ORIGINAL ARTICLES

UDC: 616-036.22:616.921.5
DOI: https://doi.org/10.2298/VSP250901080R

Influenza surveillance in the Autonomous Province of Vojvodina, Serbia, over ten consecutive seasons (2015/16–2024/25): epidemiological trends, fatal case characteristics, and vaccination

Nadzor nad gripom u Autonomnoj pokrajini Vojvodini, Srbija, tokom deset uzastopnih sezona (2015/16–2024/25): epidemiološki trendovi, karakteristike smrtnih ishoda i vakcinacija

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Abstract

Background/Aim. Influenza represents a significant public health concern. The aim of this study was to analyze indicators of influenza activity over ten consecutive seasons in the Autonomous Province of Vojvodina (APV), Serbia, including age-specific and weekly distribution, and characteristics of influenza-related mortality. In addition, influenza vaccination trends in APV over the past ten seasons were assessed. **Methods.** A retrospective study was conducted using data from sentinel surveillance of influenza-like illness (ILI) and acute respiratory infections (ARI) among outpatients, as well as severe acute respiratory infection (SARI) and acute respiratory distress syndrome (ARDS) among hospitalized patients with fatal outcomes, along with data on the number of individuals vaccinated against influenza in APV. Laboratory confirmation of influenza-related deaths was performed at the Virology Center, Institute of Public Health of Vojvodina, Novi Sad, Serbia. **Results.** ILI and ARI incidence varied seasonally, peaking typically between surveillance weeks 5 and 10. The 2020/21 season showed markedly low influenza virus activity, while the 2021/22–2024/25 seasons displayed patterns typical of influenza seasons. Throughout the surveillance period, children aged 0–4 and 5–14 exhibited the highest incidence rates. Over the ten seasons, 202 laboratory-confirmed influenza-associated deaths were recorded, predominantly among men aged 24–64 years, occurring mainly during winter months. None of the patients had been vaccinated. The most common influenza A subtype was A (H1N1)pdm09 (59.4%). Fatal cases were almost evenly distributed between SARI (49.0%) and ARDS (51.0%), with ARDS being more common in adults aged 24–64 years. No statistically significant difference in the distribution of fatal outcomes was observed between the pre- and post-coronavirus disease 2019 periods (p = 0.6870). Influenza vaccination coverage among high-risk populations remained low, peaking at 17.5% among individuals ≥ 65 years in the 2020/21 season. Among healthcare workers, coverage reached over 40.0% in 2020/21 but declined to 20.0–25.0% in the subsequent seasons. **Conclusion**. Integrated sentinel and hospital-based surveillance encompasses monitoring of outpatient, severe, and fatal influenza cases. A significant increase in influenza vaccination coverage among high-risk groups could reduce hospitalization rates, the frequency of complications, and influenza-related deaths.

Key words:
covid-19; epidemiology; influenza, human; respiratory tract infections; serbia; vaccination; virology.

Apstrakt

Uvod/Cilj. Grip predstavlja značajan javnozdravstveni problem. Cilj rada bio je da se analiziraju indikatori aktivnosti virusa gripa tokom deset uzastopnih sezona u Autonomnoj Pokrajini Vojvodini (APV), Srbija, uključujući uzrasno-specifičnu i nedeljnu distribuciju i karakteristike smrtnih ishoda povezanih sa gripom. Osim toga, analizirani su i trendovi vakcinacije protiv gripa u APV tokom poslednjih deset sezona. **Metode**. Sprovedena je retrospektivna studija korišćenjem podataka iz sentinelnog nadzora nad oboljenjima sličnim gripu (*influenza-like illness* – ILI) i akutnim respiratornim infekcijama (*acute respiratory infections* – ARI) kod ambulantnih bolesnika, odnosno nad

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teškom akutnom respiratornom bolešću (*severe acute respiratory infection* – SARI) i akutnim respiratornim distres sindromom (*acute respiratory distress syndrome* – ARDS) kod hospitalizovanih bolesnika sa smrtnim ishodom, kao i podataka o broju osoba vakcinisanih protiv gripa u APV. Laboratorijska potvrda virusa gripa kod bolesnika sa smrtnim ishodom dobijena je u Centru za virusologiju Instituta za javno zdravlje Vojvodine, Novi Sad, Srbija. **Rezultati**. Stope incidencije ILI i ARI varirale su u zavisnosti od sezone, sa pikovima uglavnom između 5. i 10. nedelje nadzora. Sezona 2020/21 imala je značajno nisku aktivnost virusa gripa, dok su sezone 2021/22–2024/25 imale obrasce tipične za sezonu gripa. Tokom perioda nadzora, deca uzrasta 0–4 i 5–14 godina imala su najviše stope incidencije. Tokom deset sezona registrovana su 202 smrtna ishoda povezana sa laboratorijski potvrđenim gripom, uglavnom kod muškaraca uzrasta 24–64 godine, koja su se dogodila pretežno tokom zimskih meseci. Nijedan bolesnik nije bio vakcinisan. Najzastupljeniji podtip virusa gripa tipa A bio je A (H1N1)pdm09 (59,4%). Smrtni slučajevi bili su gotovo ravnomerno raspoređeni između dijagnoza SARI (49,0%) i ARDS (51,0%), pri čemu je ARDS bio češći kod odraslih starosti 24–64 godine. Nije uočena statistički značajna razlika u raspodeli smrtnih ishoda između perioda pre i posle pandemije izazvane koronavirusom 2019 (p = 0,6870). Obuhvat vakcinacijom protiv gripa visokorizične populacije ostao je nizak, dostižući maksimum od 17,5% kod osoba ≥ 65 godina u sezoni 2020/21. Među zdravstvenim radnicima, obuhvat je dostigao vrednost od preko 40,0% u sezoni 2020/21, ali je u narednim sezonama opao na 20,0–25,0%. **Zaključak**. Integrisani sentinelni i bolnički nadzor obuhvata nadzor nad ambulantnim, teškim slučajevima i smrtnim ishodima povezanim sa gripom. Značajno povećanje obuhvata imunizacijom protiv gripa u populacijama sa povećanim rizikom od obolevanja od gripa moglo bi smanjiti stope hospitalizacije, učestalost komplikacija i smrtnost povezanu sa virusom gripa.

Ključne reči:
covid-19; epidemiologija; grip; respiratorni trakt, infekcije; srbija; vakcinacija; virologija.

Introduction

Influenza remains a major global public health concern, contributing significantly to morbidity and mortality, particularly among young children, older adults, and individuals with underlying medical conditions [1, 2]. Seasonal influenza epidemics cause substantial strain on healthcare systems, with considerable year-to-year and regional variation in their intensity, timing, and age distribution [3]. Continuous influenza surveillance is crucial for understanding seasonal dynamics, guiding immunization policies, and evaluating the disease burden, particularly in the context of emerging respiratory threats [4–8].

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in early 2020 profoundly disrupted the epidemiology of other respiratory viruses, including influenza [9]. Non-pharmaceutical interventions such as school closures, mask mandates, physical distancing, remote working, and international travel restrictions resulted in historically low influenza activity during the 2020/21 season in many countries, including those in the European region [10–13]. In the aftermath of the pandemic, influenza activity gradually rebounded, although with atypical timing and intensity in some seasons [14].

The Autonomous Province of Vojvodina (APV), northern Serbia, has established an integrated system that combines sentinel surveillance of influenza-like illness (ILI) and acute respiratory infection (ARI) in outpatient settings, hospital-based surveillance of severe acute respiratory infection (SARI) and acute respiratory distress syndrome (ARDS), and virological testing of respiratory samples collected from influenza-suspected cases across the province. These surveillance systems enable comprehensive monitoring of influenza activity and disease burden and have been described in detail previously [15, 16].

In Serbia, influenza vaccination is mandatory for individuals older than 6 months with chronic conditions, pregnant women, adults aged over 65 years, family members of high-risk individuals, residents and staff of gerontological and social-health institutions, as well as for health-care workers (HCWs) with chronic illnesses, pregnant HCWs, and HCWs providing medical services to pregnant women or patients at high risk of complications [17–19].

The aim of this study was to analyze the weekly and age-specific ILI and ARI incidence, compare clinical and epidemiological features of influenza-related deaths in adults (24–64 vs. ≥ 65 years), and to describe the distribution of influenza vaccination over ten seasons (2015/16–2024/25) in APV.

Methods

This observational study was based on data collected through sentinel surveillance of ILI and ARI among outpatients, surveillance of hospitalized influenza patients with SARI and/or ARDS, and virological surveillance in APV, over ten consecutive influenza seasons (from calendar week 40 to week 20 of the following year, i.e., from the first week of October to the fourth week of May). During the study period (2015/16 to 2024/25), we analyzed weekly seasonal and age-specific trends of ILI and ARI, and compared the characteristics of fatal influenza cases between individuals aged 24–64 years and those aged ≥ 65 years. We applied the same methodology for sentinel and hospital-based surveillance of ILI, ARI, SARI, and ARDS as previously reported [15, 16]. Sentinel surveillance, in line with World Health Organization (WHO) and national recommendations, was conducted in all primary health care centers of APV and covered five age groups (0–4, 5–14, 15–29, 30–64, and ≥ 65 years). Outpatient cases (ILI and ARI) were reported weekly by sentinel general practitioners and pediatricians. Hospital surveillance involved daily reporting of all SARI and ARDS cases from acute care hospitals, applying WHO case definitions. Laboratory confirmation of influenza was performed using real-time polymerase chain reaction–according to the protocols of the United States Centers for Disease Control and Prevention at the Center for Virology, Institute of Public Health of Vojvodina (IPHV), Novi Sad, Serbia [15, 16, 20].

The number of persons vaccinated against influenza, stratified by age groups within high-risk populations and by HCW status, was collected annually through collaboration between IPHV and the six district Institutes of Public Health located in Subotica, Sombor, Pančevo, Sremska Mitrovica, Kikinda, and Zrenjanin, Serbia.

Statistical analysis

Weekly incidence rates of ILI and ARI were calculated *per* 100,000 inhabitants, and age-specific weekly rates were estimated for the five previously defined age groups. The epidemic threshold (baseline) of 246.3 cases *per* 100,000 inhabitants, representing the medium level of influenza activity, was defined based on weekly ILI incidence rates from five pre-pandemic (2004/05–2008/09) sentinel seasons in APV [20].

Comparisons between the 24–64-year and ≥ 65-year age groups were performed by gender, place of residence, month of death notification, number of comorbidities, influenza virus type, clinical diagnosis (SARI or ARDS), and observation period (seasons 2015/16–2019/20 vs. 2020/21–2024/25), using the Chi-squared or Fisher's exact test, as appropriate. For continuous variables–specifically, the number of days from symptom onset to laboratory confirmation, and from symptom onset to death–Student's *t*-test was applied. A *p*-value < 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS software, version 21 (IBM Corp., Armonk, NY, USA).

Ethical considerations

Data from this retrospective study were obtained from surveillance conducted at the Center for Disease Control and Prevention of the IPHV, Novi Sad, which coordinates influenza surveillance across the entire territory of APV. As this is part of routine surveillance practice established for many years [15, 16, 20], approval from the Ethics Committee was not required in Serbia. All patient data were anonymized and de-identified in accordance with ethical standards.

Results

Influenza-like illness

Over ten consecutive influenza seasons (2015/16 to 2024/25), weekly incidence rates of ILI in APV displayed substantial seasonal variability, with epidemic activity usually occurring between weeks 5 and 10. The epidemic threshold (baseline: 246.3 cases *per* 100,000 inhabitants) was surpassed in all pre-coronavirus disease 2019 (COVID-19) seasons (2015/16–2019/20) and in the recent three influenza seasons (2022/23–2024/25). Before the COVID-19 pandemic, seasonal peaks were typically observed between weeks 5 and 7, with exceptionally high activity in 2019/20 (peak 881.1 *per* 100,000 in week 6) and other intense waves in 2017/18 (500.5 *per* 100,000, week 5) and 2018/19 (497.1 *per* 100,000, week 7). In contrast, ILI incidence remained far below the epidemic threshold throughout 2020/21, coinciding with the onset of the COVID-19 pandemic. The 2021/22 season showed a delayed and more gradual pattern compared with pre-pandemic years, with incidence peaking later than usual in weeks 11–13 (maximum 249.1 *per* 100,000) and only approaching but not exceeding the epidemic threshold. In subsequent seasons, influenza activity rebounded. In 2022/23, incidence peaked at 343.6 *per* 100,000 (week 6), while in 2023/24 a higher peak of 422.0 *per* 100,000 was recorded (week 7). Preliminary 2024/25 data indicate sustained transmission, with the epidemic threshold exceeded from week 6 and a peak of 273.6 *per* 100,000 in week 8 (Figure 1).

Across all seasons, the highest incidence rates of ILI were consistently observed in children aged 0–4 and 5–14 years, with peak weekly rates exceeding 700–1,000 *per* 100,000 inhabitants during several weeks (e.g., weeks 6–8 in 2015/16, 2017/18, 2018/19, and 2019/20). Adolescents and young adults (15–29 years) exhibited intermediate rates, while the lowest incidence was observed among individuals aged ≥ 65 years, although substantial increases were noted during high-intensity seasons (e.g., 2022/23 and 2023/24). The timing and magnitude of seasonal peaks varied between seasons. Several seasons (e.g., 2017/18, 2018/19, and 2019/20) showed sharp, early peaks dominated by pediatric age groups, whereas others, such as 2021/22, had later peaks extending into weeks 12–15, coinciding with broader age distribution of cases. The 2020/21 season showed markedly attenuated ILI activity across all age groups (Figure 2).

Acute respiratory infections

From the 2015/16 through the ongoing 2024/25 respiratory seasons, weekly incidence rates of ARI in APV fluctuated substantially, with clear seasonal peaks each year, typically between epidemiological weeks 4 and 10. Incidence rates ranged from below 200 *per* 100,000 inhabitants during inter-epidemic weeks to over 2,500 *per* 100,000 inhabitants during the peak of ARI activity. The highest peak across the surveillance period was observed in the 2022/23 season (week 6), reaching 2,703 *per* 100,000 inhabitants. Other notable high-intensity seasons included 2017/18 (peak 2,465 *per* 100,000 in week 5), 2018/19 (2,060 *per* 100,000 in week 5), and 2019/20 (2,183 *per* 100,000 in week 5). By contrast, the 2020/21 season (coinciding with the start of the COVID-19 pandemic) showed markedly lower activity, with weekly rates remaining below 1,100 *per* 100,000 inhabitants. Seasonal peaks tended to occur in February (weeks 5–7) in most pre-pandemic seasons, whereas post-2020 fluctuations

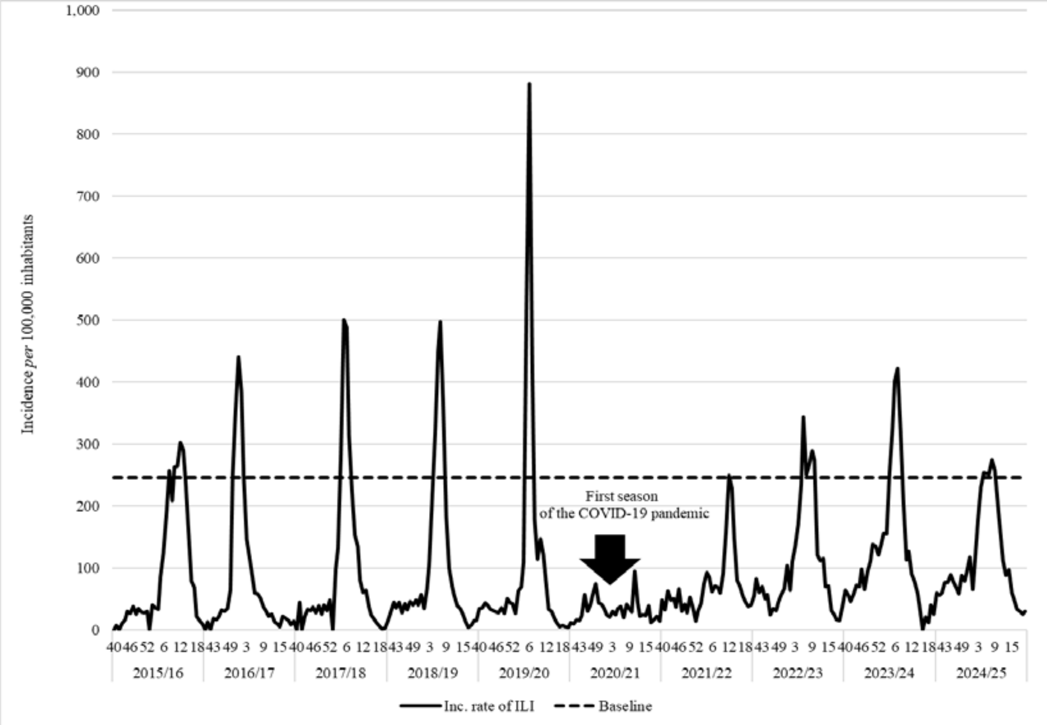

Fig. 1 – Weekly (October–May) incidence of influenza-like illness (ILI) *per* 100,000 inhabitants in the Autonomous Province of Vojvodina, Serbia, 2015/16–2024/25 seasons. COVID-19 – coronavirus disease 2019; Inc. – incidence.

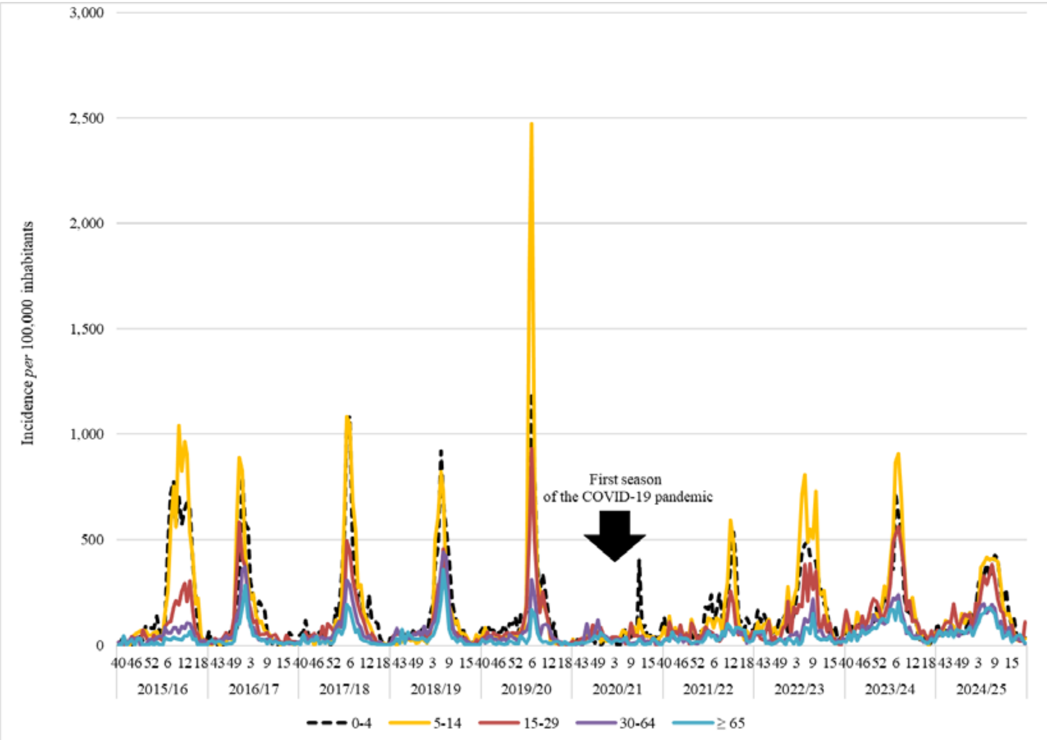

Fig. 2 – Weekly (October–May) age-specific incidence of influenza-like illness *per* 100,000 inhabitants in the Autonomous Province of Vojvodina, Serbia, 2015/16–2024/25 seasons. COVID-19 – coronavirus disease 2019.

demonstrated more variable patterns. The 2021/22 season exhibited a prolonged late peak, extending from weeks 10 to 13 with weekly rates above 1,800 *per* 100,000 inhabitants, while 2023/24 had an earlier and sharper peak in weeks 4–6 (maximum 2,396 *per* 100,000 in week 5). The current 2024/25 season shows a moderate trajectory, with incidence peaking thus far at 1,655 *per* 100,000 inhabitants (week 6) (Figure 3).

Weekly age-specific incidence rates of ARI *per* 100,000 inhabitants in APV showed that children aged 0–4 years and school-aged children (5–14 years) consistently exhibited the highest weekly ARI incidence, frequently exceeding 4,000–6,000 cases *per* 100,000 inhabitants during seasonal peaks. Adults aged 15–29 years showed intermediate incidence rates, whereas adults aged 30–64 years and those ≥ 65 years had substantially lower rates, typically below 1,000 cases *per* 100,000 inhabitants except during major peaks. Marked inter-seasonal variability was observed. Peak activity commonly occurred between weeks 5 and 10. However, the 2021/22 season demonstrated a delayed peak compared with pre-COVID-19 seasons, while the 2020/21 season recorded notably lower incidence across all age groups (Figure 4).

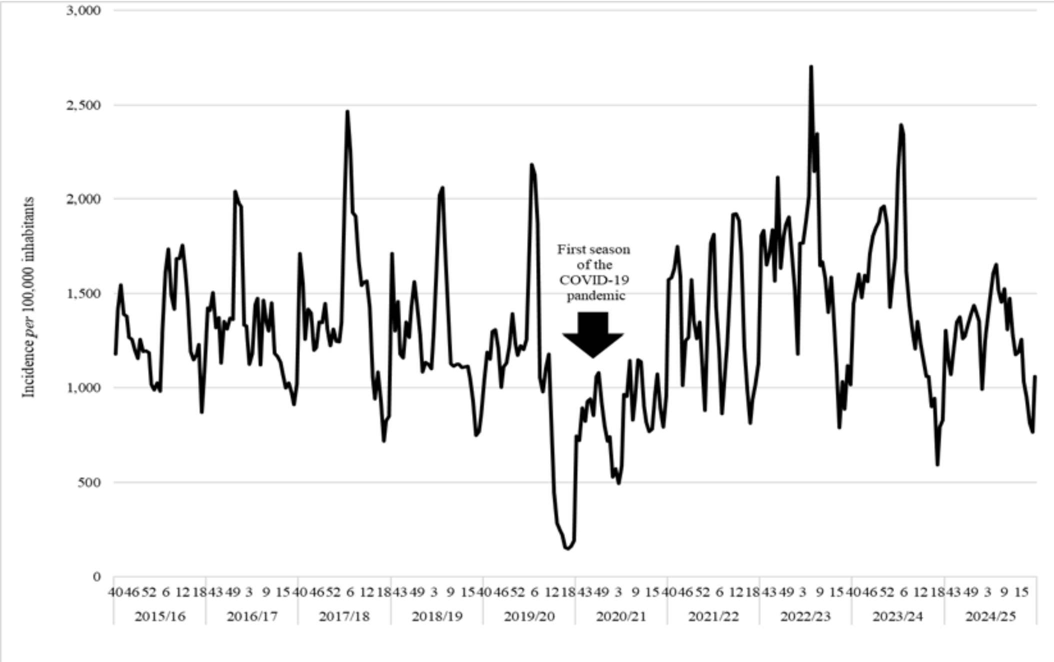

Fig. 3 – Weekly (October–May) incidence of acute respiratory infections *per* 100,000 inhabitants in the Autonomous Province of Vojvodina, Serbia, 2015/16–2024/25 seasons. COVID-19 – coronavirus disease 2019.

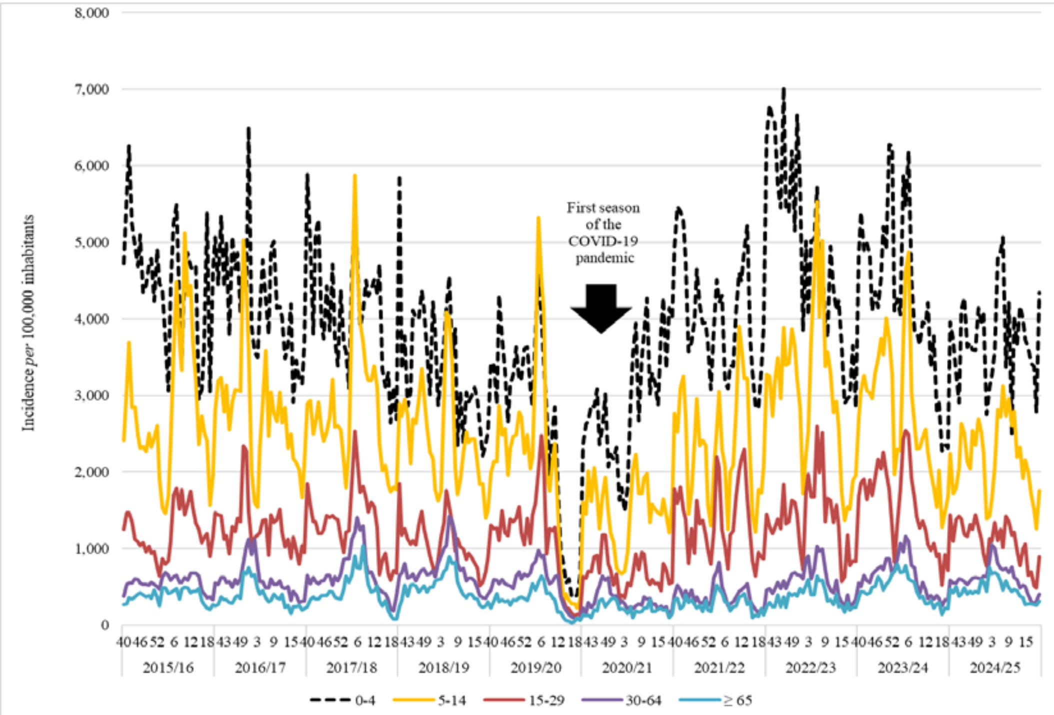

Fig. 4 – Weekly (October–May) age-specific incidence of acute respiratory infections *per* 100,000 inhabitants in the Autonomous Province of Vojvodina, Serbia, 2015/16–2024/25 seasons. COVID-19 – coronavirus disease 2019.

Laboratory-confirmed influenza-associated deaths

Between the 2015/16 and 2024/25 influenza seasons, a total of 202 laboratory-confirmed influenza-associated deaths were reported in APV. The highest number of fatal cases was recorded during the 2018/19 season, with 57 (28.2% of all reported fatalities) deaths, followed by 37 (18.3%) deaths in the 2017/18 season, and 35 (17.3%) deaths in the 2019/20 season. In contrast, no influenza-related deaths were recorded during the 2020/21 season, which coincided with the first year of the COVID-19 pandemic (Figure 5).

None of the patients with fatal outcomes had received vaccination prior to influenza. Among the 202 laboratory-confirmed fatal influenza cases, 56.4% occurred in males. The proportion of male deaths was significantly higher among individuals aged 24–64 years (65.1%) compared to those aged ≥ 65 years (50.0%) (p = 0.0326). The majority of cases resided in urban areas (54.5%), with no significant difference in place of residence between the two age groups. The mean time from symptom onset to laboratory confirmation of influenza was similar across age groups (overall mean: 3.0 ± 2.9 days; p = 0.9145). Likewise, the average duration from illness onset to death did not differ significantly across age groups (mean: 12.5 ± 10.2 days; p = 0.7277). Most deaths occurred during the winter months, with the highest number reported in February (46.5%), followed by January (25.2%) and March (19.4%), but the monthly distribution of deaths did not differ significantly between the two age groups (p = 0.7199). Regarding comorbidities, individuals aged ≥ 65 years were more likely to have multiple underlying conditions, with only 0.9% having no comorbidities, compared to 7.0% in the 24–64 age group (p = 0.0292). Over ten consecutive influenza seasons, influenza A(H1N1)pdm09 was the most frequently identified virus type (59.4%), with a similar distribution across two age groups (p = 0.7056). Other detected types included A(H3N2) (19.4%), influenza B (15.3%) and unsubtyped influenza A (5.9%). Regarding clinical presentation, 51.0% of patients were diagnosed with ARDS, which was more frequent in the 24–64 age group than in older adults (58.1% vs. 45.7%), although the difference was not statistically significant (p = 0.0808). When stratified by age and surveillance period, 84.9% of fatal cases aged 24–64 years and 82.8% of those aged ≥ 65 years occurred in the earlier period (2015/16–2019/20), with no statistically significant difference in the distribution of fatal cases between the two periods (p = 0.6870) (Table 1).

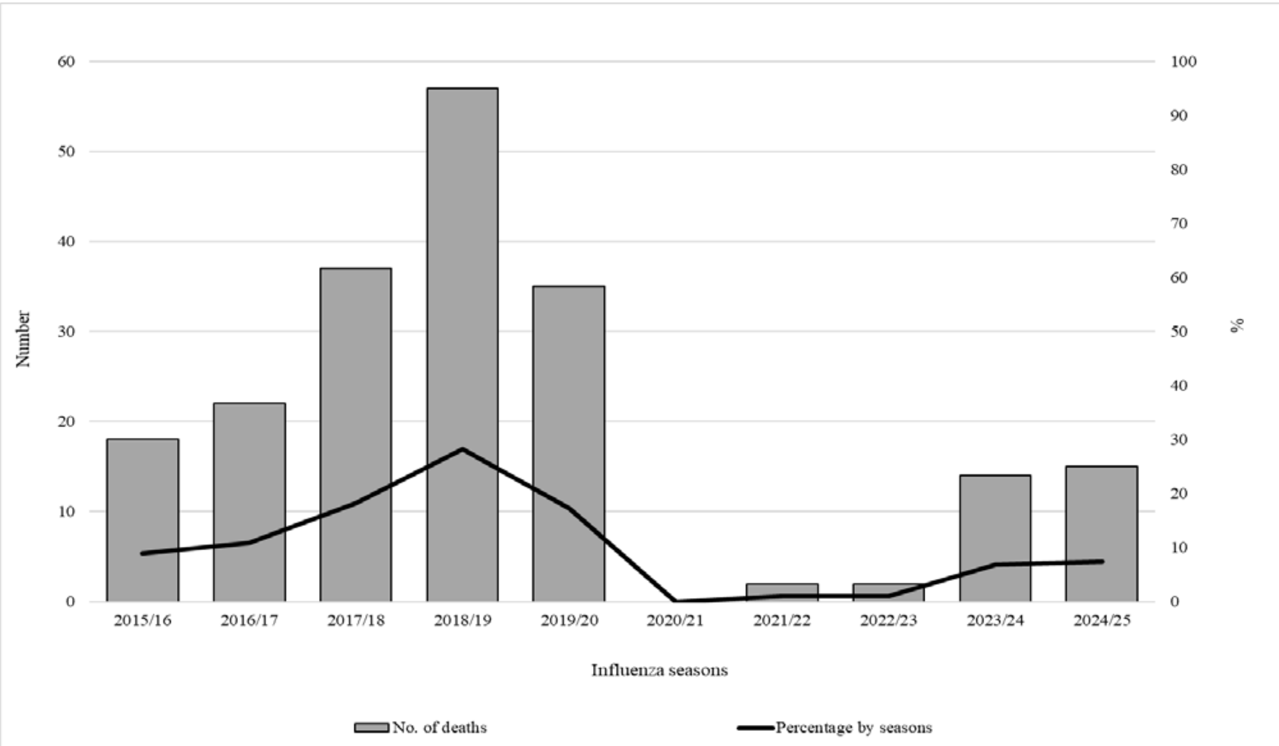

Fig. 5 – Influenza-associated deaths by years in the Autonomous Province of Vojvodina, Serbia, 2015/16–2024/25 seasons.
No. – number.

Table 1

Comparison of fatal influenza cases aged 24–64 and ≥ 65 years in the Autonomous Province of Vojvodina, Serbia, 2015/16–2024/25 seasons

Parameters	Fatal influenza cases			*p*-value
	total (n = 202)	24–64 years (n = 86)	≥ 65 years (n = 116)	
Gender				
male	114 (56.4)	56 (65.1)	58 (50.0)	**0.0326**
female	88 (43.6)	30 (34.9)	58 (50.0)	
Place of residence				
rural	92 (45.5)	41 (47.7)	51 (44.0)	0.6016
urban	110 (54.5)	45 (52.3)	65 (56.0)	
Days between onset and laboratory confirmation	3.0446 ± 2.8622	3.0698 ± 2.6112	3.0259 ± 3.0459	0.9145
Days between onset of illness and death	12.5347 ± 10.1722	12.2442 ± 9.2022	12.7500 ± 10.8699	0.7277
Month of death				
December	4 (2.0)	2 (2.3)	2 (1.7)	0.7199
January	51 (25.2)	24 (27.9)	27 (23.3)	
February	94 (46.5)	34 (39.5)	60 (51.7)	
March	39 (19.4)	19 (22.2)	20 (17.3)	
April	14 (6.9)	7 (8.1)	7 (6.0)	
Number of comorbidities*				
0	7 (3.5)	6 (7.0)	1 (0.9)	**0.0292**
1	88 (43.5)	36 (41.9)	52 (44.8)	
2	67 (33.2)	33 (38.3)	34 (29.3)	
3	32 (15.8)	8 (9.3)	24 (20.7)	
> 3	8 (4.0)	3 (3.5)	5 (4.3)	
Type of influenza				
A non-subtyped	12 (5.9)	4 (4.7)	8 (6.9)	0.7056
A (H1N1)pdm09	120 (59.4)	55 (64.1)	65 (56.0)	
A (H3N2)	39 (19.4)	15 (17.4)	24 (20.7)	
B	31 (15.3)	12 (14.0)	19 (16.4)	
Diagnosis				
SARI	99 (49.0)	36 (41.9)	63 (54.3)	0.0808
ARDS	103 (51.0)	50 (58.1)	53 (45.7)	
Period				
2015/16–2019/20	169 (83.7)	73 (84.9)	96 (82.8)	0.6870
2020/21–2024/25	33 (16.3)	13 (15.1)	20 (17.2)	

SARI – severe acute respiratory infection; ARDS – acute respiratory distress syndrome; n – number.
All values are given as numbers (percentages) or mean ± standard deviation.
Values that differ significantly ($p < 0.05$) are marked in bold.
***Note*: * – included chronic cardiovascular, cerebrovascular, pulmonary, renal, and liver diseases, immunodeficiency (including malignancy and human immunodeficiency virus), diabetes, and obesity, as well as long-term smoking and alcohol consumption.**

Immunization against influenza

Between the 2015/16 and 2024/25 seasons, the number of persons vaccinated against influenza in APV ranged from 57,570 in 2015/16 to a peak of 108,374 in 2020/21, averaging 77,842 *per* season (Figure 6).

The majority of vaccinated persons were aged ≥ 65 years (ranging from 36,989 to 66,337 annually), followed by adults aged 20–64 years (19,001–40,814). The number of vaccinated children at high risk of complications was low: 5–19 years (ranging from 306 to 1,186) and 6 months–4 years (fewer than 180 in most seasons). A sharp increase occurred in 2020/21 during the COVID-19 pandemic, after which numbers declined but stayed above pre-2019/20 levels. More precisely, the highest vaccination uptake was observed among those aged ≥ 65 years (rising from 9.8% in 2015/16 to 17.5% in 2020/21, and later stabilizing at 14.0–16.0%). Adults aged 20–64 years had modest coverage (1.9–4.0%), while adolescents (5–19 years) and young children (6 months–4 years) remained below 0.5% (Figure 7).

Between 2015/16 and 2018/19, 4,000–5,000 HCWs were vaccinated annually, corresponding to 16.0–21.0% coverage. A marked increase was observed in 2019/20 (≈ 8,900 vaccinated; 32.1% coverage), with a peak in 2020/21 when over 11,000 HCWs received the vaccine, reaching more than 40.0% coverage. After this peak, uptake declined sharply to about 20.0% in the 2021/22 season, and then fluctuated between 21.0% and 25.0% (5,400–6,800 vaccinated annually) during the 2022/23–2024/25 seasons (Figure 8).

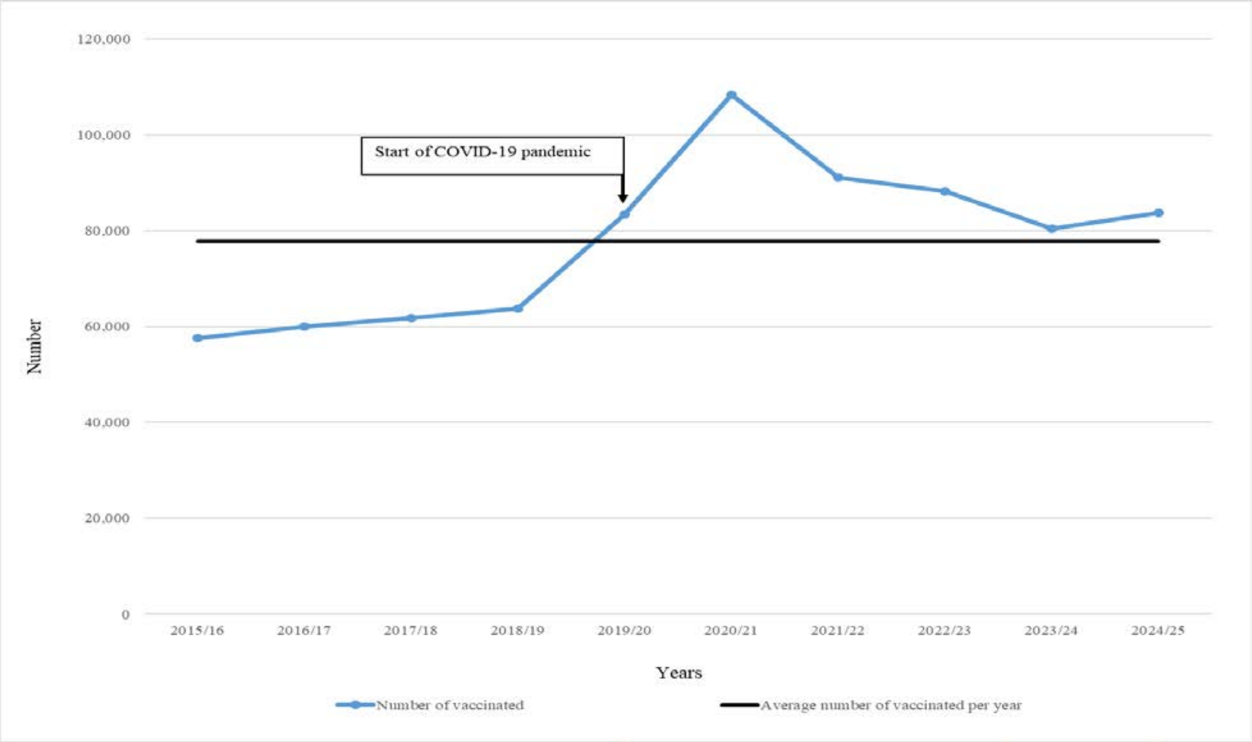

Fig. 6 – Number of high-risk individuals vaccinated against influenza in the Autonomous Province of Vojvodina, Serbia, 2015/16–2024/25 seasons.
COVID-19 – coronavirus disease 2019.

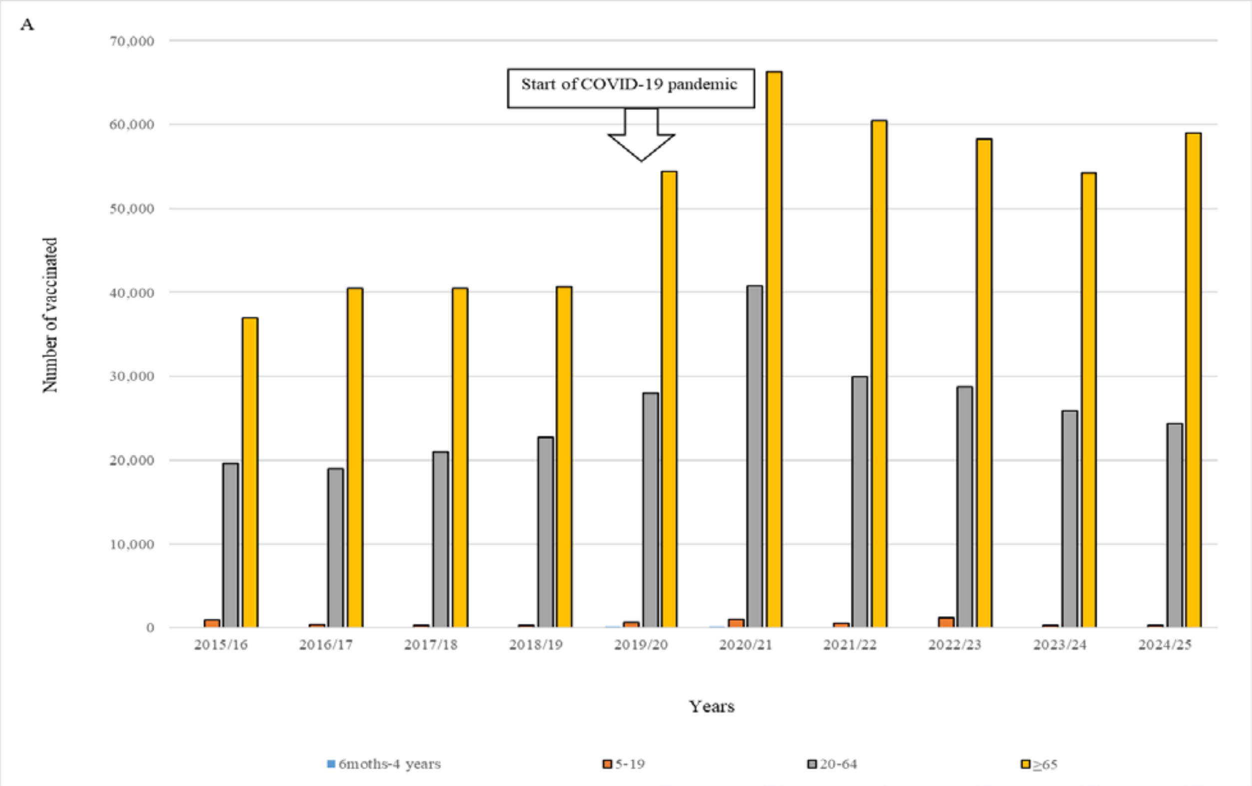

Fig. 7 – Number (A) and percentage (B) of high-risk individuals vaccinated against influenza by age groups in the Autonomous Province of Vojvodina, Serbia, 2015/16–2024/25 seasons.
COVID-19 – coronavirus disease 2019.

***Note*: Fig. 7 continued on next page.**

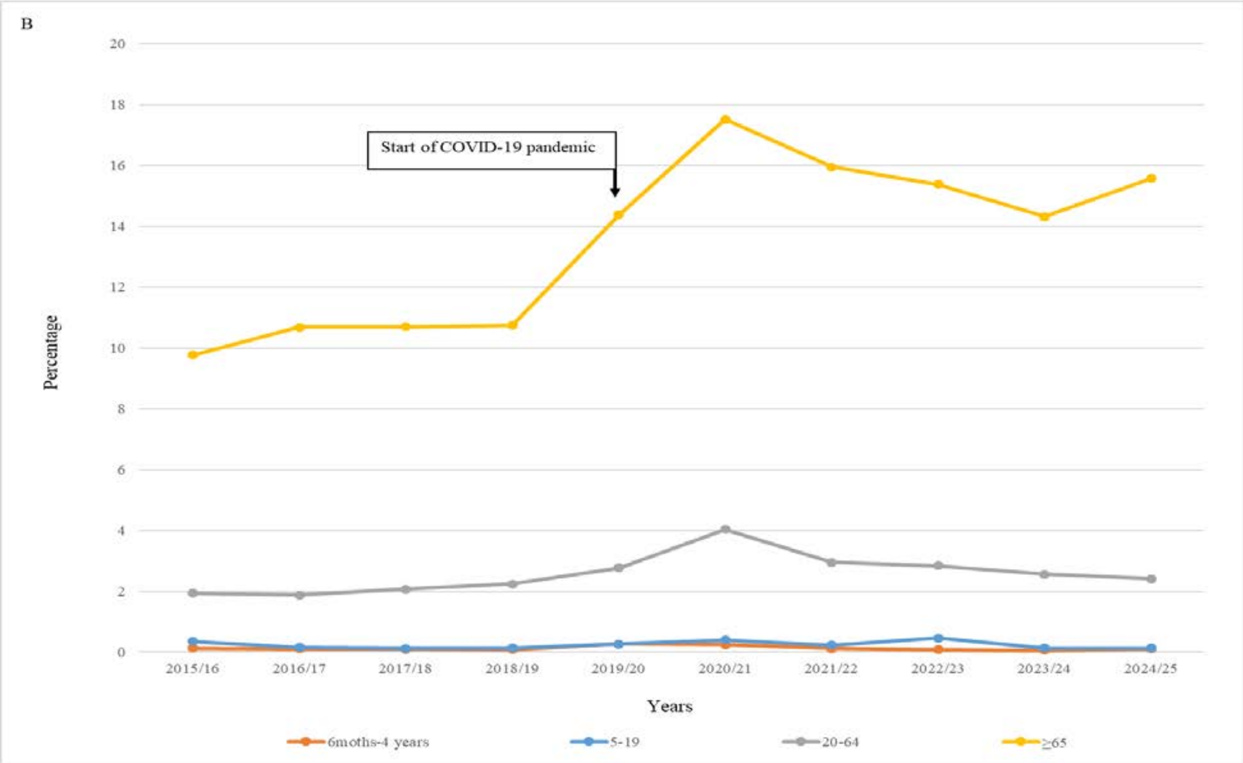

Fig. 7 (Continued) – Number (A) and percentage (B) of high-risk individuals vaccinated against influenza by age groups in the Autonomous Province of Vojvodina, Serbia, 2015/16–2024/25 seasons. COVID-19 – coronavirus disease 2019.

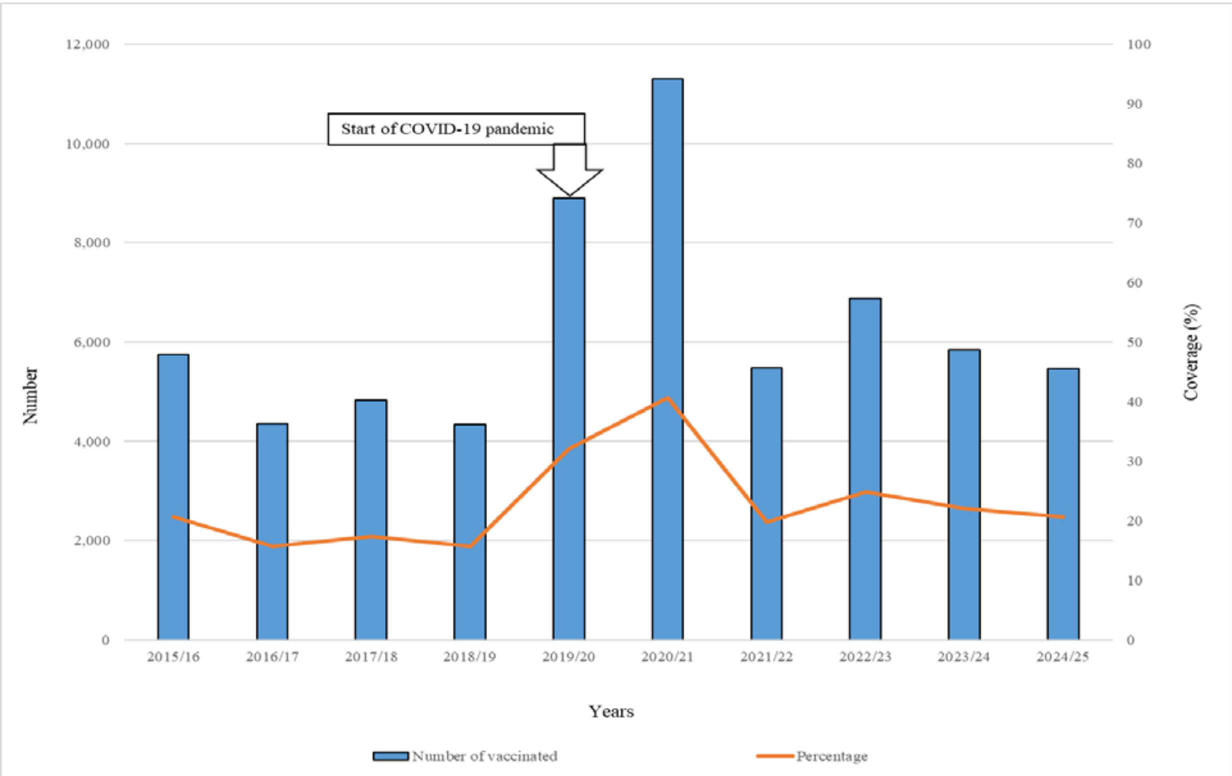

Fig. 8 – Coverage of immunization against influenza among healthcare workers in the Autonomous Province of Vojvodina, Serbia, 2015/16–2024/25 seasons. COVID-19 – coronavirus disease 2019.

Discussion

Building on previously published results of influenza surveillance in APV over five seasons (2010/11–2014/15) [15, 16], this study provides a comprehensive overview of influenza activity in the province over the subsequent ten consecutive seasons (2015/16–2024/25), encompassing both the pre- and post-COVID-19 pandemic periods.

As observed across European countries and globally, influenza activity was virtually absent during the 2020/21 season [9–12]. For instance, in the WHO European Region, the epidemic threshold of 10% positivity among tested samples was not reached during the 2020/21 influenza season, and detections of seasonal influenza, as well as ILI and ARI cases, were lower than those typically observed even during regular summer months [21]. The widespread implementation of non-pharmaceutical interventions against SARS-CoV-2, along with virus competition and the lower R_0 of influenza compared to SARS-CoV-2, likely contributed to the pronounced reduction in influenza circulation [22].

Sentinel surveillance is considered the gold standard for monitoring influenza activity, providing high-quality data from a defined outpatient population (ILI or ARI), together with virus characterization analyses [21]. Based on our sentinel surveillance results, we found that, for reasons yet unexplained, the highest weekly ILI incidence rates in APV over ten consecutive seasons were recorded in the season preceding the COVID-19 pandemic. Our results also showed that, across ten consecutive seasons, the highest weekly peak incidence was usually recorded between weeks 5 and 10. Excluding the 2020/21 influenza season (the beginning of the COVID-19 pandemic), atypical influenza dynamics persisted into 2021/22, characterized by delayed and attenuated epidemic waves, with incidence peaking later than usual, between weeks 11 and 13–a pattern also observed in other countries, and explained by the withdrawal of SARS-CoV-2 from circulation, after which influenza virus re-emerged [23, 24]. However, from 2022/23 onwards, seasonal influenza activity began returning to pre-pandemic levels in both timing and intensity, although some variation in peak magnitude and age distribution remained [25].

The highest incidence of ILI and ARI consistently occurred in younger populations, particularly among those aged 0–4 and 5–14 years, underscoring their role as key drivers of influenza virus transmission. These findings are consistent with reports from other European surveillance networks and are widely recognized in the literature [25–27]. In contrast, individuals aged ≥ 65 years showed lower incidence rates of both ILI and ARI but accounted for a substantial proportion of severe and fatal outcomes, particularly during high-intensity seasons.

Our results also showed that ARI incidence rates were highest in the 2017/18 season, but substantially higher in the post-COVID-19 period, specifically during the 2022/23 and 2023/24 seasons. The increased frequency of ARI in the post-COVID period may be attributed to the resurgence of respiratory viruses, not only influenza, which had been suppressed during the 2020–2022 period. Unlike rhinoviruses and enteroviruses, which persisted despite interventions such as masking and school closures–likely due to their greater surface stability and alternative transmission routes–many other respiratory viruses notably increased following the mitigation of the COVID-19 pandemic [28–32].

During 2020/21, ILI and ARI incidence declined in all age groups, but the highest rates were recorded in children aged 0–4 years, probably reflecting continued kindergarten attendance during the COVID-19 pandemic. The predominance of ILI in school-aged children (5–14 years)–a group considered the main reservoir for seasonal influenza transmission [30] compared with preschool-aged children (0–4 years)–was first observed at the end of the 2021/22 influenza season, coinciding with the re-emergence of seasonal influenza, and persisted until the end of the study period (2024/25 season).

Over the ten-season period, 202 laboratory-confirmed influenza-associated deaths were recorded. The highest number of fatal cases occurred over three consecutive seasons (2017/18–2019/20), during which 64% of all fatal cases were recorded, coinciding with the highest ILI incidence observed across all seasons in APV. During the 2020/21 season, when ILI incidence was below baseline, no deaths attributable to influenza were reported.

Our analysis revealed a higher proportion of male deaths among adults aged 24–64 years compared to those aged ≥ 65 years. Although the reasons for these gender differences are not yet fully understood [33, 34], there is some evidence that estradiol is a potent anti-inflammatory hormone that reduces the severity of influenza A virus infection in females [35]. This may explain the pattern observed in our cohort aged 24–64 years, but not in those aged ≥ 65 years. The equal distribution of influenza-related fatal cases among individuals aged ≥ 65 years, regardless of gender, may be explained by immunosenescence associated with increasing age and reduced physiological resilience, which together impair the ability to mount an effective immune response and increase the risk of complicated clinical forms of influenza [1–3, 8, 14, 25, 26].

Although not statistically significant, we observed a slight predominance of urban residence among fatal cases compared to rural areas, which aligns with known patterns of influenza transmission in densely populated regions [36].

We found that time intervals from symptom onset of influenza to laboratory confirmation and to death were similar across the 24–64 and ≥ 65-year age groups, suggesting comparable disease progression once severe illness developed. Although data on outcome severity and length of hospital stay are available [37–39], no evidence was found to support uniform disease progression across these two age groups, suggesting this warrants further investigation. The reasons for this are likely related to the nearly even distribution of comorbidities across both age groups studied, except for the presence of three concurrent comorbidities, which were significantly more frequent among influenza-hospitalized patients aged ≥ 65 years. The impact of comorbidities on influenza outcomes has been well described previously [40–43].

During the study period, almost 60% of all fatal cases were attributed to influenza A(H1N1)pdm09. The predominance of A(H1N1)pdm09 among fatal cases, with a similar distribution across age groups, reflects circulating strain patterns reported across Europe and globally in recent seasons [5, 44]. We also found that clinical presentations (SARI or ARDS) in fatal cases were nearly evenly distributed, with no significant trend toward more frequent ARDS diagnoses among younger adults, a finding consistent with previous studies [45, 46]. Due to the absence of notable influenza activity during the COVID-19 period, most fatal cases (84%) occurred in earlier observed seasons (2015/16–2019/20). However, no significant shifts in the distribution of fatal cases between the two age groups were observed over time, indicating stable fatality patterns despite fluctuations in influenza activity and public health interventions.

Public interest in influenza vaccination rose markedly immediately before and during the onset of the COVID-19 pandemic. In APV, during the October–November 2020 period, all influenza vaccine doses from the first distribution tranche in primary care were rapidly administered, reflecting heightened demand. However, additional vaccine supplies were delayed until late 2020, by which time interest had already started to decline [47].

The Spanish nationwide ENE-COVID study, involving nearly 29,000 adults from established risk groups, showed a marked increase in influenza vaccination coverage during the first year of the COVID-19 pandemic – from 31% in 2019 to almost 47% in 2020. The largest gains were among older adults (from 58% to 75%) and HCWs (over 20 percentage points). Only the ≥ 65-year group reached the national target, highlighting persistent gaps in other priority groups. These findings indicate that the COVID-19 pandemic boosted influenza vaccination, but structural and behavioral barriers remain, emphasizing the need for targeted strategies to further improve uptake [48].

A recent multi-country analysis from France, Italy, Spain, and the United Kingdom showed that current influenza vaccination programs, though below the WHO 75% target, prevent substantial morbidity, mortality, and healthcare costs, particularly among older adults and those with chronic conditions. In 2021/22, coverage ranged from 44% to 65%, averting an estimated 1.9 million cases and 38,000 deaths. Achieving the target could prevent nearly one million additional cases, highlighting both the value of vaccination and the need for reinforced strategies to close persistent gaps in high-risk groups [49].

Despite being mandatory, influenza immunization coverage among HCWs in APV remained suboptimal throughout the study period. Coverage rose substantially during the first pandemic year, peaking at 40.7% in 2020/21– the highest observed in the study period. This surge likely reflects a combination of pandemic-related risk perception and prior educational initiatives on the importance of influenza vaccination, conducted in 2019 across several tertiary healthcare institutions in APV, coinciding with the introduction of the quadrivalent influenza vaccine in Serbia. However, the absence of high-intensity influenza virus circulation during 2019–2021 likely reduced perceived risk, and vaccination uptake subsequently reverted to pre-pandemic levels in APV, despite influenza re-emerging from 2021/22 onwards at intensities typical of the pre-COVID era. This pattern underscores the challenge of sustaining increased uptake once the acute sense of pandemic threat dissipates.

Comparable observations have been described in other regions. A three-year evaluation of influenza vaccination among healthcare workers at a large university hospital in Pisa showed a surge from persistently low coverage, 10–12% in 2018/19–2019/20, to 39.3% in 2020/21, reflecting the COVID-19 pandemic's role as a catalyst. A survey indicated that 71% of respondents considered influenza vaccination more important in the pandemic context [50]. Similarly, a European review of 14 studies reported a 17–38% increase in influenza vaccine uptake among HCWs in 2020/21 compared with 2019/20, driven by COVID-19-related factors such as greater vaccine willingness, fear of infection, and symptom confusion. Despite these gains, hesitancy persists, suggesting that only mandatory vaccination policies may sustain high coverage in Europe [51].

Public health relevance

Our findings offer important insights into temporal trends and age-specific patterns of influenza activity before, during, and after the COVID-19 pandemic in a southeastern European context.

Similar to previously published experiences in influenza surveillance in APV [15, 16, 20, 30, 52–57], our results continually underscore the importance of maintaining resilient, comprehensive, multi-component surveillance systems that can detect atypical influenza seasons and inform timely public health responses. The consistent observation of high incidence of both ILI and ARI among children, alongside severe outcomes in older adults, supports the prioritization of these groups in seasonal vaccination programs and other preventive measures. In a typical influenza season, particularly school-aged children are most frequently affected and act as the main reservoirs for influenza transmission, while severe cases and deaths occur predominantly among older adults and individuals with comorbidities. This pattern becomes even more pronounced during seasons of higher ILI intensity. Furthermore, the disruption of typical seasonal dynamics during the pandemic underscores the need to better understand long-term shifts in population immunity and virus circulation. These findings may inform European-level strategies on pandemic preparedness, influenza vaccination, and the integration of respiratory virus surveillance.

Considering the number of individuals vaccinated against influenza in high-risk populations and among HCWs, our findings highlight the need for urgent interventions to increase influenza vaccine coverage.

Strengths and limitations of the study

This study has several notable strengths. Our study was based on integrated and continuous surveillance of ILI, ARI, and severe outcomes (SARI/ARDS) over a ten-season period in a defined geographical region. The use of standardized case definitions, consistent surveillance methodology, and age-specific incidence analysis allowed for robust monitoring of seasonal patterns and the impact of the COVID-19 pandemic. Additionally, the inclusion of virological data and fatal outcomes offers a comprehensive view of the influenza burden, going beyond outpatient trends.

However, several limitations should be acknowledged. First, although sentinel surveillance provides valuable trend data, it may underestimate the absolute number of influenza cases, particularly in populations with limited healthcare-seeking behavior. Second, hospital-based surveillance may miss severe cases who were not admitted or tested, especially during the peak of the COVID-19 pandemic when healthcare systems were under strain. Third, virological testing was not performed for all suspected cases, particularly in outpatient settings, and subtype identification was not always possible. Fourth, the lack of classification of patients by community- vs. healthcare-associated influenza may have introduced bias in the variable “Days between onset and laboratory confirmation”. Fifth, the lack of information on the number of days spent on mechanical ventilation for patients with ARDS may have influenced the calculated mean value of the variable “Days between onset of illness and death”. Lastly, except for the ≥ 65-year-old age group, we did not have access to the number (denominator) of patients with comorbidities for whom influenza vaccination is mandatory. However, given the exceptionally low percentages observed across age groups, it can be assumed that coverage in these risk groups was also extremely low. Although insufficient, influenza vaccination coverage was measured for all HCWs in institutions in APV. Therefore, it can be assumed that coverage is higher among HCWs working in departments with increased risk.

Despite the numerous limitations of this study, we believe they did not substantially affect the main findings of our research.

Conclusion

Our findings emphasize the need for preparedness for atypical influenza seasons in the post-COVID-19 era and targeted prevention strategies, including vaccination of high-risk groups. Children consistently experience the highest incidence, while most influenza-related deaths occur in seasons of peak influenza-like illness activity, with middle-aged men overrepresented among fatalities. Notably, none of the fatal cases were vaccinated, highlighting the urgent need to improve vaccine uptake through physician awareness and public health education. Persistently low vaccination coverage among high-risk individuals, contrasted with higher but unstable uptake among health-care workers, underscores the need for strengthened and sustainable immunization strategies. Temporary increases in coverage during the COVID-19 pandemic suggest that public awareness can improve uptake, but sustained efforts are essential.

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Received on September 1, 2025
Accepted on October 8, 2025
Online First December 2025