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Frequency and effects of seasonal flu vaccines on exacerbations of chronic obstructive pulmonary disease in Serbia

Učestalost i efekti vakcinacije protiv sezonskog gripa na pojavu egzacerbacija hronične opstruktivne bolesti pluća u Srbiji

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Abstract

Background/Aim. The influenza virus is often the cause of exacerbations among chronic obstructive pulmonary disease (COPD) patients, especially during the winter season. However, vaccination rates are still below recommended even in developed countries. The aim of the study was to determine the rates and examine the effectiveness of immunization against seasonal influenza in preventing exacerbations among COPD patients in Serbia. **Methods.** The prospective cohort study of stable COPD outpatients was conducted over three years (between October 1, 2014, and September 30, 2017) at the Polyclinic Department of Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia. The rates and effects of seasonal flu vaccination on COPD exacerbation rates were evaluated using univariate and multivariate logistic regression analysis, taking into account comorbidity, age, and body mass index (BMI). **Results.** The study included 840 patients. The flu vaccination rate was 37.1%. Exacerbations occurred more frequently in unvaccinated patients [176 (31.9%) vs. 375 (68.1%), $p = 0.043$]. In elderly vaccinated patients (≥ 65 years) there were fewer exacerbations compared to unvaccinated patients [89 (56.0%) vs. 188 (69.4%), $p = 0.005$]. Lower frequency of exacerbations was also observed in vaccinated patients with comorbidities [165 (61.1%) vs. 327 (69.4%), $p = 0.021$] and low BMI [27 (64.3%) vs. 78 (83.9%), $p = 0.011$]. Multivariate logistic regression analysis identified BMI < 21 kg/m^2 [relative risk (RR): 0.490; 95% confidence interval (CI): 0.318–0.758; $p = 0.001$] and heart failure (RR: 2.734; 95% CI: 1.121–6.669; $p = 0.027$) as independent predictors of COPD exacerbations. **Conclusion.** Immunization for seasonal influenza in Serbia is below recommended rates. Flu vaccination was associated with a significant reduction in COPD exacerbation rates, particularly in elderly patients and patients with heart failure and low BMI.

Key words:
influenza, human; influenza, vaccines; pulmonary disease, chronic obstructive; recurrence; risk assessment; serbia; vaccination.

Apstrakt

Uvod/Cilj. Egzacerbacije hronične opstruktivne bolesti pluća (HOBP) često nastaju usled infekcija virusima influence, posebno u zimskim mesecima. Međutim, i u razvijenim zemljama je stepen imunizacije i dalje niži od preporučenog. Cilj rada je bio da se utvrdi učestalost i efektivnost imunizacije protiv sezonskog gripa u cilju prevencije egzacerbacija kod bolesnika sa hroničnom opstruktivnom bolešću pluća (HOBP) u Srbiji. **Metode.** Prospektivna kohortna studija sprovedena je kod ambulantnih bolesnika sa HOBP, lečenih u periodu od 1.10.2014. do 30.09.2017. u Polikliničkoj službi Instituta za plućne bolesti Vojvodine, Sremska Kamenica. Povezanost vakcinacije i egzacerbacija HOBP, ali i komorbiditeta, starosti i indeksa telesna mase (*body mass index* - BMI), ispitivana je pomoću univarijantne i multivarijantne logističke regresione analize. **Rezultati.** Studijom su bila obuhvaćena 840 bolesnika. Protiv sezonskog gripa vakcinisano je 37,1% bolesnika. Egzacerbacije HOBP bile su češće kod nevakcinisanih bolesnika [176 (31,9%) vs. 375 (68,1%), $p = 0,043$]. Stariji, vakcinisani bolesnici (≥ 65 godina), imali su manje egzacerbacija u odnosu na nevakcinisane [89 (56,0%) vs. 188 (69,4%), $p = 0,005$]. Manje egzacerbacija je potvrđeno u grupi vakcinisanih bolesnika sa komorbiditetima [165 (61,1%) vs. 327 (69,4%), $p = 0,021$] i niskim BMI [27 (64,3) vs. 78 (83,9%), $p = 0,011$]. U multivarijantnoj analizi nezavisni prediktori pojave egzacerbacije su bili BMI > 21 kg/m^2 [relativni rizik (RR): 0,490; 95% interval poverenja (CI): 0,318–0,758; $p = 0.001$] i srčana slabost (RR: 2,734; 95% CI: 1,121–6,669; $p = 0.027$). **Zaključak.** Imunizacija protiv sezonskog gripa u Srbiji je i dalje ispod preporučenog nivoa.

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Vakcinacija protiv sezonskog gripa značajno redukuje egzacerbacije među HOBP pacijentima, posebno kod starijih sa srčanom slabošću i niskim BMI.

Ključne reči:
grip; grip, vakcina; pluća, opstruktivne bolesti, hornične; recidiv; rizik, procena; srbija; vakcinacija.

Introduction

Chronic obstructive pulmonary disease (COPD) is a significant sociomedical burden for both the patient and the society. It is estimated that 11–12% of the world population suffers from COPD [1, 2]. The more frequent exacerbations, the quicker the progression of the disease. The exacerbations are followed by a decrease in the quality of life, an increase in the number of hospitalizations, and mortality [3].

Viruses account for up to 50% of COPD exacerbations and the influenza virus for up to 28% of seasonal viruses (winter months) [4–7]. The World Health Organization (WHO) and European Center for Disease Prevention and Control (ECDC), Centers for Disease Control and Prevention (CDC) of the United States (US), as well as many national guides, recommend that patients with COPD undergo immunization for influenza (Evidence level A, Recommendation degree 1) [8, 9]. Vaccination against influenza leads to a reduction in viral infections by 60%, hospitalizations up to 40%, and a reduction in the occurrence of pneumonia [10–12]. Thus, the flu vaccination is recommended for all patients over 65 years of age and for the chronically ill [13, 14]. The aim of the European Union (EU) is to vaccinate 70% of patients with chronic diseases. From 2012–2016, the number of those vaccinated averaged 45%, and in the US, around 40% [15, 16].

The effects of seasonal flu vaccination among COPD patients have been demonstrated in most of the studies coming from highly-developed countries as opposed to low or middle-income countries. The vaccination rates and effects of vaccination in these settings remain largely unknown even though these countries face a high COPD burden due to high smoking prevalence and the fact that simple and inexpensive interventions such as vaccination may have a large impact on patients' health.

The aim of this study was to examine the frequency and effectiveness of vaccination against seasonal flu among COPD patients in Serbia. More specifically, we aimed to determine whether the flu vaccine reduces COPD exacerbation rates. Additionally, we examined the influence of patient-related factors such as age, comorbidities, and body mass index (BMI) in relation to the vaccination status on reducing COPD exacerbations.

Methods

Study design and population

This prospective cohort study was conducted over three years, and it included consecutive ambulatory patients with COPD (October 1, 2014 – September 30, 2017) at the Polyclinic for Pulmonary Diseases, Institute for Pulmonary Diseases of Vojvodina (IPDV) in Sremska Kamenica, Serbia. The Institute is a tertiary institution in Vojvodina (a northern province in Serbia) and covers a population of approximately 1.9 million (21.56% of the total population of the Republic of Serbia). The Polyclinic Department of the IPDV is a major outpatient clinic for the municipality of Novi Sad with surrounding settlements, covering almost 400,000 inhabitants.

The criteria for being included in the study were the following: patients over 40 years of age, established COPD diagnosis (based on a post-bronchodilator forced expiratory volume in the first second/forced vital capacity – FEV1/FVC ratio of < 0.70) [1] for at least one year, and being in the stable phase of the diseases (no systemic use of corticosteroid therapy or respiratory infection within 6 weeks prior to the study and no change in current medications). Patients who were suffering from cancer within the 5-year period prior to the study were excluded from it. Basic demographics data, comorbidities, and data regarding COPD exacerbations in the previous year were collected from the patients' medical files. The demographic data included gender, age, smoking habits (packs per year), and BMI.

At the beginning of the study, the patients were divided into two groups according to the immunization status against seasonal flu and followed for a one-year study period. Vaccination status and comorbidities were obtained from patients' files and medical history at the IPDV but were also given by the patients. The patients' vaccination status for the current year was collected. All the patients were vaccinated during the standard vaccination season (October-January) [15, 16]. Vaccinations were performed by the patients' general practitioners in their local health centers. The major outcomes were moderate/severe exacerbations during the one-year follow-up.

A patient was considered to have a moderate COPD exacerbation if treated with systemic corticosteroids or antibiotics [17]. Severe COPD exacerbations were defined as the need for hospitalization or evaluation in the emergency department [17]. We also analyzed whether vaccination influenced the stability of COPD groups according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) ABCD classification of COPD [1] over a one-year period.

Ethics committee approval

All research procedures were in accordance with the ethical standards of the Institute where the research took place, following good clinical practices and the the Helsinki Committee Declaration and its later amendments or

comparable ethical standards. The research was approved by the IPDV Ethics Committee.

Statistical analysis

Descriptive statistics were generated for all study variables, including mean and standard deviation (SD) for continuous variables and relative frequencies for categorical variables. The χ^2 test was used to determine whether there was a significant difference between the expected frequencies and the observed frequencies in one or more categories. The predictive values of evaluated variables for COPD exacerbations were evaluated with univariate and multivariate logistic regression analysis. All statistically significant predictors in univariate analysis were included in multivariate logistic regression analysis. All probability values were calculated by assuming a 2-tailed α value of 0.05 with confidence intervals at the 95% level. All statistical analyses were performed with SPSS for Windows version 17 (SPSS Inc., Chicago, IL).

Results

The study included 840 patients (468 males and 372 females); a total of 312 patients (37.1%) were vaccinated against seasonal flu. There were 741 patients with comorbidities, the most frequent being arterial hypertension (n = 597; 71.1%). During the previous year (prior to entering the study), COPD exacerbations were present in 663 (78.9%) patients. The basic demographic characteristics of the study population, comorbidities, and exacerbations are shown in Tables 1 and 2. During the one-year follow-up, 551 (65.6%) patients experienced COPD exacerbations.

Table 1

Characteristics of the study population and comorbidities

Characteristics	Values
Demography, n (%)	
males	468 (55.7)
females	372 (44.3)
Age (years), mean ± SD	65.39 ±8.6
Patients aged ≥ 65 years, n (%)	430 (51.2)
Duration of COPD (years) , mean ± SD	7.64 ± 5.44
Smoking (pack/year), mean ± SD	45.67 ± 25.09
Smoker, n (%)	348 (41.4)
Ex-smoker, n (%)	448 (53.3)
Nonsmoker, n (%)	44 (5.3)
BMI (kg/m2), mean ± SD	26.39 ± 4.77
Patients with < 21 kg/m^2, n (%)	135 (16.1)
Comorbidity, n (%)	741 (88.2)
arterial hypertension	597 (71.1)
hyperlipoproteinemia	255 (30.3)
ischemic heart disease	198 (23.6)
DM	180 (21.4)
arrhythmia	177 (21)
tuberculosis	56 (6.6)
depression	52 (6.2)
heart failure (NYHA ≥ 2)	36 (4.3)
osteoporosis	31 (3.7)
hyperplasio prostate	14 (1.6)
hypothyroidism	9 (1.1)
breast cancer	5 (0.6)
lung cancer	4 (0.5)
Number of CMB, n (%)	
1	290 (34.5)
2	233 (27.7)
≥3 CMB	185 (22.0)
CVD+DM+depression	19 (2.4)

COPD – chronic obstructive pulmonary disease; BMI – body mass index; DM – diabetes mellitus; CVD – cardiovascular disease; NYHA – New York Heart Association; CMB – comorbidity; SD – standard deviation.

Table 2

Exacerbation characteristics of the chronic obstructive pulmonary diseases patients (n = 840)

Exacerbations	Previous year	Study year
Yes	663 (78.9)	551 (65.6)
None	147 (17.5)	271 (32.3)
Pneumonia	30 (3.6)	18 (2.1)
Total number of exacerbations		
moderate	1,219	892
severe	206	217
ABCD classification		
A	240 (28.6)	351 (41.7)
B	189 (22.5)	146 (17.4)
C	96 (11.4)	62 (7.5)
D	315 (37,5)	281 (33,4)

***Note*: Values are expressed as number (%) of the patients, except total number of exacerbation.**
A – low symptom severity, low exacerbation risk; B – high symptom severity, low exacerbation risk; C – low symptom severity, high exacerbation risk; D – high symptom severity, high exacerbation risk.

Table 3

Characteristics of COPD patients with exacerbations according to the vaccination status

Characteristics	Vaccination		*p*
	yes 312 (37.1)	no 528 (62.9)	
With exacerbation (moderate/severe)	176 (31.9)	375 (68.1)	0.043
Age ≥ 65 years	89 (56.0)	188 (69.4)	0.005
Age < 65 years	103 (67.3)	171 (66.9)	0.935
With CMB	165 (61.1)	327 (69.4)	0.021
Without CMB	27 (64.3)	33 (57.9)	0.520
With heart failure (NYHA ≥ 2)	6 (66.7)	24 (88.9)	0.043
Without heart failure	186 (61.4)	335 (67.1)	0.102
Without CVD + DM + Depression	192 (61.5)	340 (66.9)	0.116
BMI ≥ 21 kg/m^2	168 (61.1)	278 (64.6)	0.353
BMI < 21 kg/m^2	27 (64.3)	78 (83.9)	0.011

***Note*: Values are expressed as number (%) of the patients.**
COPD – chronic obstructive pulmonary disease; CMB – comorbidity; NYHA – New York Heart Association; CVD – cardiovascular disease; DM – diabetes mellitus; BMI – body mass index.

Patients who were vaccinated had less frequent severe and moderate COPD exacerbations than unvaccinated patients [176 (31.9%) vs. 375 (68.1%); $p = 0.043$]. Frequencies of COPD exacerbations according to vaccinal status are presented in Table 3. Among patients ≥ 65 years, more COPD exacerbations occurred in unvaccinated compared to vaccinated patients [188 (69.4%) vs. 89 (56.0%), $p = 0.005$]. A lower frequency of exacerbations was observed in vaccinated patients with at least one comorbidity compared to unvaccinated patients [165 (61.1%) vs. 327 (69.4%), $p = 0.021$]. In patients without comorbidities, there was no statistically significant difference in the frequency of exacerbations according to the vaccination status [33 (57.9%) vs. 27 (64.3%), $p = 0.520$]. Vaccinated patients who suffered from heart failure (NYHA ≥ 2) had a lower frequency of exacerbations compared to unvaccinated patients [6 (66.7%) vs. 24 (88.9%), $p = 0.043$]. Among patients with multiple comorbidities [cardiovascular diseases (CVD), diabetes mellitus (DM), and depression], nobody was vaccinated. In this subgroup, everybody had COPD exacerbation during the follow-up (one of them passed away from exacerbation and pneumonia in the hospital). In vaccinated patients with BMI < 21 kg/m^2, there was a lower frequency of exacerbation [27 (64.3%) vs. 78 (83.9%), $p = 0.011$].

In univariate logistic regression analysis, significant predictors of COPD exacerbation were vaccination,

COPD duration, BMI < 21 kg/m^2, and heart failure, while age ≥ 65 and comorbidities were not (Table 4). In multivariate logistic regression analysis, only BMI < 21 kg/m^2 and heart failure were independent predictors of COPD exacerbations.

Table 4

Logistic regression analyses of predictors of COPD exacerbations

Analysis	RR	95% CI	*p*
Univariate			
age ≥ 65 years	0.889	0.668–1.182	0.418
CMB	1.284	0.835–1.976	0.255
vaccination	0.747	0.557–0.898	0.048
COPD duration	1.032	1.004–1.061	0.025
BMI < 21 kg/m^2	0.492	0.319–0.759	0.001
heart failure	2.701	1.111–6.567	0.028
Multivariate analysis			
BMI < 21 kg/m^2	0.490	0.318–0.758	0.001
heart failure	2.734	1.121–6.669	0.027

COPD – chronic obstructive pulmonary disease; CMB – comorbidity; BMI – body mass index; RR – relative risk; CI – confidence interval.

During the one-year follow-up, vaccinated patients were more likely to improve and move to a milder category according to GOLD ABCD stages, as shown in Figure 1. Unvaccinated patients were more likely to remain in the same stage at the end of the study.

COPD exacerbations are well known. A Cochrane meta-analysis by Poole et al. [19] has shown the results of 11 studies regarding the efficacy of the influenza vaccine in COPD. There was a significant reduction in the number of exacerbations, but because of the small number of patients, there was no observed effect on mortality. In our study, COPD exacerbations were significantly reduced in vaccinated patients. A lower number of ER visits in vaccinated patients was also observed in other studies [20]. Montserrat-Capdevila et al. [21] analyzed 1,323 patients over a three-year period and reported fewer hospitalizations among the vaccinated patients.

Our observation on the lower frequency of exacerbations among vaccinated patients older than 65 is similar to a South Korean study in which 828 (54.2% vaccinated) patients were analyzed [22]. Nichol et al. [20] noted that persons older than 65 outside the flu season are often hospitalized for the flu and pneumonia (55 of 1,000), and during the season, that number doubles. In our study, BMI < 21 kg/m^2 was an independent predictor of exacerbations, and among the vaccinated patients, those with BMI < 21 kg/m^2 experienced fewer exacerbations, which is in line with the study by Gajanan et al. [23]. Compared to our study, the Montserrat-Capdevila et al. [21] study from 2014 demonstrated similar results in the number and type of comorbidities, the most frequent being arterial hypertension and diabetes. We observed that vaccinated patients with comorbidities had a lower frequency of exacerbations compared to unvaccinated

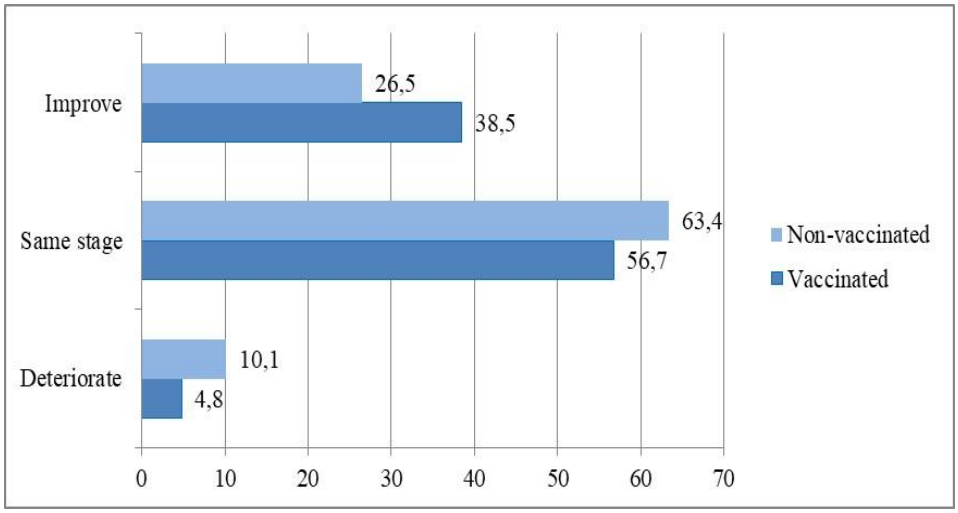

Fig. 1 – Tendency to different category of disease severity regarding vaccination status during one-year follow-up in chronic obstructive pulmonary disease patients.

Discussion

The results of the study demonstrate that only one-third of COPD patients received the seasonal flu vaccine. Those who were vaccinated experienced a significant reduction in COPD exacerbations compared to unvaccinated patients during a one-year follow-up. The observed effects were more pronounced in patients with comorbidities, low BMI, and the elderly.

The study by Aka Aktürk et al. [18] showed a similar number of vaccinated patients, 36.5%. The effects of flu vaccination on patients, which had been previously reported by Søgaard et al. [24]. Vardeny et al. [25], in 2016, reported that there was less worsening of heart failure in patients vaccinated against seasonal flu. In our study, among patients with multiple comorbidities (CVD, DM, and depression) none had been vaccinated, and all had experienced COPD exacerbations. These findings indicate that the effects of vaccination are of paramount importance in the subpopulation of COPD patients who are older, underweight, and have comorbidities.

The reason for a lower level of immunization (37.1%) could be due to the distrust of the effectiveness of immunization against seasonal flu worldwide [26, 27]. Zimmerman et al. [28] reported that 38% of unvaccinated persons thought that they could get the flu after vaccination. That study also showed that one-third of the unvaccinated persons were not informed by their doctors regarding vaccination, and similar findings were also observed by other authors [18]. The impact of health care workers is very important for promoting immunization but only 8.7% of the health staff in Serbia were vaccinated in the 2016–2017 season [29]. Interestingly, a recent study found that even health care workers who suffer from COPD are often unaware of their disease which could lead to a lower level of immunization [30].

There were two important limitations to this work. First, there was no laboratory confirmation of vaccination against seasonal flu. Immunization information was obtained from patients' files and medical histories but was also given by the patients. Second, there were probably varying criteria for hospitalization or observation in COPD exacerbation rates among health institutions. Despite these limitations, to our knowledge, this is the first longitudinal study investigating the effects of the flu vaccination in COPD patients in this region (Southeast Europe - West Balkan). The study showed that vaccination rates were far below the recommended, especially in high-risk patients. We believe our study is important as it underlines that in resource-limited settings there is a great area for improvement in COPD care using low-cost interventions such as seasonal flu vaccination.

Conclusion

There is a clear reduction in the number of exacerbations among vaccinated patients with COPD. Multivariate logistic regression analysis confirmed that patients with a low BMI and heart failure (NYHA ≥ 2) were independent predictors of COPD exacerbations. In these subgroups, vaccination led to a significant decrease in exacerbations. From the aforementioned, the study demonstrates that there is a great need for consistent information and education for all COPD patients with an emphasis on non-pharmacological prevention of exacerbation and progression of the disease.

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