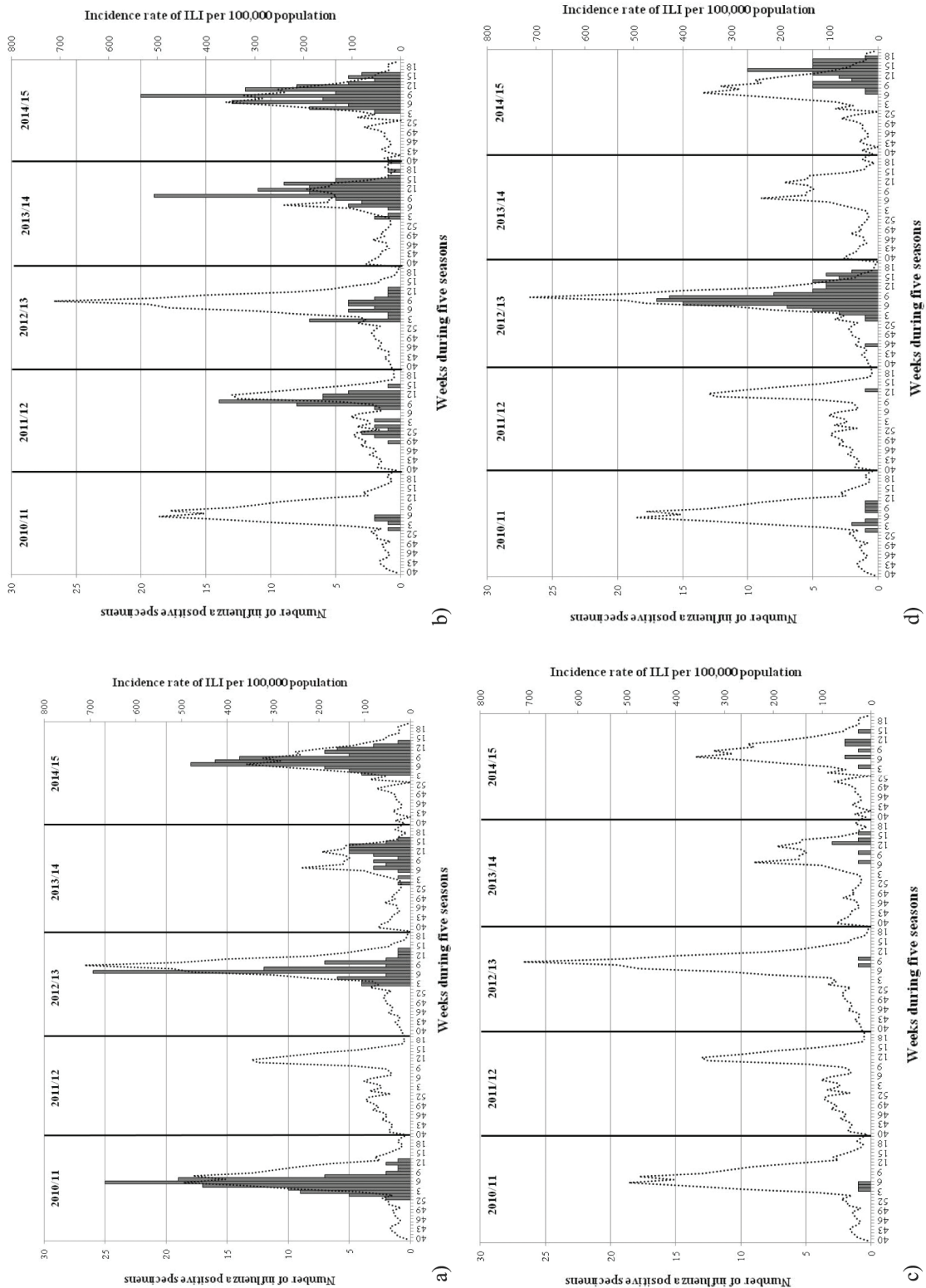
Fig. 1 – The weekly influenza like illness (ILI) incidence rate, the number of influenza positive patients by type/subtype and by week of illness onset in Vojvodina (Serbia) during five consecutive influenza seasons, 2010–2015: a) influenza A (H1N1)pdm09, b) influenza A (H3N2), c) influenza A (non-subtype) and d) influenza B.

Legend: The black vertical lines indicate the separation between different influenza seasons (2010–15).
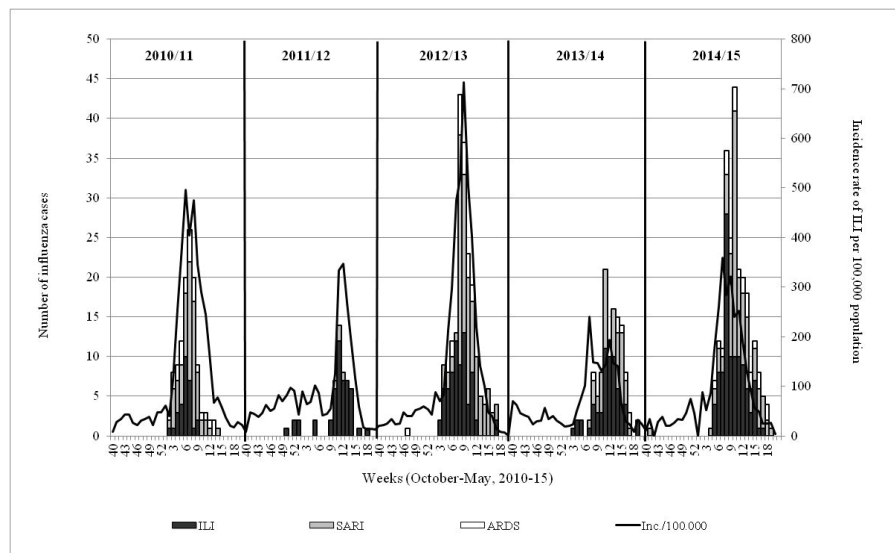
**Fig. 2 – The weekly incidence rate and distribution of laboratory-confirmed
influenza patients by clinical diagnosis of influenza in Vojvodina (Serbia)
during five consecutive influenza seasons, 2010-2015.
Legend: ILI - influenza-like illness; SARI - severe acute respiratory
infection; ARDS - acute respiratory distress syndrome.**

Table 1

**Analysis of the predictors of influenza infection by case definitions in Vojvodina (Serbia) during the
investigated period (n = 1,466)**

Years	Clinical form, n (%)			
	Total cases	ILI	SARI	ARDS
2010/11				
positive (+)	118 (100.0)	29 (24.6)	66 (55.9)	23 (19.5)
negative (-)	96 (100.0)	9 (9.4)	53 (55.2)	34 (35.4)
OR (95% CI)		3.15 (1.41–7.04)	1.03 (0.60–1.77)	0.44 (0.24–0.82)
p-value		0.0052	ns	0.0096
2011/12				
positive (+)	53 (100.0)	49 (92.5)	4 (7.5)	0 (-)
negative (-)	31 (100.0)	16 (51.6)	7 (22.6)	8 (25.8)
OR (95% CI)		11.48 (3.33–39.6)	0.28 (0.07–1.05)	0.02 (0.01–0.43)
p-value		0.0001	ns	0.0111
2012/13				
positive (+)	199 (100.0)	72 (36.2)	110 (55.3)	17 (8.5)
negative (-)	186 (100.0)	35 (18.8)	131 (70.4)	20 (10.8)
OR (95% CI)		2.45 (1.53–3.90)	0.52 (0.34–0.79)	0.78 (0.39–1.53)
p-value		0.0002	0.0023	ns
2013/14				
positive (+)	117 (100.0)	63 (53.8)	47 (40.2)	7 (6.0)
negative (-)	222 (100.0)	73 (32.9)	125 (56.3)	24 (10.8)
OR (95% CI)		2.38 (1.51–3.77)	0.52 (0.33–0.82)	0.53 (0.22–1.26)
p-value		0.0002	0.0050	ns
2014/15				
positive (+)	233 (100.00)	105 (45.1)	104 (44.6)	24 (10.3)
negative (-)	211 (100.0)	49 (23.2)	117 (55.5)	45 (21.3)
OR (95% CI)		2.71 (1.80–4.09)	0.65 (0.45–0.94)	0.42 (0.25–0.72)
p-value		0.0001	0.0231	0.0017

**OR – odds ratio; CI – confidence interval; ILI – influenza-like illness; SARI – severe acute respiratory
infection; ARDS - acute respiratory distress syndrome; ns – not significant (*p* > 0.05).**

Table 2

Epidemic periods, predominant influenza types, hospitalization rate and number of fatal outcomes by years in Vojvodina (Serbia), 2010–2015 seasons

Parametars	2010/11	2011/12	2012/13	2013/14	2014/15
Duration of epidemic period*	4–11 (8 weeks)	11–13 (3 weeks)	6–11 (6 weeks)	–	6–11 (6 weeks)
Predominant type/subtype of influenza virus	A(H1N1)pdm	A(H3N2)	B	A(H3N2)	A(H3N2)
Number of hospitalized patients with influenza (SARI or ARDS)	89	4	127	54	128
Hospitalization rate **	4.6	0.2	6.6	2.8	6.6
Number of deaths (CFR%)***	6 (6.7)	0 (-)	10 (7.9)	3 (5.6)	19 (14.8)

* **Epidemic period-week incidence rate of influenza like illness (ILI) above 246.3 per 100,000 population; ** Per 100,000 population in Vojvodina according census; ***Case fatality rate (CFR) of hospitalized cases with influenza – severe acute respiratory infection (SARI) or acute respiratory distreses syndrome (ARDS).**

There were a total of 562 influenza A and 158 influenza B virus infections confirmed during the five influenza seasons, without statisticall significant difference between gender regarding the types of influenza virus (p = 0.1257).

In the accordance with the proposed case definitions (ILI, SARI or ARS), there were no significant association with a risk of influenza A or B infection among the confirmed cases of influenza (p > 0.05).

The predominant age-range of the patients with influenza A (42.2%) and B (43.0%) infection was 30 to 64. The age distribution by the two types of influenza virus showed a significant difference only among the patients of the 15–29 age group (p = 0.0168).

Regarding the monthly distribution, influenza A and influenza B predominated during the February-March period, with 76.5% and 82.9%, respectively, in all confirmed cases. During December and January, influenza A type (17.8%) was registered more frequently than influenza B type (7.6%), and the difference was statistically significant (p = 0.0012).

The patients hospitalized during five influenza seasons were more likely to present with co-morbidity conditions, such as immunodeficiency, for different reasons.

Table 3

Characteristics of the laboratory-confirmed influenza A and B cases in Vojvodina (Serbia), during the 2010–2015 influenza seasons

Characteristics	Influenza A (n = 562)		Influenza B (n = 158)		p values*
	n	%	n	%	
Gender					
male	280	49.8	90	57.0	0.1257
Case definition					
ILI	259	46.1	59	37.3	0.0569
SARI	250	44.5	81	51.3	0.1483
ARDS	53	9.4	18	11.4	0.4529
Age					
0–4	76	13.5	14	8.9	0.1346
5–14	89	15.8	35	22.1	0.0734
15–29	83	14.8	12	7.6	0.0168
30–64	237	42.2	68	43.0	0.8558
≥ 65	77	13.7	29	18.4	0.1619
Months					
October–November	1	0.2	1	0.6	nd
December–January	100	17.8	12	7.6	0.0012
February–March	430	76.5	131	82.9	0.1031
April–May	31	5.5	14	8.9	0.1369
Comorbidities**					
chronic obstructive pulmonary disease	43	7.7	14	8.9	0.6182
diabetes mellitus	32	5.7	13	8.2	0.2643
immunodeficiency	73	13.0	34	21.5	0.0110
any cardiovascular disease	75	13.3	26	16.5	0.3637
chronic nephropathy	35	6.2	9	5.7	1.0000
overweight***	24	4.3	3	1.9	0.2351
pregnancy	12	2.1	1	0.6	0.3173
fatal outcome during hospitalization	30	5.3	8	5.1	1.0000

ILI – influenza-like illness; SARI – severe acute respiratory infection; ARDS – acute respiratory distress syndrome; nd – not determined; *Fisher's exact test; **One patient with confirmed influenza could have one or more comorbidities, simultaneously; ***Body mass index – BMI ≥ 30 kg/m^2.

The immunosuppressed patients were more likely to have influenza B than influenza A infection ($p = 0.0110$). When comparing A and B influenza types, no significant differences were found ($p > 0.05$) regarding chronic obstructive pulmonary disease, *diabetes mellitus*, cardiovascular diseases, chronic nephropathy, obesity, pregnancy and a risk of fatal outcome during hospitalization (Table 3).

Discussion

We conducted the first retrospective surveillance study among outpatients and hospitalized patients with laboratory confirmation of influenza in Vojvodina during the post-pandemic period. Data from our study showed that influenza A (H1N1) pdm09, A (H3N2) and influenza B were detected with different distribution over the observed periods. Three virus subtypes are cocirculating in Vojvodina and the predominant influenza subtypes were influenza A (H3N2) during 3 influenza seasons (2011/12, 2013/14 and 2014/15), influenza B in the 2012/13 season, while influenza A (H1N1)pdm09 was predominant during the first post-pandemic season in Vojvodina (2010/11). These findings are in good agreement with those from previously published results of the WHO reports [17–21].

Similar to the 2012/13 season, a large number of 3 subtypes of influenza cocirculated during the 2014/15 season, as reflected in high hospitalization rate of the patients with SARI and ARDS (6.6 per 100,000 inhabitants) in each of the above-mentioned influenza seasons. During both seasons, epidemic periods lasted for 6 consecutive weeks. The case fatality rate (CFR) in hospitalized influenza cases with SARI or ARDS diagnosis was the highest in the last post-pandemic season (14.8%; 19/128). Except the 2011/12 season, when no influenza-associated deaths were reported, the CFR in hospitalized patients ranged from 5.6% to 7.9% in other influenza seasons. The values of CFR during the post-pandemic influenza seasons was higher than the rates registered during the pandemic season in Vojvodina, when the CFR of hospitalized patients was 2.0% [7]. We believe that by implementing more sensitive hospital surveillance of the novel influenza virus (2009/10 season), it was possible to register more hospitalized patients (1,591) with ARDS, pneumonia, and those with acute febrile illness, than it was possible during the study period when the overall number of hospitalized patients with SARI and ARDS was 402. However, we are convinced that a total burden of influenza is often underestimated because many fatal outcomes are caused by some other secondary complications of influenza.

The case definition of ILI differs from country to country. The sensitivities and specificities of different ILI case definitions are very similar, but the positive predictive value (PPV) and positive likelihood ratio (LR+) are different, with the United States Centers for Disease Control and Prevention (US–CDC) ILI (fever defined as body temperature ≥ 37.8 °C plus cough and/or sore throat in the absence of a known cause other than influenza) having the lowest, and the WHO new ILI (fever defined as body temperature ≥ 38 °C plus cough and with onset within the last 10 days) having the highest PPV and LR+ [22–24].

In the surveillance of influenza in Vojvodina we used WHO's old ILI definition (patients with sudden onset of fever (> 38 °C) and cough/sore throat). The data of some other studies has shown that this case definition provided a slightly smaller different values of PPV and LR+ compared to WHO's new ILI. For example, it was reported that the respective values were 39% and 42% for PPV, whereas those for LR+ were 12.0 and 13.3, respectively [22]. Although there is a controversy as to whether the indicators from previous research are reliable for the estimation of efficacy of ILI case definitions [25], we found more frequently the patients with ILI among confirmed cases compared to the negative results of influenza testing during all five seasons of the sentinel surveillance of influenza. Similarly to the findings of other authors [26], the prevalence of laboratory-confirmed influenza infection in our community, during the five surveillance seasons a percentage of the patients with ILI was 63.6% (318/500). This results show that the sentinel surveillance of ILI and virological surveillance of influenza are an integrated and inseparable system for influenza monitoring.

A higher percentage of negative results of RT-PCR in patients with SARI and ARDS can be explained by the fact that the patients with suspected influenza were hospitalized in the later phases of infection, when PCR isolation of influenza is less sensitive. In accordance with that, the percentage of influenza confirmed cases might be increased if the specimens are collected only during the first few days of the illness. Likewise, the SARI and ARDS cases could be also due to other respiratory viruses, not only influenza [16, 25].

Similar to the results of our research, findings of other studies indicated that clinical features of patients infected with seasonal influenza A and B viruses are similar, despite the fact that the overall influenza A was more commonly detected than influenza B [27, 28].

We found that the influenza B virus circulated throughout the year and detection rates were mainly comparable to those of the influenza A viruses. Nevertheless, when comparing the features of the influenza A and B virus infections among the patients in Vojvodina in the 2010–2015 time frame, it comes out that the influenza A occurred more frequently than influenza B at the beginning of the influenza season (December-January) and more frequently among the 15–29 year old patients. The reasons for the increased number of influenza A positive specimens among young people can be explained by the fact that young people are tested more often [7], and that they, especially children, may shed virus more abundantly and for longer periods than adults [16]. In accordance with mentioned, among all confirmed cases of influenza, the participation of the influenza A virus was higher compared to influenza B virus (the ratio 3.6 : 1.0).

Similarly to the data of some other authors [3], we found that the influenza B followed influenza A as ILI and SARI cases when compared to clinical case definitions of influenza. Likewise, when we compared influenza infections among the patients with ARDS, no differences were found between the frequencies of the two types of influenza.

According to the WHO reports, in the 2010–2015 influenza seasons across Europe and USA, the most commonly

recognized factors for severe disease among the hospitalized adult patients were chronic respiratory disease (or asthma), cardiovascular diseases, metabolic disorders, and obesity. The most commonly reported underlying conditions among hospitalized pediatric patients were asthma, neurologic disorders, and immunodeficiency [17–21]. During the 2014/15 season, the new reports appeared on renal disease with significant presence among adult patients hospitalized because of influenza [21]. The data of the European system for monitoring excess mortality indicated that in the last winter season (2014/15), excess all-cause mortality among the elderly was higher than during the preceding 4 winter seasons [19–21]. In Vojvodina, during the last influenza season, when a large number of all three influenza subtypes were detected, the mortality rate of influenza was 1.0 per 100,000 inhabitants and it was the highest in comparison to the preceding seasons. The higher value of mortality rate of influenza (1.6 per 100,000 inhabitants) in Vojvodina was registered only during the pandemic 2009/10 season [7].

Despite the fact that vaccination plays a key role in controlling influenza transmission among high risk groups as well as in the general population, coverage of vaccination against influenza in Vojvodina remains low and includes mostly population aged 65 years or older [6, 29]. In our study, among cases with influenza-associated deaths, none of the participants had ever received an influenza vaccination.

Our results of the presenting comorbidities were similar in both groups, and the most common were immunodeficiency and cardiovascular disease. In the patients group with the influenza B confirmed infection, immunodeficiency was more commonly detected than in the other groups. A probable explanation for this is that two nosocomial outbreaks (2012/13 and 2014/15) with influenza B were registered, among patients with blood cancer receiving chemotherapy (resulting in immunodeficiency) [29].

Conclusion

The impact of influenza in Vojvodina over the past five influenza seasons has been considerable in terms of surveillance among outpatients as well as among the patients hospitalized with influenza. Earlier respiratory sampling collections for virological evaluation before hospitalization or the modification of actual case definitions of SARI and ARDS could increase the percentage of confirmed cases of influenza among the patients with suspected influenza infection. Besides, increasing number of samples among patients with influenza suspicion infection through the precise laboratory guidelines for sampling would lead to a more precise view on the distribution of influenza A and B viruses in Vojvodina. The activity to increase the coverage of immunization against influenza, particularly among the patients with risk factors for complications of seasonal influenza, could decrease the number of hospitalizations, complications and fatal outcomes due to influenza infection.

Conflict of interest

The authors declare no conflict of interest.

Ethical standards

All information about patients was anonymised and de-identified. This article does not contain any additional studies with human or animal subjects.

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