

EFFECT OF INFLUENZA VACCINATION ON SEASONAL MORTALITY VPLYV OČKOVANIA PROTI CHRÍPKKE NA SEZÓNNU ÚMRTNOSŤ

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ABSTRACT

Introduction: Seasonal influenza is one of the acute respiratory infections caused by influenza viruses. In addition to acute respiratory disease, it also causes complications of a patient's pre-existing conditions with possible fatal consequences.

The aim: To verify whether influenza vaccination has an effect on reducing seasonal mortality.

Methods: We conducted a Case-control Study. We used the administrative data of the health insurance company Dôvera (1.6 million insured persons). We monitored the vaccination coverage of all Dôvera clients, vaccination coverage by gender, and separately for persons 60 years of age and older. We compared the all-cause mortality in the group of those vaccinated against influenza with the all-cause mortality in the group of non-vaccinated. We created the group of unvaccinated by randomly pairing 1:1 with the vaccinated based on age, sex, and the most expensive diagnosis. We analyzed 5 influenza seasons – 2017/18, 2018/19, 2019/20, 2020/21 and 2021/22 (September – April). We excluded the 2020/21 influenza season from the mortality analysis, due to the increased mortality from COVID-19.

Results: The vaccination coverage rate of persons aged 60 and older was from 6.6 % in the 60 – 64-years-age group in the 2019/20 season to 23.8 % in the 80 – 84-years age group in the 2018/19 season. There were no significant differences between the vaccination coverage rates of men and women. All-cause mortality in the unvaccinated group was in the range 2.02 – 2.29 % in analysed seasons, in the vaccinated group 1.31 – 1.47 %, OR = 1.45 – 1.7. Significant differences were found in older age groups, in people over 60 years, OR = 1.47 – 1.74. Results were statistically non-significant in the group under 60 years old.

Conclusion: We consider influenza vaccination to be a suitable tool for reducing the seasonal mortality.

Key words: Influenza. Influenza vaccination. All-cause mortality.

ABSTRAKT

Východiská: Sezónna chrípka patrí medzi akútne respiračné infekcie spôsobené vírusmi chrípky. Okrem akútneho respiračného ochorenia spôsobuje pacientovi aj komplikácie už existujúcich stavov s možnými smrteľnými následkami.

Cieľ: Overiť, či má očkovanie proti chrípke vplyv na zníženie sezónnej úmrtnosti.

Metódy: Uskutočnili sme štúdiu prípad-kontrola. Využili sme administratívne údaje zdravotnej poisťovne Dôvera (1,6 milióna poistencov). Sledovali sme zaočkovanosť všetkých

klientov Dôvery, zaočkovanosť podľa pohlavia a zvlášť u osôb nad 60 rokov. Porovnali sme celkovú úmrtnosť v skupine očkovaných proti chrípke s celkovou úmrtnosťou v skupine neočkovaných. Skupinu neočkovaných sme vytvorili náhodným párovaním 1:1 s očkovanými na základe veku, pohlavia a najdrahšej diagnózy. Analyzovali sme 5 chrípkových sezón – 2017/18, 2018/19, 2019/20, 2020/21 a 2021/22 (september – apríl). Z analýzy úmrtnosti sme vylúčili chrípkovú sezónu 2020/21 z dôvodu zvýšenej úmrtnosti na COVID-19.

Výsledky: Zaočkovanosť osôb starších ako 60 rokov bola od 6,6 % v skupine 60 – 64-ročných v sezóne 2019/20, do 23,8 % v skupine 80 – 84-ročných v sezóne 2018/19. Medzi zaočkovanosťou mužov a žien neboli žiadne významné rozdiely. Celková úmrtnosť v skupine neočkovaných bola v analyzovaných sezónach od 2,02 - 2,29 %, v skupine očkovaných 1,31 – 1,47 %, OR = 1,45 - 1,7. Štatisticky významné rozdiely boli zistené v starších vekových skupinách, u osôb nad 60 rokov, OR = 1,47 – 1,74. Výsledky boli štatisticky nevýznamné v skupine do 60 rokov.

Záver: Očkovanie proti chrípke považujeme za vhodný nástroj zníženia sezónnej úmrtnosti.

Kľúčové slová: Chrípka. Očkovanie proti chrípke. Celková úmrtnosť.

INTRODUCTION

Influenza vaccination is an important tool for preventing this respiratory disease, which has the potential to cause serious complications and even death. Due to several factors, vaccination has a positive effect on both individuals and the entire population. Vaccination stimulates the immune system to produce antibodies against influenza viruses. These antibodies reduce the likelihood of infection [1]. Influenza can cause serious health problems, especially for people with weakened immune systems, the elderly and the chronically ill. Vaccination reduces the risk of complications such as pneumonia, exacerbation of chronic diseases and even death in these risk groups [2, 3].

There is a wealth of evidence on the effectiveness of influenza vaccination and its importance for individuals and the population as a whole: Among

adults hospitalized with influenza, vaccinated patients had a 26 % lower risk of admission to the intensive care unit (ICU) and a 31 % lower risk of death from influenza compared with those, who were not vaccinated [4]. Another study showed similar results. Among adults hospitalized with the influenza, vaccinated patients were 59 % less likely to be admitted to the ICU than those who were not vaccinated. Vaccinated adult patients spent an average of four days less in the ICU than non-vaccinated patients [5].

The influenza vaccine has been shown to reduce the risk of illness in healthy adults [6], and effective in preventing hospitalization and complications in children and adults [7].

The effectiveness of vaccination has also been investigated in vulnerable groups. A study in US children found that vaccine protects against life-threatening influenza symptoms in children [8]. An additional study from Valencia found the effectiveness of vaccination in preventing hospitalizations among children during the influenza season [9].

The effectiveness of seasonal influenza vaccines is influenced by the match of the circulating subtypes of the influenza virus with the vaccine, but also by other factors, causing a documented variability in the effectiveness of the vaccine [10]. These studies show that influenza vaccination brings a significant benefit and therefore support the position that it is subsequently important to constantly monitor influenza developments and adapt vaccines according to the circulating strains of the influenza virus.

AIM

The aim of our study was to verify whether influenza vaccination has an effect on reducing seasonal mortality, therefore to assess the benefits of vaccination against influenza by age, gender, and the analysed influenza seasons.

METHODS

To assess the effect of influenza vaccination by age, gender, and season, we performed a Case-control Study [11]. We tracked 5 influenza seasons:

2017/18, 2018/19, 2019/20, 2020/21 and 2021/22 (September – April). We used the anonymized administrative data of the health insurance company Dôvera, which provided data on age, sex, the most expensive diagnosis, and residence of the monitored persons. The anonymized data were available to one of the co-authors based on a contract with Dôvera. The population of Slovakia was approximately 5.4 million in 2021, of which 1.6 million were insured in the Dôvera Health insurance company. We found out the vaccination coverage rate among clients of the Dôvera, compared the vaccination coverage rate between men and women, and the vaccination coverage rate among persons according to 5-years age groups. We created a control group of unvaccinated persons by randomly pairing them with vaccinated persons 1:1 based on age, gender, and the most expensive diagnosis. The numbers are listed in Table 1.

We excluded the 2020/21 influenza season from the mortality analyses, due to the increased mortality from COVID-19. We considered every person who had a death from any cause in the records of the health insurance company to be deceased. We compared the total mortality in the group of persons who were vaccinated against influenza with the total mortality in the group of unvaccinated persons. We calculated the higher chance of dying the unvaccinated compared to the vaccinated in the observed seasons and according to 5-years age groups.

We did not evaluate the influence of the level of health care on mortality by residence, due to the potential emergence of disparities that we are not equipped to interpret accurately. This caution arises from the likelihood of varying influenza incidence across different regions.

We used the Chi-square test to compare occurrence of deaths in the vaccinated and non-vaccinated groups. We calculated the odds ratio (OR) in the groups. We used the R programs for working with data and statistical calculations. We tested the results statistically at the set significance level of $p \leq 0.05$.

Table 1 The set of persons included in the study according to the analysed seasons

Season	2017/18	2018/19	2019/20	2020/21	2021/22
Vaccinated	50 453	51 554	45 468	69 601	63 386
Unvaccinated	50 453	51 554	45 468	69 601	63 386
Total	100 906	103 108	90 936	139 202	126 772

RESULTS

Influenza vaccination of Dôvera clients (for all ages) in the five monitored seasons ranged from 3.2 to 4.6 % overall; the highest vaccination coverage rate 4.6 % was observed in the 2020/21 season. In the 2017/18 season, the vaccination coverage rate was 3.8 %, in the 2019/20 season it fell to 3.2 %, and after the COVID-19 pandemic it rose to 4 % in the 2021/22 season (Table 2).

There were no significant differences between the vaccination coverage rates of men and women in the observed seasons (Table 3).

Vaccination coverage rates were found to be low in younger age groups, with vaccination among those up to 40 reaching only 2 % maximum, rising only during the 2020/21 season to 2,6 % in the

35 – 39 age group (this is likely result of the COVID-19 pandemic). The vaccination coverage rate rises with age, reaching maximum in the 80 – 89 age group (Table 4). The highest vaccination coverage rate (23.8 %) was among people aged 80 – 84 in the 2018/19 season.

We analyzed mortality in four influenza seasons. We excluded the 2020/21 influenza season, due to the increased mortality from COVID-19 in Slovakia. The highest mortality rate of unvaccinated persons was in the 2021/22 season – 2.29/100. The lowest was 1.31/100 in the 2019/20 season for vaccinated persons. In each of the analyzed seasons, mortality was lower in vaccinated persons compared to non-vaccinated ones. In the last monitored season 2021/22, the chance of death in the group of

Table 2 Influenza vaccination coverage rate (%) of Dôvera clients in influenza seasons 2017/18 – 2021/22, Slovakia

Season	2017/18	2018/19	2019/20	2020/21	2021/22
Number of vaccinated	50 453	51 554	45 468	69 601	63 386
% of vaccinated	3.8	3.7	3.2	4.6	4.0

Table 3 Influenza vaccination coverage rate (%) of Dôvera clients by gender in influenza seasons 2017/18 – 2021/22, Slovakia

Season	2017/18	2018/19	2019/20	2020/21	2021/22
females	3.8	3.8	3.2	4.7	4.0
males	3.8	3.7	3.2	4.4	4.0

Table 4 Influenza vaccination coverage rate (%) of Dôvera clients by age groups in influenza seasons 2017/18 – 2021/22, Slovakia

Age group	Season				
	2017/18	2018/19	2019/20	2020/21	2021/22
00 – 04	0.4	0.4	0.4	0.9	0.7
05 – 09	1.3	1.2	1.0	1.8	1.4
10 – 14	1.8	1.8	1.3	2.0	1.4
15 – 19	1.5	1.6	1.2	1.9	1.3
20 – 24	0.8	0.8	0.7	1.5	1.1
25 – 29	0.8	0.9	0.8	1.6	1.2
30 – 34	1.1	1.1	1.0	2.0	1.6
35 – 39	1.3	1.4	1.2	2.6	2.0
40 – 44	1.8	1.7	1.5	3.1	2.4
45 – 49	2.3	2.3	2.0	3.6	2.8
50 – 54	3.5	3.2	2.6	4.4	3.7
55 – 59	4.9	4.7	3.8	6.0	5.0
60 – 64	7.7	7.2	6.6	8.8	7.7
65 – 69	12.1	11.6	9.6	12.4	11.7
70 – 74	15.9	15.4	12.9	15.5	15.1
75 – 79	20.1	18.9	16.8	18.3	17.6
80 – 84	22.2	23.8	19.6	19.3	19.6
85 – 89	23.2	23.1	20.7	21.1	21.7
90 – 94	21.7	21.6	19.2	20.9	21.8
95 +	16.2	20.9	19.4	19.1	16.3

unvaccinated people was 1.74 times higher compared to the vaccinated group. In previous seasons, the chance of dying was 1.45 – 1.57 times higher for non-vaccinated compared to vaccinated. The differences in mortality between vaccinated and non-vac-

inated were statistically significant in each season (Table 5).

We also analysed the mortality differences in vaccinated and unvaccinated according the age groups. Vaccination did not have significant effect

Table 5 Comparison of mortality for vaccinated and unvaccinated Dôvera clients in the analysed seasons 2017/18, 2018/19, 2019/20, 2021/22, Slovakia

Influenza season	Vaccinated			Unvaccinated			OR	95% CI		p-value
	deceased	survived	mortality	deceased	survived	mortality				
	(n)	(n)	per 100	(n)	(n)	per 100				
2017/18	735	49 718	1.46	1 143	49 310	2.27	1.57	1.43	1.72	< 0.001
2018/19	758	50 796	1.47	1 090	50 464	2.11	1.45	1.32	1.59	< 0.001
2019/20	595	44 873	1.31	917	44 551	2.02	1.55	1.4	1.72	< 0.001
2021/22	865	62 521	1.36	1 453	61 933	2.29	1.74	1.56	1.85	< 0.001

Table 6 Comparison of mortality for vaccinated and unvaccinated Dôvera clients in the analysed seasons 2017/18, 2018/19, 2019/20, 2021/22 and age groups, Slovakia

Influenza season	Age group	Unvaccinated		Vaccinated		OR	95% CI		p-value
		Deceased (n)	Survived (n)	Deceased (n)	Survived (n)				
2017/18	< 55	27	14 880	30	14 877	0.90	0.53	1.51	0.690
	55 – 59	30	4 104	25	4 109	1.20	0.71	2.5	0.499
	60 – 64	68	6 403	52	6 419	1.31	0.91	1.88	0.143
	65 – 69	108	7 911	77	7 942	1.41	1.5	1.89	0.022
	70 – 74	159	6 368	103	6 424	1.56	1.21	2.00	< 0.001
	75 – 79	206	4 976	125	5 057	1.67	1.34	2.10	< 0.001
	80 – 85	272	2 939	122	3 089	2.34	1.88	2.92	< 0.001
85+	273	1 729	201	1 801	1.41	1.17	1.72	< 0.001	
2018/19	< 55	29	15 353	30	15 328	0.97	0.58	1.61	0.891
	55 – 59	34	4 059	22	4 074	1.55	0.91	2.66	0.109
	60 – 64	83	6 168	43	6 211	1.94	1.34	2.81	< 0.001
	65 – 69	121	7 975	64	8 035	1.90	1.40	2.58	< 0.001
	70 – 74	129	6 730	106	6 756	1.22	0.94	1.58	0.129
	75 – 79	194	5 128	132	5 193	1.49	1.19	1.86	< 0.001
	80 – 85	212	3 161	155	3 221	1.39	1.13	1.72	0.002
85+	288	1 890	206	1 978	1.46	1.21	1.77	< 0.001	
2019/20	< 55	19	13 187	15	13 191	1.27	0.64	2.49	0.493
	55 – 59	21	3 356	17	3 360	1.24	0.65	2.35	0.516
	60 – 64	70	5 287	44	5 313	1.60	1.9	2.34	0.015
	65 – 69	104	7 195	55	7 244	1.90	1.37	2.64	< 0.001
	70 – 74	121	6 137	71	6 187	1.72	1.28	2.31	< 0.001
	75 – 79	169	4 765	109	4 825	1.57	1.23	2.00	< 0.001
	80 – 85	183	2 884	114	2 953	1.64	1.29	2.9	< 0.001
85+	230	1 740	170	1 800	1.40	1.14	1.72	0.001	
2021/22	< 55	31	21 436	35	21 432	0.89	0.55	1.44	0.622
	55 – 59	37	4 699	22	4 714	1.69	0.99	2.86	0.052
	60 – 64	91	6 755	41	6 805	2.24	1.54	3.24	< 0.001
	65 – 69	168	9 514	99	9 583	1.71	1.33	2.19	< 0.001
	70 – 74	247	8 752	125	8 874	2.00	1.61	2.49	< 0.001
	75 – 79	259	5 557	149	5 667	1.77	1.44	2.18	< 0.001
	80 – 85	282	3 303	155	3 430	1.89	1.54	2.31	< 0.001
85+	338	1 917	239	2 016	1.49	1.25	1.78	< 0.001	

Table 7 Comparison of mortality for vaccinated and unvaccinated Dôvera clients in the analysed seasons 2017/18, 2018/19, 2019/20, 2021/22 in two age groups, Slovakia

Influenza season	Age group	Unvaccinated		Vaccinated		OR	95% CI		p-value
		Deceased (n)	Survived (n)	Deceased (n)	Survived (n)				
2017/18	≤ 59	57	18 984	55	18 986	1.04	0.72	1.50	0.849
	≥ 60	1 086	30 326	680	30 732	1.62	1.47	1.78	< 0.001
2018/19	≤ 59	63	19 412	52	19 402	1.21	0.84	1.75	0.307
	≥ 60	1 027	31 052	706	31 394	1.47	1.33	1.62	< 0.001
2019/20	≤ 59	40	16 543	32	16 551	1.25	0.79	1.99	0.346
	≥ 60	877	28 008	563	28 322	1.58	1.42	1.75	< 0.001
2021/22	≤ 59	68	26 135	57	26 146	1.19	0.84	1.70	0.325
	≥ 60	1 385	35 798	808	36 375	1.74	1.60	1.90	< 0.001

on mortality in age groups under 60. However, we found that in all seasons in the age groups 60 years and over, or 65 years and over, there was a significant difference in mortality between vaccinated and unvaccinated (Table 6). The exception was the age group 70 – 74 years in the 2018/19 season. The chance of unvaccinated people dying was highest in the 2017/18 season in the 80 – 85 years age group (OR = 2.34).

In Slovakia, vaccination against the influenza is recommended for seniors aged 59 and over [12]. We therefore focused on the analysis of all-caused seasonal mortality in all persons aged 60 and over. In each influenza season, we found a statistically significant difference in mortality between vaccinated and unvaccinated persons in this age category, with the chance of dying among unvaccinated individuals being 1.47 – 1.74 times higher compared to vaccinated individuals (Table 7). The highest difference between vaccinated and unvaccinated mortality was in the 2021/22 season, when the chance of death in the group of unvaccinated persons aged 60 and over was 1.74 times higher compared to the vaccinated group.

DISCUSSION

The relationship between an increase in mortality and the severity of the influenza season was confirmed by several studies. Studies [13-15] highlighted the major public health burden of influenza and its severe complications, including death. The studies referred to clinical burden of severe influenza, influenza-associated all-cause mortality, the modelling of influenza-attributable contribution to excess hospitalization and mortality during the influenza seasons.

Another study measured the effect of state-level hospital worker influenza vaccination laws on pneumonia and influenza mortality in hospitals. Implementation of state laws requiring hospitals to offer influenza vaccination to their employees was associated with a 2.5 % reduction in the monthly pneumonia and influenza mortality rate [16].

In France, during eight consecutive influenza seasons (2010 – 2018) more than 90 % of excess mortality was in the group of 65+ year-olds [17]. A study that described the impact of exposure to influenza virus on hospitalization and death in the elderly residence of long term care facilities in the 2004/05 season confirmed that exposure to influenza increased the all-cause risk of hospitalization and the all-cause risk death [18].

Based on these results we assumed, that influenza vaccination could have an effect on reducing seasonal mortality. We confirmed that there was a significantly higher seasonal mortality between unvaccinated clients of Dôvera Health insurance company compared to vaccinated in all analysed seasons in the age group 60 years old and over.

Our results are also confirmed by the study [19] in which influenza vaccine prevented hospital admission for influenza and pneumonia and all-cause mortality in individuals aged 65 years or older.

In another study with similar methodology to the present study, researchers conducted a prospective cohort study in a population aged over 80 years. They compared all-cause mortality in vaccinated and unvaccinated subjects after propensity score matching to control for age, sex, and comorbidities. After propensity score matching, mortality was assessed at 20.9 % in the vaccinated group and 23.9% in the unvaccinated group (OR = 0.84 [0.75 – 0.93], p = 0.001) [20].

A similar study [21] confirmed the effect of influenza vaccination on the reduction in risk of death from all causes, with the effect increasing with age and comorbidity.

Based on the results of our analysis, we confirmed that influenza vaccination was protective, reduced the seasonal mortality. It was protective in the group of 60 years and older, which correlates with the recommendations for vaccination against influenza in Slovakia [12].

In our study vaccination did not have significant effect on mortality in age groups under 60. It could be for two reasons: either influenza is not life-threatening for younger age groups, or this is a result of very low vaccination coverage in these groups. It is possible, that if the vaccination coverage rates in the groups under 60 years of age were higher, the effect of vaccination on mortality would be revealed.

The benefit of this work is also the fact that the sample of processed data consisted of 90 – 139 thousand people in individual seasons. A total of 560,000 people were included in our sample. We are aware that vaccination coverage rate against the influenza is very low in Slovakia. Therefore, we feel the need to bring evidence to the inhabitants of Slovakia about the benefits of vaccination against the influenza, namely protecting the health and life of every vaccinated person in Slovakia. Support for vaccination is also important in view of the presented results. We feel the need to improve patient access to vaccination, e.g., by introducing vaccination in pharmacies, or by setting up vaccination centers similar to these during the COVID-19 period, since the vaccination is seasonal. Vaccination centers could also help in view of the shortage and high average age of general practitioners, who are currently the only ones authorized to vaccinate against the influenza in Slovakia. We consider the fact that the parliament approved a law in 2023, based on which it will be possible to introduce vaccinations in pharmacies, a success. This will be preceded by the accreditation of a study program aimed at educating pharmacists on this issue.

The limitation of this study is not considering the regionality of the monitored persons. Another possible limitation was that only one insurance company was used. Additionally, it is worth noting that other vaccinations in older adults, such as those against COVID-19 and pneumococcal disease, may have contributed to a lower mortality rate. Furthermore, it's possible that those who were vaccinated

were more motivated to prevent illness compared to those who were not vaccinated.

CONCLUSION

We found that the influenza vaccination coverage rate of the Dôvera Health insurance company clients in the five analysed seasons 2017/18 – 2021/22 was in the range of 3.2 – 4.6 %. Vaccination of older adults increased with age, with a maximum of 80 – 89 years. The highest vaccination coverage rate, 23.8 %, was among persons aged 80 – 84 in the 2018/19 season. There were no significant differences between the vaccination coverage rates of men and women in the observed seasons.

In each of the four analysed influenza seasons, 2017/18, 2018/19, 2019/20 and 2021/22, all-caused seasonal mortality was lower in vaccinated individuals compared to unvaccinated. This difference was statistically significant. Analyzing mortality rates by age group, we did not find significant effect of vaccination on seasonal mortality among age groups under 60. However, the effect of vaccination on seasonal mortality was found in the age groups over 60. Namely, we found statistically significant differences in favor of the vaccinated in all four analysed seasons and 5-years age groups over 65, except for the 70 – 74-yearsage group in the 2018/19 season. The results showed that the differences in mortality among vaccinated and unvaccinated clients of the Health insurance company Dôvera in the age group of 60 and over are also statistically significant.

We consider vaccination against influenza to be a suitable tool in the prevention of the influenza and its complications, including death, particularly in the elderly aged 60 and over and reduce the seasonal mortality.

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