EPIDEMIOLOGICAL ANALYSIS OF MORTALITY FROM INFLUENZA IN THE REPUBLIC OF CROATIA

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Received on 04.01.2024. *Reviewed on 19.01.2024.* *Accepted on 26.04.2024.*

ABSTRACT

Introduction: Influenza is an acute infectious disease of the respiratory system caused by one of the influenza viruses A, B or C, which inevitably appears every year in the form of larger or smaller epidemics, with a pronounced rapid spread within the population. A higher number of deaths occurs in the months when the epidemic lasts and is associated with an increased number of pneumonia, especially in older people.

Objective: Analyze the mortality from influenza in the Republic of Croatia and consider the connection of mortality with vaccination status.

Subjects and methods: A retrospective cross - sectional epidemiological study was conducted between January and April 2024. Data on deaths from influenza between January 2014 and December 2023 were analyzedin the Republic of Croatia collected at the Service for Epidemiology of Infectious Diseases of the Croatian Institute of Public Health.

Results: In the observed period in the Republic of Croatia, 65321 people fell ill with the flu, of which 227 reports had a fatal outcome caused by the flu infection. Among the deceased, 70 % are people aged 65 and older, and 20 % are people aged 30 to 65. On average, more male persons died, and 63 % of respondents were not vaccinated, 32 % of respondents did not know their vaccination status, and 5 % of them were vaccinated against influenza.

Conclusion: In all flu seasons, we record the highest number of deaths in people aged 65 and older. Most of the deceased persons were not vaccinated against influenza.

Keywords: Human Influenza, Mortality Rate, Epidemiology, Vaccination, Croatia, Prevention

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INTRODUCTION

Influenza or flu is an acute infectious disease of the respiratory system caused by one of the influenza viruses A, B or C, which inevitably appears every year in the form of larger or smaller epidemics, with a pronounced rapid spread within the population (1). Incubation of the disease lasts usually 2 days, but can last between 1 - 4 days (2). Influenza can be asymptomatic, and 50 % of patients will develop a clinical picture of the disease with elevated body temperature and respiratory symptoms in milder forms, and pneumonia and sepsis in more severe forms of the disease. Pneumonia is a serious complication of the flu that is responsible for most deaths. A higher number of deaths occurs in the months when the epidemic lasts and is associated with an increased number of pneumonia, especially in older people (1). Influenza epidemics cause numerous health, social and economic problems (3). During the epidemic, the number of patients in pediatric surgeries and primary care surgeries increased manifold, the number of sick days, school absences increased manifold, the consumption of drugs, especially antibiotics, increased, and the number of hospitalizations, especially of older people, increased. This is why influenza is a very important disease for the entire community, not only for the individual and the health service. All this significantly increases costs in the health and state system (2). A very important epidemiological feature of influenza is the increase in the mortality rate. This rate is called excess mortality, and it is most often associated with complications of the flu, especially in the elderly (1). According to data from the Centers for Disease Control and Prevention, the number of deaths caused by influenza in the USA in 2021 was 41917, with a death rate of 12.6 per 100000 population, which ranks it 13th leading cause of death (4). Considering that the flu is transmitted through droplets, respiratory secretions, and that the patients do not necessarily have a typical clinical picture, prevention measures such as eliminating the source of infection and interrupting the path of transmission of the causative agent (isolation of patients, avoiding groups of people, wearing protective masks) in practice are difficult to implement and do not achieve the expected effect, and therefore vaccination of the population is the only effective measure of influenza prevention (5). Immunity against influenza is type - specific for overcoming influenza caused by one type of virus and does not provide protection against another type of virus. Immunity depends on hemagglutinin and

neuraminidase, which are constantly changing, therefore a person is constantly exposed to infection with influenza viruses (6). In the Republic of Croatia, vaccination against the flu has been carried out for decades with the aim of reducing complications and deaths from the flu in people with chronic diseases and with the aim of reducing the impact of the flu on the productivity of the working population, reducing costs in the health and state systems (7). By monitoring morbidity and mortality during flu seasons, groups of the population that develop complications and die more often are identified, and they are given priority for vaccination. For groups at increased risk, vaccination in Republic of Croatia is free, and studies around the world show that vaccinated people die less from this infectious disease (8). According to the estimate of seasonal flu-related mortality for the European Union from the Global Influenza Mortality Research project in the period from 2002 - 2011. in 28 EU countries, 27,600 respiratory deaths were reported that were associated with seasonal influenza, with 88% of these deaths occurring among people over 65 years of age (9). Continuous epidemiological monitoring of reports of patients and deaths related to influenza is important in order to respond in a timely manner and implement appropriate preventive measures and develop strategies aimed at preventing influenza and its complications, reducing mortality and improving the health of the population. The aim of this study was to epidemiologically analyze the mortality from influenza in the Republic of Croatia and to consider the relationship between mortality and vaccination status.

SUBJECTS AND METHODS

A retrospective cross - sectional epidemiological study was conducted in the time period between January and April 2024. Data on deaths from influenza between January 2014 and December 2023 were analyzedin the Republic of Croatia collected at the Service for Epidemiology of Infectious Diseases of the Croatian Institute ofPublic Health. The Act on the Protection of the Population from Infectious Diseases of the Republic of Croatia prescribes the reporting of every case of illness or death from influenza. To monitor the flu, a system was developed, i.e. a network for reporting infectious diseases, from doctors who diagnose the disease in their area of work and report it to the competent epidemiological services of the County Institute of Public Health and the Institute of Public Health of the City of Zagreb to the Department for Epidemiology of Infectious Diseases of the

Croatian Institute of Public Health which collects and processes all incoming applications. In this system, in accordance with the regulations, each case of influenza syndrome is reported on an individual report card outside the flu season, and during the flu season, individual reporting is stopped and switched to collective weekly reporting in accordance with the reporting obligation. The criterion for the inclusion of subjects in the study was the cause of death - flu, if any other disease was entered under the cause of death variable, the subject was excluded from the study. Weekly registration in one flu season lasts from 40 to 20 calendar weeks. Data on the trend of influenza, which the Croatian Institute of Public Health collects in weekly reports in this same period, is reported to the European Surveillance System TESSy and to the European Center for Monitoring Infectious Diseases. In the rest of the year, the data is reported on a monthly basis. In this research, all influenza death reports received in consecutive ten years were processed according to age groups, gender, calendar week of influenza reporting and vaccination status.

Statistical analysis

The Statistical Program for Social Sciences (SPSS) for Windows, version 28.0, was used to analyze the obtained results. The Chi-square test was used to assess the statistical significance of the analyzed model. Next, a Cox regression model was used to estimate the overall association between vaccination status and influenza mortality. The Cox regression model is a statistical method used to evaluate the influence of several factors on the probability of an event, the analyzed factors were: age, gender and vaccination status. The purpose of using this test is to identify what effect these factors have on the risk of death from influenza.The hazard ratio (HR) and its 95 % confidence interval (CI) were calculated from the Cox regression model.Descriptive methods were used in the Microsoft Excell 2021 for Windows software system.The probability level in all tests of $p<0.05$ is taken as statistically significant.

RESULTS

In the observed ten - year period in the Republic of Croatia, 65321 people fell ill, of which 227 reports had a fatal outcome caused by influenza infection. The highest number of reported deaths, 107 was recorded in the 2018/2019 season, 29 people in the 2017/2018 season, 25 people

in 2016/2017, then 22 people in 2022/2023, and the lowest in the 2021/2022 season with 4 deceased people (Figure 1).

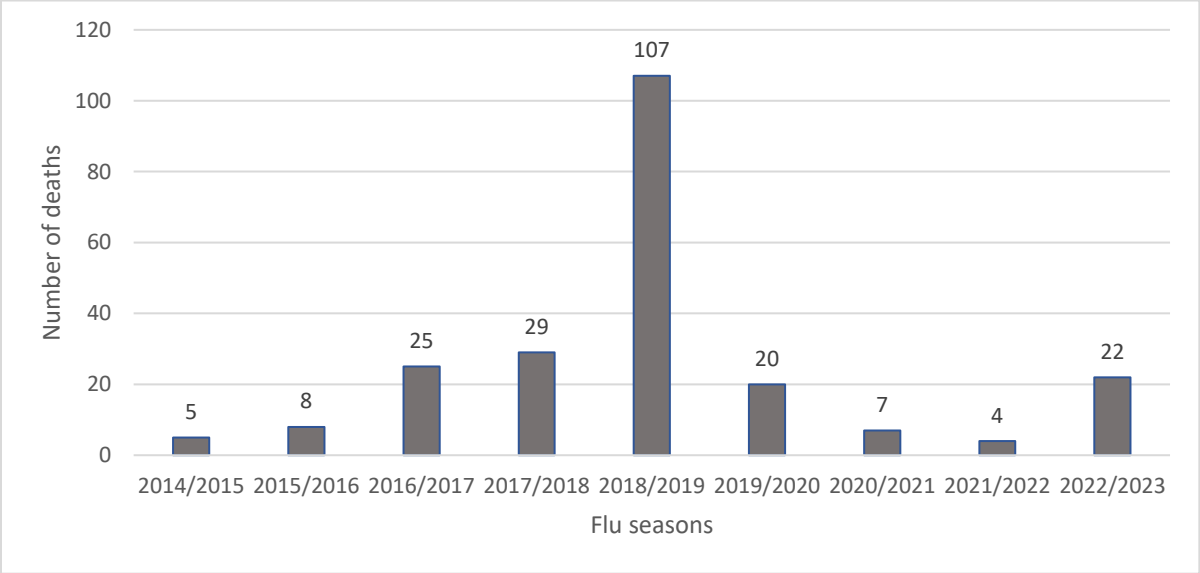

Figure 1. - *The number of reported deaths in the seasons 2014/2015 – 2022/2023 in the Republic of Croatia*

In all flu seasons in the observed period in the Republic of Croatia, mortality was higher in men, and the largest number of men died in the 2018/2019 season (Figure 2).

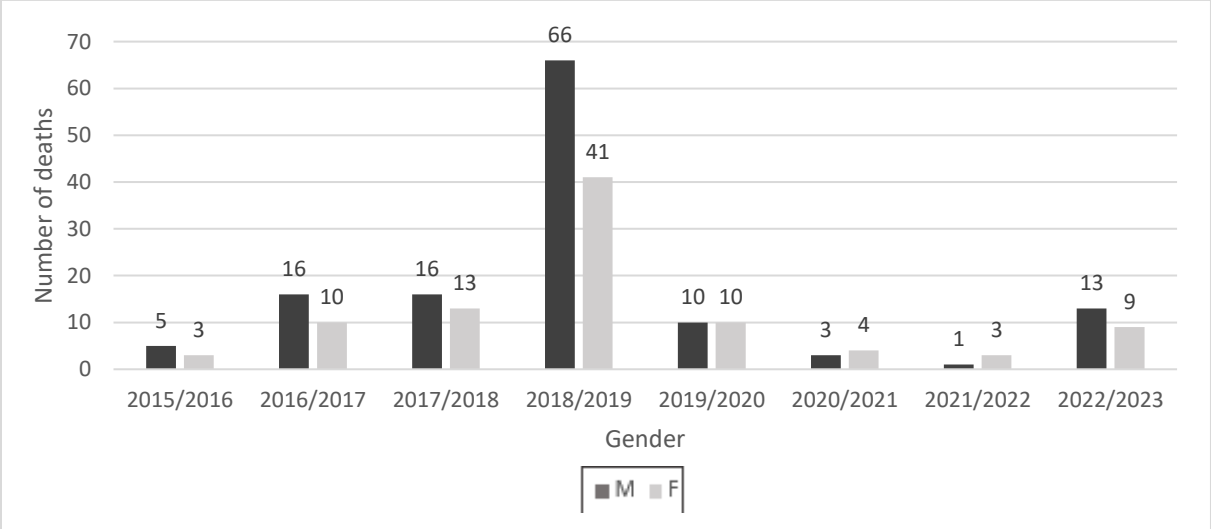

Figure 2. - *Distribution of deaths by gender in the seasons 2015/2016 - 2022/2023 in the Republic of Croatia*

We record the highest number of deaths from the 2nd (second week of January) to the 7th (end of February) calendar week, which corresponds to the time of the flu

epidemic and the highest number of patients in the flu seasons. With regard to vaccination status, the majority of deceased persons with known vaccination status were not vaccinated against influenza, despite the fact that they belong to the groups for which vaccination in the Republic of Croatia is recommended and free of charge (Figure 3).

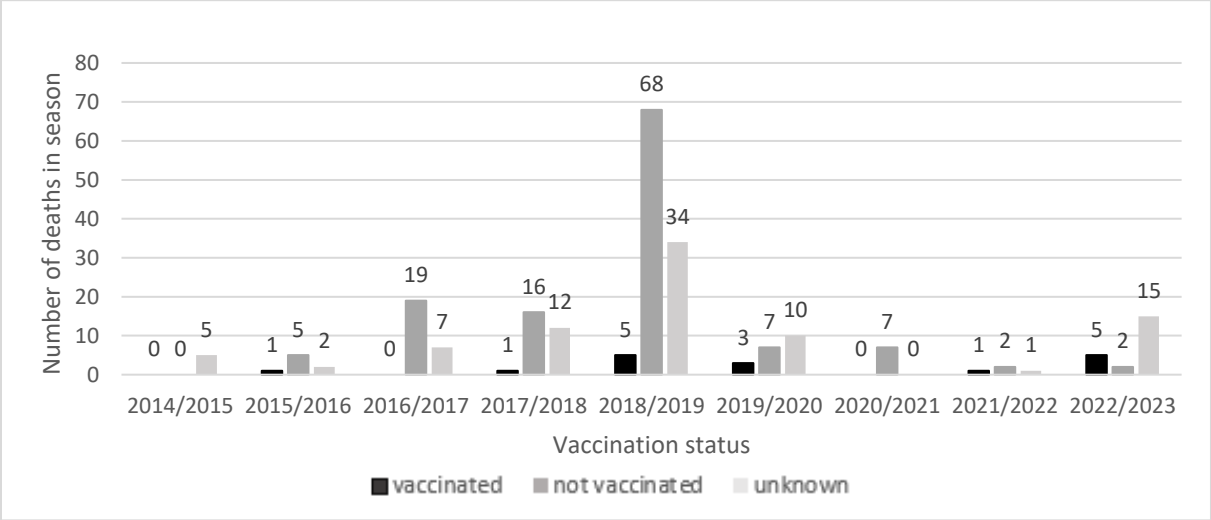

Figure 3. - *Vaccination status of those who died from influenza in the seasons 2014/2015 - 2022/2023 in the Republic of Croatia*

Among those who died due to the flu and its complications, 70 % were people aged 65 and older, and 20 % were people aged 30 to 65. On average, more men died (62 % of men) and 63 % of respondents were not vaccinated, 32 % of respondents did not know their price status, and 5% of them were vaccinated against influenza. The results of the Chi-square test show that the model is statistically significant ($\chi 2=7.417$, df =3, $p<0.05$). According to the results of the Cox regression model, we can conclude that the variables of age group (HR 0.984, 95 % CI 0.765 to 1.265, $p > 0,05$) and gender (HR 0.888, 95 % CI 0.599 to 1.317, $p>0.05$) are not statistically significant predictors of mortality, while the variable of vaccination status is statistically significant as a predictor mortality (HR 1.758, 95 % CI 1.166 to 2.650, $p<0.05$).

DISCUSSION

The analysis of epidemiological data on mortality from influenza in the Republic of Croatia during the last decade showed that in all flu seasons the highest number of deaths occurred in persons aged 65 and older, and the majority of deceased persons were not vaccinated against influenza. These results provide insight into the scale of the problem and trends associated with

this respiratory virus. Research has shown that influenza represents a significant public health challenge due to its seasonal nature, high rate of transmission, severe course of the disease in the elderly, chronically ill and people with weakened immune systems, and a heavy burden on the economy, workforce and health system. Collected results based on summary weekly reports as part of this research on deaths from influenza in the seasons of 2014 / 2015 until 2022 / 2023 in the Republic of Croatia, they continue to monitor mortality in Croatia (10). The expected number of deaths is justified by the fact that indirect death from influenza occurs more often, that is, influenza infection caused by worsening of the underlying disease or complications, such as pneumonia or sepsis (11). Many studies show that, on average, the estimated number of indirect deaths associated with influenza is higher than the estimates for direct deaths from influenza (12). For this reason, further more detailed studies of the association between influenza and other diseases are needed to obtain estimates of influenza-related mortality for a wider range of outcomes and to obtain a more comprehensive picture of the burden of influenza on mortality. A study published in 2020 in Austria estimated that globally 389000 deaths from respiratory causes were associated with influenza (13). Among those who have died due to the flu in the Republic of Croatia, people over the age of 65 predominate, which is to be expected because this is precisely the risk group for death from the flu, and it is important to protect and vaccinate this particular population and emphasize the effectiveness of the flu vaccine in elderly and immunocompromised persons (14 - 17). According to research conducted in England and Hong Kong, older men have a higher mortality rate than women, which coincides with the results of this research, which showed that in the Republic of Croatia, more men than women die from the flu (18 - 20).The highest number of deaths is recorded from the beginning of January to the end of February, which corresponds to the time of the flu epidemic and the highest number of patients in flu seasons. One of the key factors analyzed in this research is influenza vaccination and its association with mortality. The results of the research confirmed the expected statement that there is a statistically significant relationship between vaccination status and the reduction of mortality from influenza (21). The majority of deceased persons with known vaccination status in the Republic of Croatia were not vaccinated against influenza, the same correlation between

vaccination coverage rates and estimates of influenza-related mortality also appears in other European Union countries (22). The combined results of five European studies show that, in all age groups, the effectiveness of the flu vaccine in the 2017/18 season was 25 to 52 % against all types of flu (23). While a prospective cohort study in Sweden confirmed that influenza vaccination is effective in reducing mortality especially among the elderly (24). The results of this study according to the Cox regression model regarding the statistical significance of the vaccination status of the deceased agree with the results of a ten-year Swiss study that showed that the influenza vaccine has a significant protective effect in terms of mortality, reaching a mortality reduction of 13 % (25). It is therefore worrying that the mean percentage vaccination rate of the elderly for the 19 member states of the European Union was 47.1 % (ranging from 2 % to 72.8 %) in the period from 2016 to 2017 (26). Accordingly, this epidemiological analysis of influenza mortality in the Republic of Croatia emphasizes the importance of influenza vaccination as an effective strategy for reducing mortality and disease burden. Continuous monitoring of epidemiological trends and the implementation of preventive measures are key to suppressing influenza and protecting the public health of the population. Further research on this topic is needed, as this study was limited by the lack of information on patient comorbidities that affect outcomes, and integration of this data into future research would provide a better understanding of the interactions between influenza and other health conditions and help identify the most effective prevention and treatment strategies.

CONCLUSION

In all flu seasons, we record the highest number of deaths in people aged 65 and older. Most deceased persons with known vaccination status were not vaccinated against influenza. The results of this research point to the need for stronger public health campaigns that would encourage a larger percentage of the population to get vaccinated against the flu. It is important to continuously monitor epidemiological reports of cases and deaths related to influenza in order to react in a timely manner and implement appropriate preventive measures and develop strategies aimed at reducing mortality and improving the health of the population.

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EPIDEMIOLOŠKA ANALIZA MORTALITETETA OD GRIPE U REPUBLICI HRVATSKOJ

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SAŽETAK

Uvod: Influenza ili gripa je akutna zarazna bolest dišnog sustava uzrokovana jednim od virusa gripe A, B ili C koja se neizostavno pojavljuje svake godine u obliku većih ili manjih epidemija, s izraženim brzim širenjem unutar populacije. Veći broj smrtnosti pojavljuje se u mjesecima kada traje epidemija i povezuje se s povećanim brojem upala pluća, pogotovo u starijih ljudi Cilj istraživanja: Analizirati mortalitet od gripe u Republici Hrvatskoj i razmotriti povezanost mortaliteta s cijepnim statusom.

Materijali i metode:Provedena je retrospektivna presječna epidemiološka studija između siječnja i travnja 2024. godine. Analizirani su podaci umrlih od gripe od 01.01.2014. do 31.12.2023. godine u Republici Hrvatskoj prikupljeni na Službi za epidemiologiju zaraznih bolesti Hrvatskog zavoda za javno zdravstvo.

Rezultati: U promatranom razdoblju u Republici Hrvatskoj od gripe oboljelo je 65 321 osoba, od toga 227 prijava su imale smrtni ishod uzrokovan infekcijom gripe. Među preminulima 70 % prevladavaju osobe u dobi od 65 godina i starije, a 20 % osobe u dobi od 30 do 65 godina života. U prosjeku više je muških osoba umrlo te 63 % ispitanika nije bilo cijepljeno, kod 32 % ispitanika nije bio poznat cijepni status, a njih 5% je bilo cijepljeno protiv gripe. Zaključak: U svim sezonama gripe najveći broj smrtnih ishoda bilježimo u osoba u dobi od 65 godina i starije. Većina preminulih osoba nije bila cijepljena protiv gripe.

Ključne riječi: gripa, smrtnost, epidemiologija, cijepljenje, Republika Hrvatska, prevencija

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